Breakthrough Therapy Designation (BTD)	VS	Regenerative Medicine Advanced Therapy Designation (RMAT)
FDA Safety and Innovation Act of 2012 (FDASIA)	**Statute**	21st Century Cures Act of 2016
Drugs and biologics regulated by FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)	**Eligible Products**	Regenerative medicines, a class of CBER-regulated biologics that includes: • cell therapies, • therapeutic tissue engineering products, • human cell and tissue products, • gene therapies, including genetically modified cells, that lead to a durable modification of cells or tissues, • Combination products (biologic-device, biologic-drug, or biologic-device-drug) when the primary mode of action is conveyed by the biological product component 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, allogeneic (to first or second degree relatives) or reproductive use.
Products intended to treat a serious condition	**Eligible Conditions**	Products intended to treat, modify, reverse, or cure a serious condition
Preliminary clinical evidence indicating the product may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapy. FDA guidance defines "preliminary clinical evidence" as "evidence that is sufficient to indicate that the drug may demonstrate substantial improvement in effectiveness or safety over available therapies, but in most cases is not sufficient to establish safety and effectiveness for purposes of approval."	**Evidence Threshold**	Preliminary clinical evidence indicating potential to address unmet medical needs for serious diseases or conditions. Unlike BTD, RMAT designation does not require evidence indicating substantial improvement over available therapies.
FDA expects preliminary evidence would generally be derived from Phase I or II trials with sufficient numbers of patients to be credible, although data cannot be expected to be definitive. Nonclinical information could support clinical evidence of drug activity. Ideally, FDA says preliminary clinical evidence indicating a substantial improvement over available therapies would be derived from: • a study that compares the investigational drug to an available therapy (or placebo, if there is no available therapy) in clinical testing, or • a study that compares the new treatment plus standard of care to SOC alone. FDA encourages sponsors to obtain some preliminary comparative data of this type early in development. FDA is also open to other types of persuasive clinical data, including single-arm studies comparing the new treatment with well-documented historical experience. (FDA notes that generally, such historically controlled data would be persuasive only if there is a large difference between the new treatment and historical experience.)	**Sources Of Evidence**	Preliminary clinical evidence to demonstrate the potential of a regenerative medicine therapy to address unmet medical needs "generally would be obtained from clinical investigations specifically conducted to assess the effects of the therapy on a serious condition." FDA acknowledges that such investigations, particularly early in product development, may not always be prospective clinical trials with a concurrent control. The agency will consider preliminary clinical evidence from: • studies with appropriately chosen historical controls • well-designed retrospective studies or clinical case series that provide data systematically collected by treating physicians. In either case, FDA emphasizes that "it is essential that the preliminary clinical evidence be generated using the regenerative medicine therapy that is planned for clinical development, rather than a related product."

Timeline

Submit request for BTD or RMAT with an IND or after, ideally no later than the end-of-Phase II (EOP2) meeting. FDA will respond within 60 calendar days of receipt.

Sources: Adapted from FDA's May 2014 guidance on expedited programs for serious conditions (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf) and FDA's November 2017 draft guidance on expedited programs for regenerative medicine therapies for serious conditions (https://pink.pharmaintelligence.informa.com/-/media/supporting-documents/pink-sheet/2017/11/regenerative-medicine-draft-guidance-on-expedited-programs-11-16-2017.pdf)

Pink Sheet
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