Orphan Drug Development Guidebook

Building Block U211

This document defines the content of the Building Block created for each identified tool, incentives, initiative or practice introduced by public bodies or used by developers to expedite drug development in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	Regenerative Medicine Advanced Therapy (RMAT) Designation
References	https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-therapy-designation https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-regenerative-medicine-therapies-serious-conditions Cumulative CBER Regenerative Medicine Advanced Therapy (RMAT) Designation Requests Received by Fiscal Year
Description	The RMAT is one of the designation programs which specifically addresses the expedited development and review of certain regenerative medical therapies designated as RMATs. It allows companies to interact with the FDA earlier and more frequently during the clinical development of their product. An RMAT-designated therapy is eligible for priority review and accelerated approval. The early interactions with FDA can be used to discuss potential surrogate or intermediate endpoints to support an accelerated approval of the product. Many candidate therapies in development for orphan diseases also qualify for the Regenerative Medicine Advanced Therapy designation. Regenerative medicine is a rapidly expanding field that has the potential to treat serious conditions, particularly in patients with unmet medical needs. The Center for Biologics Evaluation and Research (CBER) recognizes the importance of regenerative medicine therapies and is committed to helping ensure they are licensed and available to patients with serious conditions as soon as it can be determined that they are safe and effective. This is intended to facilitate development and review of regenerative medicine therapies intended to address unmet medical need in those with serious conditions.

	No later than 60 calendar days after receipt of the designation request, CBER will notify the sponsor as to whether the regenerative medicine therapy has received the RMAT designation. If CBER determines that the regenerative medicine therapy does not meet the criteria for RMAT designation, CBER will include a written description of the rationale for the determination. As with other expedited development programs, if RMAT designation has been granted but, later in development, the product no longer meets the qualifying criteria, then CBER may rescind the RMAT designation. This is because FDA needs to focus its resources on RMAT product development programs that continue to meet the program's qualifying criteria.
Category	Regulatory Building Block
Geographical scope	United States of America
Availability	Applicants developing regenerative medicine therapies, which comprise: "Cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. Additionally, gene therapies, including genetically modified cells that lead to a durable modification of cells or tissues may meet the definition of a regenerative medicine therapy. A combination product (biologic-device, biologic drug, or biologic-device-drug) can be eligible for RMAT designation when the biological product component provides the greatest contribution to the overall intended therapeutic effects of the combination product (i.e., the primary mode of action in the combination product is conveyed by the biological product component)"
Scope of use	Early and frequent interactions with FDA for discussions e.g. study design, endpoints, extent of safety data required to support approval, dose-response concerns, and use of biomarkers.
Stakeholders	• Medicinal product developers • The Center for Biologics Evaluation and Research (CBER)
Enablers /	An investigational drug is eligible for RMAT designation if:

Require ments	• It meets the definition of regenerative medicine therapy • It is intended to treat, modify, reverse, or cure a serious condition; and • Preliminary clinical evidence indicates that the regenerative medicine therapy has the potential to address unmet medical needs for such condition. In order to apply for RMAT designation, a developer should submit a request to CBER either with a new investigational new drug application (IND) or in an IND amendment. CBER will not accept requests for RMAT designation for INDs that are inactive or on clinical hold. Unlike BTD (Building Block U204), RMAT designation does not require evidence indicating substantial improvement over available therapies.
Output	The output is a designation which grants access for Priority Review Designation and Accelerated Approval.
Best time to apply and time window	Either with the IND request or after, once there is clinical evidence of the drug efficacy. No later than end of phase 2.
Submissi on guidance	In general, the RMAT request should contain a concise summary of information that supports the RMAT designation, including: • A description of the investigational product, including a rationale for the investigational new drug meeting the definition of a regenerative medicine therapy; • A discussion to support that the disease or condition, or the aspect of the disease or condition, that the product is intended to treat is serious; • A summary of the risks and benefits associated with the therapies, if any, currently available for this condition; • A description of the unmet medical need that the product has the potential to address; and • The preliminary clinical evidence that the product has the potential to address the specified unmet medical need for this serious condition. Please note that the preliminary clinical evidence may not always come from prospective clinical trials with concurrent control and well-designed retrospective studies, or clinical case series could be used to support RMAT designation request. However, the preliminary clinical evidence must be generated using the product the sponsor intends to use for clinical development.

Expert tips

RMAT, especially when the product is also eligible for Priority Review, may greatly expedite the timeframe for a qualifying product to obtain marketing authorization. The early and more frequent interactions with FDA also help de-risk the development of products that are often facing novel development challenges in the regenerative space.

PROs:

	Breakthrough Therapy Designation	Regenerative Medicine Advanced Therapy Designation
Statute	Section 506(a) of the FD&C Act, as added by section 902 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)	Section 506(g) of the FD&C Act, as added by section 3033 of the 21st Century Cures Act
Qualifying criteria	A drug that is intended to treat a serious condition, **AND** preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	A drug is a regenerative medicine therapy, AND the drug is intended to treat, modify, reverse, or cure a serious condition, AND preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition
Features	• All fast track designation features, including: ▪ Actions to expedite development and review ▪ Rolling review • Intensive guidance on efficient drug development, beginning as early as Phase 1 • Organizational commitment involving senior managers	• All breakthrough therapy designation features, including early interactions to discuss any potential surrogate or intermediate endpoints • Statute addresses potential ways to support accelerated approval and satisfy post-approval requirements
When to submit	With the IND or after and, ideally, no later than the end-of-phase 2 meeting	
FDA response	Within 60 calendar days after receipt of request	
Designation Rescission	Designation may be rescinded later in product development if the product no longer meets the designation-specific qualifying criteria	

- Guaranteed interactions with the FDA resulting in intensive FDA guidance on efficient drug development
- Eligible for priority review
- Eligible for accelerated approval

CONs:

- Restricted to regenerative medicines
- RMAT is not available for human cell and tissue products that are minimally manipulated and are intended for homologous use, and either:

  (1) have no systemic effect or do not depend on metabolic activity of living cells, or

  (2) are for autologous, allogenic (to first- or second-degree relatives) or reproductive use.

	- RMAT designation has significant overlap with BTD, so it is not easy to disaggregate the effect of each one individually