February 9, 2018

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

RE: Draft Guidance Documents

- Docket No. FDA-2017-D-6154 for "*Evaluation of Devices Used with Regenerative Medicine Advanced Therapies; Draft Guidance for Industry*"
- Docket No. FDA-2017-D-6159 for "*Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Draft Guidance for Industry*"

To Whom it May Concern:

The Foundation for the Accreditation of Cellular Therapy (FACT) appreciates the opportunity to submit comments regarding the draft Food and Drug Administration (FDA) guidance documents referenced above. We support the FDA's efforts to clarify and streamline its regulation of regenerative medicine therapies.

The mission of FACT is to improve the quality of cellular therapy through peer-developed standards, education, and accreditation for the benefit of patients. As the non-profit Standards and accreditation arm of the American Society for Blood and Marrow Transplantation (ASBMT) and the International Society for Cellular Therapy (ISCT), FACT is founded on the idea that collaboration and advice from peers drive continuous improvement. Professionals expert in their respective fields who hold themselves to a higher standard are in the best position to maintain quality, safety, controlled clinical trials, and appropriate data. A grass roots approach such as this promotes patient safety, increases public confidence, and eases pressure on regulatory agencies such as the FDA. These all protect an environment of research and development that fosters advancement of the field.

Our comments are divided into two sections: 1) the role of FACT accreditation in advancing cellular therapy for regenerative medicine, and 2) specific comments regarding the draft guidance documents.

1. The Role of FACT Accreditation in Advancing Cellular Therapy for Regenerative Medicine

   Development of professional standards and voluntary accreditation can play an important role in advancing cellular therapies for regenerative medicine. FACT accreditation serves as a bridge between the manufacturing and administration of cellular therapy products for early clinical trials and licensure, and can be a benefit not only to trial sponsors but also to the FDA.

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In 2015, FACT published its first edition of the *FACT Common Standards for Cellular Therapies* to promote quality medical and laboratory practice in a broad range of cellular therapies. These Standards represent the basic fundamentals of cellular therapy applicable to any cell source or therapeutic application, and are intended to be used throughout the life cycle of a product from early development through clinical trials and post-licensure administration. Through the Common Standards, FACT has expanded its services to professionals and facilities utilizing cellular therapy products to improve outcomes in patients suffering from a variety of diseases and conditions. The Standards require a comprehensive quality management program; validation of manufacturing processes, equipment, and supplies; and evaluation and reporting of safety endpoints and clinical outcomes, preferably via the Center for International Blood and Marrow Transplant Research (CIBMTR).

Ideally, various discipline-specific (e.g., cardiology, orthopedics, and neurology) or product-specific standards would be added in the future with the input, collaboration, and acceptance of those experts actively involved in the specialized field along with the clinical and laboratory programs who volunteer to contribute to and comply with the standards. As a demonstration of this approach, we have recently accomplished this goal for immune effector cellular therapy, including chimeric antigen receptor (CAR) T cells, via the publication of the *FACT Standards for Immune Effector Cells* in 2017. These Standards are applicable to immune effector cell therapies wherever they are administered, and have already contributed to the safety and quality of clinical trials, regulatory approval, and reimbursement, thereby increasing patient access to these lifesaving cells. FACT-accredited immune effector cell programs will be educated, trained, and well equipped to safely administer and manage these therapies.

We believe FACT is in a unique position to assist both the FDA and sponsors by balancing the needs for controlled innovation and investigation in early trials with rigorous data collection for regulatory approval. FACT-required quality management programs thread together each phase of clinical trials. The use of such a program begins the orderly creation of documents and records, ensures use of adequate vendors and materials, provides data regarding successful procedures, and provides suitable safety and efficacy data required for regulatory submissions. Equally important, the FACT requirements establish a quality-based culture at accredited programs.

By encouraging FACT accreditation, the FDA will receive more complete submissions that are ready for regulatory advancement, thereby decreasing pressure on limited resources and time. This greatly supports the FDA's worthwhile goals of streamlining and expediting review of cellular therapy applications for regenerative medicine, and may even serve as a surrogate approval in early clinical trials in order for the FDA to focus on later-stage biologics license applications (BLAs).

The draft guidance, "*Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Draft Guidance for Industry,"* Docket No. FDA-2017-D-6159, includes numerous references to the importance of early clinical data, controlled processes, and records to allow for expedited review and approval of RMATs. The following examples demonstrate how FACT accreditation would be of benefit to each.

- Page 5, *"Advantages of the RMAT designation include . . . early interactions with sponsors."*

  FACT accreditation would enhance the effectiveness and productivity of these interactions by confirming that sponsors have established and maintained a quality management system that requires standardized process controls, use of appropriate materials, record keeping, and evaluation of patient outcomes. For example, sponsors will be able to demonstrate the level of quality of ancillary materials because FACT accreditation requires qualification of these materials and written agreements with vendors to meet an adequate quality of service and regulatory compliance.

- Page 6, *"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."*

  FACT-accredited facilities are required to archive Standard Operating Procedures (SOPs) and maintain records, which together are used for retroactive analysis and investigation. This provides a mechanism to compile reliable historical clinical data based on processes in place at the time of the therapy. Confidence in this approach is bolstered by FACT requirements for personnel training and systematic audits to promote and assess compliance with SOPs. The procedures themselves must also be validated to determine reproducibility of procedures.

- Page 7, *"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."*

  All of the elements listed in this outline of preliminary clinical evidence are required by FACT to be incorporated into an accredited establishment's quality management program. Therefore, it is likely that FACT-accredited programs will submit complete descriptions to the FDA.

FACT welcomes the opportunity to discuss productive alignments we may be able to offer the FDA as it works to achieve your stated goal of bringing innovative, scientifically proven regenerative cell therapies to patients more quickly. We encourage the FDA to consider how the *FACT Common Standards for Cellular Therapies* may assist investigators, their clinical units and laboratories, and the FDA with improving the quality of Investigational New Drug (IND) applications, especially Regenerative Medicine Advanced Therapies (RMATs), to reduce capacity strains on the FDA and increase the number of cellular therapies that eventually reach market approval.

2. Specific Comments Regarding the Draft Guidance Documents

Docket No. FDA-2017-D-6154 for "Evaluation of Devices Used with Regenerative Medicine Advanced Therapies; Draft Guidance for Industry."

- Page 10, "*Consistent with the Agency's approach . . . RMAT-based combination products are generally reviewed under a single application.*"

  We find this approach useful and efficient.

- Page 10, *". . . separate marketing applications for each product may be appropriate, particularly if the delivery device may ultimately be labeled for use with multiple RMATs that have similar characteristics and administration requirements. In instances where there are separate applications for the RMAT and delivery device, fulfillment of regulatory requirements may be simplified or streamlined by reducing redundancy in data requirements . . ."*

  Acknowledging that devices may eventually be used for more than one specific RMAT offers important insight for accelerating approval of products in the future. Is the FDA referring to only additional RMATs under development by the same sponsor, or will data be published regarding the types of RMATs under review and device classification decisions, including the basis for those decisions? Please clarify the potential extent of this provision.

Docket No. FDA-2017-D-6159 for "Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Draft Guidance for Industry."

- Page 9, *". . . 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."*

  The guidance lists examples of data sources, including patient registries. We propose that the FDA consider collaboration with the CIBMTR to create a data registry. The CIBMTR has experience with collecting data from providers, auditing data for accuracy, providing data back to the providers for analysis, and establishing risk-adjusted algorithms for evaluating patient outcomes. The CIBMTR holds the contract for the Stem Cell Therapeutic Outcomes Database (SCTOD), awarded by the Health Resources and Services Administration of the U.S. Department of Health and Human Services. As the contract holder, the CIBMTR is charged with collecting data on all allogeneic (related and unrelated) hematopoietic cell transplantations (HCTs) performed in the United States.

  The CIBMTR has recently established its Cellular Therapy Registry (CTR) for collecting non-HCT data for cellular therapies for regenerative medicine, and has the ability to provide its services for a wide variety of cellular therapy products. The CIBMTR is currently working with CAR-T manufacturers to incorporate FDA requirements into its forms, and the manufacturers have indicated they will be using the CTR as their registry. This allows efficient use of resources

and a consistent source and format of data for evaluation. The CIBMTR has the potential to be a valuable resource to the FDA in this effort.

- Page 11, *"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."*

  We agree the use of multicenter data is reasonable and will expedite the approval of RMATs. We request the FDA to consider if individual BLAs are practical in terms of the number of applications that may result and the duplicative resources required of the sites. Although individual site data would still be necessary, we suggest that the FDA consider permitting BLAs that utilize multicenter data to include all participating sites.

Thank you for considering these comments. We hope you find them useful. If you have any questions, please do not hesitate to contact us.

Sincerely,

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