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Opinion

Planning for progress: A US regulatory approach to advancing the clinical development of gene therapies

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While the gene-therapy field has experienced tremendous scientific, technological, and regulatory advances, understanding the factors that are slowing the rate of development and approval is important to ensure that barriers are addressed.[1] This article reflects on progress made under the Regenerative Medicine Advanced Therapy (RMAT) designation program, discusses barriers to efficient clinical development of gene-therapy products, and opines on the role of PDUFA VII as a key driver in facilitating efficient development of, and access to, gene therapies in the United States.

IS THE RMAT DESIGNATION PROGRAM DELIVERING ON ITS INTENDED BENEFITS?

The 21st Century Cures Act, enacted in December 2016, introduced the RMAT designation program to accelerate development and approval of regenerative medicines, including gene therapy.[2] A regenerative-medicine therapy may qualify for RMAT designation if preliminary clinical evidence indicates a potential to address unmet medical needs for a serious or life-threatening disease or condition. Ideally, a product with an RMAT designation would benefit from increased flexibility in clinical trial design and opportunities to explore more efficient regulatory paths including accelerated approval, and close guidance from, and engagement with FDA leadership. With the recent 5-year anniversary of the RMAT program, a reflection on its performance is timely to evaluate whether the program is delivering on its promise to expedite and facilitate product development and approval.

Since the inception of the RMAT program, the FDA has received 187 requests, granted 72 (~38%), and denied 101 (~54%) (see Table 1).[3] However, as of March 31, 2022, only three RMAT-products have been approved (one of which is a gene therapy)—sharply contrasting the Breakthrough Therapy Designation (BTD) program,[1] which saw 94 approvals in the first 5 years, despite similarities in the rates of designation, goals, and benefits.[4,5] While RMAT designated products are in varying stages of development, the limited number of designated products approved underscores the need to assess whether we (FDA and industry) are leveraging it to its full potential. Finally, there appears to be a downward trend in RMAT designation requests since the program's inception. This may indicate key frustrations with the program and potentially a misalignment of expectations. Some of the unrealized expectations, as highlighted across many ASGCT forums, include: 1. securing FDA leadership guidance across all RMAT products; 2. clarity on when to apply and the amount of data that would suffice; and 3. frequent multiple interactions after the RMAT designation is granted.

With the additional resources expected under PDUFA VII,[6] CBER should be better positioned to support RMAT. Given the current misalignment between sponsors' expectations from the program and what the Agency is currently resourced to deliver, incorporating metrics to track the impact from PDUFA VII—especially on the speed and ease of product development, on Agency resource utilization, and leadership engagement—would be valuable to help close the gap. ASGCT membership expect RMAT to enable frequent Agency and leadership engagement to expedite development. With PDUFA VII, there is an expectation that more live meetings will be granted for RMAT-designated products instead of written response only (WRO) communications. Additionally, it is important for CBER to accept communication plans when proposed, as having a clear engagement strategy will help streamline development.

The lack of understanding and alignment on the data necessary to obtain an RMAT designation needs to be addressed. Clarification in guidance and relevant workshops with examples highlighting the amount, type, and duration of data (especially for products evaluating efficacy based on biomarker data) will save time and resources for sponsors and the FDA alike. Additionally, brief pre-submission meetings, similar to what is currently in place for BTD, would help reinforce sponsors' understanding of whether they are ready to submit an RMAT request. Overall, the first five years of RMAT has provided some benefits. However, many challenges still exist, and there are opportunities to ensure that RMAT becomes a better mechanism for earlier, more reliable alignment to avoid surprises, de-risk programs, and deliver innovative treatments to patients efficiently.

WHAT ARE OTHER CHALLENGES TO THE EFFICIENT DEVELOPMENT OF GENE THERAPIES?

Several challenges remain with progressing clinical trials and generating sufficient data to support approval. This article highlights difficulties with clinical development and does not address chemical, manufacturing and control (CMC), nonclinical, or safety, which have been extensively discussed in the literature.[6–12]

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Table 1. RMAT designation by year

Fiscal year (FY)	RMAT requests received	RMAT requests granted	RMAT requests denied	RMAT requests withdrawn
2017	31	11	18	2
2018	47	18	27	2
2019	37	17	18	2
2020	34	13	21	0
2021	24	8	14	2
2022 (as of 03/31/2022)	14	5	3	0

Determining the ideal approach for first-in-human (FIH) studies can be challenging given the important goals of ensuring patient safety and adequacy of the dose-selection strategy in light of the inability to re-dose. FIH development strategies are further complicated by questions regarding the translatability of nonclinical to clinical data and the lack of appropriate animal models. Thus, a thoughtful approach to FIH trial design is critical. For example, guidance suggests staggering dosing in FIH trials. However, practical approaches, including the number of participants per dose cohort, amount of time in between dosing, and the involvement of data-monitoring committees, likely run the gamut with approaches being either too fast or too slow. As the field collectively gains more experience with advanced therapies in the clinic, approaches that may have been appropriate in the early days may need to be re-examined. As an example, for AAV gene therapies, we now can understand and predict some toxicities that are related to capsid serotype, dose, and route of administration; this knowledge may now allow for more efficient trial design, dosing schema and staggering schedules, and a certain level of standardization of nonclinical packages for a FIH trial. With FDA's broad view across many programs, providing more specific learnings and considerations that balance patient safety and trial efficiency could prove useful for the field.

Challenges remain with understanding the ideal approach to aligning with CBER on the use of novel endpoints. There is a spectrum of biomarkers: validated biomarkers, biomarkers that are "reasonably likely" surrogate endpoints, and emerging biomarkers. Therefore, continued dialogue, especially for emerging biomarkers, and new approaches to assessing the totality of data that would support approval are critical. Taking factor activity in hemophilia as an example, while guidance was ultimately released highlighting the acceptability of factor activity as a surrogate endpoint for accelerated approval of hemophilia gene-therapy products, the community would benefit by increasing transparency of the decision-making process, including discussions regarding the amount of data that supported the determination that factor activity was a reasonable surrogate endpoint. While the initial hurdle has been crossed with the uncertainty of leveraging surrogate endpoints for hemophilia, there are many other diseases where this uncertainty is rate limiting. Clearly articulating an accelerated development path leveraging a surrogate endpoint would be useful. For example, diseases such as Beta thalassemia, Sickle Cell Disease, Congenital Adrenal Hyperplasia, and Canavan disease, could benefit from ongoing dialogue that balances supporting innovation while ensuring safety and effectiveness of the product.

Gene replacement provides a unique opportunity for biomarker use, particularly in the setting of rare diseases. We (FDA and industry) need to ensure a clear path and openness to engaging in dialogue around how available data, an understanding of the mechanism of disease process, and the unique approach to gene replacement create an opportunity that could accelerate development and patient access. Flexibility around biomarkers is critical, as gene-therapy programs are typically focused on rare and ultra-rare diseases; in such diseases, there is often a paucity of rigorous, prospective natural-history data available to define disease trajectory clearly and confidently. Generally, sponsors would benefit tremendously from more guidance on the considerations for planning a nonclinical/clinical package to support such a relationship that could result in an accelerated or traditional approval.

DOES PDUFA VII HAVE THE POTENTIAL TO ADDRESS OUTSTANDING BARRIERS TO THE DEVELOPMENT OF GENE THERAPY PRODUCTS?

Based on the commitment letter, PDUFA VII advancements are largely driven by a focus on cell and gene therapies.[13] Importantly, for the first time in PDUFA history, CBER will receive substantial resources and greater targeted hires than CDER to meet demands from the current and anticipated influx of cell- and gene-therapy applications (Table 2). Substantially strengthened CBER staff capacity and capability will help overcome existing resource limitations, allowing staff to spend additional time on meetings and submission reviews, including those with RMAT designation, expand stakeholder outreach, invest in new policy and guidance, and facilitate development and use of regulatory tools and scientific technologies. The proposed PDUFA VII commitments include several cross-center goals that would support CDER and CBER programs. Specifically, there are opportunities to address challenges

Table 2. Metric goals for targeted hires within the human drug review program staff during PDUFA VII

	FY 2023	FY 2024	FY 2025	FY 2026	FY 2027
CBER	132	48	29	15	4
CDER	77	31	15	0	0
Other FDA	1	0	0	0	0
Total Full Time Employees (FTEs)	210	79	44	15	4

FY, fiscal year.

with investigational new drug (IND)-enabling and FIH studies. Notably, the INTERACT meeting, typically held before a pre-IND meeting, will become a formal meeting under PDUFA VII, ensuring dedicated resources and predictable timelines.

Model-informed drug development (MIDD) approaches will help advance and integrate the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources in gene-therapy development and regulatory review. While more characterization and mechanistic information is needed to enhance the value and application of MIDD approaches for gene therapy, MIDD could be used to better understand variability and durability based on predictive modeling to inform regulatory decision-making.

Tools available in PDUFA VII may help address challenges with gaining alignment on the use of novel or surrogate endpoints with the Agency. The new Type D meeting focused on a narrow set of issues should be availed to address novel issues such as discussions on innovative technology, novel clinical trial design, patient engagement to provide input on trial design, selection of clinical endpoint, or other clinical-outcome assessment tools.

PDUFA VII builds on the prior PDUFA iteration by retaining Type C meetings specifically pertaining to early consultations regarding the use of new surrogate endpoints as the primary basis of product approval—this meeting should be leveraged more for gene-therapy programs. Also, active CBER participation in the Rare Disease Endpoint Advancement (RDEA) Pilot Program will inform best practices for novel endpoint development. Factors often associated with rare diseases targeted by gene therapy include the lack of regulatory precedent, small trial populations, and/or limited understanding of a disease's natural history. This creates unique challenges when selecting appropriate efficacy endpoint(s)—making the RDEA pilot especially relevant for gene therapies.

FDA's PDUFA VII commitment to leverage public-private partnerships to seek public input on challenges faced by gene-therapy developers will be critical for the field. Also, the planned guidance on evaluating efficacy in small patient populations using novel trial designs and statistical methods, and how these concepts can be applied to common diseases, will be helpful to clarify expectations for gene therapies.

Lastly, the Agency may solicit and address frequently asked questions and answers (Q&As) in guidance under PDUFA VII to facilitate clinical development. The proposed iterative approach to the guidance allows new Q&As to be addressed in a timely menner and made available to stakeholders. It would be helpful for the first draft to include Q&As to clarify data-sufficiency expectations to proceed to FIH trials, use of novel and surrogate endpoints, and sufficiency of the clinical data package.

This paper comes at a key inflection point in the regulatory landscape for gene therapy. It reflects on the last five years of RMAT and looks ahead to the implementation of PDUFA VII over the next five years, considering approaches to address key challenges with new regulatory tools. While progress has been made with the implementation of RMAT, much more is needed to continue advancements in the field. Additionally, challenges remain with progressing clinical trials and generating sufficient data to support approval. Resources and commitments included in the proposed PDUFA VII package should help address many difficulties developers face. With the influx of new reviewers under PDUFA VII, ensuring education, openness, and awareness on novel approaches will be important to continued advancement of innovation in the field. The new resources provided under PDUFA VII come with a commitment to integrating new staff, engaging external stakeholders, staying current with regulatory science and innovation, and advancing industry communication and engagement, all of which, with careful implementation, could be transformational for the field.

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DECLARATION OF INTERESTS

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