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The Race to Market: *Regulation of Cell-Based Therapies and Considerations for Process Development*

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Introduction

The cell therapy industry is positioned to make major changes in healthcare and disease treatment. The Alliance for Regenerative Medicine (ARM) recently reported on the robust state of the industry and identified that revenue from cell therapy products grew from $460 million in 2010 to $1.3 billion in 2013.[1] There are currently more than 40 commercially available cell therapy products with indications ranging from cardiovascular to cancer and non-healing wounds. The pipeline for these therapies is also expanding. ARM reports nearly 270 trials underway (Phase 1 through Phase 3). Another 58 projects are in the research stage and 245 in pre-clinical. Adding to this total, there are 77 industry-sponsored cell-based immunotherapy trials.

Cell therapy represents a very different approach to treatment when compared to small molecules or many biologics. As such, regulatory authorities are evolving and adapting their approach to help ensure patient safety and efficacy of these innovative and complex therapeutics. A recent decision by regulatory authorities in Japan allows for an accelerated pathway for approval. This presents a tremendous opportunity for the industry, but at the same time, exerts tremendous pressure on developers to rapidly and efficiently characterize their products and processes in order to take advantage of such accelerated pathways.

This article provides an overview of current regulations for cell-based therapies in the United States (US), European Union (EU), and Japan, and considerations for working successfully within these frameworks. It also describes a structured approach to process development that can help achieve accelerated timelines.

What is a Cell-Based Therapy?

Human cell and tissue-based products offer enormous promise in the treatment of chronic conditions such as heart failure, type 1 diabetes, and steroid-resistant asthma. Current therapeutic options manage these conditions but do not repair the underlying causes. The field of regenerative medicine has the potential to change the approach to these and other conditions by replacing damaged tissue and/or by leveraging the body's own resources to heal itself.

Cell-based therapies are derived from diverse and complex biological sources, including differentiated cells derived from adult organs, and stem cells of varying origins.[2] These therapies offer distinct and certainly intriguing therapeutic capabilities versus traditional small molecule drugs and biologics. For example, these cells may be able to sense and integrate signals within their environment, execute complex responses, and migrate to other sites in the body.[3] While it is expected that these capabilities can be leveraged to treat many different diseases and conditions, the complexity of these cells, the precise manipulations required, and the need for controlling their actions within a patient pose challenges for both developers and regulatory authorities.

Regulation of Cell-Based Therapies

Understanding how a cell-based therapy will be regulated can be confusing, as these products do not lend themselves to a "one size fits all" concept of development and regulation.

Cell-based therapies can be generally categorized as "patient-specific" or "off-the-shelf." A patient-specific therapy is specifically (and separately) produced for each patient (*i.e.*, an individual production lot for each patient). Autologous therapy is sometimes misconstrued as being synonymous with patient-specific because the therapy is produced from cells extracted from the patient's own body, and therefore, inherently patient-specific. However, patient-specific also includes matched donor allogeneic approaches where the therapy is produced from cells extracted from a donor with a matched immune profile to the patient (*e.g.*, donor stem cell or cord blood transplant).

Although a patient-specific therapy more closely resembles a medical procedure, these therapies may fall under elevated levels of regulatory authority. For instance, in *United States v. Regenerative Sciences*, the US District Court for the District of Columbia recently concluded that the US Food and Drug Administration (FDA) has the authority to regulate certain autologous stem cell procedures—in this case, those that are more than minimally manipulated.[4]

Off-the-shelf therapies, which can also be referred to as "universal donor allogeneic therapies," use cells that have been derived from donors and are not specific to the patient. The properties of the cells do not require a matched immune profile to avoid immune rejection. These therapies are considered off-the-shelf since they provide doses for many patients to be produced from one or more donors in advance. They are placed on the shelf, figuratively speaking; typically in a cryopreservation storage tank.

Off-the-shelf therapies inherently require manipulation of the cells collected from donors to create the immune-privileged properties of the therapy, as well as extensive culture-based expansion to yield cell quantities for many patients. As a result, more than minimal manipulations have occurred and they always fall under elevated regulatory authority (*e.g.*, classified as a "Category 351" product within US regulations, as discussed below).

The extent of regulation required for each treatment (*e.g.*, whether the product requires full clinical testing) will be determined by the extent to which the cells have been manipulated before being introduced into a patient. For some types of cell-based therapies, only minimal or no manipulation is needed to obtain a product that retains the original features and function of the cell type extracted from the body. Other therapies require more extensive manipulation, however, including proliferation and/or differentiation to expand a particular cell type or genetic modification. For example, if stem cells are taken from one part of the body, manipulated to function differently and then engrafted at a different site of the body in the same patient, the treatment could be regulated as a device, a transplant, and/or as a cell therapy.

Additional regulatory challenges center on the need for precise product characterization, the potential for allogeneic therapies to spread communicable disease, and the need for tailored manufacturing and delivery for patient-specific therapies. A broad range of considerations to evaluate include the potential for immunogenicity, genetic instability, cell differentiation to undesired cell types, migration of cells away from the treatment site, and uncontrolled cell proliferation or tumorigenicity.

Current Regulatory Landscape

Regulations set the criteria that must be fulfilled in evaluating cell-based therapeutics encompassing safety, identity, purity, potency, and clinical efficacy. As the field of regenerative medicine advances, regulatory authorities are steadily evolving the guidelines and requirements that are placed on manufacturers, and providing greater clarification on the approach.

Table 1 provides a summary of key attributes of the regulatory frameworks in the US, EU, and Japan.

TABLE 1. Key attributes of regulatory frameworks.

Region	Regulatory Framework	Key Attributes
United States	Part 1271 of Title 21 of the Code of Federal Regulations (21 CFR Part 1271): Human Cellular and Tissue-Based Products	• Tiered, risk-based approach to regulation • Categorized and regulated based on the potential safety risk that the manufacture and distribution of each type of product poses to patients • Pre-pre-IND meetings allow FDA to advise companies very early in their product development
European Union	Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products (ATMPs); Committee for Advanced Therapies (CAT)	• Tiered, risk-based approach to regulation • Consolidated all advanced therapies (gene, cellular, and tissue-based) under a single European regulatory framework to ensure consistency across member states • EMA's Committee for Advanced Therapies (CAT) is responsible for assessing product quality, safety, and efficacy • CAT encourages companies to partner with the agency early in their product development
Japan	Pharmaceutical Affairs Law (PAL); Act regarding Ensuring of Safety of Regenerative Medicine (Regenerative Medicine Law)	• Accelerated approval may be granted if safety is demonstrated in Phase 1/3 clinical studies and effectiveness is anticipated • Post-market surveillance period will further characterize safety and efficacy profiles, and will ultimately determine final approval • Studies must be conducted on Japanese people, even if in limited number

United States

The FDA has a tiered approach in place for the regulation of cell-based therapies (21 CFR 1271) that addresses the agency's major safety concerns. These include: preventing the use of contaminated cells or tissues, which can spread communicable diseases such as HIV and hepatitis; preventing inadequate handling or processing that may damage or contaminate these products; and ensuring the clinical safety of products that are manipulated and/or combined with other drugs or devices. Under this framework, cell-based therapies are categorized and regulated based on the potential safety risk that the manufacture and distribution of each product type poses to patients.[2] The categories for cell-based products are as follows:

- **Category 1** products are not regulated under 21 CFR 1271 rules because their manufacture involves little to no manipulation and their use is considered homologous (the cell or tissue product directly replaces the function for which it was intended). Examples of Category 1 products include human organs for transplantation, whole blood, and blood-derived products.
- **Category 2** ("361") products represent a higher safety risk compared to those in Category 1, and are regulated under Section 361 of the Public Health Service Act. In brief, these products are minimally manipulated, are intended for homologous use, and cannot be combined with a drug or device. Although "361" products are guided by the FDA's tiered rules set forth in 21 CFR 1271, manufacturers of "361" products are not required to follow the biologics license application (BLA) pathway and are not subject to current good manufacturing practices (cGMP). An example of a "361" product is replacement of cartilage from one knee with cartilage derived from the other knee in the same patient or first-degree cousin.
- **Category 3** ("351") products are also subject to "361" and are either more extensively manipulated than Category 1 and "361" products, or are intended for non-homologous use (the cells are not being used clinically to do what they naturally do), or both. As such, they present a higher level of safety concern. Therefore, they are regulated as a biologic drug or a medical device under Section 351 of the Public Health Service Act and are subject to pre-market review procedures and full clinical testing. However, because of the expense and available supply of each treatment, trials of "351" products may be of a much smaller size compared to traditional pharmaceutical trials.

  Additionally, entities involved in any step for the manufacture of "351" products, from recovery through distribution, as well as screening or testing of the donor, are classified as manufacturers by the FDA. Therefore, they are subject to cGMP regulations (21 CFR 210 and 211) and applicable parts of 21 CFR 1271, particularly Part C (donor eligibility requirements). Part C sets the requirements for determining donor eligibility, including donor screening for high-risk behavior, medical history, and testing for communicable diseases.

European Union

The EU has also adopted a tiered, risk-based approach to cellular therapies, of which the European Medicines Agency (EMA) regulates only the highest risk products. In December 2008, a new regulatory framework specific to these therapies (Regulation [EC] 1394/2007 on advanced therapy medicinal products [ATMPs]) was established to help spur the growth of this emerging industry.[5] Regulation 1394/2007 consolidated all advanced therapies (gene, cellular, and tissue-based) under a single European regulatory framework to ensure consistency across member states. Prior to the implementation of Regulation 1394/2007, products derived from genes and cells were classified as drugs, tissue-engineered products were partially classified as a drug or a device, and regulations were not harmonized across EU member states.

Central to the regulation of ATMPs is the EMA's Committee for Advanced Therapies (CAT), a multidisciplinary scientific committee responsible for assessing the quality, safety, and efficacy of ATMPs that follow a centralized marketing authorization procedure. CAT conducts two procedures on behalf of companies developing ATMPs. They determine whether a given product meets the scientific criteria that define an ATMP (classification), and they evaluate all available quality and non-clinical data (certification). By evaluating early-stage data, CAT can serve as a regulatory advisor during development, and the committee strongly encourages companies to take advantage of these opportunities.[6] CAT's early evaluation can also help companies attract financial support for further product development (*e.g.*, conducting clinical trials). It should be noted that CAT provides recommendations to EMA only—the EMA makes the ultimate approval decisions. Additional incentives have been put in place to support small and medium-sized companies developing ATMPs, including fee reductions.

Japan—*Marking a Major Shift*

In November 2013, a great deal of discussion ensued when Japan revised its Pharmaceutical Affairs Law (PAL) as it applies to drugs, medical devices, and regenerative medicine, and enacted the Regenerative Medicine Law to ensure the safety of regenerative medicine. The revised PAL defines stem cells as regenerative medicine products. The Regenerative Medicine Law is designed to accelerate the clinical development of cell therapies by providing temporary conditional approval if a given cell-based therapy demonstrates a strong safety profile in Phases 1–3 clinical studies with the anticipation of effectiveness (Figure 1).[7] This means that the potential exists for a cell-based therapy to reach the marketplace without demonstrating the usual efficacy requirements.

This new framework also mandates studies to be conducted on the Japanese population, even with limited patient numbers. The Regenerative Medicine Law certainly has the potential to greatly accelerate time-to-market for cell-based therapies. This presents a very interesting situation for developers of therapeutic products. Typically in Phase 1, there has not been much time spent on process and analytical development or product characterization, as these activities usually take place during the clinical trial process. The question becomes: "Is there a structured and rational way to approach process development and risk mitigation that can help advance time-to-market even in these accelerated situations?" See the discussion below for a structured approach to process development that can help achieve accelerated timelines.

Considerations for Industry

The cell-based therapy industry is relatively young compared to the traditional pharma/biotech industry. The cellular therapy industry is still finding its way in terms of understanding what is needed to ensure safety, consistently deliver the desired efficacy, and operate within a regulated environment. The industry is learning how to best partner with regulatory agencies to help move products through development. Understanding when to engage, and most importantly, how to engage with the regulators are key attributes to the success of any clinical development program. This includes discussions regarding product and process development.

Regulatory agencies are assuming a collaborative role within the industry to expand their knowledge base on cell therapies, and in turn, help manufacturers achieve the highest quality product to ensure patient safety. For example, the FDA has developed a collaborative working relationship with ARM to help create clear and predictable regulatory pathways for cell therapies. The European Innovative Medicines Initiative (IMI), an industry/regulatory collaboration, has been formed to facilitate the development of new safety evaluation methods through pre-competitive data-sharing. The FDA has also created pre-pre-investigational new drug (IND) meetings to advise companies very early in their product development, and the EMA's CAT supports a similar collaborative approach. These early, informal meetings are meant to help manufacturers design the right pre-clinical package, including the most appropriate series of pharmacology and toxicology studies. Such meetings can be particularly valuable when determining how to best evaluate the safety of cell-based products, especially with respect to identifying the most relevant animal models.

A recent article by Goldring *et al.*[8] offers an in-depth discussion of assessing the safety of stem cell therapeutics. Highlighting the challenge and the need for collaboration with regulatory authorities, the authors note: "Importantly, the stem cell therapy field needs to interact at the level of therapy provider, safety scientist, and drug regulator in order to define the 'acceptable risk' associated with a particular treatment, and to set in place a framework for accurate assessment of that 'risk'."

Product developers should take advantage of every opportunity to partner with the applicable regulatory

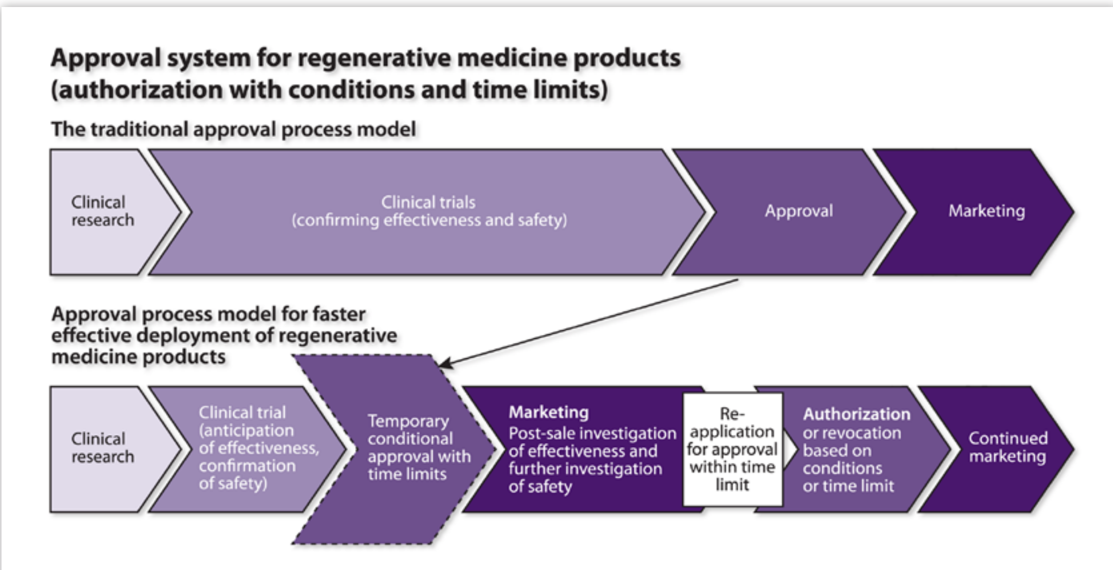

FIGURE 1. Japan's new regenerative medicine law is designed to accelerate the clinical development of cell therapies. (Adapted from reference[6].)

agency throughout clinical development, including EMA's CAT and FDA's pre-pre-IND meetings, to gain a better understanding of the regulatory requirements that pertain to their specific product. Developers should also be encouraged to engage with the agency as early in development as possible—and as much as possible—to establish study criteria, particularly to assess the safety of stem cell therapies. Understanding how to effectively partner with the applicable agency will help manufacturers accelerate products through the pipeline. Additionally, the knowledge gained by regulatory agencies will help to advance the cell therapy field overall.

Development by Design

Regulatory pathways that provide accelerated paths to approval, such as in Japan, are opportunities for products to reach market sooner. However, the path for process and product development that would have been otherwise leveraged will not be sufficient. "Development by Design," an approach used by Progenitor Cell Therapy (PCT), presents a rationale and incremental framework to approach process development to identify and mitigate risk. This allows the overall goal of sustainable manufacturing to be achieved in both traditional and accelerated pathways.

Process development usually takes place up through Phase 2, with lock-down and validation at Phase 3 to prepare for approval (Figure 2). A key challenge in any development program is that, while quality realization must occur early in development and be well-established by Phase 2 trials, realization of cost of goods sold (COGS), scale, and sustainability are not required until much closer to commercialization (Figure 3).

This approach puts significant pressure on cell therapy developers to defer investment in COGS, scale, and sustainability until it is, to some extent, too late. Or to define it another way, developers often defer such considerations until

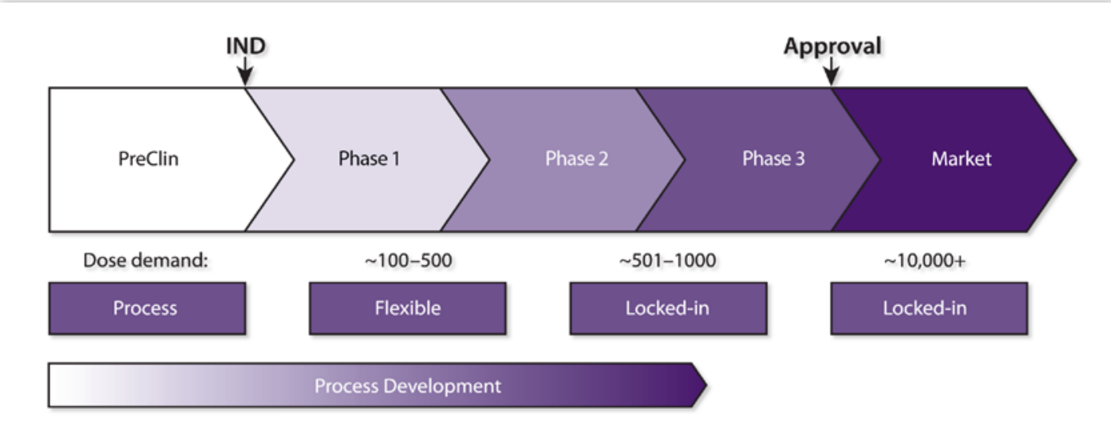

FIGURE 2. Process development typically occurs through Phase 2 with lock-down and validation at Phase 3 in preparation for approval.

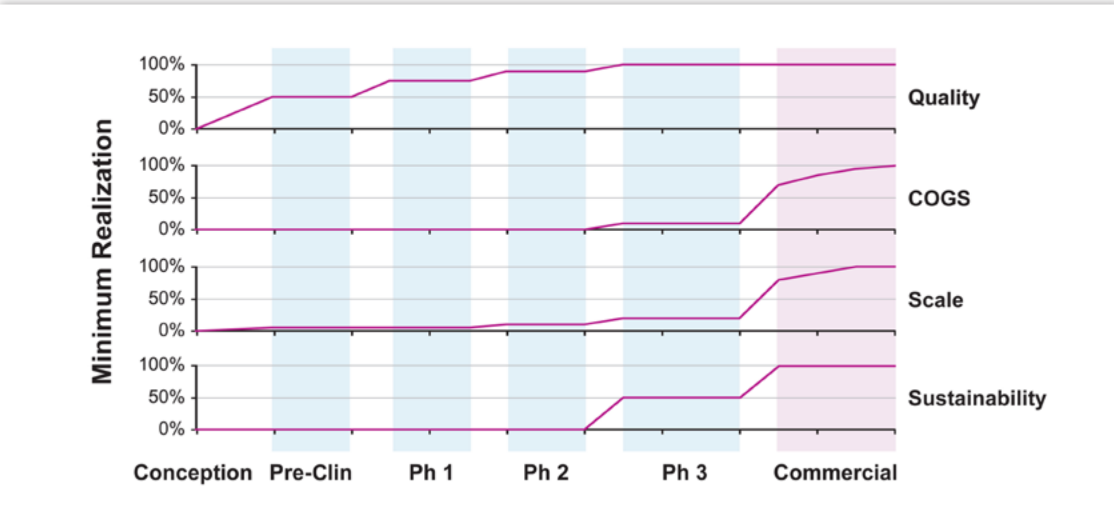

FIGURE 3. Realization of cost of goods sold, scale, and sustainability are not required until much closer to commercialization.

the comparability risks of making changes to address these concerns is substantial. Additionally, any extreme change in scale of process as a developer moves toward commercialization can quickly create quality risks never encountered before.

Development by Design is a process that PCT applies in which each critical success factor—quality, COGS, scale, and sustainability—can be addressed in a systematic and rational way. The Development by Design process addresses:

- **Quality.** The strength of the process is directly related to reducing the risk of failure to treat the patient. Automation, integration, and closed system designs are key tactics to elevate robustness of the process.
- **COGS.** As processes mature, the focus on COGS for commercial viability becomes critical. Development by Design allows for prospective approaches to addressing COGS appropriate for scale and stage of development.
- **Scale.** Cell therapy products inherently possess high complexity with one or more mechanisms of action that are often incompletely understood. Scaling up or out requires analytical tools and *in vivo* models to judge product comparability.
- **Sustainability.** Manufacturing must be sustained over the full product life cycle and companies need to methodically assess the full range of supply chain inputs across every unit operation, in both process and testing.

Conclusion

Unprecedented developments in cell-based therapies carry the hope of new treatments for many types of chronic diseases and conditions. The success of this burgeoning new industry will, in part, rely on how well it collaborates with regulatory agencies to ensure the development of safe and effective products.

Developers of cell-based therapeutics who work with contract development and manufacturing (CDMO) partners can benefit from the combined expertise of these organizations and find innovative approaches to address the challenges of commercialization. An experienced CDMO can facilitate the regulatory compliance process and ensure that best practices are applied.

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