ACRO Innovate Advocate Collaborate

November 21, 2025

Andrew C. Harvan
Center for Biologics Evaluation and Research
Grace R. Graham,
Deputy Commissioner for Policy, Legislation, and International Affairs
Food and Drug Administration

RE: ACRO comment submission on *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions* – Docket (FDA-2017-D-6159)

Dear Mr. Harvan and Ms. Graham,

Founded in 2001, the Association of Clinical Research Organizations (ACRO) is a non-profit trade association representing the world's leading clinical research and technology organizations, which provide specialized services that are integral to the development of drugs, biologics and medical devices that enable patients to live longer, healthier, and more productive lives. ACRO members provide a wide range of services and digital technologies across the entire spectrum of development – from pre-clinical, proof of concept, and first in human studies through post-approval, pharmacovigilance, and health data research. ACRO member companies employ nearly 400,000 people worldwide and conduct research in every global region.

General Comments

ACRO welcomes the Draft Guidance for Industry on *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions*. As with all guidance documents, this draft guidance helps enable effective drug development. Biomedical innovation abhors a vacuum. Regulatory uncertainty and unpredictability can create industry caution and risk aversion about the adoption of innovative approaches to clinical research. Guidance documents – including this draft guidance on expedited programs for CGTs – help de-risk the expensive, lengthy drug development process by providing transparency into the FDA's current, best thinking through pragmatic, risk-based recommendations. Because of their legally non-binding status – providing recommendations that enable flexibility – guidance documents foster a nimble, agile approach to drug development and provide a stable, predictable business environment where drug developers can make business decisions with confidence. A key component of FDA's leadership amongst regulators worldwide is thanks to its prescient issuance of guidance documents on emerging, timely issues.[1]

[1] Just a handful of examples of FDA's global leadership in regulatory innovation are the following guidances:

- *Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products* (draft) https://www.fda.gov/media/184830/download
- *Integrating Randomized Controlled Trials for Drug and Biological Products into Routine Clinical Practice* (draft) https://www.fda.gov/media/181871/download
- *Conducting Clinical Trials with Decentralized Elements* (final) https://www.fda.gov/media/167696/download
- *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (final) https://www.fda.gov/media/155022/download

ACRO welcomes the additional clarity provided in the draft guidance on the different expedited programs and designations available for regenerative medicines (including "Fast Track," "Breakthrough Therapy," and "Regenerative Medicine Advanced Therapy" (RMAT)). This clarity will be helpful for ACRO members when developing and implementing clinical development plans with sponsors.

Specific Comments

Lines 259-276; 303-306, 408-411
ACRO welcomes the transparency on expectations for preliminary clinical evidence which would be necessary to demonstrate the potential of a regenerative medicine therapy to address unmet needs, to potentially be eligible for Regenerative Medicine Advanced Therapy (RMAT) designation. In addition, ACRO welcomes the comparison of Breakthrough Therapy Designation and RMAT Designation. In particular, it is useful to see the explanation of the differences in the level of clinical evidence needed for both – with a clear contrast that the RMAT designation requires evidence to indicate *"that the drug has the potential to address unmet medical needs for such disease or condition the potential to address unmet needs,"* while the Breakthrough Therapy Designation requires evidence to indicate *"that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies."*

A number of conditions with unmet needs may have small patient populations (as referenced in lines 545-547) and, therefore, there is limited ability to conduct prospective randomized clinical trials at an early stage of development. It is useful that the draft guidance includes reference to the potential acceptability of external controls and alternative study designs (such as retrospective studies or clinical case series) as part of the preliminary clinical evidence.

Lines 315-346
ACRO welcomes the inclusion of hypothetical examples whose detailed descriptions provide industry with valuable illustration and clarification of the draft guidance recommendations.

Lines 397-403
The draft guidance indicates that RMAT designation may be rescinded if the qualifying criteria are no longer met. We believe the draft guidance could be strengthened by further discussion and elaboration about the circumstances under which RMAT designation can be withdrawn. We would also welcome recommendations for planning in order to help mitigate that risk. ACRO recommends inclusion of a clear, narrative description of rescission scenarios, processes, and expectations. It would be helpful to specify the circumstances under which the RMAT designation may be reconsidered and possibilities for remediation (e.g., submission of mitigations or corrective actions).

Lines 529-531
The current draft guidance references collecting data from a "meaningful number of study sites" and notes considerations for accelerated approval. The guidance does not give further details on what is meant by "meaningful number." Given the very small numbers of patients and sites in ultra-rare indications, lack of clarity on the interpretation of "meaningful number" may impact the ability to design feasible studies in ultra-rare indications. Further clarification and interpretation of "meaningful number" in different contexts and on acceptable alternatives would be welcome.

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ACRO recommends the clarification that "meaningful number of study sites" is context-dependent and, for ultra-rare indications, may include international pooling across harmonized protocols with centralized data capture and adjudication.

ACRO also recommends the addition of text to reflect that other flexibilities may be considered, such as registry-based approaches supplemented by external controls, and federated data from qualified registries. Alternatives should be supported by a comprehensive statistical analysis plan and evidence of data integrity and comparability across sites.

Lines 534-602
ACRO welcomes the support for innovative trial designs in order to provide flexibility for certain study populations and conditions, such as rare diseases.

Thank you for the opportunity to provide feedback on this draft guidance. Please contact ACRO (knoonan@acrohealth.org) if we can answer any questions.

Respectfully submitted,

Karen Noonan

Karen Noonan
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