Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

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Draft Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

Draft Guidance for Industry

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I. INTRODUCTION

This guidance provides sponsors engaged in the development of regenerative medicine therapies for serious or life-threatening diseases or conditions[1] with our recommendations on the expedited development and review of these therapies, including as provided under section 506(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as added by section 3033 of the 21st Century Cures Act (Cures Act).[2] Under section 506(g) of the FD&C Act, a regenerative medicine therapy can be designated as a regenerative advanced therapy if it meets certain criteria. FDA refers to such designation as "regenerative medicine advanced therapy" (RMAT) designation (see section III.C of this document). This guidance describes the expedited programs available to sponsors of regenerative medicine therapies for serious conditions, including those products designated as RMATs. To that end, the guidance provides information about the provisions in the Cures Act regarding the use of the accelerated approval pathway for regenerative medicine therapies that have been granted designation as an RMAT. Finally, the guidance describes considerations in the clinical development of regenerative medicine therapies and opportunities for sponsors of such products to interact with the Center for Biologics Evaluation and Research (CBER) review staff. As a general matter, this guidance addresses regenerative medicine therapies regulated by CBER as biological products under the FD&C Act, section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262), and applicable regulations.

This draft guidance, when finalized, will supersede the final guidance of the same title dated February 2019. FDA is issuing this guidance in accordance with a commitment outlined in the reauthorization of the Prescription Drug User Fee Act (PDUFA VII) under the 2022 FDA User Fee Reauthorization Act.[3]

[1] As explained in section III of this guidance, all references to serious conditions include life-threatening conditions, and, for purposes of this guidance, the terms "condition" and "disease" are used interchangeably.
[2] Public Law 114-255.
[3] See Section I.O.3 of the PDUFA VII commitment letter available at https://www.fda.gov/media/151712/download.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Regenerative medicine is a rapidly expanding field that has the potential to treat serious conditions, particularly in patients with unmet medical needs. CBER recognizes the importance of regenerative medicine therapies and is committed to helping ensure they are licensed[4] and available to patients with serious conditions as soon as it can be determined they are safe and effective. The programs described in this guidance are intended to facilitate development and review of regenerative medicine therapies intended to address an unmet medical need in patients with serious conditions. In addition to the programs described in this guidance, regenerative medicine therapies may also be eligible for FDA's Platform Technology Designation Program.[5] Sponsors may be able to leverage information and relevant prior knowledge, when scientifically justified and legally permissible, outside of the platform technology designation program.

In particular, this guidance addresses regenerative medicine therapies which are defined in section 506(g)(8) of the FD&C Act as including cell therapies[6], therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the PHS Act (42 U.S.C. 264) and Title 21 of the Code of Federal Regulations Part 1271 (21 CFR Part 1271). Based on FDA's interpretation of section 506(g), human gene therapies[7], including genetically modified cells, generally meet the definition of a regenerative medicine therapy[8] (Ref. 1).

[4] Biological products are licensed under section 351 of the PHS Act while drugs are approved under section 505(c) of the FD&C Act; this guidance generally refers to "approval" and "accelerated approval" consistent with the terminology in section 506(c) of the FD&C Act, which authorizes FDA to grant accelerated approval for drugs, including biological products that are drugs, under their respective authorities.

[5] For additional information regarding FDA's Platform Technology Designation Program, please see Platform Technology Designation Program for Drug Development; Draft Guidance for Industry (May 2024), available at https://www.fda.gov/media/178938/download. When finalized, this guidance will represent FDA's current thinking on the topic.

[6] FDA interprets cell therapies, for purposes of section 506(g)(8) of the FD&C Act, to include both allogeneic and autologous cell therapies.

[7] For additional information regarding human gene therapies, please *see, e.g.,* Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs); Guidance for Industry (January 2020), available at https://www.fda.gov/media/113760/download.

[8] Based on FDA's interpretation of section 506(g) of the FD&C Act, microorganisms (e.g., viruses, bacteria, fungi) that are not genetically modified, products that are genetically modified but do not express a foreign transgene (e.g., an adenovirus vector that has been genetically modified with a deletion), and peptide therapeutic vaccines do not meet the definition of regenerative medicine therapy.

Further, as FDA interprets section 506(g), xenotransplantation products may also meet the definition of a regenerative medicine therapy (Ref. 1). Additionally, a combination product (biologic-device, biologic-drug, or biologic-device-drug) can be eligible for RMAT designation when the biological product constituent part is a regenerative medicine therapy and provides the greatest contribution to the overall intended therapeutic effects of the combination product (i.e., the primary mode of action of the combination product is conveyed by the biological product constituent part).[9]

III. EXPEDITED PROGRAMS FOR REGENERATIVE MEDICINE THERAPIES

In 1988, FDA issued regulations in 21 CFR Part 312 (Subpart E)[10] on expediting the availability of promising therapies to patients with serious conditions. The regulations call for earlier attention to drugs that have promise in treating such conditions, including early consultation with FDA for sponsors of such products. In subsequent years, the FD&C Act has been amended several times to include several new programs for expedited product development and review, including fast track designation, accelerated approval, and breakthrough therapy designation. In December 2016, Congress amended section 506 of the FD&C Act (21 U.S.C. 356) by adding new section 506(g), which specifically addresses the expedited development and review of certain regenerative medicine therapies designated as RMATs.

Regenerative medicine therapies intended to treat, modify, reverse, or cure serious conditions are eligible for FDA's expedited programs, including fast track designation, breakthrough therapy designation, RMAT designation, accelerated approval, and priority review designation, if they meet the criteria for such programs. This guidance provides additional information about the application of those programs to regenerative medicine therapies, as well as information about the RMAT designation program, which CBER intends to administer in a manner that is consistent with the other expedited programs, where applicable. Sponsors should consult the "Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics" dated May 2014 (Expedited Programs Guidance) (Ref. 2) for generally applicable information, including the criteria for, and benefits of, fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation.[11] As with other biological products, regenerative medicine therapies receiving fast track designation, breakthrough therapy designation, and RMAT designation must meet the evidentiary standards for approval, including demonstrating safety and effectiveness (regardless of whether the product receives accelerated or traditional approval).[12]

[9] For additional information, see 21 USC 353(g)(1)(C) and 21 CFR 3.2.

[10] Food and Drug Administration, Interim Rule, Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses (53 FR 41516, October 21, 1988).

[11] For additional information regarding FDA's policies and procedures for accelerated approval as well as the threshold criteria for drugs, see the "Draft Guidance for Industry: Expedited Program for Serious Conditions – Accelerated Approval of Drugs and Biologics" dated December 2024 (Ref. 3). When finalized, this guidance will represent FDA's current thinking on the topic.

[12] Section 505(d) of the FD&C Act and section 351(a) of the PHS Act. See also section 506(e) of the FD&C Act.

Fast track designation, breakthrough therapy designation, and RMAT designation are distinct designation programs with different programmatic requirements. Sponsors may apply for and receive more than one designation for a given product, but sponsors should apply for each designation separately. Information that supports more than one designation may be submitted in each separate designation request.

Early-phase clinical studies involving small study populations may also provide early evidence of effectiveness in addition to focusing on safety assessments, such as for rare diseases. In cases where early-phase clinical studies are used to establish evidence of effectiveness in support of a marketing application, sponsors should ensure that appropriate quality controls for the clinical products are implemented during the early clinical development phase. Such quality controls should be based on a thorough evaluation of the product's critical quality attributes (CQAs) and manufacturing critical process parameters (CPPs). Additionally, a designation under any of the expedited programs does not change the chemistry, manufacturing, and controls (CMC) information required to assure product quality (including manufacturing facility compliance with applicable current good manufacturing practices) for approval. For approval it is important to demonstrate process control to ensure a consistent product with predefined CQAs for product strength, potency, identity, and purity. 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 CMC readiness for expedited development, sponsors of regenerative medicine therapies may need to pursue a more rapid CMC development program to accommodate the faster pace of the clinical program. Elements to consider for assuring CMC readiness may include designing the product quality control strategy based on a good understanding of relevant CQAs, planning for analytical assay validation and commercial process validation, and developing a risk-based strategy for managing manufacturing changes including scale-up and scale-out manufacturing. For example, sponsors are encouraged to perform product characterization studies early and throughout development to prevent future delays in the product development program due to an inability to identify relevant CQAs and reliably ensure product quality. Sponsors are strongly encouraged to discuss CMC readiness, including any perceived manufacturing challenges, through increased interactions with FDA under the auspices of these expedited programs.

For the purposes of this guidance, the terms *serious disease or condition, unmet medical need, surrogate endpoint, intermediate clinical endpoint,* and *clinically significant endpoint* have the same meanings as described in the Expedited Programs Guidance (Ref. 2). These terms are summarized briefly as follows:

> A *serious disease or condition* is a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more

serious one.[13] Of note, all conditions meeting the definition of *life-threatening* as set forth in 21 CFR 312.81(a) would also be serious conditions.

An *unmet medical need* is a condition whose treatment or diagnosis is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs).

A *surrogate endpoint* is a marker such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit, but is not itself a measure of clinical benefit.

An *intermediate clinical endpoint* is a measurement of a therapeutic effect that can be measured earlier than an effect on irreversible morbidity and mortality (IMM) and is considered reasonably likely to predict the drug's effect on IMM or other clinical benefit.

Clinically significant endpoint generally refers to an endpoint that measures an effect on IMM or on symptoms that represent serious consequences of a disease. It can also refer to findings that suggest an effect on IMM or serious symptoms.

In this guidance, the terms "condition" and "disease" are used interchangeably, and any serious or life-threatening disease or condition, or serious aspect of a disease or condition, is further referred to as a 'serious condition' hereafter. With respect to the expedited programs, for the purposes of this guidance, all references to drugs or drug products refer to human drugs, including drugs that are biological products, unless otherwise specified. As a general matter, however, this guidance addresses regenerative medicine therapies regulated by CBER as biological products under the FD&C Act, section 351 of the PHS Act (42 U.S.C. 262), and applicable regulations.

A. Fast Track Designation

An investigational new drug that is intended to treat a serious condition, and for which nonclinical or clinical data demonstrate the potential to address an unmet medical need in patients with such condition, can receive fast track designation.[14] Advantages of fast track designation include actions to facilitate development and expedite review of the product, such as the possibility for rolling review if FDA determines, after preliminary evaluation of clinical data submitted by a sponsor, that the fast track product may be effective. In addition, such a product could be eligible for priority review if supported by adequate scientifically valid information, including clinical data, in the complete marketing application submission.

[13] 21 CFR 312.300(b).

[14] Fast track designation is also available for an investigational new drug that is intended to treat a serious condition and that has been designated as a qualified infectious disease product under section 505E(d) of the FD&C Act.

CBER bases the decision to grant fast track designation on nonclinical or clinical data demonstrating that the product has the potential to address an unmet medical need. For example, at an early stage of development, evidence of the product's effect in a relevant in vitro or animal model could constitute sufficient evidence of the product's potential to address an unmet medical need. If nonclinical or clinical data demonstrate such potential, and the product development program is adequately designed to determine whether the regenerative medicine therapy will address an unmet medical need in those with a serious condition, then CBER would consider granting fast track designation.

B. Breakthrough Therapy Designation

Under the breakthrough therapy program, an investigational new drug that is intended to treat a serious condition, and for which preliminary clinical evidence indicates that the product may demonstrate substantial improvement over available therapies on one or more clinically significant endpoints, may qualify for breakthrough therapy designation. Advantages of this designation incorporate all the benefits of fast track designation and also include intensive FDA guidance on efficient drug development, as well as an organizational commitment to involve senior management in facilitating the product's development program.

It should be noted that the level of evidence required for breakthrough therapy designation is higher than for fast track designation. Specifically, fast track designation requires only that nonclinical or clinical data demonstrate the potential to address an unmet medical need, whereas for breakthrough therapy designation, preliminary clinical evidence must indicate that the product may demonstrate a substantial improvement over existing therapies on one or more clinically significant endpoints.

The following are hypothetical examples of regenerative medicine therapies that CBER may consider for breakthrough therapy designation:

- In metastatic breast cancer that is refractory to available therapies, administration of allogeneic tumor cell lines expressing tumor-specific antigens are associated with complete responses in a substantial portion of subjects in an open-label, first-in-human study.

- In advanced forms of age-related macular degeneration, subretinal administration of retinal pigment epithelium cells is associated with substantial improvement in either visual acuity or visual fields, or a substantial reduction in the area of geographic atrophy, at one year post-administration.

- In severe osteoarthritis limiting mobility, intra-articular administration of cells derived from hematopoietic stem cells suspended in a balanced buffer solution, when compared to the administration of the balanced buffer solution alone, is associated with a substantial decrease in pain and improvement in function.

In each of the above examples, the preliminary clinical evidence of substantial improvement over available therapies on a clinically significant endpoint could generally be derived from Phase 1 or Phase 2 trials.

C. Regenerative Medicine Advanced Therapy Designation

An investigational drug is eligible for RMAT designation if:

- It meets the definition of regenerative medicine therapy (see section II of this document);
- It is intended to treat,[15] 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.

Advantages of the RMAT designation include all the benefits of the fast track and breakthrough therapy designation programs, including early interactions with FDA (see Comparison of Breakthrough Therapy Designation and Regenerative Medicine Advanced Therapy Designation table below, which sets forth key similarities and differences between breakthrough therapy designation and RMAT designation). Section 506(g)(5) of the FD&C Act specifies that these early interactions may be used to discuss potential surrogate or intermediate endpoints to support accelerated approval (see section III.E in this guidance).

Regarding the preliminary clinical evidence to demonstrate the potential of a regenerative medicine therapy to address unmet medical needs, we generally expect that such evidence would be obtained from clinical investigations specifically conducted to assess the effects of the therapy on a serious condition. Such clinical investigations may not always be prospective clinical trials with a concurrent control. In some cases, clinical evidence obtained from relevant clinical investigations with appropriately chosen external controls[16] may provide sufficient preliminary clinical evidence of the potential to address an unmet medical need. In other cases, preliminary clinical evidence could come from well-designed retrospective studies or clinical case series that provide data systematically collected by treating physicians. Such clinical evidence may be from studies conducted outside of the United States[17] (Ref. 4). While preliminary clinical evidence does not need to demonstrate the substantial evidence of effectiveness that would be necessary for approval, such information should not be purely hypothetical and should show the potential to address an unmet medical need. For example, preliminary clinical evidence may include information from relevant clinical studies that show

[15] As described in section III.A.2 of the Expedited Programs Guidance (Ref. 2), FDA considers a product to be intended to treat a serious condition when the drug is intended to have an effect on a serious condition, or a serious aspect of a condition, such as a direct effect on a serious manifestation or symptom of a condition.

[16] See Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products; Draft Guidance for Industry (February 2023), available at https://www.fda.gov/media/164960/download. When finalized, this guidance will represent FDA's current thinking on the topic.

[17] 21 CFR 312.120.

potential for the regenerative medicine therapy to achieve clinical benefit for the serious condition. Additionally, preliminary clinical evidence should be clinically relevant to the serious condition that the regenerative medicine therapy is intended to address.

In any case, it is essential that the preliminary clinical evidence be generated using the product[18] that the sponsor intends to use for clinical development. If there are differences between the product used to collect the preliminary clinical evidence and the product planned for clinical development due to manufacturing changes, then it is recommended that the sponsor provide comparability data to establish relevance of the preliminary clinical evidence. If comparability between the intended clinical product and the product used to generate preliminary clinical evidence cannot be established, then the preliminary clinical evidence would generally not be supportive of an RMAT designation. If product manufacturing changes are made after receiving the RMAT designation, the post-change product may no longer meet the qualifying criteria for RMAT designation if comparability cannot be established with the pre-change product that was used to generate preliminary clinical evidence (Ref. 5). When changes to the product manufacturing process are planned or anticipated, sponsors should conduct a risk assessment of the impacts on product quality and, if deemed necessary based on the risk assessment, perform a comparability study.

When determining whether the preliminary clinical evidence is sufficient to support RMAT designation, CBER intends to consider factors, including but not limited to: the rigor of data collection; the consistency and persuasiveness of the outcomes; the number of patients or subjects, and the number of sites, contributing to the data; the severity, rarity, or prevalence of the condition; and whether the product used to generate the preliminary clinical evidence is comparable to the product under development. In addition, CBER intends to consider the potential that bias (e.g., bias in the study design, treatment assignment, or outcome assessment) may be a factor in the evidence provided in support of RMAT designation. CBER will review the preliminary clinical evidence in each designation request and will make designation decisions on a case-by-case basis. As opposed to breakthrough therapy designation, RMAT designation does not require evidence to indicate that the drug may offer a substantial improvement over available therapies on one or more clinically significant endpoints. As with breakthrough therapy designation, an RMAT designation is not the same as an approval and does not change the statutory standards for demonstration of safety and effectiveness needed for marketing approval.[19]

[18] FDA acknowledges that the issue of manufacturing changes is complex; however, manufacturing changes and product comparability are beyond the scope of this guidance. Manufacturing changes made to products during the development program would not necessarily preclude initial RMAT designation or cause RMAT designation to be rescinded. Such considerations will be made on a case-by-case basis.

[19] See section 506(e) of the FD&C Act. See also FDA's Standard Operating Policy and Procedure (SOPP) 8212, entitled "Management of Breakthrough Therapy-Designated Products: Sponsor Interactions and Status Assessment Including Rescinding" (Ref. 5), which explains that breakthrough therapy designation is not the same as an approval and does not change the statutory standards for marketing approval.

The following are hypothetical examples of preliminary clinical evidence that CBER would consider sufficient to demonstrate a product has the potential to address unmet medical needs in those with a serious condition:

- In a single-arm, open-label study conducted in a center treating patients with severe and extensive skin burns, use of allogeneic keratinocyte- and fibroblast -based cell therapy is associated with rapid and substantial wound re-epithelialization of deep partial thickness burns in the majority of treated wounds.

- In a dose-finding study, intra-myocardial administration of allogeneic human mesenchymal precursor cells to patients with advanced chronic heart failure refractory to available medical therapies is associated with dose-dependent improvement in several physiological measurements of left ventricular performance.

- In an open-label trial, the implantation of a vascular prosthesis comprising allogenic smooth muscle cells seeded on a degradable polymeric scaffold resulted in improved graft longevity when used as an arteriovenous graft for providing vascular access in patients requiring hemodialysis.

- In an open-label first-in-human study, one time administration of a clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9)-based gene editing therapy knocking down expression of a misfolded protein resulted in sustained reduction of the protein level in serum that was correlated with clinical benefit in subjects with hereditary disease caused by the misfolded protein.

- Repeated topical application of a gel formulation containing non-integrating, replication-incompetent viral vector-based gene therapy delivering functional copies of a gene to subjects with hereditary disease is associated with continued expression of the delivered gene and improved wound healing.

- One time administration of an autologous T-cell immunotherapy to patients with treatment-refractory unresectable or metastatic cancer led to an objective response rate higher than in patients historically treated with chemotherapy alone.

In each of the above examples, the preliminary clinical evidence could support a determination that the regenerative medicine therapy has potential to address unmet medical needs for a serious condition.

In order to apply for RMAT designation, a sponsor should submit a request to CBER either with a new investigational new drug application (IND) or in an IND amendment. CBER will not review or grant requests for RMAT designation for INDs that are inactive. If the IND is on clinical hold, or partial clinical hold, at the time the RMAT designation

request is received or if the request was received with the original IND submission and it is placed on clinical hold during the initial 30 day review period, the circumstances of the hold or partial hold will be considered to determine how they may affect the review of the request for RMAT designation, e.g., whether the hold issues preclude a determination of whether preliminary clinical evidence indicates the product has the potential to address an unmet medical need.

If you submit an RMAT designation request as an amendment to your IND, the cover letter should specify that the submission contains an RMAT designation request. The request should be in bold, uppercase letters as follows: **REQUEST FOR REGENERATIVE MEDICINE ADVANCED THERAPY DESIGNATION**. If the request is submitted with an initial IND, the cover letter should specify that the submission contains both an initial IND and a request for RMAT designation. The request should be in bold uppercase letters as follows: **INITIAL INVESTIGATIONAL NEW DRUG SUBMISSION** and **REQUEST FOR REGENERATIVE MEDICINE ADVANCED THERAPY DESIGNATION**.[20]

In general, such a 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.

A request for designation as an RMAT should describe the preliminary clinical evidence supporting designation. A description of the preliminary clinical evidence should include, for example, the conditions for product administration, outcome assessment, and patient monitoring; a description of the patients and their outcomes, including the number of patients who have received the drug; and the design, conduct, and analyses of any clinical investigations.

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

[20] For additional information on submitting requests for RMAT designation, *see* SOPP 8215 entitled "Management of Regenerative Medicine Advanced Therapy Products: Request for Designation, Sponsor Interactions, and Status Assessment" (September 2023), available at https://www.fda.gov/media/172173/download.

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.

A comparison of the key features of Breakthrough Therapy Designation and Regenerative Medicine Advanced Therapy Designation is provided in the table below:

Comparison of Breakthrough Therapy Designation and Regenerative Medicine Advanced Therapy Designation

	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	

D. Priority Review Designation

A product, including those that received fast track, breakthrough therapy, or RMAT designation, may be eligible for priority review, if it meets the criteria for priority review at the time the marketing application is submitted. At the time of a pre-biologics license application (pre-BLA) meeting with CBER, sponsors of regenerative medicine therapies,

including those under expedited development programs, should consider discussing their eligibility for priority review. For example, a regenerative medicine therapy may receive priority review if it treats a serious condition, and, if approved, would provide a significant improvement in the safety or effectiveness of the treatment of the condition.

A decision about granting priority review is made within 60 calendar days of receipt of the marketing application or efficacy supplement. If priority review is granted, CBER has a 6-month goal for reviewing the biologics license application (BLA) or efficacy supplement after filing.[21]

E. Accelerated Approval

As explained in the "Draft Guidance for Industry: Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics"[22] dated December 2024 (Accelerated Approval Draft Guidance) (Ref. 3), accelerated approval has been used primarily in settings in which the disease course is long and an extended period of time would be required to measure the intended clinical benefit of a drug. Section 506(c) of the FD&C Act provides that FDA may grant accelerated approval of a product,[23] including regenerative medicine therapies, "for a serious or life-threatening disease or condition… upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments." Sponsors of products that have been granted accelerated approval have been required to conduct post-approval confirmatory studies to verify and describe the anticipated effects of their products on irreversible morbidity and mortality or other clinical benefit (Ref. 3).[24]

Section 506(g)(6) of the FD&C Act explains that FDA may grant accelerated approval to products that have received RMAT designation. Under this provision, as appropriate, RMATs may be eligible for accelerated approval based on:

- previously agreed-upon surrogate or intermediate endpoints that are reasonably likely to predict long-term clinical benefit, or

- reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate.

[21] For additional information on review goals, see the PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 through 2027, available at https://www.fda.gov/media/151712/download.
[22] When finalized, this guidance will represent FDA's current thinking on this topic.
[23] Approval is under FD&C Act section 505(c) (for drugs) or PHS Act section 351(a) (for biological products). Also see 21 CFR Part 314, Subpart H; 21 CFR Part 601, Subpart E.
[24] See 21 CFR 601.41.

The use of surrogate or intermediate endpoints that are reasonably likely to predict long-term clinical benefit to support accelerated approval is discussed in greater detail in the Accelerated Approval Draft Guidance (Ref. 3).

Regarding reliance upon data obtained from a meaningful number of investigational sites, we expect that the determination of whether the number of investigational sites, even if limited, is "meaningful" will depend on factors such as whether the evidence of effectiveness is likely to be affected by a site-specific or investigator-specific bias, such that any conclusions regarding the product's effectiveness could not be reliably generalized to other sites. Thus, we anticipate that this determination will be a BLA review issue that will be considered on a case-by-case basis. If an RMAT receives accelerated approval based on this provision, it may be appropriate for the sponsor to provide post-approval clinical evidence about the product through expansion to additional sites.

As further specified in section 506(g)(7) of the FD&C Act, sponsors of products that have been granted RMAT designation and which receive accelerated approval may be able to fulfill the post-approval requirements from clinical evidence obtained from sources other than the traditional confirmatory clinical trials. Under this provision, as appropriate, the post-approval requirements for RMATs receiving accelerated approval may be satisfied by the following:

- The submission of clinical evidence, clinical studies, patient registries, or other sources of real-world evidence such as electronic health records;
- The collection of larger confirmatory data sets as agreed upon during product development; or
- Post-approval monitoring of all patients treated with such therapy prior to approval of the therapy.

Upon review of a BLA, CBER will determine what type(s) of post-approval requirements (e.g., confirmatory clinical trials, patient registries, electronic health records, or other data collections) will be necessary to confirm the clinical benefits of an RMAT that receives accelerated approval. Considerations that CBER anticipates will determine the type of post-approval requirements that are necessary include, but are not limited to, the nature of the product and its administration, the evidence supporting marketing approval, the nature and magnitude of the anticipated benefit, the size of the target population, and the feasibility of obtaining confirmatory evidence. Thus, CBER intends to determine post-approval requirements for verification of clinical benefit, including certain types of real-world evidence (RWE)[25], on a case-by-case basis. FDA may require, as appropriate, a

[25] For purposes of this guidance, FDA defines real-world evidence (RWE) as follows: the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world data (data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources). Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products; Guidance for Industry (August 2023), at 2, available at https://www.fda.gov/media/171667/download.

study or studies to be underway prior to approval, or within a specified time period after the date of approval, of the applicable product. The clinical evidence for fulfilling post-approval requirements for products granted accelerated approval should be collected timely and with due diligence.[26] In certain limited instances, RWE may be used to fulfill gaps in confirmatory evidence to verify and describe the clinical benefit of a regenerative medicine therapy granted RMAT designation and approved via accelerated approval. Such cases may involve the use of RWE generated from real-world data (RWD) serving as a treatment and comparator in an observational study or as a control arm (e.g., natural history data) in an externally controlled study.

The acceptability of RWE as confirmatory evidence will depend on multiple factors, such as:

- Reliability (data accrual and data quality control) and relevance of the RWD sources.
- Comparability of populations, missing data and incomplete capture of data, selection bias, data heterogeneity, and potential immortal time bias, among others.
- Inability to use a parallel assignment control arm due to limited disease prevalence or ethical concerns in rare disease settings.
- Diagnostic variability of clinical outcomes.
- Impact of blinding on the assessment of clinical outcomes.[27]

As with any biological product approved under the accelerated approval pathway, FDA may withdraw such marketing approval of a regenerative medicine therapy, including an RMAT, as described in section 506(c)(3) of the FD&C Act.

Sponsors of regenerative medicine therapies, including products designated as RMATs, may pursue either accelerated approval or traditional approval. The selection of the pathway to approval will include review of the design, conduct, and results of the studies that provide the primary evidence of effectiveness. CBER encourages sponsors interested in pursuing accelerated approval for their regenerative medicine therapies to consult with the Agency early in development. These interactions can be used to discuss whether accelerated approval is appropriate, proposed surrogate or intermediate clinical endpoints, plans to collect data obtained from a meaningful number of study sites, other clinical trial design issues, and any considerations related to product quality and manufacturing.

[26] See section 506(c)(3)(A)(i) of the FD&C Act.

[27] For additional information on the use of RWE/RWD in supporting regulatory decisions for drug and biological products, see: Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products; Guidance for Industry (July 2024), available at https://www.fda.gov/media/152503/download.; Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products; Guidance for Industry (December 2023), available at https://www.fda.gov/media/154449/download; and Data Standards for Drug and Biological Product Submissions Containing Real-World Data; Guidance for Industry (December 2023), available at https://www.fda.gov/media/153341/download.

IV. CONSIDERATIONS IN CLINICAL TRIAL DESIGN

Many regenerative medicine therapies are being developed to address unmet medical needs in patients with serious conditions, including rare diseases. To help facilitate the development of data to demonstrate the safety and effectiveness of these products, CBER will work with sponsors and encourage flexibility in clinical trial design. We will consider clinical trials in support of a BLA that incorporate adaptive designs (Ref. 6), enrichment strategies (Ref. 7), or novel endpoints.

CBER recognizes that, for regenerative medicine therapies for rare diseases, certain aspects of drug development that are feasible for common diseases may not be feasible, and that development challenges can be greater with increasing rarity of the disease. For example, in some rare diseases, there will likely be a limited number of affected individuals eligible to enroll in clinical trials. Innovative trial designs, such as trials that compare several different investigational agents to each other and a common control, may be particularly useful in studies of regenerative medicine therapies to treat rare diseases. Historical controls may be considered, if appropriate. Natural history[28] data 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.

As an alternative to a traditional multi-center clinical trial, innovative trial designs whereby multiple clinical sites participate in a trial investigating a regenerative medicine therapy with the intent of sharing the combined clinical trial data to support BLAs from each of the individual centers/institutions could be considered. In such trials, manufacturing may be performed at all clinical sites using a common manufacturing protocol and product quality testing specifications. For example, this type of trial design could be considered for the use of stem cells derived from adipose tissue for the treatment of debilitating osteoarthritis, whereby the trials are conducted at a specified number of orthopedic practices. In this situation, each practice could submit a BLA that relies on both the data from the individual practice and the combined data from all practices that participated in the clinical trial. Each practice would also be required to meet the BLA requirements, and product manufacturing would be required to meet current good manufacturing practice (CGMP) requirements. We encourage potential sponsors who are considering this trial design to engage in early discussions with FDA.

Furthermore, CBER will work with sponsors to determine the types of endpoints that might be appropriate for various phases of clinical development. We encourage sponsors to obtain input from the affected patient communities regarding the endpoints that might be clinically

[28] In this guidance, the "natural history" of a disease refers to the course a disease takes from its onset, through the presymptomatic and clinical stages, to a final outcome in the absence of treatment.

meaningful.[29] The following are examples of how CBER could consider the use of novel endpoints for regenerative medicine therapies:

- Visual acuity is generally accepted as an efficacy endpoint for products used to treat visual impairment. In conditions that lead to advanced visual impairment, such as Leber congenital amaurosis, it might not be possible to achieve a statistically significant change in visual acuity. As such, CBER could consider an effect on a novel endpoint, such as an improvement in functional vision (i.e., improvement in performance of tasks that require visual function) as evidence of effectiveness.

- For regenerative medicine therapies that are cellular or tissue constructs intended to replace a tissue or organ, CBER recognizes that assessment of the long-term effectiveness of the construct might not be feasible prior to marketing approval. For these products, CBER could consider short-term performance to be novel, clinically meaningful efficacy endpoints.

Due to their distinctive features, regenerative medicine therapies are likely to raise unique safety considerations that would benefit from long-term safety monitoring. Many regenerative medicine therapies are intended to be administered once and designed to achieve prolonged biological activity. Since the biological activity of many regenerative medicine therapies may develop or manifest differently when compared to conventional pharmaceuticals (e.g., small molecules), monitoring plans for clinical studies should include assessments for both safety and any pharmacologic activity that presents product-specific safety concerns. We recommend that sponsors include in their specific monitoring plans both short-term and long-term safety monitoring, where the duration of long-term safety monitoring should be based on the type of the regenerative medicine therapy product.[30] Sponsors are encouraged to explore the feasibility of leveraging digital health technologies for collecting the safety information necessary for achieving the goals of monitoring and follow up.[31]

We encourage sponsors of regenerative medicine therapies to have early discussions with CBER about clinical trial design (Ref. 8), including the appropriate study population and the number of study subjects that might be necessary to provide sufficient evidence of safety and effectiveness.

V. INTERACTIONS BETWEEN SPONSORS AND CBER REVIEW STAFF

CBER recommends that sponsors of regenerative medicine therapies engage in discussions with the Office of Therapeutic Products (OTP) review staff early during product development (Ref.

[29] For additional information, see Patient-Focused Drug Development: Collecting Comprehensive and Representative Input; Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders (June 2020), available at https://www.fda.gov/media/139088/download.

[30] See Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry (June 2015), available at https://www.fda.gov/media/106369/download.

[31] See Digital Health Technologies for Remote Data Acquisition in Clinical Investigations; Guidance for Industry, Investigators, and Other Stakeholders (December 2023), available at https://www.fda.gov/media/155022/download.

9). The draft guidance entitled "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products; Draft Guidance for Industry" (Ref. 10) describes standardized procedures for requesting, preparing, scheduling, conducting, and documenting formal meetings between sponsors of Prescription Drug User Fee Act products and the FDA.[32] In particular, the Type B meetings described, including the pre-IND, end-of-phase 2 or pre-phase 3, and pre-BLA meetings, represent critical points in the product development life cycle.

For some regenerative medicine therapies, it may be necessary for OTP to engage in consultative review with staff from other CBER offices or other FDA Centers. For example, CBER may consult with other Centers on review of regenerative medicine therapies that are combination products, in accordance with the Staff Manual Guide (SMG) 4101 (Ref. 11). More generally speaking, for regenerative medicine therapies, as for other products, a consultative review may occur when a unique aspect of a product's indication, formulation, design, or performance raises concerns that require review by another Office or Center or when the expertise to review a particular aspect of the product resides in another Office or Center. If OTP determines that a consultative review is necessary, OTP will initiate contact with the appropriate Office or Center and seek advice on specific questions or issues. The consultative review is used to ensure a comprehensive review of the product.

[32] For additional information, *see* SOPP 8101.1 entitled "Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products" (July 2024), available at https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/UCM324381.pdf, and see also Best Practices for Communication Between IND Sponsors and FDA During Drug Development; Guidance for Industry and Review Staff, (December 2017), available at https://www.fda.gov/media/94850/download.

VI. REFERENCES

1. Food and Drug Administration, Notice, Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products (58 FR 53248, October 14, 1993), available at https://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/UCM148113.pdf.

2. Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014, available at https://www.fda.gov/media/86377/download.

3. Draft Guidance for Industry: Expedited Program for Serious Conditions – Accelerated Approval of Drugs and Biologics, December 2024*, available at https://www.fda.gov/media/184120/download.

4. Guidance for Industry and FDA Staff: FDA Acceptance of Foreign Clinical Studies not conducted under an IND Frequently Asked Questions, March 2012, available at https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf.

5. SOPP 8212: Management of Breakthrough Therapy-Designated Products: Sponsor Interactions and Status Assessment Including Rescinding, June 2016 and last updated August 2023, available at https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/UCM506016.pdf.

6. Guidance for Industry: Adaptive Designs for Clinical Trials of Drugs and Biologics November 2019, available at https://www.fda.gov/media/78495/download.

7. Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products, March 2019, available at https://www.fda.gov/media/121320/download.

8. Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products, June 2015, available at https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf.

9. Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products, November 2013, available at https://www.fda.gov/media/87564/download.

10. Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products, September 2023*, available at https://www.fda.gov/media/172311/download.

11. SMG 4101: FDA Staff Manual Guides, Volume IV – Agency Program Directives: Combination Products: Inter-Center Consult Request Process, June 2004 and last updated

November 2023, available at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffManualGuides/UCM283569.pdf.

* When finalized, this guidance will represent FDA's current thinking on this topic.