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FDA PREPARES FOR THE NEXT GENERATION OF REGENERATIVE MEDICINES

In its new regulatory framework for regenerative medicines released in November 2017, FDA takes a flexible approach, creating opportunity for manufacturers.

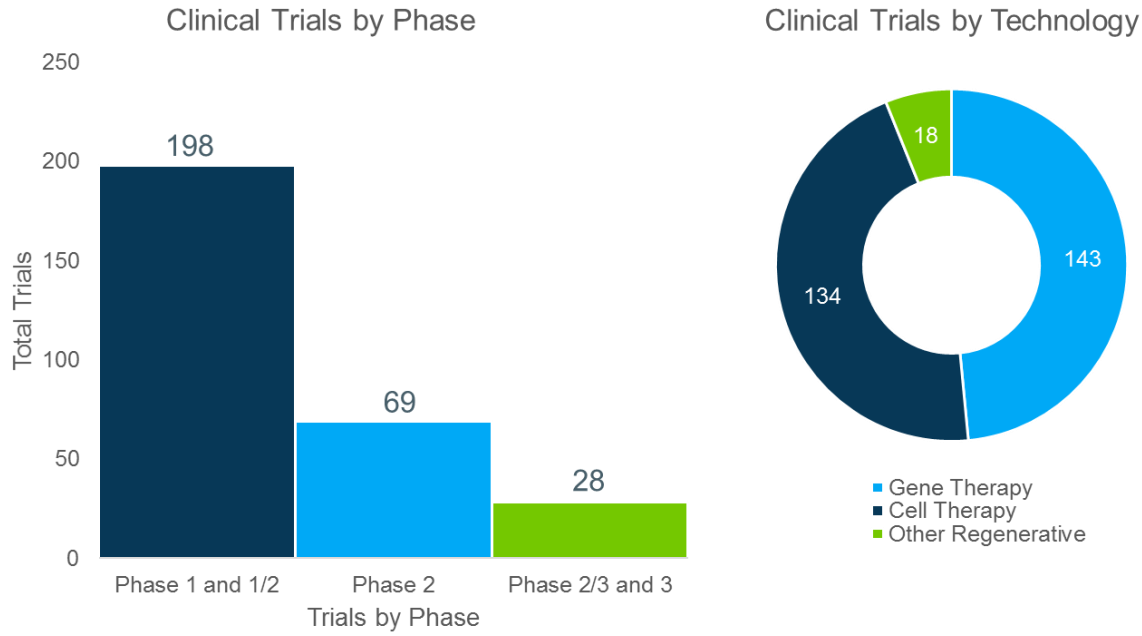
Regenerative medicines are therapies that augment, repair, replace, or regenerate organs and tissues. They include cell therapies, gene therapies (including genetically modified cell therapies), and tissue engineering or biomaterials. Regenerative medicine holds the promise to treat and cure a wide range of debilitating diseases in a single course of treatment. Over the last 30 years, significant research has been devoted to developing new tools and strategies for delivery of regenerative medicines, making it possible to overcome previous safety and efficacy challenges.

In 2017, FDA approved the first two genetically modified cell therapies—chimeric antigen receptor T-cell (CAR-T) therapies for the treatment of cancer—which has stimulated strong interest in the regenerative sector. FDA is currently reviewing a gene therapy for the treatment of hereditary blindness, Spark Therapeutics' voretigene neparvovec, which received unanimous support from an FDA advisory committee on October 12, 2017.

Robust Regenerative Medicine Pipeline

Based on Avalere's review of ClinicalTrials.gov, there are 295 industry-sponsored clinical trials underway for gene therapies, cell therapies, or other regenerative medicines including engineered tissue and other biomaterials (see Figure 1).

Figure 1: Current Pipeline of Regenerative Medicines



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Regenerative medicines are under development in numerous therapeutic areas. Oncology represents the single largest area of development, with 53% of regenerative medicine clinical trials worldwide, according to the Alliance for Regenerative Medicine. Other major areas of development include cardiovascular, central nervous system, musculoskeletal, autoimmune, endocrine, dermatologic, ophthalmic disorders, and infectious disease.

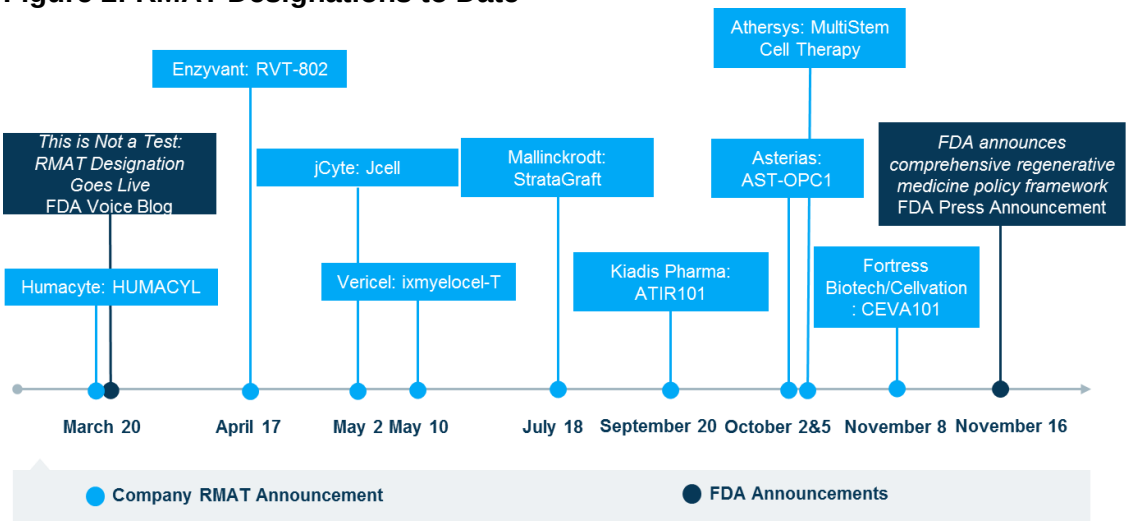
FDA's Regenerative Medicine Framework

On November 16, FDA released two final and two draft guidance documents, which collectively comprise the FDA's framework for the development and oversight of regenerative medicines. Within this framework, FDA details the Regenerative Medicine Advanced Therapy (RMAT) designation, which was created in the 21st Century Cures Act. Like other expedited regulatory programs, the RMAT designation gives the product sponsor an opportunity for early and frequent interaction with the agency, which can be critical in helping speed a product's development and path to approval.

The framework acknowledges that not all aspects of traditional drug development are feasible for regenerative medicines, particularly those intended to treat rare diseases. The new guidance indicates regulatory flexibility around both the preliminary clinical evidence used to request the RMAT designation as well as the clinical trial designs used in later phases of product development. The guidance also explicitly encourages the use of innovative approaches to development and approval of these novel products.

To date, 9 products have received an RMAT designation, according to public announcements made by manufacturers (see Figure 2). Several of the RMAT-designees also received an additional expedited designation.

Figure 2: RMAT Designations to Date



Key Considerations for Manufacturers

The regulatory flexibility demonstrated in the FDA's regenerative medicine framework presents product developers with several opportunities for innovation and engagement:

- **Innovative clinical trials designs** including the use of adaptive designs, novel endpoints, and enrichment strategies. Designs that incorporate a diverse range of patients could increase access while generating a broader and potentially more real world data set. For preliminary clinical evidence, FDA is open to the use of historical controls, retrospective studies, and clinical case series, particularly in the development of treatments for rare diseases.

- **Real-world evidence generation strategy** for long-term monitoring of both safety and efficacy. FDA recognizes that assessment of the long-term efficacy of regenerative medicines might not be feasible prior to marketing approval, making a robust plan for long-term monitoring critical. Real-world evidence would likely be of value to other stakeholders, including payers and HTAs.

- **Patient Engagement** in the development of clinical trials, registries, biobanks, and novel endpoints can greatly enhance development of regenerative medicines. For example, Spark Therapeutics won praise for its novel endpoint, developed with input from FDA and patients, to assess efficacy of the company's gene therapy. Rather than simply measuring the ability to see light, Spark's patient-focused endpoint involves navigating a random course in various lighting levels. This test more closely approximates the "real world" situations a patient would encounter in normal daily activities.

METHODOLOGY

To examine the current pipeline of regenerative medicines in clinical development, an advanced search was conducted in ClinicalTrials.gov on November 29, 2017 using the following search terms: "gene therapy", "cell therapy", and "regenerative medicine". Search parameters were limited to: trials in phases 1-3; conducted in the U.S.; funded by industry; and not yet recruiting, recruiting, enrolling by invitation, active but not recruiting, or completed.

The number of RMAT designations granted was determined by reviewing press releases generated from a simple web search for "RMAT designation".

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