What's New In FDA's Latest Cell And Gene Therapy Guidance

By **Michael Werner and Sara Klock** (October 31, 2025)

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On Sept. 20, the U.S. Food and Drug Administration issued draft guidance outlining how sponsors can utilize the FDA's expedited review pathways to facilitate development and streamlined review of cell and gene therapies and other regenerative medicine products.

Once finalized, the draft guidance will supersede earlier FDA guidance on this topic from February 2019.

This action was one of several agency initiatives designed to promote cell and gene therapy product development, especially when targeted at unmet medical needs.

History of RMAT

The 21st Century Cures Act added the regenerative medicine advanced therapy, or RMAT, designation to the Federal Food, Drug and Cosmetic Act in 2016.

According to the FDA, a sponsor can request RMAT designation if:

> a. The drug is a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, except for those regulated solely under Section 361 of the Public Health Service Act and part 1271 of Title 21, Code of Federal Regulations;
>
> b. The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and
>
> c. Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition.

The RMAT designation was designed to support development and approval of regenerative medicine products, including cell and gene therapies that target unmet medical needs in patients with serious conditions.

RMAT designation provides sponsors more interaction with the FDA on drug development, including early interactions to discuss any potential surrogate or intermediate endpoints, organizational commitment involving senior managers, and potential ways to support accelerated approval.

As of September, the FDA received almost 370 designation requests and approved 184 (though not all approvals are publicly disclosed). As of June, 14 of the RMAT-designated products were approved for marketing.

Previous Guidance Compared to Draft Guidance

The new draft guidance reiterates FDA policies regarding RMAT eligibility, including how the

agency determines whether a sponsor has provided sufficient evidence to support a designation request.

It also provides details for sponsors about the application process. As in the earlier guidance, the FDA provides an in-depth discussion of clinical trial design considerations for trials for rare diseases.

In such situations, the FDA pledges to work with sponsors and will encourage flexibility in clinical trial design. Some specific examples detailed by the FDA in the draft guidance include:

- Innovative trial designs, such as those that compare several different investigational agents to each other and a common control; and
- Natural history data that may provide the basis of a historical control, but only if the control and treatment populations are adequately matched in terms of demographics, concurrent treatment, disease state and other relevant factors.

The draft guidance encourages trial designs where multiple clinical sites participate in a trial investigating a regenerative medicine therapy with the intent of sharing the combined clinical trial data to support biologics license applications from each of the individual centers or institutions.

The FDA further states that manufacturing may be performed at all clinical sites using a common manufacturing protocol and product quality testing specifications.

The FDA also encourages sponsors to obtain input from the affected patient communities regarding the clinical endpoints that would be clinically relevant to the patients suffering from the disease.

The draft guidance differs from previous guidance on safety issues. For example, the draft guidance notes that regenerative therapies "are likely to raise unique safety considerations that would benefit from long-term safety monitoring."

Consequently, the FDA recommends that monitoring plans for clinical trials should include both short-term and long-term safety assessments. In a new development, sponsors also are encouraged to explore using digital health technologies to collect safety information.

In addition, the FDA specifies that an RMAT or other expedited review designation does not change the chemistry, manufacturing and controls information required to assure product quality.

The draft guidance notes regenerative medicine therapies with expedited clinical development activities may "face unique challenges in expediting product development activities to align with faster clinical timelines."

To ensure chemistry, manufacturing and controls readiness for expedited development, sponsors of regenerative medicine therapies may need to pursue a more rapid chemistry, manufacturing and controls development program to accommodate the faster pace of the clinical program.

If product manufacturing changes are made after receiving the RMAT designation, the post-

change product may no longer qualify for the designation if comparability cannot be established with the prechange product. If manufacturing changes are planned or anticipated, the FDA recommends that sponsors conduct a risk assessment to determine whether the changes affect product quality.

The draft also notes that sponsors can use real-world evidence to support an accelerated approval application. For purposes of this guidance, the FDA defines real-world evidence as the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world data.

Next Steps

The FDA is accepting comments on the draft guidance through Nov. 24. Sponsors should view the draft guidance as a reflection of the agency's thinking and its recommendations for sponsors.

Though the document reiterates many FDA views expressed in earlier guidance, it provides sponsors with specific recommendations on several new topics. Sponsors should consider submitting comments to ensure FDA takes into account any concerns before it finalizes the guidance.

The draft guidance on expedited review is one of three draft guidances issued by the FDA on the same day, all related to cell and gene therapy.

The others were "Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations," which provides examples of how companies can use different methodologies to demonstrate safety and efficacy as compared to larger studies, and "Postapproval Methods to Capture Safety and Efficacy Data for Cell and Gene Therapy Products," which discusses how companies can use techniques such as real-world evidence, electronic health records and patient registries to understand how products work.[1]

Taken together, these guidances are part of a broader effort by FDA leadership to advance cell and gene therapy product development. Since the spring, FDA Commissioner Martin Makary has announced several such initiatives. Some, like these guidances, are specific to cell and gene products, while others focus on products for rare diseases but have direct implications for cell and gene products.

These include:

- Makary's announcement in April of a conditional approval pathway for ultra-rare conditions;
- A June cell and gene therapy roundtable hosted by FDA leaders, in which they pledged to reduce regulatory barriers and support custom CRISPR gene-editing therapies;
- Makary's announcement in June of a new priority review program and flexible trial designs; and
- A September announcement of a new Rare Disease Accelerated Approval Program.

While many of the details of these programs remain unclear, cell and gene medicine

sponsors and researchers may have new opportunities to work with the FDA in the days ahead.

The FDA recommends that sponsors of regenerative medicine therapies engage with the Office of Therapeutic Products staff early in product development. This will allow sponsors to get FDA input on their clinical trial design, safety monitoring and other components of their clinical plan.

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[1] This article's scope is limited to the RMAT draft guidance.