

# Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

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## Draft Guidance for Industry

**This guidance document is for comment purposes only.**

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research  
November 2017

**Contains Nonbinding Recommendations**

*Draft – Not for Implementation*

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### I. INTRODUCTION

We, the Center for Biologics Evaluation and Research (CBER), are providing you, sponsors engaged in the development of regenerative medicine therapies for serious or life-threatening diseases or conditions,<sup>1</sup> 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 21<sup>st</sup> Century Cures Act (Cures Act).<sup>2</sup> 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 CBER review staff.

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the 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.

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<sup>1</sup> 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.

<sup>2</sup> Public Law 114-255.

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### **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 and available to patients with serious conditions as soon as it can be determined that 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 unmet medical need in those with serious conditions.

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, 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 Public Health Service Act (PHS Act) (42 U.S.C. 264) and Title 21 of the Code of Federal Regulations Part 1271 (21 CFR Part 1271). As FDA interprets section 506(g), 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. Additionally, 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).

### **III. EXPEDITED PROGRAMS FOR REGENERATIVE MEDICINE THERAPIES**

In 1988, FDA issued regulations in 21 CFR Part 312 (Subpart E)<sup>3</sup> 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 and efficient trial design. 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. Most recently, 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 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. Sponsors should consult the "Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics" dated May 2014 (Expedited

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<sup>3</sup> 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).

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Programs Guidance) (Ref. 1) for generally applicable information about FDA’s expedited programs and the criteria for, and benefits of, fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation. This guidance provides additional information about the application of those programs to regenerative medicine therapies, as well as information about the new RMAT designation program, which CBER intends to administer in a manner that is consistent with the other expedited programs, where applicable.

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. 1). These terms are summarized briefly as follows:

*A serious disease or condition* is a disease or condition associated with morbidity that has a 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.<sup>4</sup> 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 (Ref. 1).<sup>5</sup>

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

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<sup>4</sup> 21 CFR 312.300(b).

<sup>5</sup> See Ref. 1, section VI.A.4.

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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 those with such condition can receive fast track designation. 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 clinical data at the time of marketing application submission.

CBER bases the decision to grant fast track designation on either preclinical or clinical data 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. 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, there must be preliminary clinical evidence that the product may demonstrate a substantial improvement over existing therapies on one or more clinically significant endpoints.

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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, allogeneic tumor cell lines expressing tumor-specific antigens are associated with complete clinical responses in a substantial portion of the study 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 come from Phase 1 or Phase 2 clinical 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 I of this document);
- It is intended to treat,<sup>6</sup> modify, reverse, or cure<sup>7</sup> 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 of the benefits of the fast track and breakthrough designation programs, including early interactions with sponsors (see Table below, which sets forth the key similarities and differences between breakthrough 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).

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<sup>6</sup> As described in section III.A.2 of the Expedited Programs Guidance (Ref. 1), FDA considers a drug 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.

<sup>7</sup> This guidance uses the term “treat” to refer to the terms “*treat, modify, reverse, and cure,*” as used in section 506(g).

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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 investigations, particularly at the initial stages of product development, may not always be prospective clinical trials with a concurrent control. In some cases, clinical evidence obtained from studies with appropriately chosen historical controls, may provide sufficient preliminary clinical evidence of the potential to address an unmet 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. In either case, 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.

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 nature and meaningfulness of the outcomes; the number of patients or subjects, and the number of sites, contributing to the data; and the severity, rarity, or prevalence of the condition. 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 designation, the RMAT designation does not require evidence to indicate that the drug may offer a substantial improvement over available therapies. As with breakthrough 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.<sup>8</sup>

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 phase 2, 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

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<sup>8</sup> FDA's SOPP 8212, entitled *Management of Breakthrough Therapy-Designated Products: Sponsor Interactions and Status Assessment Including Rescinding* (Ref. 2), explains that breakthrough therapy designation is not the same as an approval and does not change the statutory standards for marketing approval.



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improvement in several physiological measurements of left ventricular performance.

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 accept requests for RMAT designation for INDs that are inactive or on clinical hold. Additionally, FDA will not further process a pending RMAT designation request for an IND that is placed on inactive or hold status while the designation request is under review. If you submit a RMAT designation request as an amendment to your IND, the cover letter should specify that the submission contains a RMAT 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 RMAT. The request should be in bold uppercase letters as follows: **INITIAL INVESTIGATIONAL NEW DRUG SUBMISSION and REQUEST FOR REGENERATIVE MEDICINE ADVANCED THERAPY DESIGNATION**.

In general, such a request should contain a concise summary of information that supports the designation, 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 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

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meets the qualifying criteria, then CBER may rescind the 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:

	<b>Breakthrough Therapy Designation</b>	<b>Regenerative Medicine Advanced Therapy Designation</b>
<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	

### **D. Priority Review Designation**

A product that receives fast track, breakthrough, or RMAT designation may be eligible for priority review, if supported by clinical data 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 under expedited development programs should consider discussing their eligibility for priority review.

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.

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### **E. Accelerated Approval**

As explained in the Expedited Programs Guidance (Ref. 1), 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 to drugs,<sup>9</sup> which include regenerative medicine therapies, that treat serious conditions, provide a meaningful therapeutic advantage over available therapies, and demonstrate an effect on: (1) a surrogate endpoint that is reasonably likely to predict clinical benefit, or (2) a clinical endpoint that can be measured earlier than irreversible morbidity and mortality that is reasonably likely to predict an effect on irreversible morbidity and mortality or other clinical benefit (i.e., an intermediate clinical endpoint). Sponsors of drugs 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. 1).

Section 506(g) of the FD&C Act, as added by the Cures 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.

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 Expedited Programs Guidance (Ref. 1). 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 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

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<sup>9</sup> See also 21 CFR Part 314, Subpart H; 21 CFR Part 601, Subpart E.

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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 a 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 intended 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 on a case-by-case basis.

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, if the sponsor fails to comply with the requirements described in section 506(c) of the FD&C Act and 21 CFR 601.43(a).

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 depend on 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.

#### **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

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consider clinical trials in support of a BLA that incorporate adaptive designs (Ref. 3), enrichment strategies (Ref. 4), 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.

For regenerative medicine therapies for more common diseases, innovative trial designs whereby multiple clinical sites participate in a multi-center trial with the intent of sharing the combined clinical trial data to support BLAs from each of the individual centers/institutions may also be appropriate. In such trials, manufacturing would be performed at all clinical sites using a common manufacturing protocol and product quality testing specifications. For example, this 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.

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 meaningful. 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.

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We encourage sponsors of regenerative medicine therapies to have early discussions with CBER about clinical trial design (Ref. 5), including 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 Tissues and Advanced Therapies (OTAT) review staff early during product development (Ref. 6). The “Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products; Draft Guidance for Industry” (Ref. 7) describes standardized procedures for requesting, preparing, scheduling, conducting, and documenting formal meetings between sponsors of Prescription Drug User Fee Act products and the FDA. 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 RMATs, it may be necessary for OTAT to engage in consultative or collaborative review with staff from other CBER offices or other FDA Centers. As described in the Staff Manual Guide (SMG) 4101 (Ref. 8), a consultative review is performed when a unique aspect of a product’s indication, formulation, design, or performance raises concerns and when the expertise to review that particular aspect resides in another CBER office or FDA Center. If OTAT determines that a consultative or collaborative review is necessary, OTAT will initiate contact with the appropriate reviewer and seek advice on specific questions or issues. The consultative review is used to assist OTAT in its decision making.

In the case of a collaborative review, also described in SMG 4101 (Ref. 8), OTAT will work closely with the appropriate CBER office or FDA Center to reach a consensus regulatory decision.

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### VI. REFERENCES

1. Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014 available at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>.
2. SOPP 8212: Management of Breakthrough Therapy-Designated Products: Sponsor Interactions and Status Assessment Including Rescinding, available at <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/UCM506016.pdf>.
3. Draft Guidance for Industry, Adaptive Design Clinical Trials for Drugs and Biologics, dated February 2010\*, available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf>.
4. Draft Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products, December 2012\*, available at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf>.
5. 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/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf>.
6. Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products, November 2013, available at <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm376136.htm>.
7. Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products; Draft Guidance for Industry, March 2015,\* available at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf>.
8. SMG 4101: Intercenter Consultative/Collaborative Review Process, June 2004 and updated August 2013, available at <https://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm135860.htm>.

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