Building from the Ground Up
The Regenerative Medicine Industry Applies Lessons from the Past to Finances for the Future

by S. Anne Montgomery

New treatment modalities — as transformative as they may be of our approaches to human healthcare — still need to be profitable for their developers, provide the sorts of returns desired by investors, and be accessible to patients financially. As many industry experts have told us, the venture capital climate these days is much different from that of the early, giddier days of monoclonal antibodies. And with criteria still-emerging around the world for how regenerative medicines are and will be assessed for reimbursement, the message is clear: The extent to which cell-therapy developers can integrate pricing, reimbursement, and marketing strategies early in development will determine much of their success.

A number of contributors to this month’s supplement spoke with us about these topics as we put it together (see box, right). Additionally, speakers at the recent Cell and Gene-Therapy Forum, organized by Phacilitate Ltd. (24–26 January 2011, in Washington DC; www.phacilitate.co.uk) presented detailed insights into the interconnected elements of business models and eventual pricing and reimbursement strategies. I include here a few of their comments relevant primarily to cell therapies rather than other forms of regenerative medicine. One difficulty lies of course in dealing with very few examples of marketed cell-therapy products so that patients alike still have steep learning curves to traverse. BPI will be soliciting more in-depth discussions of these topics in future issues (hoping to present to you some excellent examples of business models currently in the works). Here, for now, is a brief presentation of critical elements.

**Funding Issues and Investor Perceptions**
As more than one analyst has mentioned, Wall Street valuations are no longer based on blockbuster expectations. The sobering reality is that billions of investor dollars have been lost over the past couple decades as products failed to make it to market. Company valuations currently are based on probability of success and the credibility of management. In vying for funding, cell therapy companies have to address a certain
Investors want more than nifty SCIENCE; they want to see solid TECHNOLOGY.

Annemarie Moseley (CEO of Repair Technologies, http://repairtechnologies.net) offered a slightly different take on cost perspectives in her conversation with us: “The Provenge story is still in progress, but its cost of $93,000 for a three- to four-month survival is different from some of the outcomes in graft-versus-host disease, heart failure, and diseases that have a more chronic component. The cost of Prochymal stem-cell therapy (Osiris Inc.) at $10,000 per dose may be more appealing, for example, depending on the number of treatments needed. So far, the cell therapies haven’t come close to the costs to treat diseases such as Gaucher’s and Fabry’s — so maybe it is fair to say that stem cell therapies may be cheaper for the mainstream than orphan products. Quality of life will have to play a role, but also clearly clinical endpoints are important based on the Osiris story.”

Another element is, of course, the need to educate physicians along with the investment community: Physicians who don’t understand these new therapies will not recommend them for their patients. Doctors also need to know how to present these options to patients who may balk at incurring the related expenses (even if reimbursed) — explaining real and perceived risks and the greater savings possible over the long term. To this end, several Phacilitate speakers emphasized the importance of presenting at medical conferences — reaching an audience outside of the more familiar pharmaceutical development arena. Many people involved in developing regenerative medicines come from medical fields, but for those with
Business models must consider geographically dispersed facility NETWORKS.

backgrounds primarily in pharmaceutical development, such conferences may involve rethinking their networking expectations to help inform and expand their eventual market.

Emerging Business Models
Business models within the regenerative medicines sector show general similarities with the rest of the biotechnology industry. As new companies head from academia and research laboratories into development, they face decisions over whether to
- build or buy a dedicated facility
- lease a facility
- contract for existing capacity with a contract manufacturing organization (CMO)
- partner with other manufacturers
- implement a combination of the above depending on the intended market and logistics/distribution requirements.

As one example, David Urdal (CSO of Dendreon Corporation) outlined Dendreon’s mix of capacity strategies (2). The company scaled up geographic manufacturing capabilities by expanding its New Jersey facility and established 10-year leases (with purchase options) in Atlanta, GA, and Seal Beach, CA. In Europe, the company is using a CMO as a launch facility and plans to build a facility of its own in Germany.

Urdal explained key sourcing decisions related to establishing supply chains for Dendreon’s various centers — with emphasis on cost control and economic use of resources. Call centers were outsourced; a company has to be able to contact doctors and patients quickly, and such resources are already established. Apheresis centers provide

specialized services when such expertise does not exist within a cell-therapy company. (Urdal mentioned that his company works with 150–200 centers around the United States, which suggests that this aspect alone can entail documentation and logistical requirements that may come as a surprise to a fledgling company.)

Transportation services were outsourced, given that existing services suited the needs of both the company and its product. That is not always possible; some companies will need to develop their own shipping services (a good example is Advanced BioHealing), and others may still need to make use of couriers for critical shipments of patient materials. Manufacturing, however, was kept in-house at Dendreon to ensure control and monitoring of the process and thereby “ownership” of risk.

Recognizing the need always to address future markets, the company has an advanced planning system to help manage its supply chain.

As a later speaker summarized, cell-therapy business models must consider geographically dispersed networks of cell-collection facilities, engineering services, manufacturing, distribution, logistics, and treatment facilities. Robert Preti (president and CSO of Progenitor Cell Therapy, LLC) emphasized that cell therapy companies need to think through their phase-specific development needs with an eye toward integrating available solutions. He and others stressed the importance of anticipating evidence requirements throughout a product’s lifecycle, generating a “stream of evidence.”

Reimbursement
In our discussions with supplement contributors, common points appear regarding reimbursement for (therefore access to) cell and gene therapies. A good point to make at the outset is that the FDA’s approval of a drug or therapy doesn’t guarantee favorable clinical and reimbursement decisions. To make their best argument for reimbursement, companies need to show favorable outcomes in real-world applications, demonstrating that a proposed therapy is “reasonable and necessary.” As one source describes it, determining medical necessity is often far from simple.

The dilemma comes from several factors, the first of which is terminology. There are almost as many definitions of medical necessity as there are payors, laws, and courts to interpret them. Generally speaking, though, most definitions incorporate the principle of providing services that are “reasonable and necessary” or “appropriate” in light of clinical standards of practice. A lack of objectivity inherent in those terms can lead to widely varying interpretations by physicians and payors, so the care provided may not meet the definition. And the ultimate decision as to whether services are medically necessary is likely to be made by a payor reviewer who never even sees the patient.

In the United States, for example, Medicare defines medical necessity as services or items reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. Although that sounds like a pretty solid rule, the Centers for Medicare and Medicaid Services have the power under the Social Security Act to determine whether a treatment method is reasonable and necessary in each case. Even if a service meets the necessary criteria, coverage can be limited if that service is provided more frequently than allowed under a national coverage policy, a local medical policy, or a clinically accepted standard of practice (3).

Among other factors, a manufacturer has to show that its therapy will improve quality of life when measured against an existing standard of care (not a placebo, for this class of therapeutics). Another point that might surprise some readers is that in Medicare’s perspective, reimbursement decisions don’t rest on a cost-effectiveness analysis. But like other payers, that agency might certainly consider the continuing impact of the economic burden of the disease without a new treatment regimen or modality.
The European approach to making reimbursement decisions is surprisingly similar, as outlined in the Phacilitate presentation by Wilfried Dalemans, CTO and vice president of regulatory affairs for TiGenix in Belgium (4). He said that a company needs to demonstrate its product’s clinical benefit, effect on quality of life, safety and side effects, cost-effectiveness, and durability of treatment effect. Data should be presented comparing a product with relevant other treatments. His advice for companies developing their business plans is to
- Start early in anticipating reimbursement issues
- Involve all stakeholders in the company
- Understand national regulatory expectations and requirements
- Use relevant endpoint parameters in clinical trials and seek out the right target population (which will show the highest benefit/value of the treatment)
- Include a subpopulation analysis and a relevant comparator group.

"Obtaining and defending reimbursement is ongoing for the lifetime of a product," supplement contributor Dawn Driscoll told me. "It is never ‘achieved,’ never ‘done.’ For cell therapies in particular, reimbursement may at worst need to be defended for each patient. At best, every payer has annual budgets to balance, so pricing and reimbursement for costly therapies will always be under pressure.”

Considering the emphasis on target-population analysis for personalized medicine, the implication is that companies might find better success by pursuing therapies for more focused indications (rather than those that are broad-population-based) — diseases/conditions with few other existing standards of care, that is. Because cell therapies and personalized medicines offer tools for more specific genetic analysis of target populations, the tradeoff against the blockbuster model may be in a greater percentage of efficacy in a more focused market.

Medicare Decision Process: Going into greater detail about how some reimbursement decisions are made, Clifford Goodman (vice president of The Lewin Group, www.lewin.com, and chair of the Medicare Evidence Development and Coverage Advisory Committee, www.cms.gov/FACA/02_MEDCAC.asp) talked about the importance of “evidence requirements in the era of comparative effectiveness.” Research into comparative effectiveness involves demonstrating a therapy’s impact on outcomes of healthcare decisions (5). It entails attributes such as
- direct “head-to-head” comparisons against standards of care, not placebos (considering all types of accepted interventions, with emphasis on real-world effectiveness rather than efficacy/ideal conditions)
- emphasis on health outcomes
- use of diverse methods and data sources as appropriate
- ability to discern subgroup differences (heterogeneity of treatment effects).
As his example, Goodman outlined questions and related “scores” as applied to Provenge cell therapy, the first such product to be subject to comparative effectiveness research and related inquiries to support policymaking by MEDCAC. Analyzed and scored were the following issues:

- Confidence level for survival outcomes, control of disease-related symptoms, and “avoidance of minimization of the burdens associated with anticancer therapy while maintaining overall survival and control of disease-related symptoms”
- Confidence level for evidence supporting improvement in overall survival time and control of disease-related symptoms
- Confidence that conclusions are generalizable to unlabeled uses and that they apply generally to patients in demographic groups that may not have been represented (or were underrepresented) in enrolled clinical trial populations
- Ability to predict how patients will respond based on evaluation pretreatment of factors such as site(s) of metastases, blood levels of biomarkers, and associated pain ($).

**A POSITIVE BEGINNING**

All these points admittedly only touch the surface of policies in development. It is clear, though, that opportunities do exist for regenerative medicine companies to work toward developing lucrative relationships with potential partners and investors even in these sadder-but-wiser economic times. Understanding the intracacies of business planning and incorporating current knowledge of reimbursement issues early in that planning — as well as realizing the need to educate physicians and target patient populations — will help regenerative medicines achieve the success that these efforts so richly deserve.

**REFERENCES**


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