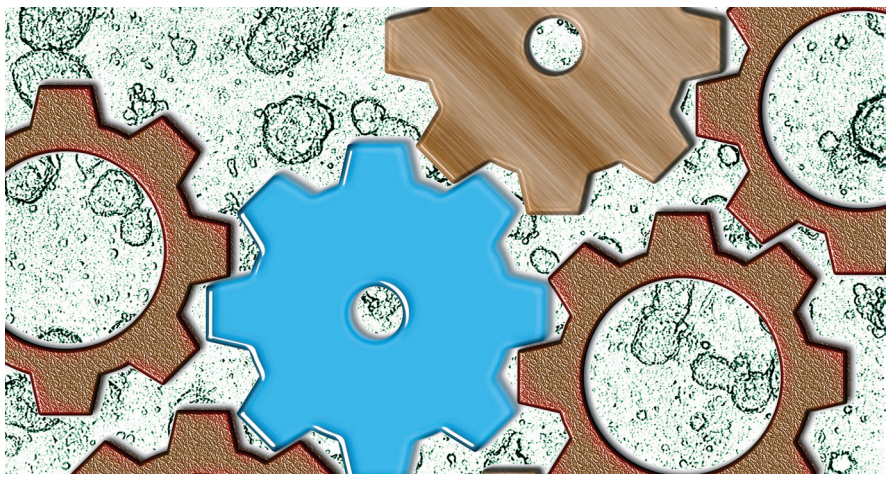
Mastering Industrialization of Cell Therapy Products

An Opportunity for Dedicated CMOs

by Jean-Paul Prieels, Patrick Stragier, François Lesage, Didier Argentin, and Alex Bollen

Incomes currently generated by the global cell therapy market are estimated to be ~US$400 million. That value represents 10 main products, some of which have been on the market since the late 1990s (e.g., Dermagraft and Apligraf, with >$100 million yearly revenues each). Cell therapy product revenues are low compared with those of the biopharmaceutical market (~$100 billion). But the market's growth potential and clinical pipeline are leading to higher expectations. The sector's compound annual growth rate (CAGR), for example, is predicted to reach at least 20% (1).

Recent filings support those market growth expectations. Two products received FDA approval in 2011, LaViv dermal filler based on autologous fibroblasts (Fibrocell) and Hemacord cord blood hematopoeitic progenitor cells for blood disorders (NY Blood Center). Moreover, Provenge therapeutic cancer vaccine for prostate cancer (Dendreon) and Chondrocelect product for cartilage regeneration (Tigenix) continue to gain momentum in their respective markets. A relatively strong clinical pipeline (~300 clinical trials, including ~200 using mesenchymal adult stem cells) also supports potential market growth.



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A Segmented Market

Clinical and commercial pipelines can be categorized into three different primary segments: ex vivo gene therapy, immunotherapy, and regenerative medicine. The latter can be further subdivided into "low-dose" and "high-dose" subsegments.

Ex vivo gene therapy — currently a segment with fewer clinical trials in progress than other markets — brings safety advantages over traditional gene therapies. For example, ex vivo gene therapy clinical development is currently investigated at the San Rafaele/Telethon Foundations, in collaboration with GlaxoSmithKline. It addresses rare monogenetic disorders such as adenosine deaminase deficiency (ADA-SCID) (2), metachromatic leukodistrophy (MLD) (3), and wiskott-aldrich syndrome (WAS) (4).

The **immunotherapy** segment has almost 100 clinical trials in progress and one marketed product (Provenge). Doses are generally limited to a few tens of millions of cells (except for human stem cell transplantations, which require a few billion cells). Such doses should not be a production issue because most immune system cells are grown in suspension and may be processed in Wave bioreactor bags (GE Healthcare).

The **regenerative medicine** (RM) market is the most widespread in terms of doses, which vary from less than one million cells (epithelial/

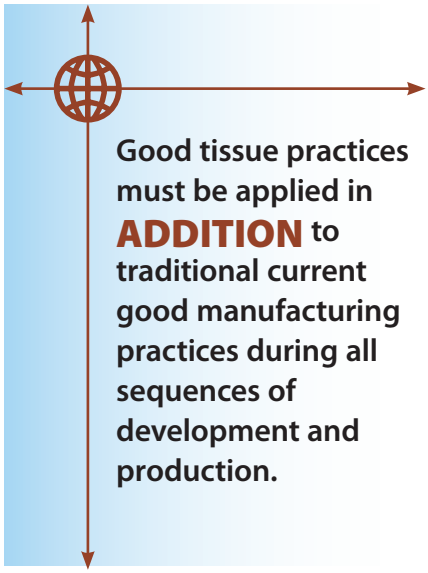
neural cells) to a few billion cells (cardiovascular applications). Consequently, production needs vary by nearly 4 logs. The main technical difficulty lies in the fact that most RM cells are anchorage-dependent, and suitable bioreactors for such cells are not yet widely available on the market. The RM market can be divided into two subsegments: a "low-dose" range (million cells range, such as for orthopedics and CNS applications) and "high-dose" range (billion cells range, such as for heart and diabetes therapies).

"Low-dose" therapies do not present a particular problem in scaling up because million-cell quantities can easily be produced in disposable, commercially available flasks. The technical issue lies in process automation. Some specialized companies (e.g., TAP Biosystems, CaridianBCT, Invetech, and ATMI) can deliver standard or customized equipment for that purpose.

"High-dose" therapies present unique challenges. One dose can easily require up to 10–20 Cell Factory system (Nunc) or tray stacks. That is already a challenge in phase 1–2 clinical trial production. Although such systems can be upscaled and automated, the solutions remain expensive and space-consuming. Innovative bioreactors such as the Xpansion system developed by Artelis and ATMI might constitute a cost-effective solution.

Dedicated CMOs

Burger et al. clearly identified pros and cons for subcontracting cell therapy production to academic or commercial CMOs (**2**). On one hand, although up-to-date expertise in cell therapy is available in academia, that CMO infrastructure may lack in ad hoc and distinct human resources to guarantee appropriate quality assurance (QA) and quality control (QC). By contrast, commercial CMOs generally offer well-established experience in manufacturing biologics and pharmaceutical and in coping with GMP standards. Nonetheless, they may lack specific cell therapy expertise and capabilities. Those limitations are critical because cell therapy manufacturing demands very specific equipment, procedures, and technical know-how. The very few ad hoc service providers available for product development and manufacturing can pose a threat (in project planning and timelines) to product-based companies lacking the appropriate infrastructure and seeking to outsource manufacturing.



Cell therapies must comply with stringent regulations and standards in handling, production, and delivery operations. For example, the requirements to be associated with a registered tissue bank organization and to handle human donor-derived tissues in accordance with the ATMP 61394/2007 regulation have become key compelling constraints to all players in the cell therapy sector. Good tissue practices (GTPs) must be applied in addition to traditional current good manufacturing practices (CGMPs) during all sequences of development and production. Preventing diseases transmission, cross contamination, and sample mix-ups as well as product tracking and traceability are of paramount importance to provide safe and reliable services and products.

Any cell therapy–dedicated CMO also needs to develop and apply reliable, inexpensive, simple, and rapid analytical methods. These methods are quite different from those used in the traditional pharmaceutical sector. Cell therapy developent and production have no "standard" QA or QC. Instead, dedicated and sophisticated methods are adapted for a given product. Cell-based assays such as fluorescence activated cell sorting (FACS) and potency assays are required. In addition, gene expression profiling and genome sequencing may soon become mandatory.

Specific equipment and devices are needed in cell therapy production, including closed systems for cell expansion, separation, purification, and enrichment. Semiautomated processes for critical production steps also should be included in overall production lines. Manufacturing cell therapy products carries specific challenges in cell banking and cultivation methods, regulatory compliance, QC, and logistics. Regulations will undoubtedly evolve according to scientific and technological progress.

The translational process, from scientific concepts and discoveries to innovations and commercialized cell therapy products, remains a risky and costly business. So cell-therapy–dedicated CMOs have a key role to play in this rapidly growing market.

Outsourcing

Access to adequate cleanrooms and resources to manufacture clinical lots can be a major challenge for some cell therapy companies. Outsourcing production activities might be one solution. A CMO would need adequate infrastructure to provide the critical steps (described below) before performing clinical manufacturing. The complete process (excluding development activities) usually takes about six to eight months.

Technology Transfer Phase: Every process that a cell therapy company develops is particular to a product. The initial small-scale process is usually labor intensive and performed at research or hospital units. In most cases, draft procedures are incomplete and raw materials and disposables are not properly qualified (reliable source and quality) or might not even be available as GMP.

The first step in a technology transfer process consists of evaluating basic operations and establishing flow diagrams, bill of materials, bill of testing, and lists of specific equipment. In the next step, CMO experts monitor a process run at a client's facility. CMO personnel then execute a run at the CMO facility (technology transfer laboratory) under client supervision. The run should include quality testing (in process and final).

Process and assay development may not be required always (depending on process phasing and on the project development status). The aim is to develop a robust process leading to reliable and reproducible production as well as a good characterization of a final product.

Equipment qualification and validation may be necessary, even when a CMO has validated cleanrooms and equipment. During this step, check that a solid QC system is in place and have it approved by local regulatory authorities.

GMP Documentation: Once the process is clearly established, a CMO will need to write specific procedures and manufacturing batch records. This document should comply with the CMO's quality system.

Engineering Runs and Training: A CMO should perform a number of engineering runs to demonstrate that the process can be performed reproducibly. This phase can also be used to train operators and finalize manufacturing batch records.

Aseptic Process Validation Runs (Media-Fill Tests): A CMO should prepare a reduced protocol based on a risk analysis of the developed process. All critical steps where a product might be contaminated should be included. Each operator should perform three runs to demonstrate an ability to deliver a sterile product.

Validation Runs: Before starting GMP operations, a CMO should conduct a last phase in performing three runs with patient material. This should take place in a cleanroom with validated equipment and final manufacturing batch records. The products generated during those runs should be tested according to quality control procedures to prove that specifications are met.

Advantages of a CMO

Cell therapy is a promising, emerging sector with major opportunities for existing or newly created companies involved in healthcare. The entrance of this market requires assets in terms of capabilities and know-how. Moreover it often requires an expensive and fastidious infrastructure (buildings, validated cleanrooms, implemented quality system, personnel recruitment and training, facility monitoring and maintenance). That can take up to two and a half years before production activities can be started.

Dedicated CMOs will be key players because they have much of the expertise, equipment, and regulatory tools that may be lacking to most new companies. They can bring added value, including specific tools — bearing in mind regulatory constraints applied to cell-based medicines (EMA ATMP 1394/2007 and FDA HCT/Ps 21 CFR part 1271). The fact that 75% of clinical and commercial applications are still autologous cell transplantations increases cost-of-goods issues and makes dedicated CMOs even more important players.

In addition to having the expertise required for handling and processing particular stem cells, cell therapy CMOs should also master operations involving the application of viral vectors. That process requires a BSL2 level facility, cell transduction, including transduced stem cells populations QC, genome sequencing, and related analytical procedures. CMOs should have a wide diversity of constantly updated expertise. Such know-how may not be available in all CMOs dedicated to the production of ATMPs-HCT/Ps. A CMO's facility should have adequate production spaces (cleanrooms with all necessary HVAC, pressure cascades, confinement, environmental monitoring), validated and approved by regulatory authorities. Its quality systems should cover all aspects of operations (from suppliers qualification program to final product release testing, including a master validation plan, recall procedure, training, waste decontamination. Finally, a CMO should have qualified trained staff in logistics, QA, QC, manufacturing, technology transfer, project management, engineering, and validation.

References

1 *Etude de Thérapie Cellulaire*. Bionest Partners/Leem. February 2010.

2 Burger S. *World Stem Cell Report*. World Stem Cell Summit, Baltimore Maryland, 2009; 150; www.worldstemcellsummit.com.

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