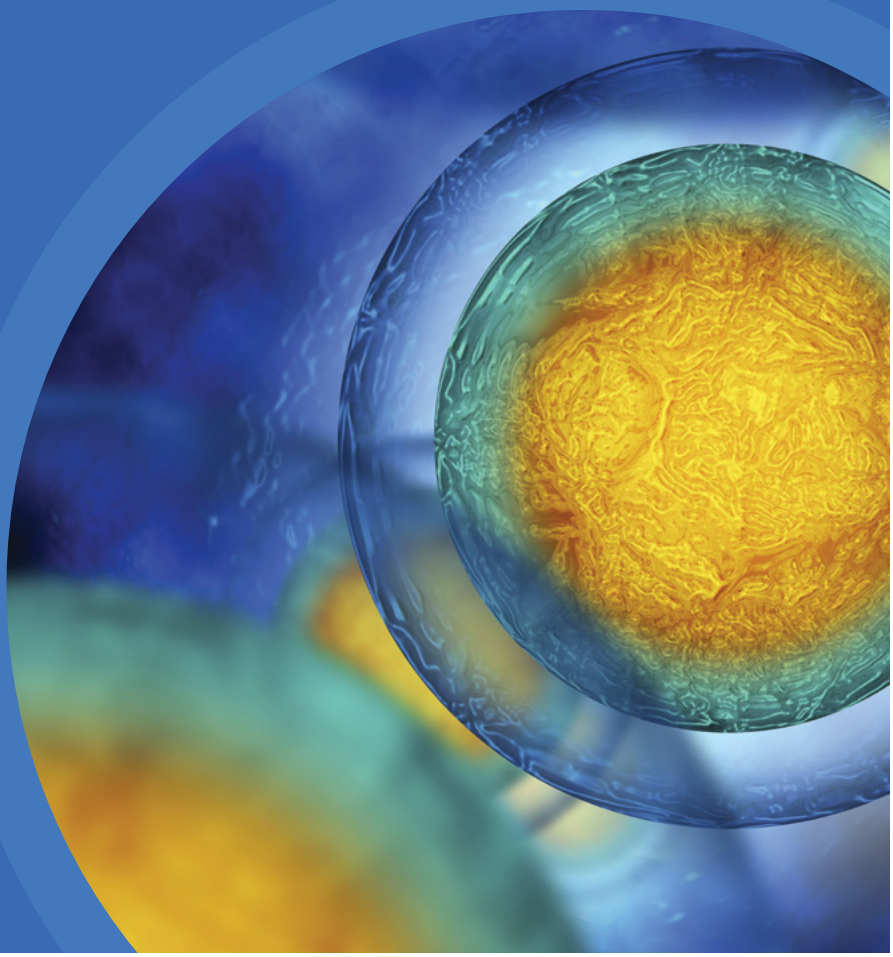
Nsight

NB Research Report

Manufacturing Matters in Cell Therapy

2016



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Report Goals and Objectives

The focus of this report is to outline recent key advances in the manufacturing of cellular therapies and to clearly outline the state of the cell therapy market. Here we delineate the manufacturing process in detail, including key factors that influence companies to manufacture in-house or to outsource, elements essential to the success of current leaders in the cell production field, and competitive intelligence on large and small scale automated cell culture equipment.

Recent market trends are analyzed for a clear view of the cell therapy industry landscape, revealing near term opportunities for growth in manufacturing as well as market entrance and adoption strategies for providers of products and services for cell manufacturing.

Purpose

Valuable competitive intelligence provides more than just the numbers. Shifts in industry landscape and drivers of change can occur well before there is data to analyze. This report provides powerful competitive intelligence, bringing unique insights and first-hand experiences with current systems, key factors driving change in the industry, and the requirements for adoption of new manufacturing alternatives.

Intended Audience

This report will be useful to organizations and individuals within the cell and gene therapy industry, including therapeutics companies, commercial manufacturing organizations, institutional manufacturing facilities, providers of manufacturing equipment products and solutions, the investment community, and stakeholders who are critical in advancing the industry.

Methodology and Information Sources

The market research within this N-Sights report was conducted using both primary and secondary resources. We spoke in depth with key opinion leaders in the industry, CEOs, directors, scientists, regulatory consultants, research institutions, government organizations and the investment community involved in developing and manufacturing cell and gene therapies.

A variety of secondary source material was used including, but not limited to, clinicaltrials.gov, company websites and press releases, white papers, reports from industry and government organizations, industry news sources, industry trade journals, and scientific journals.

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Executive Summary

Cell and Gene Therapy Manufacturing

Cell and gene therapy represent a new human health paradigm, with the potential to provide curative solutions rather than just chronic treatments for a variety of human diseases and genetic disorders. The rapid growth in this new industry is driving increased demand for cellular manufacturing. Given that manufacturing can single-handedly make or break the commercial success of a clinically promising cellular therapeutic, decisions on how and where manufacturing occurs are critical.

First, each therapeutic has unique manufacturing requirements depending on cell type, growth requirements, cell numbers, donor source, and clinical indication. Consequently, there is no typical, one-size-fits-all manufacturing process. In addition, the cost of manufacturing remains high, with negative consequences for the economics and therefore the commercial success of these novel therapies.

Beyond standardizing manufacturing processes, solutions that reduce the cost of goods sold (COGS) remain a significant issue. Finally, the cost-benefit analysis of in-house manufacturing versus outsourcing is complex, but the availability of new systems should shift the balance, making these decisions easier for both companies and their investors.

Here we address the variety of systems currently in use including applications, capabilities, constraints, and new developments. Included are detailed analyses and comparisons of more than 15 commonly used systems such as flasks, bags and bioreactors, as well as nine options recently marketed or currently in beta-testing that provide closed, partially or fully automated manufacturing solutions.

The changing landscape from pre-clinical and clinical development through commercially available cell therapies and the requisite manufacturing requirements is reviewed. For example, immunotherapies have grown to almost 50% of cell therapies in clinical trials. These shifts in

therapeutic areas in development and their impact on the future of manufacturing are covered. Additional factors driving the shift in manufacturing include:

- increasing demand for small-scale as full-scale
- changing FDA recommendations for closed systems and parallel processing
- decreasing the COGS to ensure commercial success, not just clinical efficacy

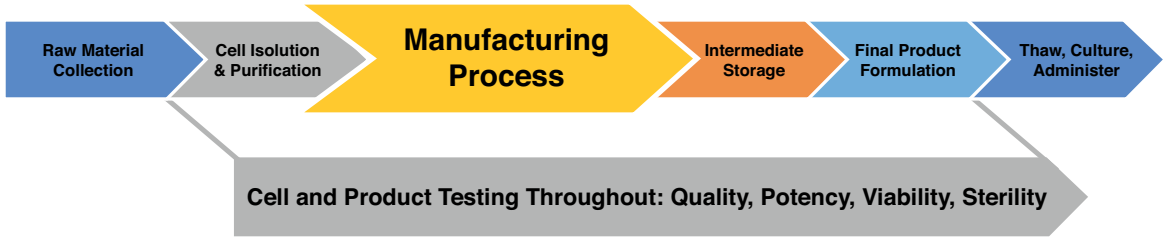
This report provides an overview of key phases where manufacturing decisions occur and the factors influencing these decisions from start-up to commercial scale development. A variety of systems in use and in development are covered, outlining the potential benefits and limitations, as well as current applications. Industry trends and private-public partnerships working to develop more efficient and cost-effective solutions for manufacturing are highlighted. Success in these areas is required, for both the growth of the industry and the successful treatment of patients beyond investigative clinical research.

1. Pre-Clinical Through Commercial Manufacturing

Manufacturing at a Glance

Developing a cell therapy product is a multi-step process, of which manufacturing is only one component (Figure 1). This process and the specific steps involved can vary depending on whether the cell therapy is autologous or allogeneic, fresh or frozen, genetically modified or a combination product. While each step is critical to both a clinical program and a company's commercial success, this report focuses specifically on the manufacturing process.

Figure 1: Cell Therapy Bioprocessing Production Flow



Source: Adapted from R. Lee Buckler, The Cell Therapy Group

Manufacturing Begins at Institutions

Given the surge in academic stem cell research over the past decade, many research institutions have set up on-campus bioprocessing facilities. Due to their lower price point and proximity to additional core facilities, these institutional manufacturing facilities are the outsourcing vendor of choice for early-stage companies. Many companies use these facilities to manufacture cells from pre-IND through Phase II studies. While academic centers primarily provide services for early stage clinical work, there are instances where such centers continue to provide manufacturing services through Phase III studies and in support of a Biological Licensing Application ("BLA").

A handful of institutional facilities report that up to 50-60% of their clients are commercial entities (Table 1). What differentiates these more commercially focused and successful institutional manufacturing centers from their counterparts? ***We found three distinguishing characteristics:***

1. 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 new 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.

The UC Davis facility reported that 50% of their clients are commercial entities. This may increase as companies shift their manufacturing to California in order to be eligible to apply for funding from the California Institute of Regenerative Medicine (CIRM). Similarly, 50-60% of City of Hope's manufacturing workload is for industry clients. The most common cell types that these centers manufacture are hematopoietic stem cells, adult mesenchymal stem cells (MSCs), induced pluripotent stem (iPS) cells and human embryonic stem cells. They also cite examples of manufacturing T cells, dendritic cells and tissue-based products. In terms of numbers of cells manufactured per program, or length of time for manufacturing, academic facilities stated that there are no typical, or average manufacturing programs.

These highly focused Institutional Centers and others like them should be the starting point for both early-stage cell therapy companies needing manufacturing expertise, and corporations seeking validation and adoption of novel manufacturing solutions.

Table 1: Select Institutional Manufacturing Facilities

Facility	Clinical Stage				Resources	Growth
	Pre-IND	Ph I	Ph II	Ph III		
Waisman Biomanufacturing	○	●	●	○	5 suites; 5 staff	
City of Hope	○	●	●	○	2 GMP facilities, 26,000 ft2; 60 staff, most with industry experience	Demand increasing; Want to close, speed up, standardize system
Fred Hutchinson	●	●	●	●	4 suites; 35 staff, most with industry experience	High demand; doubled staff every year for the past two years
UC Davis	●	●	●	●	6 suites	Anticipate growth as companies translate to clinical manufacturing; funded by CIRM

These facilities offer their services to academic researchers and cell therapy companies alike.

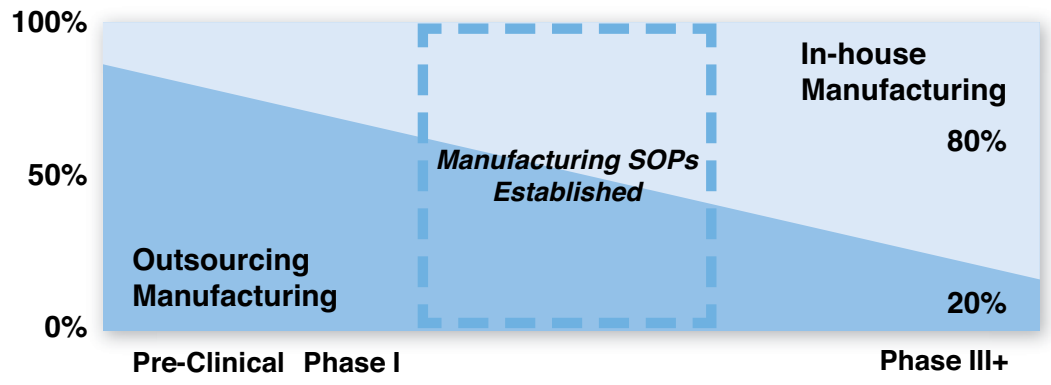
Sources: Primary Interviews | ● Provided ○ Not Provided

The Transition To Commercial Manufacturing

The typical early stage cell therapy company lacks the resources for implementing internal manufacturing capabilities. Instead they outsource to fulfill their manufacturing demands, particularly during pre-clinical and early stages of clinical development. In fact, our research shows that **80% of early stage cell therapy companies outsource their manufacturing** from pre-Investigational New Drug ("pre-IND") through Stage II studies. At later stages of clinical development less than 20% of companies outsource. Instead they develop in-house manufacturing capabilities. Companies typically develop their commercial manufacturing processes and determine

whether to continue to outsource manufacturing or bring it in-house between Phase I and Phase III clinical trials (Figure 2).

Figure 2: Manufacturing Decisions During Clinical Development



Sources: Primary Interviews

The Role of Contract Manufacturing Organizations

As companies mature to conducting later stage clinical trials, a small percentage (less than 20%) of companies continue to outsource their manufacturing. Most who do continue outsourcing use commercial CMOs instead of academic manufacturing facilities because of their increased expertise and manufacturing capabilities. Based on feedback from industry interviews, for companies requiring U.S.-based manufacturing, Lonza, Progenitor Cell Therapy (PCT) and WuXi AppTec are considered the industry leaders and are preferred by cell therapy companies when outsourcing later stage cell manufacturing. There are several other smaller and/or newer companies growing to address the demand for manufacturing of cell and gene therapies including Brammer Biopharmaceuticals, Cognate, and Pacific GMP.

- **Lonza** is the recognized leader in development, manufacturing and testing services for cell-based therapeutics, with expertise in process development, manufacturing, biopreservation, storage and distribution, and regulatory support. Recently, Lonza and Nikon announced an exclusive collaboration in the field of cell and gene therapy manufacturing in Japan. Nikon will have access to Lonza's quality and operating systems, facility design and ongoing consulting services for the establishment of a wholly owned Nikon cell and gene therapy contract manufacturing business. Nikon's newly formed subsidiary, Nikon CeLL Innovation Co., Ltd., will actively contribute to the early realization of Japan's regenerative medicine market

and over time will expand its business domain into adjacent technology areas. Furthermore, Nikon will also develop equipment and disposables needed to optimize the manufacture of high-quality cells, along with hardware and software from Japan to the international market.

- **PCT** is also focused on manufacturing for the cell therapy industry, having manufactured over 30,000 products and worked with over 100 cell therapy clients. Interestingly, the goal of PCT's newly created Engineering and Innovation department is to address the challenges associated with scale-up and cost effectiveness. A recently announced partnership between Invetech and PCT is focused on the development of a new closed processing system (the "System") for cell therapy manufacturing.

- **WuXi AppTec** offers a range of solutions and GMP manufacturing suite capacities for the expansion or processing of cells for therapeutic or vaccine applications, with clients running clinical programs through commercial manufacturing needs. WuXi is constructing a second cell therapy manufacturing facility in the U.S. – with 45,000 square feet of cGMP manufacturing and support space – featuring flexible clean room design and single-use disposable systems, and will accommodate both planar and microcarrier cell culture systems to meet the critical demands of clinical and commercial supply. WuXi is also expanding their manufacturing capacity in China.

- **Brammer Biopharmaceuticals** is a new CMO being established to provide manufacturing and testing services for cell-based therapeutics, with expertise in process development, manufacturing, biopreservation, storage and distribution, and regulatory support.

- **Cognate Bioservices** provides full development and cGMP manufacturing services to organizations engaged in the clinical and commercial development of cell-based therapeutics. Cognate offers a range of expertise and services to help companies navigate clinical and commercial spaces to optimize and validate manufacturing processes, quality control, clinical trial design, and regulatory support.

- **Pacific GMP**, which primarily manufactures master cell lines for producing therapeutic proteins, has some capacity for cell therapy manufacturing. However, cell therapy clients represent a minority of their business. The cell therapy projects that they do take on are very well defined, well planned, and logistically easy for Pacific to carry out.

Factors Determining 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 that 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.

For this reason and others, the majority of later stage companies (>75%) turn away from outsourcing altogether and develop in-house manufacturing facilities. In order to set up these complex, highly regulated systems, companies seek the input of experienced manufacturing service providers and consultants with knowledge of the regulatory process. They may also in-license manufacturing technology. While in-house manufacturing offers the highest degree of control and the ability to adapt and adjust protocols as needed, 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.

The majority of later stage companies (>75%) turn away from outsourcing altogether and develop in-house manufacturing facilities.

Table 2: Factors Influencing Manufacturing Decisions by Clinical Stage of Development

Early Stage	Late Stage	
Academic Facility	**CMO**	**In-House**
● Process adaptability ● Easy transition to in-house manufacturing ● 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

Sources: Primary Interviews | ● Advantage ○ Disadvantage

The good news is that new manufacturing systems in development will increase process control and adaptability so that trade-offs and transitions between outsourcing and in-house manufacturing will become less significant. 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.

2. The Manufacturing Process

Progression of a cellular or gene therapeutic through the phases in development from early preclinical to late clinical and commercial requires scale-up. However, generating appropriate numbers of the desired cell type necessary to treat patients presents a challenge. A wide range of technologies for cell culturing operations exist. Expansion technology choices for scale-up are driven by cell type (stem cell, immune cell, primary cell), growth conditions (adherent vs. suspension), donor source (autologous vs. allogeneic), and phase in development (early or late).

During manufacturing, cells are expanded in number to reach the desired doses for either individual patient treatment or the establishment of cell banks. Cells may also be manipulated, including stimulation with specific factors, co-culture with other cell populations, or genetic alterations. Cell expansion and manipulation may be done manually or by using an automated system. Currently, the manual approach is the most common, with some steps in the process being automated. The design of the process and the materials used will also depend heavily on the cell type. In general, the devices used during a manual or semi-automated manufacturing may be grouped into several broad categories.

Manufacturing Methods

Methods for scale-up include planar technologies (flasks, plates), bags, bioreactors (stirred tank, perfusion systems, rocking motion) and suspension platforms (microcarriers); see Table 3. In general, scale-up consists of increasing surface area and volume to accommodate a greater number or density of cells. For example, in planar systems scale-up is achieved by increasing the size and number of layers per vessel (e.g. stacked plate cell factories). Similarly, scale-up of bags and bioreactor technologies also requires an increase in size and number of vessels. Some bioreactors contain substrate scaffolds (hollow fibers, fibers or porous structures) that cells adhere to increasing the surface area to volume ratio and hence cell density. The same rationale applies to microcarriers, small beads that can be placed inside bioreactor systems as a scale-up method for adherent cells.

Table 3: Select Cell Manufacturing Solutions		
Sample Products	**Description**	**Sample Providers**
Single layer plates and flasks (T25, T75, T175)	Single layer plates or flasks for both adherent or suspension cells. Used in manual procedures for smaller scale cultures (for example autologous therapies or in the early steps of a process if only a small number of cells are available).	Corning, Falcon, NUNC, BD Bioscience and other manufacturers
Multi-layer stacked flasks	Multilayer flasks allowing for process scale-up while still maintaining the basic principle of flasks. Products include: - Triple-layer T175 flasks (525 cm2 growing area) - Stacked flasks, from 1 – 40 layers, up to 25,440 cm2 growing area - Low profile stacked flask, for example HyperStack 36 layer, 18,000 cm2 growing area	Corning, Falcon, NUNC, BD Bioscience and other manufacturers
Multi-layer flask accessories	Specialized tubing sets and sterile containers for closed-system liquid transfer.	Corning, and other manufacturers
Bags	For cells in suspension. Bags can range in volume from ~30ml to over 3L.	AFC (American Fluoroseal Corp), Gibco, Miltenyi and other manufacturers
Bag accessories	Specialized tubing sets for closed system liquid transfer; sterile welders for sealing of bags; bagged media (frequently by custom order).	Lonza, Gibco, Miltenyi, AFC and other manufacturers

Source: Adapted from R. Lee Buckler, The Cell Therapy Group; Nelsen Biomedical analysis

Table 3: Select Cell Manufacturing Solutions *(cont.)*		
Bioreactors (stirred suspension, rolling and rocking systems, perfusion, hollow fiber)		
Spinner flasks	Simplest dynamic system available, precursor of today's more advanced bioreactors. An open system consisting of an upright bottle with magnetic paddle. For small scale suspension cells or in combination with microbeads.	Various manufacturers, such as Integra
Roller bottle bioreactors	Simple open system bottles, placed in mechanical rotator.	Various manufacturers, such as Integra
ICELLis Bioreactor	Perfusion type bioreactor. Uses a fixed bed with custom macrocarriers automatically perfused with media. Up to 500m2 growing area, 25L volume.	Pall Corporation, Applikon Biotechnology
WAVE Bioreactor systems	Rocking bioreactor system, using a rocking platform and bags. Disposable bags, ranging between 100ml to 500L in volume. Includes aeration, heating and temperature control.	GE Healthcare
CelliGen BLU Bioreactor	Single use, rigid walled stirred tank design, in vessels ranging from 5L, 14L and 50L capacity.	Eppendorf, LabX
Quantum	Hollow fiber bioreactor. Automated cell culture using disposable cartridges in a functionally closed environment. 2.1m2 growing area.	Terumo BCT
Xpansion	Multi-plate bioreactor for adherent cell expansion, containing 10 to 200 plates and dedicated controller for aeration and media changes. Surface area of up to 122, 400 cm2.	Pall Corporation
Nucleo Bioreactor and PadReactor	Similar to the classic stirred tank bioreactor, but using a single use bag with integrated paddle mixing and sparger systems. For various cell cultures.	Pall Corporation, Applikon Biotechnology
FiberCell	Hollow fiber bioreactor for adherent cells, including pump system for media and gas exchange.	FiberCell Systems Inc
Biostat B-DCU II	Stirred suspension bioreactor system for suspension cells and fermentation.	Sartorius
Mobius cell culture Bioreactors	Stirred tank bioreactor, single use, 3L capacity. Systems go up to 200L, more for fermentation, biotechnology (e.g. antibody production etc.).	EMD Millipore
BioLevitator	Bioreactor using magnetic microcarrier beads to culture cells. Includes temperature and gas control.	Global Cell Solutions, VWR
Microbeads	Made of a variety of materials, such as polystyrene, glass and others. Used to culture adherent cells in suspension.	Various manufacturers
G-Rex bioreactor	Modified cell culture flask with a proprietary gas permeable membrane and increased volume capacity. Used for cells in suspension.	WilsonWolf

Source: Adapted from R. Lee Buckler, The Cell Therapy Group; Nelsen Biomedical analysis

Closed, Automated Systems

While there are a number of available technologies to scale-up manufacturing, efficiencies need to be improved in order for therapies to reach more patients. Automation and greater capacities for parallel processing within closed systems are needed.

The concept of an automated, fully closed cell manufacturing system is not unique. A number of products have been introduced into the market (Tables 4 and 5). Automated cell manufacturing systems use robotic arms to perform various cell culture operations. These systems may utilize traditional cell culture flasks or a specifically designed plate, flask or other bioreactor configuration. The more automated systems incorporate plating and harvesting capabilities, media reservoirs and incubators, and enable automated detection of cell parameters, such as cell numbers and viability. All lack capabilities for early stem cell growth and selection. Almost all are lacking automation of the final stages of high-throughput harvesting, freezing, and storage, the exception being the Miltenyi CliniMACS Prodigy System. However, this system has a small capacity, long process times, and no options for scaling up without the purchase of additional units. Overall, users of the CliniMACS Prodigy gave it very high marks for its capabilities, with the major limitation cited as the small size and throughput. Most often, users commented that they wished it came in a larger format.

Market adoption and growth has been high for those products that integrate easily into current traditional CMO facilities and practices, such as the WAVE bioreactor. Sales and adoption have been much slower for those products (TAP and Terumo systems) that are not used by CMOs, but facilitate in-house manufacturing capabilities by cell therapy companies. **There is clearly an opportunity for growth of fully automated, closed systems as a solution for in-house manufacturing.** However channels for use and adoption may need to be found outside of commercial CMO facilities adoption.

Table 4: Automated Features of Selected Closed Manufacturing Systems

System	Features Automation	Fully Enclosed System	Culture	Split & Plate	Automated Sampling	Harvest, Fill, and Finish	Cell Observation	Automated Barcode Tracking	Parallel Processing
Autoculture™ Kawasaki	◓	●	●	●	●	◓	●	●	●
CompacT SelecT™ Sartorius Stedum (TAP Biosystems)	◓	●	●	●	●	○	○	●	●
PANsys3000/4000 PAN SysTech GmbH	◓	●	●	●	○	○	●	○	●
Cellerity™ Tecan	◓	◓	●	●	●	◓	●	○	●
CliniMACS Prodigy® Miltenyi Biotec	●	●	●	N/A	●	●	●	◓	○
Cell Host Hamilton and Life and Brain	◓	●	●	●	○	◓	●	●	○
Quantum® Terumo	◓	◓	●	N/A	○	○	○	◓	○
Xpansion® ATMI (Pall Corporation)	◓	◓	●	N/A	○	○	●*	◓	○
WAVE GE Healthcare	◓	◓	●	N/A	○	○	○	◓	○
G-Rex WilsonWolf	◓	◓	●	N/A	○	○	○	◓	○

*optional microscope attachment
Fully enclosed: From seeding through cell collection.
Automated sampling: Includes cell analysis functions.
Parallel Processing: Allows multiple manufacturing programs simultaneously within the same system.
N/A: Not applicable; due to the design of the system this function is accomplished in an alternate manner or is not required at all for the propagation of cells.

Sources: Company websites; journal articles; white papers; primary interviews | ● *Complete* ○ *Not At All* ◓ *Partial*

Table 5: Specifications of Selected Closed Manufacturing Systems

System	Differentiating Benefits	Limitation	Vessel	Scale Up	Typical Capacity (1 unit)
Autoculture™ Kawasaki	Parallel processing and automatically track via barcode	Requires manual seeding	T flask	increase # vessels	33.6 L (60x T-500 flasks)
CompacT SelecT™ Sartorius Stedum (TAP Biosystems)	Generates assay-ready plates	No cell separation function/ centrifuge	T flask or roller bottles	increase # vessels	4.725 L (90x T-175 flasks)
PANsys3000/4000 PAN SysTech GmbH	Live-Cell Imaging paired with extensive analysis and optional add-ons allowing for Raman spectroscopy and metabolism assay	Requires manual sampling	microtiter plates or flasks	interface for connection with stack incubator	0.405 L (18x T-75 flasks)
Cellerity™ Tecan	CellGEM software (see appendix)	Not fully enclosed	plates or flasks	increase # platforms	15 L (500 Roboflasks)
CliniMACS Prodigy® Miltenyi Biotec	Integrated cell separation by fractionation or magnetic means/ full automation including harvest, fill, and finish	Limited volume	bag	increase # platforms	0.3 L (1 centricult unit)
Cell Host Hamilton and Life and Brain	Pipettes w/out tubing, removing potential source of contamination	Limited volume	multiwell plates	increase # vessels	3.4 L (189x 6-well plates)
Quantum® Terumo	High density manufacturing with small footprint (0.3m2)	Not fully enclosed	hollow fiber	increase # platforms	10.5 L (11,500 hollow fibers with a surface area of 2.1 square meters)
Xpansion® ATMI (Pall Corporation)	Fluoresence-based pH and DO measurement avoids need for physical probes; reduced contamination risk	Difficulty of sampling and visual inspection	multiplate	increase # platforms	21.9 L (200x 2D multiplates)
WAVE GE Healthcare	Affordability with a closed, simple design	Difficulty of sampling and visual inspection	bag	increase # platforms	100 L (2x 50-L cell bags)
G-Rex WilsonWolf	Allows removal of up to 90% of media prior to cell recovery Affordability with a closed, simple design	Difficulty of sampling and visual inspection	gas permeable device	increase # platforms (devices)	2L (10^8 cells per device)

Sources: Interviews, company websites, articles and white papers

3. Emerging Trends in Manufacturing

Biomanufacturing overall is moving to disposable, small-footprint solutions. In addition, semi- or fully-automated, entirely enclosed manufacturing systems are being developed to address critical requirements for the manufacture of cell therapies. Such systems improve manufacturing efficiency by increasing cell density, reducing contamination, and using less space. This shift is essential in the cell therapy industry where the cost of goods sold has been a significant barrier to success. In our discussions with stakeholders, three key factors are contributing to the shift in manufacturing.

Three Key Factors Driving Change

1. Cost of Clean Rooms

> ***"When small-scale is full-scale; the industry needs to find a way to run 3-4 patients simultaneously in fully closed systems without cross contamination."***
> - COO of Commercial Manufacturing Organization

For manufacturing cells from a single donor, or for a single program, one of the bottlenecks associated with current cell manufacturing systems from both a time and cost perspective is the need for a clean room suite that meets ISO Class 7 (Class 10,000) standards – featuring HEPA-filtered air supply, continuous monitoring of environment and equipment, and back-up system redundancy. Scaling up a manual, clean room-based process involves installing additional clean rooms, but clean rooms are expensive to build, maintain, and staff. Simultaneous production of cells from multiple donors is limited in this setting.

2. Variability and Contamination

Inconsistent manufacturing represents yet another challenge solved by new, automated, "plug and play" systems that maintain consistency and quality between batches of cells difficult to achieve with manual processing. Contamination is extremely costly and time consuming leading to the shut down of clean rooms for decontamination and to setbacks in clinical development. Closed systems significantly reduce the contamination risk.

3. Parallel and Small-Scale Processing

For autologous cell therapies, where each donor is a single batch, the requirement for separate production in individual clean rooms presents a significant problem. Given that therapies in clinical trials have shifted significantly to immunotherapies - most of these autologous - in the past several years, there is an unmet need for small scale manufacturing solutions and parallel processing.

Table 6: Voice-of-Customer on Key Unmet Needs

Closed Systems Providing Reduction in Contamination	Simultaneous Multi-Donor Expansion in "Plug-and-Play" cGMP Box	Automated Selection, Inspection, and Testing for Regulatory Compliance
"We just had to put a clinical trial on hold because of contamination in the manufacturing process. Something that decreases this would be a big bonus."	"Simultaneous or concurrent processing is a very real need. A clean room can only process one patient or cell type at a time for fear of cross-contamination. Often CMOs will lock up a clean room for a client because they will not risk cross-contamination. This is what is so compelling about an automated, closed system."	"The problem with bioreactors, and suspension systems is the inability to visually inspect, and to quantify cell density."
"Simply reducing the contamination rate below 0.05%, that would be a big deal."	"This would create an exponential decrease in cost. Instead of 5-10 clean rooms for 5-10 cell manufacturing programs you may not even need one. It would also significantly reduce the number of FTEs required. Overall it would significantly reduce COGS."	"Anything that can help with regulatory compliance is of great benefit. Typically with 10 day culture selection and expansion you want to be able to take data at certain points and demonstrate that it is always the same [manufacturing proficiency] process."
	"The biggest bang would be the plug and play aspect, allowing even the smallest group of clinical trials or therapies to have GMP manufacturing capabilities."	"Selected expansion will be a growing area. You can't do this in a bioreactor or bag. It is difficult to take aliquots over time to look at cell morphology."

Sources: Interviews with CMOs, regulatory experts, and cell therapy companies

50% of up and coming cell therapy programs require a scale-up just to the size of a biological safety hood to reach full scale, meaning that the small-scale will be full-scale for these applications. Key features that reduce contamination, facilitate cell qualification throughout manufacturing, automate features of regulatory compliance and allow parallel processing are desired.

"In a single company that we are talking to right now, if all of the different development programs actually work, the company would require 100 different clean rooms in order to do the manufacturing because each product needs to be separated from another product, either by a clean room or by a closed automated system. Obviously building out 100 clean rooms is not feasible."

- CEO of Commerical Manufacturing Organization

Looking Forward in Manufacturing

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.

The emphasis is on single-use, disposables and a small footprint. Current manufacturing solutions improve efficiency by increasing cell density, reducing media and supplement use, 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 production can occur for multiple batches on a smaller scale with decreased sources of contamination.

Automated, hands-free, "plug and play" systems have the potential to transform the cellular manufacturing landscape. In fact, several systems shown in Tables 4 and 5 are capable of manufacturing cells from multiple donors at the same time, eliminating scale-out issues typically associated with clean rooms. Collectively, the shift towards automated, enclosed systems offers more efficient and cost-effective manufacturing solutions that translate to a significant reduction in cost of goods sold benefiting both CMOs and smaller companies alike. These new systems address a noted desire within the industry to close, speed-up and standardize manufacturing. More important, **the simple design and user interface will allow companies to move from outsourcing the manufacturing process during early-stage development to using in-house manufacturing with ease.**

Private-Public Partnerships

The need to improve manufacturing processes in order to successfully bring cellular therapeutics to market is the focus of newly created manufacturing partnerships developed between a variety of industry players, academic institutions, government bodies, and non-profits. The goal of these new manufacturing centers is to develop improved, cost-effective manufacturing solutions. Here are three recently announced efforts:

- **Marcus Center for Therapeutic Cell Characterization and Manufacturing (MC3M):** Georgia Research Alliance, Georgia Tech and the Atlanta-based Marcus Foundation together launched the $23 million Marcus Center for Therapeutic Cell Characterization and Manufacturing (MC3M) at Georgia Institute of Technology. The goal of this research center is to develop processes that will ensure consistent manufacturing of high quality cell-based therapeutics at a low-cost. This is the first center of its kind in the US and will manufacture cellular therapeutics in collaboration with research and clinical institutions around the world.

- **Catapult:** This organization focused on building the Cell and Gene Therapy industry in the UK recently began construction on their new £55 million manufacturing center. Upon its completion in 2017, this is expected to be the world's first facility of its kind, with the goal of providing an infrastructure to enable manufacturing of cell therapeutics for late phase clinical trials and commercial supply. The facility will operate like a "manufacturing hotel". Clients will work with experienced personnel and core equipment, avoiding the commitment of capital to a permanent commercial facility before the clinical success of the product is known.

- **Centre for Advanced Therapeutic Cell Technologies (CATCT):** GE Healthcare recently teamed up with the Canadian Government and Centre for Commercialization of Regenerative Medicine (CCRM) to establish this $28 million center in Toronto, Ontario. The goal of this new center is to accelerate the development and production of approved and commercially available cellular therapeutics for patients. This goal will be strategically accomplished by introducing new technologies to solve manufacturing challenges and providing cell therapy companies with facilities, equipment and expertise to establish and optimize manufacturing workflows. This will allow the production of large numbers of cells required for clinical and commercial use. While GE and CCRM are spearheading this initiative, they have already built a strong industry consortium of nearly 50 collaborators, ranging from large multinationals to emerging biotechnology companies, to help implement their vision. Key companies include Invetech, PCT, Sartorius Stedim, Pall, and others.

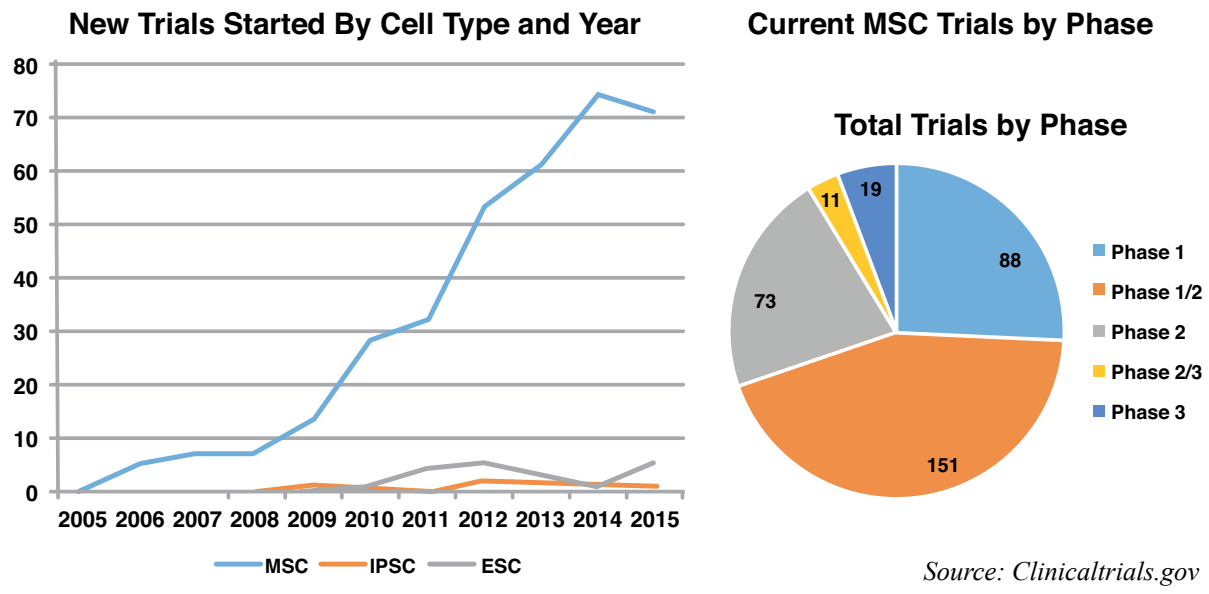
In their effort to avoid commercial failure of clinically-promising cell therapeutics, these public-private manufacturing centers will begin to address the need for increased manufacturing capacity and improved solutions for scale-up and commercialization of gene and cellular therapeutics in a reliable, efficient, and cost-effective manner. It is laudable that those in the industry are joining forces to develop solutions for these foundational issues that hold all stakeholders back.

4. Near-Term Manufacturing Opportunities

Mesenchymal Stem Cells (MSCs)

The largest near-term commercial cell therapy requiring adherent growth conditions remains primarily Mesenchymal Stem Cells (MSCs) and dendritic cells. iPS and ES cells remain largely in the basic research, rather than the clinical domain in the United States and Europe. The number of new clinical trials using MSCs has increased steadily since 2005, while iPS and ES cells have remained at a very low level (Figure 3).

Figure 3: Trends in MSC and Stem Cell Clinical Trials



Source: Clinicaltrials.gov

MSCs have been the most frequently used cell type in regenerative medicine because they can differentiate into a variety of cell types with therapeutic potential. In addition, they can evade the immune system, which makes them attractive for use in allogeneic therapies. Consequently, the industry has focused on large-scale manufacturing of MSCs for commercial production. Historically, MSCs manufactured for clinical and commercial use have been cultured using flasks, with scale-up to hyperflasks and hyperstacks. However, the industry is now moving to microcarriers and Xpansion systems for MSCs. "Hyperstacks are great for visualizing the cells, and for recovery during harvesting, but this is a highly labor and space intensive approach. The FDA wants closed systems, so even cell factories will not be acceptable". (Scientist II, CMO)

Institutions Use Cell Factories:

"For manufacturing MSCs, we use cell factories and for a production run we need to use 24 cell factories and several incubators to get to a desired yield of 3-5x10^9 cells per batch."

- Director of Academic cGMP Facility

Industry Uses Microcarriers and Xpansion:

"While they (MSCs) have been done in hyperflasks, they grow well using microcarriers and for large scale this approach will be best – to avoid the manual labor time."

- Manager of Technology and Business Development, CMO

In the future, cell therapy companies focused on allogeneic MSC approaches may not need to manufacture MSCs on their own. Instead they can rely on companies, such as RoosterBio, to produce high volumes of clinical grade cells that are readily available.

Dendritic Cell Derived Cancer Vaccines

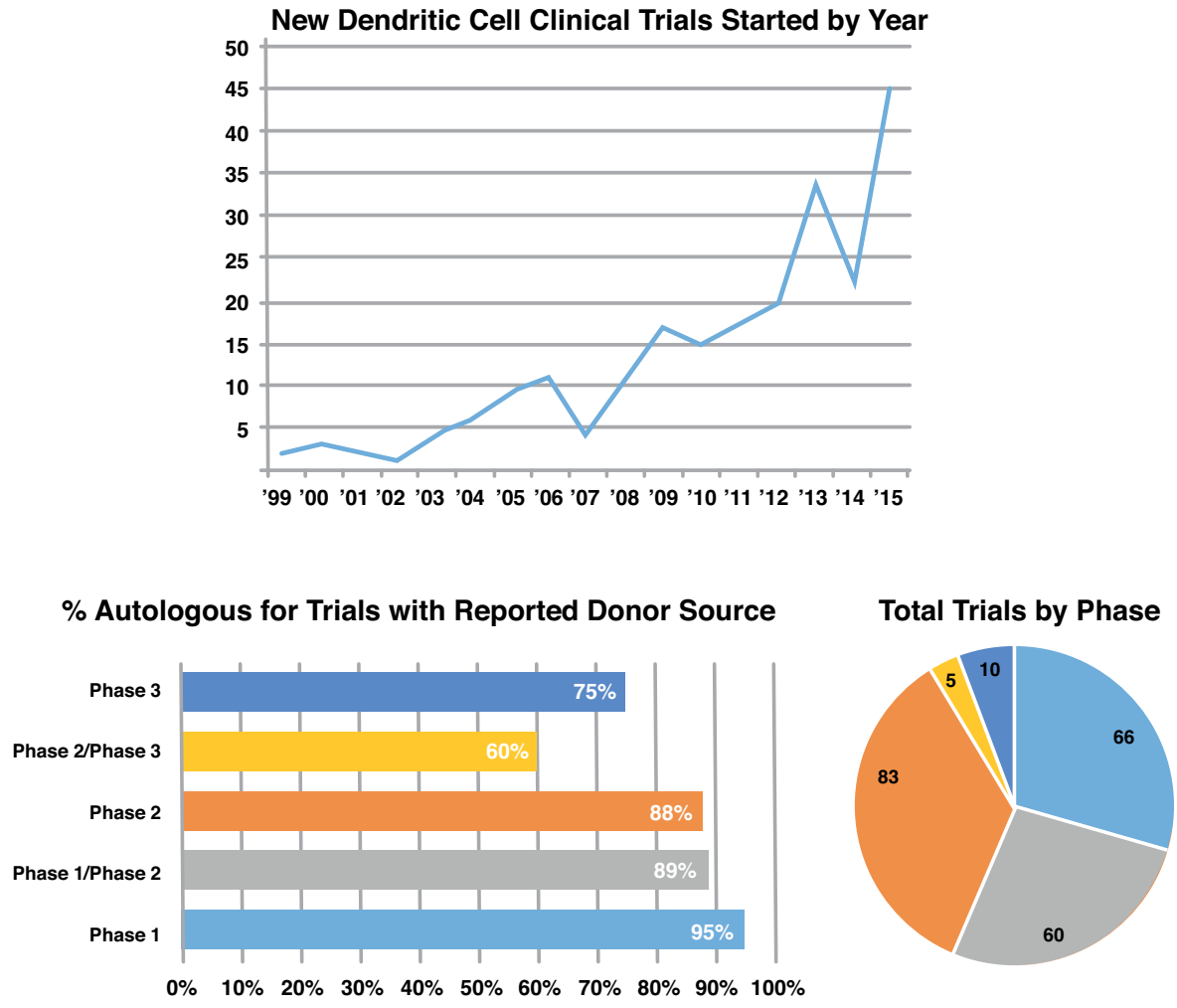
Dendritic cells must grow in a flask because they're very special, difficult, and fragile cells. They can't take the stress of being rocked back and forth in a WAVE Bioreactor.

- Scientist II, CMO

The first FDA-approved dendritic cell therapy, Provenge, was developed by Dendreon. Dendritic cells stimulate antigen-specific cytolytic, helper, and memory T cell responses. This capability has been used as a strategy to develop autologous cancer vaccines. Despite the efficacy of Provenge, the commercial challenges posed by manufacturing contributed to Dendreon filing for bankruptcy. In spite of this, clinical development of new therapeutics using dendritic cells continues, with growth in the number of new clinical trials every year. (Figure 4).

Hopefully, compact, closed systems available and in development will improve the economics of the small-scale manufacturing requirements for these therapies improving the odds for commercial success.

Figure 4: Trends in Dendritic Cell Clinical Trials



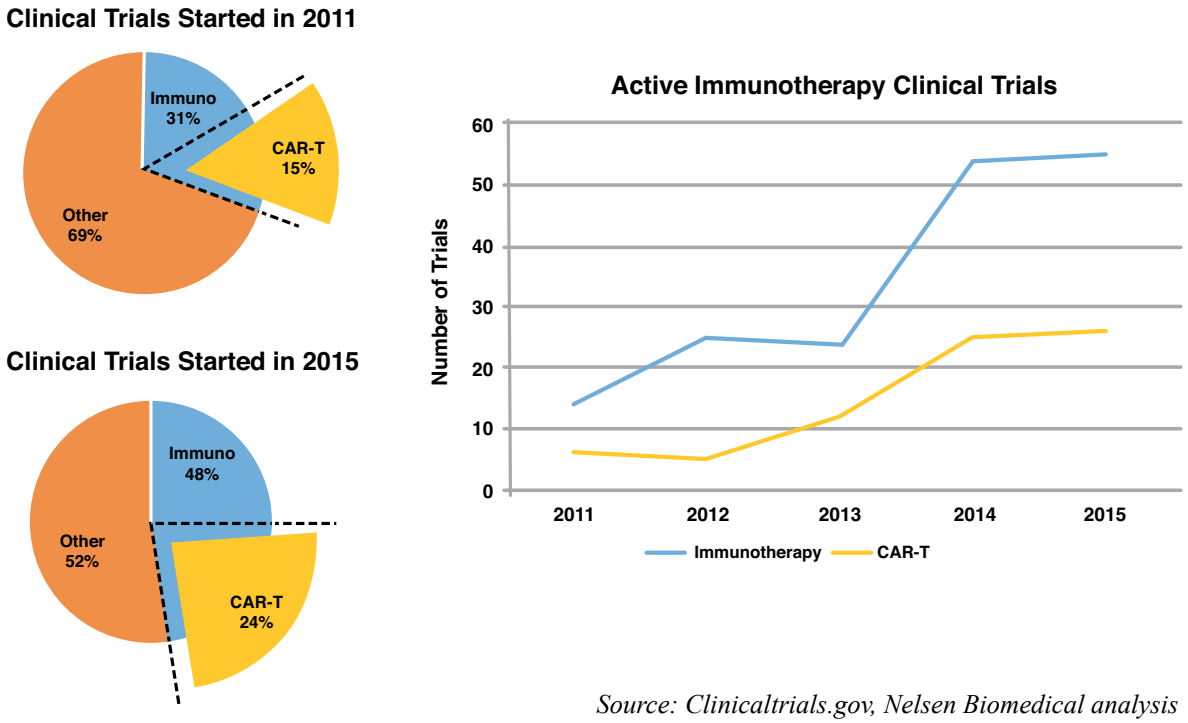
Source: Clinicaltrials.gov, Nelsen Biomedical analysis

In the past five years the number of clinical trials started using dendritic cells has more than tripled. Moreover, for trials where donor source is reported, more than 80% are autologous where small-scale is full-scale.

Immunotherapies

Cell therapies are being developed for treating a vast array of conditions, from cancer, neurodegenerative diseases and ocular pathologies to spinal cord injuries and non-healing wounds. **The most rapidly growing area is immunotherapy.** Immunotherapy clinical trials have increased dramatically in the past five years, as nearly 50% of all new cell therapy clinical trials initiated are immunotherapies, up from 30% in 2011. (Figure 5).

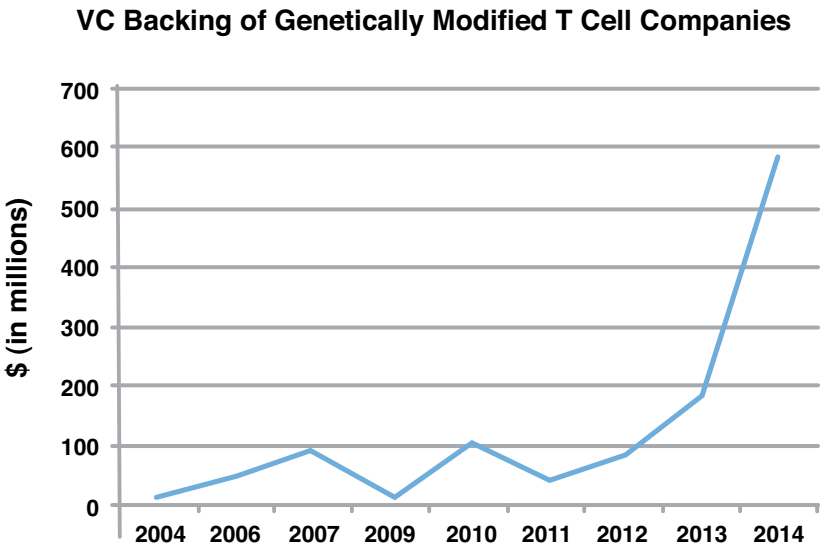
Figure 5: Trends in Immunotherapy Clinical Trials



Source: Clinicaltrials.gov, Nelsen Biomedical analysis

This growth of cellular immunotherapies is not just a clinical phenomenon, but a commercial one as well. Funding from venture capital (VC) firms and partnerships with Big Pharma have been key drivers in the growth of cellular immunotherapy companies with a significant investment in genetically modified T cell approaches in the past five years (Figure 6). With clinical efficacy rates of 90% for some applications, these therapies have a high likelihood of clinical success and commercial adoption, with expected growth well into the future. Overall the T cell immunotherapy market is expected to grow to be a $30 billion market by 2030 (1).

Figure 6: Venture Capital Investment



Sources: Press releases, company websites

Table 7: Pharma Partnerships With Immunotherapy Companies

Large Pharma	Immunotherapy Partner	Year
Novartis	University of Pennsylvania	2012
Celegene	Bluebird Bio & Baylor College of Medicine	2013
Pfizer	Cellectis	2014
Johnson & Johnson	Transposagen	2014
GlaxoSmithKline	AdaptImmune	2014
Amgen	Kite Pharma	2015
Celgene	Juno Therapeutics	2015
Merck	Intrexon & Ziopharm	2015
GE Global Research	Kite Pharma	2015
Roche	SQZ Biotech & Pieris Pharma	2015

Sources: Press releases, company websites

Manufacturing Requirements for Immunotherapies

Cellular immunotherapy approaches use T cells, B cells, NK cells, dendritic cells, and several other cells involved in immune function. The large majority of immunotherapy approaches currently in clinical development are those using modified T cells, such as chimeric antigen receptor modified T cells (CAR-T).

Flasks, roller bottles, WAVE bioreactors and other bag systems, and G-Rex are typically used for manufacturing immunotherapies, typically requiring expansion in suspension, such as CAR-T.

While most of immune cells are grown in suspension, some have total adherent growth requirements and many need one or more steps to be completed under adherent conditions. In general, flasks, roller bottles, bags, and G-Rex are typically used for growth of cells in suspension, such as T cells (and CAR-T).

We interviewed manufacturing personnel from highly active research institution cellular manufacturing facilities and commercial CMOs in order to learn current practices, as well as new approaches likely to be adopted in manufacturing. All those interviewed use a variety of the systems mentioned above, with no one system standing out as more heavily used. Of those interviewed, many academic and commercial manufacturing facilities use the WAVE system and other closed bags. These provide a closed system that can grow up to 15 billion cells in a two week manufacturing cycle. All suggested satisfaction with the benefits provided by these closed bag systems, with the following caveats:

- 50% loss of cells with harvesting, much greater than the 25% seen with other systems.
- Cell stress (cells go from 15 micrometers in size to 10 micrometers by harvest time, indicating suboptimal cell health).
- Instability of the system can lead to a non-uniform distribution of cells.
- Bag breakage.

All those interviewed on T cell manufacturing commented that T cells need gentle manufacturing and harvesting approaches. Improvements to suspension manufacturing systems to provide enhanced recovery may be needed.

Autologous: Where Small-Scale is Full Scale

Autologous cell therapy has been proven to be a highly effective therapeutic approach. Historically however, commercial products have focused on allogeneic therapies because they have been more cost effective to manufacture in large batches similar to traditional pharmaceuticals. However, there is a significant value to tailoring the therapy for individual patients. Additionally, there are negative consequences to over-expanding cells when manufacturing large batches, which may result in decreases in potency and phenotypic drift.

The shifts in the industry toward improving manufacturing efficiencies will lead to a positive change in the cost structure of personalized medicine. Specifically, this will allow for more cost-effective manufacturing of autologous cells. Of the currently marketed cell therapy products, 35% are autologous and 65% are allogeneic, but the inverse is true for clinical development where about 60% of products in clinical trials are autologous (clintrials.gov, Nelsen Biomedical analysis). These up-and-coming autologous cell therapy programs require a scale-up just to the size of a biological safety hood to reach full scale, meaning that the small-scale will be full-scale for these applications.

5. Adoption of New Systems and Services

Optimizing cell therapy manufacturing processes occurs throughout pre-clinical and early clinical development. Some experts interviewed suggested that it would be ideal to optimize the manufacturing process as early as possible, even prior to clinical stages. Others are concerned about standardizing processes while still learning about the biology. All agreed that, manufacturing SOPs should be completed by the end of Phase II clinical trials. The current realities are that:

- There is very little money available at research institutions to do such optimization of processes or to purchase novel systems.
- CMOs state they are constrained in optimization by the processing procedures established at the investigative stage because once something works therapeutically there is a reluctance to change processing significantly.
- Existing organizations, both institutional and commercial, have established infrastructure and processes.

So what's the best way to introduce new systems and gain market adoption? New and expanding CMOs and institutional manufacturing facilities are interested in implementing efficient new manufacturing processes. These facilities present an ideal opportunity for adoption of new automated and closed manufacturing systems.

As academic institutions often are the starting point for manufacturing of a cell-based therapy, adoption of a novel manufacturing system or process in the academic realm will ensure its use through the entire life cycle of the therapy.

This approach for gaining early adoption has been successful in other industries. For example, in the 1980s Apple placed its computers into high schools and colleges for students to use, gaining users early in the lifecycle. In order to reduce initial barriers and facilitate the adoption of novel manufacturing systems in these academic settings, approaches can include: creative purchasing or rental programs, "try before you buy" programs, or inclusion as "beta testers". Early application will also facilitate the transition and adoption of new systems for in-house manufacturing.

6: Summary

The cell therapy industry is experiencing an unprecedented rate of growth. Cell therapies are being developed for treating a vast array of conditions, from cancer, neurodegenerative diseases and ocular pathologies to spinal cord injuries and non-healing wounds. Historically, commercial products have focused on allogeneic therapies because they allowed for more cost-effective manufacturing using large batches, similar to traditional pharmaceuticals. However, **in recent years there has been a shift in clinical and commercial focus from allogeneic to autologous approaches.**

With this shift comes an imperative to solve the economics and efficiencies of individualized cell manufacturing. There is no one-size-fits all manufacturing solution. There are standard transitions that occur through clinical development and during scale-up, where critical decisions regarding manufacturing are made. Young companies use academic institutions for their early stage manufacturing needs. The majority shift to in-house manufacturing at later stages of clinical development, with a small percentage moving to commercial manufacturing organizations. Cost and control are the major factors that influence where companies manufacture.

To reduce costs and increase control of producing cell-based therapies, the industry is heading away from manual-based clean room manufacturing. Closed systems, parallel processing, and automated functionality are the future. Bio-manufacturing overall is moving to disposable, small-footprint solutions. Such systems improve manufacturing efficiency by increasing cell density, reducing contamination, and requiring less clean room capacity.

There has been a greater appreciation by all stakeholders that manufacturing is a critical component in the commercial success of promising cellular therapeutics. Consequently, industry, institutions, and government agencies are collaborating to create new manufacturing centers and to develop improved, cost-effective manufacturing solutions. With these improvements, the promise of these novel therapies can become a reality.

Key Take-Aways

For Cell Therapy Companies

- Partner with commercially trained staff at key institutional manufacturing centers for early-stage 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 to in-house manufacturing or CMOs in later stages.

For Companies Developing 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.

For Cell Manufacturing Organizations

- Target companies developing autologous cellular therapies, specifically immunotherapies and CAR-Ts for near-term commercial manufacturing growth.
- Invest in closed, automated systems with parallel processing capabilities.
- Diversify your business model to grow with the future of “plug-and-play” cGMP systems that will drive in-house manufacturing.

Appendix I:
Selected Manufacturing Systems

AutoCulture™ – Kawasaki

Benefits

- Barcode tracking
- Eliminate need for large cell processing facility
- Culture cells from multiple donors simultaneously
- Decontamination function
- Adaptable for variety of protocols
- Automated media exchange
- Internal observational device (microscope)
- Advanced robotics technology

Potential Limitations

- No automated fill and freeze

Examples of Clinical Applications

- Cells grown in flasks

Cellerity – Tecan

Benefits

- Automated
- Up to 8 cell lines simultaneously
- Harvest module
- Cell count function
- CellGEM software
  - Based on user input, the software estimates media and reagent needs and sends reminders to re-stock

Potential Limitations

- Not fully enclosed
- Cells are collected in a beaker- not ready to freeze and store

Examples of Clinical Applications

- Adherent, Stem cells

Cellmate – Sartorius Stedum

Benefits

- High volume
- Generates assay ready plates
- Accommodate for T-flask or roller bottles

Potential Limitations

- Isolator incubator

Examples of Clinical Applications

- Adherent, allogeneic

Cell Host – Hamilton, Life and Brain

Benefits

- Automated media changes, cell harvesting, plating, addition of growth factors and compounds
- Pipettes without tubing, removing potential source of contamination

Potential Limitation

- Plate-based
- Limited volume

Examples of Clinical Applications

- Adherent
- Embryonic stem cells

CliniMACS Prodigy – Miltenyi Biotec

Benefits

- Automation of complete process
- Internal disposable centrifuge
- Cell Separation
- Integrated microscope
- Manufacture own reagents compatible with system
- Collection into freezing bag

Potential Limitations

- Limited capability, expansion

Examples of Clinical Applications

- Adherent cells and cells grown in suspension
- Stem cell enrichment, virus reactive T cells, including CAR T

CompacT SelecT Cellmate – Sartorius Stedum

Benefits

- Fully automated
- Multiple cell lines simultaneously
- Barcode tracking
- Cell count and other assays
- Automatic harvest, but not into freeze/storage media

Potential Limitations

- No centrifuge

Examples of Clinical Applications

- Adherent
- Stem cells

G-Rex – WilsonWolf

Benefits

- Minimal culture manipulations required
- Less media usage
- No mixing or perfusion
- Linearly scalable from R&D to commercial
- Closed system
- Allows removal of up to 90% of media prior to cell recovery
- Static, functions in a standard incubator
- Cost effective scale up and scale out

Potential Limitations

- No online monitoring system

Examples of Clinical Applications

- Cells grown in suspension
- Cytotoxic T cells, CAR T, TCR, Tumor Infiltrating Lymphocytes, Hematopoietic Stem Cell, NK, T reg

PANsys3000/4000 – PAN SysTech GmbH

Benefits

- Automated microscopy
- Live cell imaging paired with extensive analysis
- 6 cell culture chambers simultaneously under different conditions

Potential Limitation

- Requires manual sampling

Examples of Clinical Applications

- Adherent
- Stem cells

Quantum – Terumo

Benefits

- Semi-automated
- Monitoring system for environmental conditions
- Hollow fiber bioreactor
- Small footprint
- Automated harvest into bags

Potential Limitations

- Difficulty of cell observation

Examples of Clinical Applications

- Adherent cells
- Stem cells

WAVE/Xuri – GE Healthcare

Benefits

- Semi-automated
- Closed
- Monitoring system
- Affordable
- Cost effective scale up and scale out

Potential Limitations

- Rocking speed may affect cell quality and yield
- No visual inspection

Examples of Clinical Applications

- Cells grown in suspension
- T cells including CAR T cells

Xpansion – Pall Corporation

Benefits

- Up to 200 plates can be stacked in small closed footprint
- Cell density and morphology are monitored by optical system
- Automated and closed seeding and feeding
- Fluoresence-based pH and DO measurement-reduced contamination risk

Potential Limitations

- No cell visualization

Examples of Clinical Applications

- Adherent cells
- Stem cells

Xvivo – Biospherix

Benefits

- Scalable
- Customizable
- Modular expansion
- Microscope can be incorporated
- Adaptable for any protocol

Potential Limitation

- Manual procedures only

Examples of Clinical Applications

- Adherent
- Stem cells (cancer, MSC, hESC, hematopoietic)

Appendix II: Glossary of Terms

Adult Stem Cells	Cells from adult tissue that meet the criteria of stem cells. There is a wide diversity of these cell types, including hematopoietic stem cells (HSCs) or mesenchymal stem cells (MSCs).
Allogeneic therapies	Cells are harvested from a donor patient's body, cultured and expanded ex vivo and later infused into a different patient or multiple patients.
Autologous therapies	Cells are harvested from a patient's body, cultured and expanded ex vivo and later re-infused to the same patient.
Biological Licensing Application (BLA)	A biological license application is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical effects of the biologic product. If the information provided meets FDA requirements, the application is approved and a license is issued allowing the firm to market the product.
CAR-T cell therapy	T cells are isolated from a patient or donor, activated, expanded and genetically engineered with CARs *in vitro* and (re-)infused into patient.
Clinical Phase I, II, III	Clinical trials involve three or four steps: • Phase I trials, usually in healthy volunteers, determine safety and dosing. • Phase II trials are used to get an initial reading of efficacy and further explore safety in small numbers of sick patients. • Phase III trials are large, pivotal trials to determine safety and efficacy in sufficiently large numbers of patients. • Phase IV trials are post-approval trials that are sometimes a condition attached by the FDA, also called post-market surveillance studies.
CMO	Contract Manufacturing Organizations provide clients with comprehensive services including process development, pre-clinical and Phase I clinical trial materials, late-stage clinical trial materials, formal stability, scale-up, registration batches and commercial production.
Dendritic cells	Cells that present antigens at the cell surface in the context of Major Histocompatibility Complex (MHC) to be detected by T cell receptors (TCR) on T cells.
Dendritic cell therapy	Hematopoietic progenitor cells or monocytes are isolated from a patient, cultured and stimulated *ex vivo* to produce dendritic cells that are already loaded with antigens. Dendritic cells are then (re-)infused into patient and present antigens to T cells.
Embryonic Stem Cells (ESCs)	Cells derived from an embryo or the embryonic fluid. These cells are pluripotent, meaning they can differentiate into cells of all three germ layers (ectoderm, mesoderm, endoderm).

Genetically modified/ engineered/ redirected T cells	T cells that have been genetically engineered to respond to a specific antigen, often tumor associated antigens (TAA). This is achieved by inserting genes into T cells that encode cell surface receptors able to detect TAAs. These receptors can be T cell receptors (TCRs) or chimeric antigen receptors (CARs).
Immunotherapy	Inducing, enhancing, or suppressing an immune response through modifying function of immune cells, including T cells, B cells, natural killer (NK) cells and dendritic cells.
Induced Pluripotent Stem Cells (iPSCs)	Differentiated cells are harvested and genetically reprogrammed to revert to a pluripotent state that enables them to differentiate into multiple different cell types. These cells are the newest to the field and are still undergoing extensive basic research.
Mesenchymal Stem Cells (MSCs)	Multipotent stem cells that can differentiate into multiple cell types, including adipocytes, chondrocytes, myocytes, and osteoblasts.
Natural Killer (NK) Cell	Lymphocytes that can recognize and destroy non-self or diseased cells in the absence of Major Histocompatibility Complex (MHC)-presented antigens or antibodies.
Pre-IND	Development stage prior to filing for Investigation New Drug status with the FDA. Also called pre-clinical.
Scale-up	Expanding cells in culture to clinically relevant numbers.
Scale-out	Expanding manufacturing capacity for commercial activity.
Stem cell	Undifferentiated cells that are able to self-renew and have the potential to differentiate into specialized cell types (potency) to become any cell type (totipotent), several cell types (pluripotent) or multiple cell types (multipotent). Potency is determined by the source and type of stem cell (embryonic, adult or genetically modified).
T cell	Encompasses several subtypes of lymphocytes with distinct roles in supporting immune responses, such as identifying antigens, destroying diseased cells and remembering past infections. They are particularly targeted against viral infections.

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