

## 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	<a href="https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm585414.pdf">https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm585414.pdf</a>
Description	<p>The RMAT Designation is analogous to the Breakthrough Designation designed for traditional drug candidates but applies to regenerative medicine treatments, and allows companies to interact with the FDA more frequently during the clinical development of the therapy. An RMAT-designated therapy is eligible for priority review and accelerated approval.</p> <p>“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.”</p> <p>All matters related to regenerative medicines (FDA-CBER definition) intended to treat, modify, reverse or cure a serious condition especially at early stage of product development. Many candidate therapies in development for orphan diseases also qualify for the Regenerative Medicine Advanced Therapy designation.</p> <p>CBER will notify the sponsor 60 days after receipt of the request. In case of Orphan drug</p>

	designation granted, fees waiver according to section 736 of the FD&C.
Category	Regulatory Building Block
Geographical scope	United States of America
Availability	<p>Applicants developing regenerative medicine therapies, which comprise:</p> <p>“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)”</p>
Scope of use	Frequent interactions with FDA for discussions e.g. study design, extent of safety data required to support approval, dose-response concerns, and use of biomarkers.
Stakeholders	<ul style="list-style-type: none"> <li>• Sponsors</li> <li>• The Center for Biologics Evaluation and Research (CBER)</li> </ul>
Enablers / Requirements	<p>An investigational drug is eligible for RMAT designation if:</p> <ul style="list-style-type: none"> <li>• It meets the definition of regenerative medicine therapy</li> <li>• It is intended to treat, modify, reverse, or cure a serious condition; and</li> <li>• Preliminary clinical evidence indicates that the regenerative medicine therapy has the potential to address unmet medical needs for such condition.</li> </ul> <p>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.</p> <ul style="list-style-type: none"> <li>– Products intended to treat, modify, reverse, or cure a serious condition.</li> </ul>

	<ul style="list-style-type: none"> <li>– Preliminary clinical evidence indicating potential to address unmet medical needs for serious diseases or conditions.</li> <li>– Unlike BTM (Building Block U204), RMAT designation does not require evidence indicating substantial improvement over available therapies.</li> </ul>																					
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.																					
Expert tips	<p>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.</p> <p>PROs:</p> <table border="1" data-bbox="338 1099 1270 1727"> <thead> <tr> <th></th> <th>Breakthrough Therapy Designation</th> <th>Regenerative Medicine Advanced Therapy Designation</th> </tr> </thead> <tbody> <tr> <td><b>Statute</b></td> <td>Section 506(a) of the FD&amp;C Act, as added by section 902 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)</td> <td>Section 506(g) of the FD&amp;C Act, as added by section 3033 of the 21<sup>st</sup> Century Cures Act</td> </tr> <tr> <td><b>Qualifying criteria</b></td> <td>A drug that is intended to treat a serious condition, <b>AND</b> preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies</td> <td>A drug is a regenerative medicine therapy, <b>AND</b> the drug is intended to treat, modify, reverse, or cure a serious condition, <b>AND</b> preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition</td> </tr> <tr> <td><b>Features</b></td> <td> <ul style="list-style-type: none"> <li>• All fast track designation features, including: <ul style="list-style-type: none"> <li>▪ Actions to expedite development and review</li> <li>▪ Rolling review</li> </ul> </li> <li>• Intensive guidance on efficient drug development, beginning as early as Phase 1</li> <li>• Organizational commitment involving senior managers</li> </ul> </td> <td> <ul style="list-style-type: none"> <li>• All breakthrough therapy designation features, including early interactions to discuss any potential surrogate or intermediate endpoints</li> <li>• Statute addresses potential ways to support accelerated approval and satisfy post-approval requirements</li> </ul> </td> </tr> <tr> <td><b>When to submit</b></td> <td colspan="2">With the IND or after and, ideally, no later than the end-of-phase 2 meeting</td> </tr> <tr> <td><b>FDA response</b></td> <td colspan="2">Within 60 calendar days after receipt of request</td> </tr> <tr> <td><b>Designation Rescission</b></td> <td colspan="2">Designation may be rescinded later in product development if the product no longer meets the designation-specific qualifying criteria</td> </tr> </tbody> </table> <ul style="list-style-type: none"> <li>- Guaranteed interactions with the FDA resulting in intensive FDA guidance on efficient drug development</li> <li>- Flexibility in the number of clinical sites used and the possibility to use patient registry data and other sources of “real-world” evidence for post-approval</li> </ul>		Breakthrough Therapy Designation	Regenerative Medicine Advanced Therapy Designation	<b>Statute</b>	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 21 <sup>st</sup> Century Cures Act	<b>Qualifying criteria</b>	A drug that is intended to treat a serious condition, <b>AND</b> 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, <b>AND</b> the drug is intended to treat, modify, reverse, or cure a serious condition, <b>AND</b> preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition	<b>Features</b>	<ul style="list-style-type: none"> <li>• All fast track designation features, including: <ul style="list-style-type: none"> <li>▪ Actions to expedite development and review</li> <li>▪ Rolling review</li> </ul> </li> <li>• Intensive guidance on efficient drug development, beginning as early as Phase 1</li> <li>• Organizational commitment involving senior managers</li> </ul>	<ul style="list-style-type: none"> <li>• All breakthrough therapy designation features, including early interactions to discuss any potential surrogate or intermediate endpoints</li> <li>• Statute addresses potential ways to support accelerated approval and satisfy post-approval requirements</li> </ul>	<b>When to submit</b>	With the IND or after and, ideally, no later than the end-of-phase 2 meeting		<b>FDA response</b>	Within 60 calendar days after receipt of request		<b>Designation Rescission</b>	Designation may be rescinded later in product development if the product no longer meets the designation-specific qualifying criteria	
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	<p>studies (pending FDA approval)</p> <ul style="list-style-type: none"><li>- Eligible for priority review</li><li>- Eligible for accelerated approval</li></ul> <p>CONs:</p> <ul style="list-style-type: none"><li>- Restricted to regenerative medicines</li><li>- RMAT is not available for human cell and tissue products that are minimally manipulated and are intended for homologous use, and either:<ul style="list-style-type: none"><li>(1) have no systemic effect or do not depend on metabolic activity of living cells, or</li><li>(2) are for autologous, allogenic (to first- or second-degree relatives) or reproductive use.</li></ul></li><li>- RMAT designation has significant overlap with BTM, so it is not easy to disaggregate the effect of each one individually</li></ul>
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