*White Paper*

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# Guide to Planning for Commercial Success of Cell and Advanced Therapies

Key Considerations for Successfully Moving from the Clinic to Commercial-scale Production

# Abstract

Much mystique and mystery surround the emerging industry of cell and advanced therapies. As companies progress toward commercial manufacture with potential game changers, such as cures for cancer and diabetes, the industry could be on the verge of significant breakthroughs; however, with no real successes to date, an important question is raised: What core attributes are required to achieve commercial success?

Since 2004, Invetech has been developing innovative new research platforms and commercial production systems for cell and advanced therapies. Based on our experiences, we've identified five key elements essential to successfully moving from the clinic to commercial-scale production. In this white paper, you'll find steps to achieving each, plus learn about some of the trade-offs and decisions that must be made to avoid the "valley of death" and enable successful progression to commercialization.

# About the Author

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Richard Grant is the Global Vice President of the Cell Therapy Group at Invetech. Richard has more than 30 years of product development experience across the biomedical, cell therapy, and industrial product fields. A member of Invetech for more than 15 years, Richard has been instrumental in building Invetech's cell therapy automation capability and continues to have a deep involvement in projects ranging from drug discovery and cell separation instruments to functionally closed, automated cellular therapy production systems.

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Since early 2004, Invetech has worked with organizations dedicated to cell and advanced therapies, helping them develop and implement commercial-scale manufacturing for a wide range of therapies. Over the years, we've identified five key elements that are essential for game-changing product development in these fields.

They are:

1. Efficacy
2. Manufacturability
3. Cost of goods
4. Reimbursement
5. Needle-to-needle logistics

## Efficacy

Efficacy is the primary (and in some cases, sole) focus of most young companies. Biotechnology startups are launched on the merit of technology developed in academic institutions, and their initial focus is to produce positive experimental results—without them, product development would stall before it even began.

To take a treatment from concept to proof in cells involves jumping several hurdles: proving potential in small-animal models, advancing to larger animal models, winning grants to complete their work, convincing technology transfer-office agents to fast-track their technologies, running experimental programs, and finally patenting and publishing their work.

This entire process is a result of a desire to meet the appropriate clinical trial milestones. It's a crucial operation, but only the first step in a broader production plan for businesses looking to mass-produce treatment once tested and approved. Biotech startups need to also focus on practices that will allow them to scale production while staying fiscally solvent in the long run—efficacy is a must, but it's just the beginning.

***Although a company has nothing without clinical efficacy, achieving such without other successful business practices in place is a fast road to failure.***

The emphasis on efficacy is understandable, but addressing the other four fundamental factors for product success—manufacturability, cost of goods, reimbursement, and needle-to-needle logistics—cannot be postponed for long.

### *Thinking Beyond Efficacy*

Once Phase 1 clinical trials have proven a therapy to be safe—and, in planning for reimbursement, even before then—concrete plans should be developed for other aspects of a successful business. The following must be addressed when starting a planning process:

- How will we manufacture consistently good product?
- How will we manufacture an affordable product?
- How will we receive starting materials, manage manufacturing at industrial scale, and deliver the product to our patients?
- Is there enough headroom between standard of care and reimbursement for us to exist as a business?

# Manufacturability

Like all manufacturers looking to create market-winning products, cell therapy manufacturers must develop and refine their processes to be robust and error-proof.

They need to instill confidence in providers, patients, and regulatory bodies that each step in the manufacturing and supply chain process will contribute to a consistent, reliable product. This requires attention right at the outset to things like workflow, facilities and equipment, use of disposables, data flow, and quality testing.

*Cell therapy manufacturers must develop and refine their processes to be robust and error-proof, using manufacturing equipment that produces consistent and repeatable processes.*

To assist you on the road to cell therapy commercialization, we've created a step-by-step guide to achieving manufacturability, based on our experience in guiding companies to marketing-winning product manufacturing.


### Step 1:
### Understand Your Process and the Requirements to Define Your Problem

Piece together a comprehensive picture of your requirements early on to prepare your business for commercial manufacturing. See if you can answer high-level questions like,"What does commercial scale look like to you?"

Then continue with additional questions to flesh out specifics, such as:

- If you aim to process a certain number of patients per year, how does that translate to doses processed per day?
- What is required (equipment, manufacturing, storage space, staff) to perform each process every day?
- If there are long incubation steps, how will the facility accommodate the number of batches that need to be in incubation in the facility at any one time?
- What will be the effects of scaling up on process flow?
- What is your desired facility utilization?
- What is your ideal manufacturing shift pattern?

In considering the above, if your company is processing 100 patients a day and the incubation time is seven days, even with 24/7 production, there will be a minimum of 700 batches in the incubators every moment of every day. However, with any interruption in processing, or ebb and flow of incoming material, significantly more product needs to be processed. The increased processing will drive down facility use and drive up required equipment capacity (e.g., capital cost) to process that peak load.

### Step 2:
### Turn Your Operation Into an Industrial Process

Reliable manufacturing calls for consistency in quality and low risk for error. A great starting point for this step is to evaluate ways to remove operator error and process variability. Can the current process be validated?

For example, if your worry is loading errors, you could design disposable sets to be quickly and easily loaded onto equipment in only one way. Additionally, you could build in mechanisms that detect errors in loading. These types of design tweaks eliminate or reduce the possibility for operator error, particularly those associated with batch records and data transcription.

As you evaluate your current process, validation should be at the forefront of everyone's mind. A robust industrial process must be able to repeatedly perform complex actions and motions to achieve the same result as the manual process.

### Step 3:
### Eliminate Skill-based Processing Steps

It's important to minimize human interaction in areas that affect product yield or quality. As you complete Step 2, you'll likely identify and prioritize those steps that contain an "art" or skill—an inherent trait of manual tasks that have high variability. Once you've honed in on them, such steps can be made consistent and repeatable by selectively applying engineering design and innovation.

Several examples of skill-based steps are common in cell therapies: manipulating the input sample (selecting cells of interest in an autologous process), manual pipetting, cell counting, or estimating confluence and knocking flasks to release adherent cells. Finding a way to lower variability may require you to repurpose existing technology—or perhaps invent a closed and automated solution to the problem—but a solution is almost always possible.

### Step 4:
### Integrate Data Flows

Reliable data can take your product from viable in theory to successful in practice. Without it, results may never be accurately measured, recorded, and used to make life-saving decisions.


At least 50% of process errors are manual transcription and recording mistakes, rather than errors in process or incursion breaches. Manufacturing execution systems (MES) and batch records should be automated to avoid numbers getting lost or altered along the way. You can significantly reduce the need to manage variations and achieve a faster product release by mapping your process and transferring it to an integrated data management, batch record, and product tracking system. Automatic batch records can significantly reduce the number of operators required, thus reducing recruitment effort and minimizing the staff turnover—an important factor in scaling a manual, open process to a closed commercial-scale manufacturing operation.

### Step 5:
### Manage Cost of Goods

Even with efficacy and a validated manufacturing process, commercial success requires your company to stay financially healthy. You can keep CoG under control by working toward the lowest cost it takes to consistently produce a product that meets identified critical quality attributes (CQAs). Whether or not you meet this goal depends on the following:

- Process development – defining CQAs and refining the process for cost, yield, and reproducibility.
- Manufacturing system development – optimizing use of equipment, disposables, and facilities.
- Timing facility bulids and equipment development – determining the lowest cost path to market.

### Step 6:
### Think in Terms of Scaling Up

Translating your bench-scale laboratory process to industrialized commercial manufacturing is an exercise in efficiency and innovation. You will have no product (or worse, no company) if that cannot be done. You must understand the technology, develop your process, and apply innovation to develop manufacturing solutions that deliver an optimal scale-up solution and final manufacturing process. To this end, the critical factors are:

- Product characterization - what are your CQAs?
- Process robustness and stability – can you make the same product every time?
- Process integrity – how can you error-proof your process?
- Labor and variability – how can you eliminate human-introduced variability?
- Cost – when do you invest in development and pur chasing of Current Good Manufacturing Practices (cGMP) process equipment?

Your process development team must work closely with your engineering development team to refine the manufacturability of your process. The combined team should be thinking in terms of characterization, CQAs,

manufacturing process transformation, equipment use and manual labor, and development time, considering the following inputs:

***Characterize the Product and Identify CQAs***

This sets the stage for your whole scaling plan. Characterizing the product and determining CQAs will identify the impact of process changes—big and small—on your cells. Move away from the “product is the process” paradigm to the true intent of GMP, which is to have a characterized process that is open to continuous improvement. CQAs are not only release parameters, but also process control measures that determine whether you have a manufacturing process, or you’re just flailing around in the dark.

***Transform the Manufacturing Process***

For a company to scale manufacturing, the process should consist of closed-unit operations in the lowest-class clean space possible. One way to do this is by leveraging single-use technologies, where a process is functionally closed and allows manufacturing to be performed in a lower-class cleanroom, e.g., Class C instead of Class B. Doing this can significantly affect both your facility costs and ongoing operating costs.

***Translate the Manual Process***

To move from manual processes to automated ones, choose technologies and equipment that will ensure quality with each interaction.

For example, move from a manual, open Ficoll (GE Healthcare) selection step or a range of traditional centrifuge wash and media exchange steps to performing a counterflow centrifugation process. This is performed in a closed, single-use disposable that can be aseptically connected to both upstream and downstream unit operations which is more suited to commercial manufacturing.

Another example would be to transition from a manual formulation step to one performed as an automated, closed formulation process. This minimizes operator interaction, reducing it to connection of closed processing vessels (both empty and those containing fluid and product) and initiation of the process (pushing the start button).

***Maximize Equipment Use***

Optimize the use of capital tied up in your manufacturing equipment by ensuring high throughput and minimal residence time of products on the most expensive equipment. Transfer long-duration process steps, such as incubation either for transfection or expansion, to low-cost equipment or low-cost spaces (e.g., shared incubators).

***Manage Development Time***

Development of a manufacturing system is at least an 18–24 month project for even the most simple therapies. However, an immediate benefit upon completion is that process validation can occur at your manufacturing site. The timing of your expenditure and finding the resources to support it must be planned in advance and match the deadlines of the clinical program and funding availability.

To be prepared, perform an early assessment of manufacturing feasibility and develop a plan that envisions what the manufacturing operation will look like. This step is key for corporate decision-making, as it paints a vision for the future of your company and provides a useful tool for communication to boards and investors.

***We suggest performing an early assessment of manufacturing feasibility and develop a plan that envisions what the manufacturing operation will look like.***

## Step 7: Plan for Success

Successful commercialization of cell and advanced therapies depend on resolving many complex challenges simultaneously. Failure to resolve just one element can put your entire enterprise at risk, and developing a plan early is crucial to success. Understand how and when to address each element in your manufacturing process so that a viable business can be established when the therapy is approved after Phase 3 clinical trials.

# Cost of Goods

Manufacturability is broadly defined as the extent to which a good or product can be manufactured with relative ease at minimum cost and maximum reliability. By definition, there is significant overlap between manufacturability and Cost of Goods (CoG) as the two are intricately intertwined.

As was mentioned earlier, achieving the lowest cost for a consistently producible product that meets identified critical quality attributes (CQAs) depends on three things:

1. Process development – defining CQAs and refining the process for cost, yield and reproducibility.
2. Manufacturing system development – optimizing use of equipment, disposables and facilities.
3. Timing facility and equipment development – determining the lowest cost path to market.

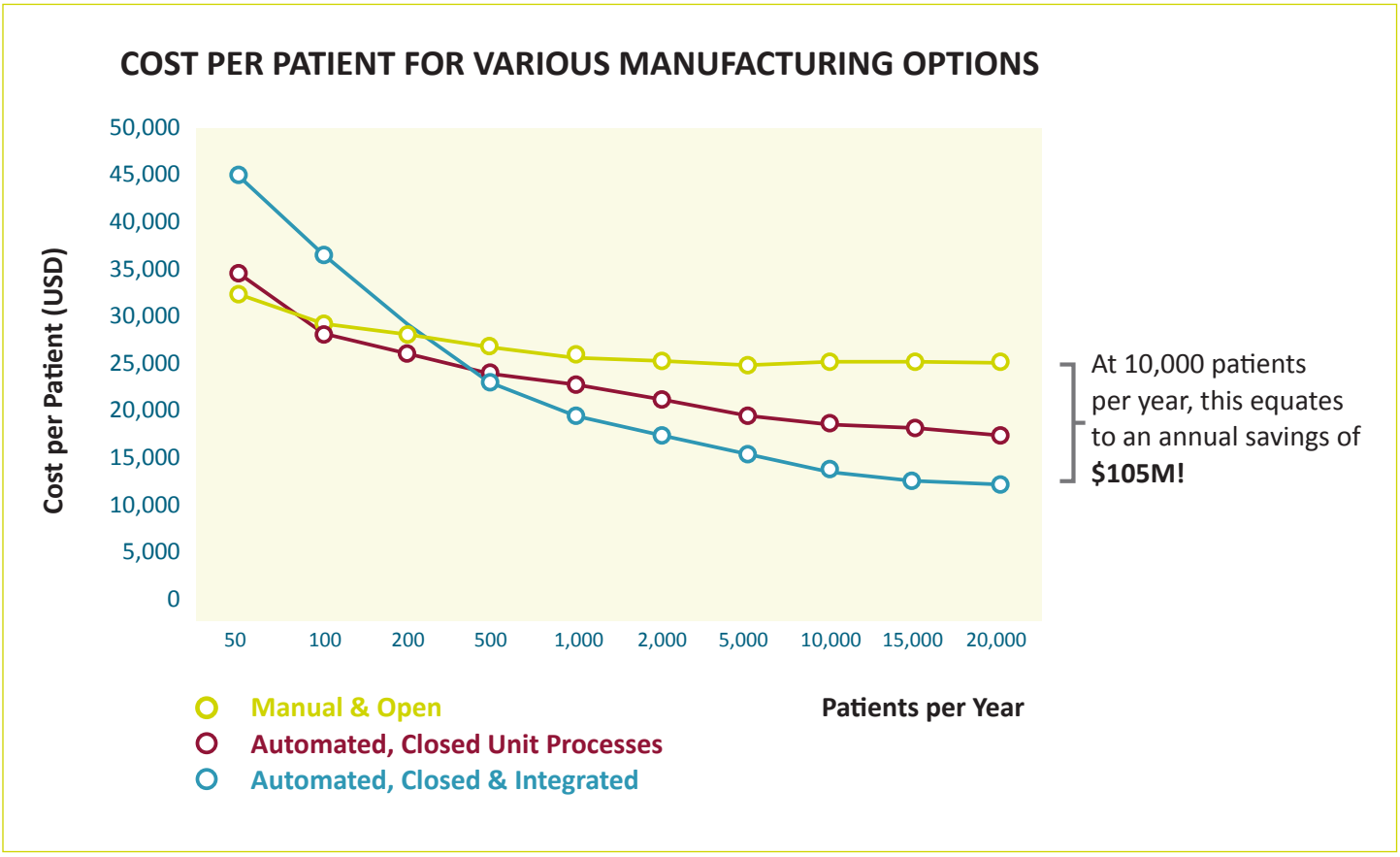
In relation to the CoG for cell therapies, this issue has been a frequent discussion point—especially because of the significant difference between autologous (patient-specific) therapies and allogeneic therapies. The latter sits much more comfortably with conventional biologics and drug manufacturing in relation to CoG: the larger a batch size, the more the manufacturing costs can be distributed across the number of doses produced. On the other hand, with autologous therapies the batch size is one patient. This creates a huge challenge in reducing CoG.

***It's much more challenging to reduce cost of goods for autologous therapies, where batch size is essentially one.***

When looking to reduce CoG for patient-specific therapies, there are two key aspects to consider. The first is moving to a closed process using single-use disposables, which allows significant savings on clean room costs. The second is automation, which allows the development of a more repeatable and reliable process. Automation will not only minimize labor requirements resulting in reduced labor costs, it will also enhance product quality by reducing variability in the process. Single-use disposables and automation are closely connected, since without them it is very difficult to move the process into lower-grade clean room space.

Figure 1.1 shows the scale-up of a patient-specific therapy and what happens to the cost per patient for three process scenarios: manual and open, automated closed unit, and automated closed and integrated. As can be seen, there is a significant savings, greater than $105M (USD), when using single-use disposables on integrated automated equipment.

**Figure 1.1**



Further breakdown of the CoG shows that the key cost drivers are remarkably consistent across the three process scenarios; however, through the combination of closed processing, process optimization and automation, a significant reduction in CoG can be achieved. (Figure 1.2)

**Figure 1.2**

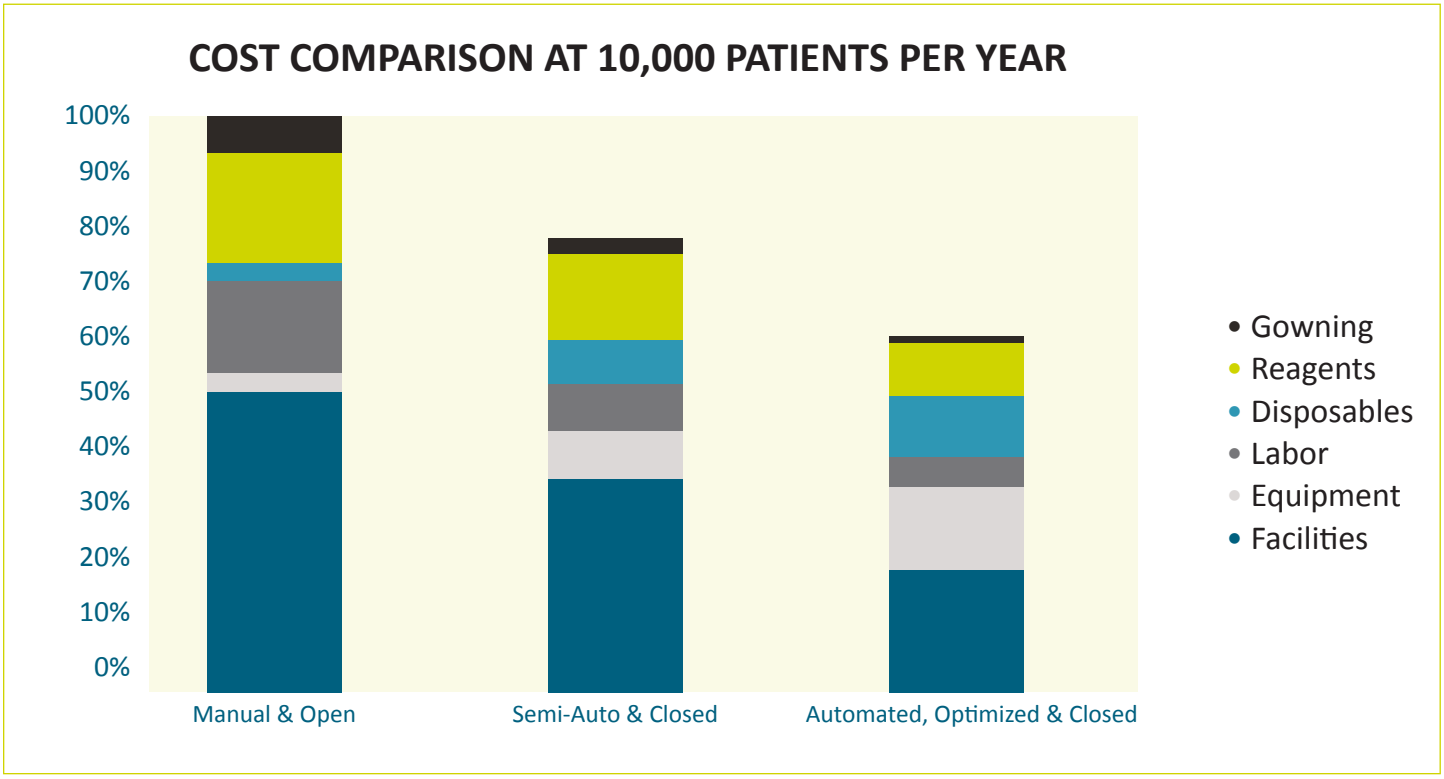
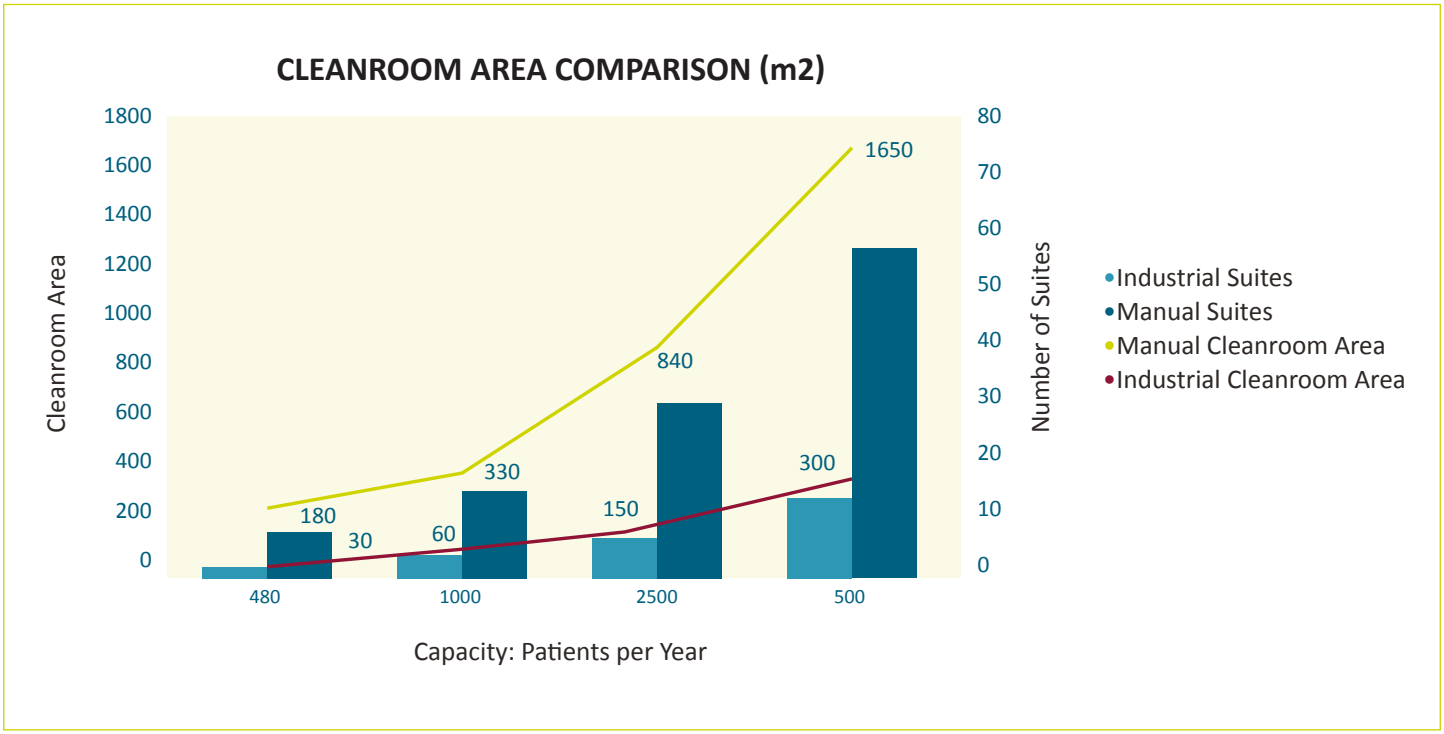


Figure 1.3 shows a comparison of the clean room area required for a scaled manual process and that for an optimized industrialized process. When considering the cost of operating in higher grade clean rooms, it is important to consider not only the initial cost, but also the annual operating cost as the latter is generally much more significant.

**Figure 1.3**



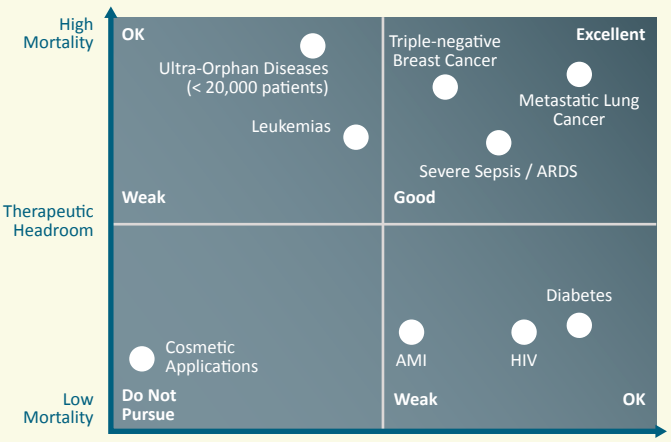

Although process equipment typically represents less than 5 percent of the total CoG, when tailored to the process, it can deliver significant advantages in terms of:

- Scalability
- Cost of therapy
- Labor requirements
- Facility requirements
- Quality

# Reimbursement

Although cell therapies are revolutionary and have instilled much excitement in the biotechnology industry, they can be expensive to produce and deliver. Furthermore, they are arriving at a time when healthcare payers are weighing up the benefit-versus-cost equation. For cell therapies to be successfully adopted into healthcare systems, developers must be critical of cost-effectiveness from the earliest stages of development. Although reimbursement is the last milestone in the long path to revenue generation, it is perhaps the first consideration to make when deciding the viability of a cell therapy product for a particular indication.

**Figure 2.1**




## Mortality

Analyzing mortality data is perhaps the simplest approach. Mortality in a patient population represents the shortcomings of an existing standard of care. Where mortality is high, standard of care is low, and willingness to pay by reimbursement providers is high. Conversely, where mortality is low, standard of care is high, and payers exhibit considerably less willingness to pay (Figure 2.1).

To illustrate this point, consider two hypothetical therapies: a mesenchymal stem cell line being developed for treatment of acute respiratory distress syndrome (ARDS) and a bone-marrow progenitor cell line being developed for treatment of acute myocardial infarction (AMI). The mortality resulting from ARDS is 40%, whereas that of a single AMI is only a few percent. The margin in which a cell therapy developer can show an improvement over standard of care in ARDS is quite large, whereas there is virtually no room for improvement in the way AMI is currently managed by physicians. The amount that a reimbursement provider should be willing to pay for either of these technologies is quantifiable and can be calculated readily.

*Although reimbursement is the last milestone in the long path to revenue generation, it is perhaps the first consideration to make when deciding the viability of a cell therapy product for a particular indication.*

## Average Age at Incidence

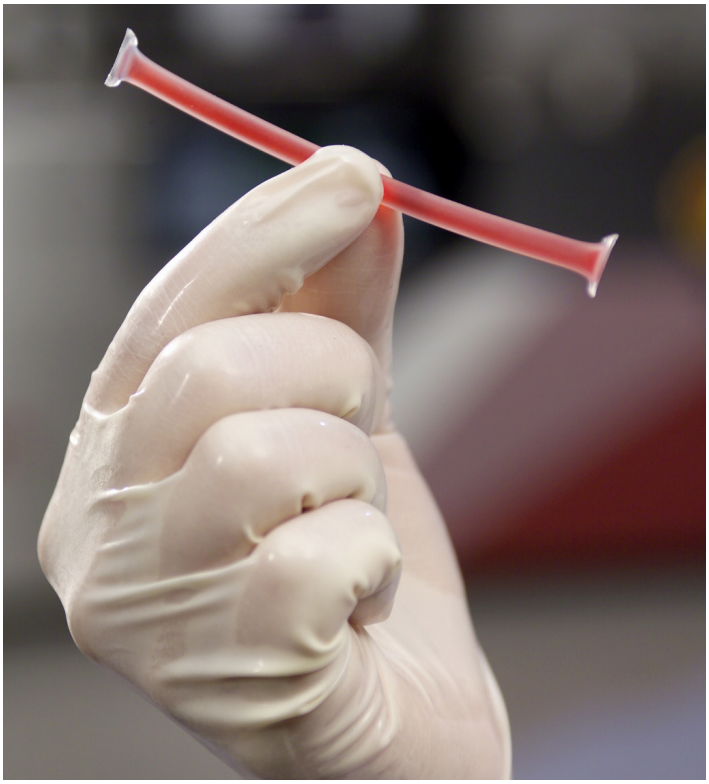
An equally important factor for maximizing payout from reimbursement providers is average age at incidence. For example, the fewer years remaining in life, the lower the willingness to pay. To view this from another perspective, the fewer years remaining in life reduces the opportunity for a therapy to deliver a health impact to a patient. Would it be a rational decision to develop a macrophage cell therapy to treat pneumonia in elderly patients? No. The average age of incidence of pneumonia in this patient group is about 75, whereas the average life expectancy in the Western world is about 80. Even for diseases with high mortality rates, the willingness to pay for such disease therapies would be nominal because cost-effectiveness calculations would incorporate five years of remaining life.

Now flip that scenario on its head. Would you develop a macrophage cell therapy to treat pneumonia in the pediatric population? Many people would say that this is an idea with commercial potential. Necrotizing pneumonia associated with methicillin-resistant Staphylococcus aureus (MRSA) has an average age at incidence of 14 and mortality of 50%, which is an optimal setting for reimbursement; however, the incidence of this indication may be prohibitively low to warrant commercial development. Other subsets of pediatric pneumonia patients provide more attractive markets. For example, premature babies often experience difficulties with their lungs and frequently get infections if intubation is required.

### Reimbursement Trends

Mortality data and age of incidence are high-level approaches that allow for rapid assessment of reimbursement potential. Given the high cost of cell therapies, they should be an integral part of indication selection. Studying the reimbursement landscape to identify trends in payers' treatment of various products also is important. For example, a company developing nanoparticle therapies would need to know that Medicare lumps cellular and acellular products into the same reimbursement category for wound healing, creating significant challenges for cell therapy technologies.

*CoG reduction, process development, and optimization are critical components of a cell therapy development plan.*



A company can evaluate its therapeutic candidate's reimbursement potential (and subsequent long-term viability of the company itself) by:

1. Understanding the mortality and standard of care for the therapy
2. Calculating willingness to pay in quality-adjusted life years
3. Calculating CoG to be 25% or less of willingness to pay

## *Deciding on an Acceptable Cost of Goods*

When deciding on an acceptable CoG for a potential cell therapy, it is best to identify the target indication and work backward. Once an indication is selected, calculate a willingness-to-pay value using mortality or quality-of-life data (willingness to pay generally ranges between $50,000 and $100,000 per quality-adjusted life year, depending on jurisdiction). The best-case scenario is that your CoG will be about 25% of that value. But generally it will need to be less than that value to account for costs associated with labor, manufacturing, logistics, quality control assays, and release testing. CoG reduction and process development and optimization are critical components of a cell therapy development plan.

# Needle-to-Needle Logistics

Needle-to-needle logistics is an industry term that refers to all of the little details that need to be performed well to make a business function. For cell therapy companies to successfully transition to profitable operation at commercial scale, it is essential to explore the variability of the entire process—from sample collection through administration—and identify the impact that process may have on product quality, and ultimately efficacy.

There are several critical issues needle-to-needle logistics addresses: overcoming the logistical challenges of distributing, delivering, and administering outgoing product; approaching inventory management and industrial-scale manufacturing; and managing the challenges of shipping, receiving, and tracking incoming items like cells, reagents, and disposables. Each of these are significant and time-critical.

*It is essential to explore the variability of the entire process—from sample collection through administration—and identify the impact that process may have on product quality, and ultimately efficacy.*

Cell therapy manufacturers seeking to distribute and administer market-winning products must develop and refine logistical processes to be robust, repeatable, and error-proof while allowing and recording traceability to guarantee chain of custody. These processes must cover:

- Packaging and storage (both temperature-controlled and ambient)
- Management of inventory (stock control and temperature-monitoring systems, both in stores and during distribution)
- Clinical-site capabilities that affect product and administration quality
- Timeliness to ensure that patient-specific therapies are delivered to the correct patients

Below are some of the questions cell therapy companies should answer as a means of successful organizational planning and process implementation:

## Incoming Logistics

### *Source Materials*

- Do they need to be temperature controlled?
- Will they be fresh or frozen?
- How long will they take to ship and what abnormal temperature events might take place during transportation?

### *Reagents*

- What format (fresh, frozen, or lyophilized) will your reagents come in?
- What is the right packaging for appropriate batch size?
- Will you need a sterile connection to closed processing disposables?
- Consider also implications on stock control of "Use by" dates.

### *Sterile Disposables*

- What packaging will be used?
- What kind of sterile connections are needed for closed processing?
- Stock control and storage life should also be considered here.

### *Data*

- How will patient IDs be created, stored, and tracked?
- How will batch and lot numbers be maintained?
- Where and how will receipt, manufactured, and expiration dates be recorded?

## Outgoing Logistics

### *Product*

- Will the product be frozen or fresh?
- How will you manage and monitor temperature, both in transit and in storage?

### *Quality Control*

- How and where will testing occur (in-house or external)?
- Where will retained samples be stored and for how long?

### *Final-Product Vessel*

- Will the vessel come from a custom or an original equipment manufacturer (OEM)?
- How will you match the selected dose container to the appropriate final shipping container?
- Make sure to consider the ease of access and administration of dose when determining the vessel.

### *Waste*

- What are the storage and quarantine implications?
- Will you incinerate on site, or hire an external contractor for biological waste disposal?

### *Data*

- What will be the chain of custody for data?
- How will you retain shipment records, including temperature history and proof of waste destruction?

## Clinical Site Logistics

### *Receiving and Storage*

- Does the clinical site have the facilities and processes to receive and appropriately store the product?

### *Dose Preparation*

- Can the clinical site thaw the product and conduct whatever preparation is needed (preferably minimal) before administration?

### *Administration*

- Is staff adequately trained to administer the therapy?
- Does its administration differ from a standard method?
- Additional training and complexity will affect uptake and likelihood of compliance with specified methods.

### *Data*

- What will be the chain of custody?
- How will you handle the record of administration and clinician training records?

## Inventory, Work-in-Progress Manufacturing Logistics

### *Patient Material*

- How will you ensure that cold-chain supply has been maintained within set boundaries?

### *Reagents*

- How will you manage inventory?
- How will you prepare batches and/or mix them before use?
- How will you manage first-in/first-out (FIFO) and expiration control?

### *Disposables*

- Consider inventory control as well as FIFO and expiration control.

### *Scheduling*

- What software and processes will you use for production scheduling, equipment availability/use, and operator availability/use?

### *Freeze–Thaw Decision*

- Will you use a freezing step to simplify planning?
- How will you manage temperature control and history of products at key processing steps?

### *Data*

- How will you manage manufacturing execution system (MES) selection and integration?
- How will you manage batch records, traceability, and chain of custody, including matching patient IDs, patient material, reagent and disposable batch and lot numbers, received dates, manufactured dates, expiration dates, and processing operator IDs?
- How and where will you store equipment calibration history, as well as operator history and training records?

## Conclusion

Successful commercialization of a cell therapy requires more than just proving safety and efficacy to the regulators. Although efficacy is important—without it, there is no therapy—it is critical for cell therapy companies to think beyond efficacy and have a plan in place for how they will successfully move from the clinic to commercial-scale production. To enable a successful progression to commercialization, each of the five essential elements—manufacturability, cost of goods, reimbursement, needle-to-needle logistics, and efficacy—must be considered in order to build a solid foundation for game-changing product development.

## About Invetech

Since 2004, Invetech has been partnering with clients ranging from small start-ups to Fortune 500 companies to develop innovative new research platforms and commercial production systems for cell and advanced therapies. Our team has the design, engineering and manufacturing expertise essential to delivering solutions that are as practical as they are marketable. Our skillset spans the entire product life cycle—from concept development through to manufacture—making us the ideal partner to help successfully move your products from the clinic to commercial-scale production.

For more information, or to discuss your project, visit **www.invetech.us** or email us at **connect@invetech.us.**

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