February 15, 2018
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2017-D-6159: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments to the Draft Guidance on Expedited Programs for Regenerative Medicine Therapies for Serious Conditions.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

BIO commends FDA on this Draft Guidance which provides important information on the expedited programs available to sponsors of regenerative medicine therapies for serious conditions.

General Comments

- BIO recommends FDA provide further guidance to sponsors on which designation, RMAT or Breakthrough Therapy, is more appropriate for different types of programs.

- The Agency should consider including an explicit statement similarly to the FDA's FAQ on Breakthrough Therapies[1] clarifying that a Sponsor can submit a request for RMAT designation for multiple indications of the same product.

- BIO believes strong communication between Sponsors and the Agency are critical in successful and efficient regulatory review process. To that end BIO recommends adding an opportunity for preliminary RMAT Designation Request Advice, similar to the Preliminary Breakthrough Therapy Designation Request Advice.

- BIO also recommends the Agency provide further clarity on how accelerated approval and post approval requirements may be used for RMAT designated

[1] FAQ, Question 11.
https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/ucm341027.htm

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products. Specifically, sponsors should be encouraged to seek stage-appropriate advice through meetings with FDA on topics such as:

  - FDA's interpretation of whether a surrogate endpoint is reasonably likely to predict long-term clinical benefits.

  - Early discussion of FDA's scientific concerns that could eventually lead to Post-Marketing Requirements.

- BIO suggest that Section V, Interactions Between Sponsors and CBER Review Staff, highlight the continued collaboration between CBER Review Staff and other FDA staff with expertise on specific topics, such as endpoints, companion diagnostics, and clinical aspects of disease.

BIO appreciates this opportunity to submit comments on the Draft Guidance on Expedited Programs for Regenerative Medicine Therapies for Serious Conditions. We provide additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Sesquile Ramon, Ph.D.
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
II. BACKGROUND		
Page 2 Section II.	It is not clear what the Agency means by the phrase "durable modification of cells or tissues."	BIO suggest the Agency further expand on its interpretation of "durable modification of cells or tissues."
Page 2 Section II.	It is not clear the criteria FDA uses for RMAT designation. In particular, what is meant by the "potential" to address unmet medical needs.	BIO suggest FDA clarify the what is meant by "potential" and that FDA develop FAQs reflecting its interpretation and case examples.
Page 2 Section II.	Guidance should provide more examples of gene therapies for clarity purposes.	BIO suggest the Agency consider the following edit: "As FDA interprets section 506(g), gene therapies, including virally delivered vectors, *in vivo* genome editing, genome editing with nucleases or CRISPR systems, genetically modified cells, that lead to a durable modification of cells or tissues may meet the definition of a regenerative medicine therapy."
III. EXPEDITED PROGRAMS FOR REGENERATIVE MEDICINE THERAPIES		
C. Regenerative Medicine Advanced Therapy Designation		
Page 6 Section III. C.	The guidance should clarify that the RMAT designation does not require evidence to indicate that the drug may offer a substantial improvement over available therapies, but that it has the potential to address the unmet medical need in those with a serious condition.	BIO suggests the Agency make the following change: "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 but has the potential to address an unmet medical need in those with a serious condition."
Page 6 Section III. C.	Provide clarity regarding "the nature and meaningfulness of the outcomes"	BIO suggest the following edit: "~~the nature and meaningfulness of the~~ outcomes that are clinically meaningful or a valid measure"

SECTION	ISSUE	PROPOSED CHANGE
Page 7 Section III. C.	Further clarification of what constitutes a "concise summary".	BIO suggest that the "concise summary" include a description of the product.
Page 8 Section III. C.	The "Features" row in the table should reference the Draft Guidance Section E for completeness.	BIO suggest the following edits to the table: "Statue specifically addresses potential ways to support accelerated approval and satisfy post-approval requirements (see Section E)"
E. Accelerated Approval		
Page 9 Section III. E.	The guidance should further clarify what types of data from a meaningful number of sites will be accepted for accelerated approval.	BIO suggests FDA include novel clinical endpoints as types of data accepted.
IV. CONSIDERATIONS IN CLINICAL TRIAL DESIGN		
Page 10 Section IV.	The section on considerations in clinical trial design has limited examples.	BIO suggest the FDA expand Section IV to include more examples of clinical trial design beyond common controls, which may be applicable for products seeking RMAT.
Pages 10 and 11 Section IV.	Given that Accelerated Approval can apply to both, original BLAs or supplemental BLAs, the draft guidance should include supplemental BLAs.	BIO suggest the following edits: "Upon review of a BLA or significant efficacy sBLA, 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." "We will consider clinical trials in support of a BLA or significant efficacy sBLA, that incorporate adaptive designs (Ref. 3), enrichment strategies (Ref. 4), or novel endpoints."

SECTION	ISSUE	PROPOSED CHANGE
Page 11 **Section IV.**	In the paragraph: "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". The example provided (innovative trial designs, such as trials that compare several different investigational agents to each other and a common control) would not be applicable when there are no additional investigational agents under study or available to collaborate in the same trial.	BIO suggest the Agency add additional examples for when adaptive or innovative trial designs may be employed, or when historical controls can be used instead of a traditional control arm. In addition, we suggest the following edit: "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,~~ Innovative trial designs, such as adaptive clinical trials, single arm trials, open label studies, and use of historical controls, may be particularly useful in studies of regenerative medicine therapies to treat rare diseases."
V. INTERACTIONS BETWEEN SPONSORS AND CBER REVIEW STAFF		
Page 12 **Section V.**	In the first paragraph, the March 2015 Formal Meetings guidance has not yet been updated to reflect the PDUFA VI meeting timelines.	BIO suggest FDA add a reference to CBER SOPP 8101.1.