ALLIANCE for Regenerative Medicine

Subject: Comment on FDA Draft Guidance for Industry titled: "Expedited Programs for Regenerative Medicine Therapies for Serious Conditions"

Docket No. FDA–2017–D–6159

ARM is an international multi-stakeholder advocacy organization based in Washington, D.C. that promotes legislative, regulatory, and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM comprises more than 290+ leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community.

ARM takes the lead on the sector's most pressing and significant issues, fostering research, development, investment, and commercialization of transformational treatments and cures for patients worldwide.

It is out of that dedication today that we submit our comments:

We commend FDA on the rapid implementation of the 21st Century Cures Act, and particularly Section 3033. ARM was also pleased with the rapid implementation of the Regenerative Medicine Advanced Therapy (RMAT) designation by the FDA Center for Biologics Evaluation and Research (CBER). This implementation has already led to the designation of a significant number of regenerative medicine therapies as RMATs. Similarly, we are pleased that CBER took the initiative to promptly generate the above mentioned draft guidance for industry specifically focused on expedited programs for regenerative medicine therapies, including RMAT designation, which complements the information already available on the FDA's website[1].

This draft guidance is helpful in clarifying key concepts and definitions, in providing illustrative examples, and in explaining how expedited programs can support the accelerated development of regenerative medicine therapies for patients with serious conditions and unmet medical needs.

Below are our general comments. Detailed comments are provided in Attachments.

Terminology and scope

The use of the terms "regenerative medicine therapy" and "Regenerative Medicine Advanced Therapy" can be somewhat confusing, and the guidance would be clearer if organized differently.

In the Introduction, the draft guidance uses the term regenerative medicine therapy in place of Regenerative Medicine Advanced Therapy (RMAT) – see Attachment 2. This

[1] https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm

creates potential confusion about the scope of the guidance as to whether it is solely for RMATs (i.e. regenerative medicine therapies that have received RMAT designation, i.e. "RMATs") or whether it is for regenerative medicine therapies in general. We had originally understood the guidance would be for the development of RMATs only; however, either would be useful as long as it is clear.

If the guidance were to be focused solely on RMATs, the guidance could be organized into two key sections: 1) criteria for designation and 2) benefits of having RMAT Designation.

If the guidance were to have a broader scope and intended to be relevant to all expedited programs for regenerative medicine therapies, we suggest the guidance could be organized in three key sections: 1) Detailed definition of regenerative medicine therapies, 2) Description of existing regulatory programs to expedite development (which would include Fast Track, Breakthrough Therapy designation, RMAT Designation, Priority Review, etc.) with clear distinctions between each program, and 3) Discussion on the specific requirements and benefits of the RMAT Designation compared to Breakthrough Therapy designation.

We see the benefits of the second approach as it encourages all regenerative medicine therapies to evaluate which of these programs designed to expedite the development of their product is most applicable, and makes it clear that all these programs are potentially applicable. We recognize this approach could create some redundancy between the draft guidance and the existing "Expedited Programs for Serious Conditions – Drugs and Biologics" dated in May 2014. The FDA should consider including a brief reference to RMAT in the next version of the 2014 guidance if the two guidance documents remain separate.

To avoid confusion between "Regenerative Medicine Therapy" and "Regenerative Medicine Advanced Therapy" we recommend the Agency includes the following sentence in the Introduction: "RMATs are a subset of regenerative medicine therapies." (See Attachment 2.)

The Agency should expand the scope of the guidance to include key considerations for the development of platform technologies that are applicable to several regenerative medicine therapies.

Definition of regenerative medicine therapy

We welcome the agency's definition of regenerative medicine in paragraph 2 on page 2, and the additional clarity that gene therapies are included in regenerative medicine therapies and are therefore potentially eligible for RMAT designation provided they meet the criteria for such designation. We note that the definition provided in section 506(g)(8) of the FD&C Act is broader in scope than some definitions of "regenerative medicine" (for example, see the NIH definition[2]) and commend FDA for its inclusive definition in keeping with Congressional intent.

We suggest further clarification on the concept of durability in the definition of "gene therapies […] that lead to a durable modification of cells or tissues." Durable in this

[2] Such as for example the NIH definition: https://report.nih.gov/NIHfactsheets/ViewFactSheet.aspx?csid=62

context is vague. We recommend removing "that lead to a durable modification of cells or tissues". If this is not possible, we recommend the Agendy defines what "durable" means in the guidance and provide illustrative examples. If durable cannot be readily defined, we recommend the Agency adds in the guidance that the concept of durability is evaluated on a case by case basis.

As this field of medicine and science is rapidly evolving, we would also like to take this opportunity to ask the FDA to consider updating the available definition of gene therapy[3] which refers to the Federal Register Volume 58, No. 197, from Thursday October 14, 1993.

In an October, 2017 letter to CBER Director, Dr. Peter Marks, ARM defined gene therapy as follows: "Gene therapy is defined as a medical intervention intended to prevent, treat, cure, or diagnose a disease or medical condition by regulating, repairing, replacing, adding, modifying, or deleting a genetic sequence or sequences, in somatic cells."

We encourage including the updated definition in the draft guidance the Agency has prioritized for publication in 2018 related to gene therapy (Guidance Agenda: Guidance Documents CBER is Planning toPublish During Calendar Year 2018[4]).

RMAT vs. Breakthrough Therapy designation

It is understood that a product with RMAT designation gets all features of the breakthrough therapy designation with regard to interactions with the Agency and organizational commitment (e.g. early involvement of senior managers). However, although sponsors can anticipate the same level of attention from the FDA regardless of whether they are granted RMAT or Breakthrough Therapy designation, there are differences in the statutory language for the criteria and benefits for the two designations. These differences are apparent in the clinical evidentiary standard, which could allow for an earlier RMAT designation, and the specified postapproval standards for the RMAT designation. It would be useful for FDA to add details in the table on page 6 as proposed in Table 1 below.

It would also be helpful to clarify in the guidance whether there are any additional benefits of Breakthrough Therapy designation if a sponsor has already received RMAT designation for a specific regenerative medicine therapy, or vice versa. Also, clarifying whether one designation is favorable versus the other depending on the product type or stage of development of the product, or some other important criterion, would help sponsors.

[3] https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm573960.htm
[4] https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM431409.pdf

Table 1- RMAT and Breakthrough Therapy Designation Compared

	Breakthrough Therapy Designation	RMAT Designation

Features	• All Fast Track designation features, including:
	  • Actions to expedite development and review
	  • Meetings with FDA throughout development
	  • Rolling review
	• Intensive guidance on efficient product development, beginning as early as Phase 1
	• Organizational commitment (e.g. early involvement of senior managers)
	• Other actions to expedite review (eg. Cross disciplinary project lead)
	• Possible eligibility for priority review
		• All breakthrough therapy designation features, including early interactions with FDA to discuss any potential surrogate or intermediate endpoints
		• Statue addresses potential ways to
		  • support accelerated approval (based on 1) surrogate or intermediate endpoints or 2) reliance on data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate) and
		  • satisfy post approval requirements via the use of patient registries, real world evidence such as electronic health records, collection of larger confirmatory data sets, or post-approval monitoring of all patients treated with drug prior to approval.

In addition, in Section C (page 5), FDA should further clarify the benefits of RMAT designation regarding post-approval requirements, including the possibility of using real world evidence to meet post-approval requirements, as provided for in the statute.

FDA has provided an opportunity to have early consultation on Breakthrough Therapy designation using the "Preliminary Breakthrough Therapy Designation Request (BTDR) Advice" form. We urge CBER's Office of Tissues and Advanced Therapies (OTAT) to use a similar form to request early consultation for RMAT designation.

Considerations on clinical trial design

The section on considerations in clinical trial design should be expanded and may deserve placement in a separate guidance focused on clinical trial design for regenerative medicine therapies. For example, providing illustrative examples on "flexibility" in trial design would be beneficial. Innovative trial design may include use of historical controls, or prospective real world evidence cohorts.

Transparency and predictability in regulatory decision making

Predictability in regulatory decision making is important for the entire field of regenerative medicine therapies, including to support investment in this very innovative area of science and medicine. We believe that publishing a list of regenerative medicine therapies that have received RMAT designation as well as metrics on the time between when RMAT designation was granted and when initial BLA approval is granted would be helpful in the future for all stakeholders. We would also value a summary of why products were deemed ineligible for the designation.

In addition, CBER may consider writing a Frequently Asked Question document on RMAT designation, and making it available on the RMAT webpage.

Agency interactions

We suggest additional clarification in either Section III.C or Section V, that for a regenerative medicine therapy that has received RMAT designation, sponsors may request "Early Interaction Meetings" (as mentioned in the last paragraph on page 5).

We urge the FDA CBER to consider expanding the type of meetings feasible for regenerative medicine therapies to "portfolio and/or platform" meetings. These meetings could be restricted to one per year for each sponsor. Portfolio and/or platform meetings would be very helpful for example for companies that are targeting the development of several regenerative medicine therapies for ultra-rare diseases where expediting the development of each program by identifying synergies between them may be essential to the financial sustainability of these programs.

We would also welcome including reference in Section III.C or in Section V, to the availability of having pre-pre-IND meetings with OTAT/CBER. These early meetings are particularly important for innovative first-in-human regenerative medicine therapies because of the lack of precedent, particularly for nonclinical and manufacturing (CMC) development.

We look forward to the publication of the final guidance and to providing FDA with our comments on future draft guidance supporting the development of regenerative medicine therapies. In particular, we look forward to contributing in commenting on potential future guidance documents on how the CMC development of RMATs could be accelerated to support accelerated approval.

ARM appreciates the opportunity to provide feedback on this guidance. We also sincerely appreciate your time and consideration of our comments. We look forward to working with you in the days ahead.

Respectfully submitted,

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Co-Founder and Senior Policy Counsel

Alliance for Regenerative Medicine

ATTACHMENT 1 – Detailed comments on FDA Draft Guidance: "Expedited Programs for Regenerative Medicine Therapies for Serious Conditions"

Page / Section	Comment and Rationale	Proposed change (if applicable)
Page 1	The terminology in the introduction could be improved for increased clarity.	See suggested edits in Attachment 2.
Page 2	The fact that gene therapies are included in the FDA's interpretation of the definition of regenerative medicing therapy (section 506(g) of the FD&C Act) should be made more clear.	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. *Note: if "may" cannot be deleted, we recommend to replace it by "can".*
Page 6	"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". In this complex field, sponsors may need to better understand what standards FDA will utilize to consider that a product is a related product.	Can the Agency elaborate on the CMC changes that would constitute the creation of a "related product"? Alternatively, should sponsors be directed to describe, where there have been significant manufacturing changes, how the current products is comparable to the product utilized to provide the preliminary clinical evidence?
Page 6	In the paragraph comparing RMAT to Breakthrough Therapy (BT) designation, it would be helpful to explicitly clarify the differences between the two designations.	After this sentence "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", consider lising all the other key differences between BT and RMAT designation.
Page 7	In the concise summary of information that supports the designation, a description of the product should also be	Consider including a bullet on "brief description of the proposed product".

	included.	
Page 8 Section III. C.	Comparison Table In the row for "Features" see suggested edits in **bold** to the right. Consider adding a Table number and a title for ease of reference.	Features – RMAT Designation • Statue **specifically** addresses potential ways to support accelerated approval and satisfy post-approval requirements (**see Section E**)
Page 11	In the paragraph where 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, we suggest including additional examples for when innovative trial designs may be employed.	Suggested wording: "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 (so called "basket trials"), or adaptive clinical trials, or use of historical controls or prospective real world evidence cohorts, may be particularly useful in studies of regenerative medicine therapies to treat such rare diseases.
Page 12 Section V. Paragraph 1	Since this draft guidance was issued, FDA has newly released the following guidance documents: 1) Best Practices for Communication Between IND Sponsors and FDA During Drug Development (Dec 2017) 2) Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products – Draft (Dec 2017)	Consider the need to replace existing text with reference to newly available guidance.

ATTACHMENT 2 – Proposed highlighted changes for Introduction to improve clarity on terminology

"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, 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 Medicine Advanced Therapy (RMAT) if it meets certain criteria. FDA refers to such designation as an ""RMAT designation." Regenerative medicine therapies that receive RMAT designation are referred to as RMATs, RMAT products, or as Regenerative Medicine Advanced Therapy(ies) interchangeably. RMATs are a subset of regenerative medicine therapies.

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 RMATs. 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.