Guide to Accelerated Regulatory Pathways for Cellular Therapeutics & Advanced Therapies

The regulatory landscape for cell therapy development has grown increasingly complex. There are now accelerated pathways for advanced therapy medicinal products (ATMPs) in several countries worldwide, including the U.S., Japan, and South Korea.
1. Accelerated Approval Regulator Pathways Worldwide

Over the past few years, the regulatory landscape for cell therapy development has grown increasingly complex. There are now accelerated pathways for advanced therapy medicinal products (ATMPs) in several countries worldwide, including the U.S., Japan, and South Korea. While the possibility for accelerated commercialization has resulted from these changes, substantial complexity has also been introduced, making it a more elaborate process to move cell therapy products from “bench to bedside.”

The United States, Japan, and South Korea are countries that have accelerated pathways unique for cell and gene therapies. Legislation took effect in Japan in late 2014, in South Korea in 2016, and in the United States in 2017.

Additionally, the EU has a program for product acceleration – the Adaptive Pathways. Although it is not explicitly for cell and gene therapies, they have been given a lot of attention by the group.

The types of pathways that exist in these countries include:

- **United States: Regenerative medicine advanced therapy (RMAT) designation**
  Cell therapies that aim to treat serious medical conditions with high unmet need and have preliminary favorable clinical data can get the designation. It allows for accelerated approval (i.e., the use of biomarkers and intermediate endpoints for BLA, priority review).
• **Japan: Conditional time-limited marketing authorization**
  This program allows for regenerative therapies (cell, gene, and tissue therapies) to receive conditional marketing authorization for up to seven years, following confirmation of safety and an initial proof of efficacy in Japan in diseases that are serious and have a high unmet need.

• **South Korea: Conditional marketing authorization for cell therapy**
  As in Japan, this program allows for cell therapies to receive conditional marketing authorization for a limited time, following an initial proof of efficacy in serious diseases.

• **European Union (EU): Adaptive Pathways pilot program**
  This program is a pilot program established by the EMA to explore ways in which the EMA can assist in streamlining the development of new promising therapies for serious conditions with high unmet need. Although this program is not explicitly for cell or gene therapy, it is the focus of the group.

Furthermore, there are differences in how each country defines advanced therapy medicinal products (ATMPs), cell therapies, and regenerative medicine products. All EU countries have a joint definition for ATMPs as set by EU regulation. Other countries have separate definitions that only partially overlap.

Only few countries in the world are willing to be the first to provide marketing authorization for novel therapies. For ATMPs, European regulation does not allow individual countries in the union to provide marketing authorization, so the **EMA is the only gateway for ATMPs in Europe.**

The U.S. FDA, Japan PMDA, and South Korea KFDA are the **only other regulatory bodies that are willing to be first to approve ATMPs.** Currently, the EMA and PMDA are leading with four marketing approvals of cell and gene therapies each.
2. U.S. Regulation of Cellular Therapeutics

In the United States, cellular therapeutics are regulated by the FDA’s Office of Cellular, Tissue, and Gene Therapies (OCTGT) within the FDA Center for Biologics Evaluation and Research (CBER). According to the FDA, “The Center for Biologics Evaluation and Research (CBER) regulates cellular therapy products, human gene therapy products, and certain devices related to cell and gene therapy.” CBER uses both the Public Health Service Act and the Federal Food Drug and Cosmetic Act as enabling statutes for oversight.

In the U.S., human tissues intended for transplantation are regulated by the FDA as “Human cells, tissues and cellular and tissue-based products” or “HCT/Ps.” Under U.S. law, any company that engages in the collection, processing, storage, screening/testing, packaging, or distribution of HCT/Ps must register with the FDA.

Currently, the FDA’s Center for Biologics Evaluation and Research (CBER) is responsible for regulating HCT/Ps and it has two different paths for cell therapies that it constructed to reflect what it considers to be “relative risk”. These pathways are commonly called “361” and “351” products. Cell therapies can potentially be regulated under either pathway.

- **361 Products**: 361 products that meet all the criteria outlined in 21 CFR 1271.10(a) are regulated as HCT/Ps and are **not required to be licensed or approved by the FDA**. These products are called “361 products,” because they are regulated under Section 361 of the Public Health Service (PHS) Act.

- **351 Products**: In contrast, if a cell therapy product does not meet all the criteria outlined in 21 CFR 1271.10(a)), then it is regulated as a “drug, device, or biological product” under the Federal Food, Drug, and Cosmetic Act (FDCA) and Section 351 of the PHS Act. These 351 products **require clinical trials to demonstrate safety and efficacy** in a process that is nearly identical to that what is required for pharmaceutical products to enter the marketplace.

To further complicate the situation, the FDA has four draft guidances that outline how HCT/Ps are viewed by U.S. regulators.
The four FDA draft guidances that affect the regulation of human HCT/Ps in the U.S. are:

1. “Same Surgical Procedure Exception under 21 CFR 1271.15(b)”
2. “Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products; Draft Guidance for Industry and Food and Drug Administration Staff”
3. “Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry”
4. “Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products; Draft Guidance for Industry and FDA Staff”

Because cell therapy is a new field that the FDA is exploring how to regulate, the FDA held a widely attended Public Hearing held at the NIH in September 2016, that reviewed its draft guidances pertaining to the regulation of Human Cell and Tissue-Based Products (HCT/Ps). The event attracted more than 600 attendees, with representatives from nearly every U.S. state. Attendees of that public hearing spent two days discussing the regulation of human cell and tissue-based products (HCT/Ps), defined by the FDA in § 1271.3(d) as “articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.”

As Dr. Weissman of the FDA pointed out in his Keynote Address during the FDA Public Hearing, the term “stem cell” is often misused, often being used to describe “mixtures of cells.” This is a key point, because the mechanism of action of a single cell type may vary substantially if the cell population also includes a range of other cell types. Similarly, Dr. Arnold Caplan, widely regarded as the “Grandfather of MSCs”, also spoke up to urge the FDA and the scientific community at large to stop referring to MSCs as “mesenchymal stem
cells” and instead identify them as “medicinal signaling cells.” This language change is meant to recognize the ability of MSCs to have strong medicinal effects, while identifying that they not exert their effects by regenerating tissue, but rather by leveraging sensory capabilities, positively affecting the microenvironment, and being sentinels for injury. As Dr. Caplan accurately stated, “Almost every cell in the body is paracrine in nature.”

Finally, it is imperative to note that the four FDA guidances are only that, guidances and not laws. The purpose of the guidances are to provide cell therapy industry stakeholders with language and tools through which they can assess their compliance. As such, the FDA’s draft guidances must adhere to existing law and it is unclear whether they do so. Clearly, the FDA is still working to figure out how it will regulate human cell and tissue-based products (HCT/Ps).

It is anticipated that the FDA will release updated guidelines for HCT/Ps in late 2017.
3. 21st Century Cures Act and REGROW Act

Details of the 21st Century Cures Act (which passed in the U.S. in December 2016) and the earlier REGROW Act (which did not pass) are described below.

Senator Kirk, who suffered from a stroke, sponsored the REGROW Act designed to amend the Public Health Service Act to require the U.S. FDA to “conditionally approve certain cellular therapeutic products without initiation of large-scale clinical trials.” If approved, it would have permitted the FDA to approve stem cell treatments conditionally, without a large, final-stage clinical trial that is usually required.\footnote{Congress.gov. (2017). S.2689 - 114th Congress (2015-2016): REGROW Act. [online] Available at: https://www.congress.gov/bill/114th-congress/senate-bill/2689 [Accessed 26 Sep. 2017].} Although this pathway would have allowed regenerative medicine products to enter the market much more quickly, REGROW was highly controversial due to concerns of allowing potentially dangerous or ineffective drugs to enter the market before the sponsor provided sufficient evidence on safety and efficacy.

The “REGROW Act” did not pass. However, on December 13, 2016, President Barack Obama signed the 21st Century Cures Act (H.R.34), which passed Congress with bipartisan support. It was a broad healthcare spending bill that included several provisions pertaining to stem cell therapy research and clinical approval. The bill does not mandate the significant changes to the regulatory approval of stem cell therapies expressed in REGROW, but it does incorporate several sections designed to allow a greater number of regenerative therapies to come to market. The growing movement to expand the adoption and implementation of regenerative medicine is reflected in this legislation.

Key relevant provisions within the 21st Century Cures Act include:

- Does not allow new regenerative medicine products, which include stem cell therapies, to skip the Phase III clinical trials. However, it does permit FDA to grant them accelerated approval if they show that surrogate endpoints might indicate that
the therapy works, subject to further evaluation. Regulators can approve a therapy without waiting on a demonstrated clinical benefit.

○ Example: a clinical study that proves a therapy shrinks a tumor could be used for approval, rather than requiring a study with the more onerous endpoint of improved survival.

● Mandates the NIH, in coordination with FDA, to award $10 Billion in each of FY 2018-2020 for “grants and contracts for clinical research to further the field of regenerative medicine using adult stem cells, including autologous stem cells” contingent on matching contributions from recipient.

● Requires FDA consult with stakeholders and the National Institute of Standards and Technology to facilitate an effort to establish standards, to support the development, evaluation, and review of regenerative medicine and advanced therapies products.

  ○ These standards are expected to play a significant role in advancing the early-stage cell therapy industry, because creating FDA-recognized standards will eliminate the need for companies to create and validate their own.

  ○ It is also an opportunity for stakeholders to weigh in on the future of regenerative therapies, and thereby, influence the regulatory and clinical environment at large.
4. Accelerated Approval Pathways in Japan

New regulations accelerating the approval of regenerative therapeutics in Japan took effect November 25, 2014. The significance of these regulations is that they allow companies to receive conditional marketing approval and **commercialize regenerative medicine products while clinical trials continue through later stages**. The accelerated commercialization of cell therapies is part of the economic revitalization plan initiated by Prime Minister Shinzō Abe.

Under Shinzō Abe, Japan has been pursuing regenerative medicine and cellular therapy as key strategies to the Japan’s economic growth. Japan’s Education Ministry also indicated that it is planning to spend 110 billion yen ($1.13 billion) on induced pluripotent stem cell research during the next 10 years, and the Japanese parliament has been discussing bills that would “speed the approval process and ensure the safety of such treatments.”

Although regenerative medicine is a huge priority for Japan, regenerative medicines have been limited because of the difficulty getting through Japan’s Pharmaceuticals and Medical Devices Agency (PMDA), with only two approved allogenic cell therapy products and fewer than 15 clinical trials as of May 2014.

**TWO NEW REGENERATIVE MEDICINE LAWS IN JAPAN**

In late 2014, Japan exercised two new acts: One is the Act on the Safety of Regenerative Medicine (**Law 85/2013**) and the other one is the Pharmaceuticals and Medical Device (PMD) Act (**Law No. 84/2013**). The aim of the first act was to accelerate the clinical application and commercialization of innovative regenerative medicine therapies. It covers clinical research and medical practice using processed cells and specifies the procedure required for clearance to administer cell procedures to humans. These guidelines are very important to the use the cells within clinical stages.

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Similarly, the PMD Act introduces a specific regulatory framework for regenerative medicine products. Under the PMD Act, conditional and time-limited marketing approval can be given to a regenerative medicine product after exploratory clinical trials have demonstrated probable benefit and proven safety.

Under these new laws, once a company has demonstrated safety and basic efficiency data in humans and has the cell product manufactured to the standards described within the Pharmaceutical and Medical Devices (PMD) Act, the cell therapy can be given conditional approval for up to seven years. This allows for commercial use with data reporting requirements and the potential for national insurance coverage.

As Kaz Hirao, CEO of Cellular Dynamics International (a Fujifilm Company), told BioInformant, “This has made Japan a ‘gate country’ for developing innovative cell therapies with the potential to address major unmet medical needs.” This has provided a strategic opportunity to American companies, because they can benefit from fast track applications through doing clinical testing within Japan and subsequently develop their cell therapy products across the rest of the world.

The intent of the Japanese laws is to accelerate the commercialization of cell therapeutics within Japan by allowing companies to benefit from conditional marketing authorization.

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Therefore, cell therapies that show safety and probable efficacy during Phase I and Phase II trials can get conditional approval for up to seven years, during which time:

1) Larger-scale, later-stage clinical trials are performed
2) Revenue from the cell therapy is pursued within the Japanese market

During the seven-year conditional approval period, companies must continue filing clinical trial data, either applying for final marketing approval (the equivalent of a Biologic License Application) or withdrawing the product within seven years.

This safety data can subsequently be used by non-Japanese participants, which is a substantial benefit to foreign companies, such as those located in the United States. The regulatory environment in Japan provides companies with the unique opportunity to “fast track” a clinical trial and seek approval of a new cell therapy product within the Japanese market.
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