Investing in the life sciences industry without an understanding of the key regulatory factors that could determine a product’s success or failure could cost you millions of dollars.

As the industry readies itself for the 2019 edition of the annual pilgrimage to the J.P. Morgan Healthcare Conference in San Francisco, our market-leading Global Regulatory Team has prepared a series of updates covering the following topic areas that we hope will help guide your 2019 investment decisions.

- Drug pricing and reimbursement
- Regulatory changes in Europe
- Medical device and technology
- Digital health
- Data privacy and cybersecurity
- Value-based purchasing
- Cell and gene therapies
- CFIUS reporting obligations

FDA’s efforts to speed development and approval of cell, tissue, and gene therapies enhance investment opportunities

In the last several years, Cell, Tissue, and Gene Therapies (CTGTs) have entered development at an exponential rate, with 44 unique CTGT products already approved and in clinical practice worldwide, according to a November analysis in the Journal of Cell Therapy. In 2017, the U.S. Food and Drug Administration (FDA) approved the first three gene therapies to ever be marketed in the United States: Novartis’ Kymriah and Kite Pharma’s Yescarta (each treating specific forms of lymphoma), and Spark Therapeutics’ Luxturna (which treats a form of hereditary blindness). Additionally, in June 2018, FDA granted marketing approval to MD Anderson’s Cord Blood, marking the sixteenth approval by FDA’s Office of Tissues and Advanced Therapies (OTAT) for a CTGT.
The increasing rate of trials and approvals for CTGTs in the U.S. coincides with FDA’s heightened focus on advancing research and development of the treatments. On July 11, 2018, FDA published six draft guidances relating to gene therapy, three of which cover products for specific disease categories (hemophilia, rare diseases, and retinal disorders), and three of which address manufacturing and clinical study design issues related to gene therapy (chemistry, manufacturing and control information; long term follow-up study design; and testing of retroviral vector-based products).

This spate of FDA guidances for gene therapy developers reflects the agency’s enthusiasm for advancement in the field. In a press release announcing the availability of these draft guidance documents, FDA Commissioner Scott Gottlieb, M.D. highlighted “great promise” in the gene therapy space, saying the guidances “are aimed at fostering developments in this innovative field.” He also acknowledged that for some gene therapies, FDA “may need to accept some level of uncertainty” at the time of approval regarding questions related to long-term efficacy of the drug, as well as product manufacturing and quality. Such uncertainty establishes “an increased need for robust long term follow-up of patients in the post-market period.” As a result, one of the draft guidance documents that FDA issued in July 2018 describes factors, including product characteristics and patient-related factors, that should be considered when assessing the need for long term follow-up. This draft guidance also describes the features of effective post-market follow-up.

**Expedited CTGT approval through RMAT designation**

The 21st Century Cures Act (enacted in December 2016) created FDA’s Regenerative Medicine Advanced Therapy (RMAT) designation. This new program allows FDA to expedite approvals of regenerative medicine products, such as CTGTs, so long as preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for a serious or life-threatening condition. An FDA draft guidance published in November 2017, expressly included “gene therapies, including genetically modified cells, that lead to a durable modification of cells or tissues” in FDA’s interpretation of a “regenerative medicine therapy” that may be eligible for RMAT designation.

RMAT designation provides the sponsor more opportunities to meet with FDA officials to discuss potential surrogate or intermediate endpoints. CBER Director Peter Marks, M.D., Ph.D. has highlighted the great value of early interactions provided under the RMAT program to address the unique manufacturing challenges associated with regenerative medicine products. RMAT designation is also beneficial because FDA can grant the product accelerated approval based on a surrogate endpoint using patient registries, or other sources of real world evidence (RWE), such as electronic health records to satisfy post-approval requirements.

Dr. Gottlieb tweeted on August 29, 2018 that the agency is seeing the “pace quicken” for RMAT designations. As of December 5, 2018, FDA had granted 26 RMAT designations.
FDA Enforcement Activities and Policies Aim to Narrow the Regenerative Medicine Field to Legitimate, Safe Products

At the same time that FDA is helping to accelerate development and approval of ground-breaking new therapies, FDA has announced a policy of cracking down on unscrupulous stem cell clinics and others marketing unsafe and illegal products. FDA regulations define a narrow category of human cells, tissues, and cellular and tissue-based products (HCT/Ps) that may legally be marketed without prior FDA approval. These are transplanted tissues and cells that are minimally manipulated, that are not promoted as pharmaceuticals, and that meet other criteria consistent with the principles of transplant medicine. Under the guise of that category, however, rogue actors have increasingly been promoting many untested and risky products as cures for serious diseases, like cancer and Alzheimer’s Disease.

In November 2017, FDA issued a comprehensive regenerative medicine policy framework to draw a clear line between HCT/Ps legitimately marketed without prior FDA approval and those that are illegal. The Agency concurrently announced a 36-month enforcement discretion period following the issuance of its framework to allow companies to sort out where their products fall, and to initiate clinical studies on products that will require FDA approval after the enforcement period is over in November 2020. FDA made clear, however, that it would continue to take enforcement actions immediately against regenerative medicine products that pose undue safety risks to patients.

More recently, FDA Commissioner Gottlieb announced that in coming months FDA will step up actions to stop stem cell clinics from illegally marketing unapproved stem cell treatments that put patients’ health at risk. He also noted that the agency is “discouraged by the overall lack of manufacturers wanting to interact with the agency in this enforcement discretion period.” As part of this enforcement initiative, FDA issued a series of letters to manufacturers, healthcare providers and clinics on December 20, urging them to contact the FDA to discuss how to come into compliance.

If FDA is effective in reducing the products illegally on the market, it should strengthen the regenerative medicine field in at least two ways. First, it will reduce competition from illegitimate products, strengthening the market for legitimate regenerative medicines, both those requiring FDA approval and those that do not. This means that companies with products that pass muster as not requiring FDA approval, and companies that succeed in bringing CTGTs through the approval process, should have robust markets in which to market their products. For investors, it means that understanding where and how FDA is drawing the lines in this field will be increasingly important.

Second, FDA’s policies, if successful, will decrease the risk that the regenerative medicine field might be tainted from adverse events caused by illegal cell, tissue, or gene therapies. Citing serious safety concerns, FDA initiated legal enforcement action against two stem cell clinics in
May 2018. In an agency press release related to these actions, Commissioner Gottlieb stated that "[c]ell-based regenerative medicine holds significant medical opportunity, but we've also seen some bad actors leverage the scientific promise of this field to peddle unapproved treatments that put patients' health at risk. In some instances, patients have suffered serious and permanent harm after receiving these unapproved products." Several media outlets have reported that some patients were permanently blinded as a result of their treatment at these clinics. FDA's increased vigilance should help prevent any event that might chill progress in the regenerative medicine space.

Ultimately, opportunities are clearly expanding for investment in the burgeoning area of cell, tissue, and gene therapies. FDA's commitment to supporting expedited development and approval of CTGTs, while acting to remove illegitimate cellular therapies from the market, contributes to a bright outlook for companies in this space, and for investors who have a solid understanding of the regulatory environment.

Our Global Regulatory Team

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Our Global Life Sciences and Health Care Team

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