American Society of Gene + Cell Therapy

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

RE: Comments for Docket No. FDA-2022-D-2983, "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Guidance for Industry"

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on the draft guidance document Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Guidance for Industry. ASGCT is a nonprofit professional membership organization comprised of nearly 6,000 scientists, physicians, and other professionals working in cell and gene therapy (CGT) in settings such as universities, hospitals, and biotechnology companies. Many of our members have spent their careers in this field performing the underlying research that has led to today's robust pipeline of transformative therapies. The mission of ASGCT is to advance knowledge, awareness, and education leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease.

The Society would like to thank the Agency for considering the need of sponsors and investigators to utilize externally controlled clinical trials to provide evidence of the safety and effectiveness of drug products. The Society believes that the externally controlled trial guidance should establish standardized protocols and guidelines to ensure trials are conducted safely and effectively, as cell and gene therapy developers focused on rare diseases with high morbidity and mortality rates face both practical and ethical hurdles in deploying traditional, randomized placebo-controlled trials.

This draft guidance, however, does not meaningfully advance the use of external controls, including controls based on real world evidence (RWE), potentially limiting sponsors' ability to overcome practical and ethical challenges in developing treatments for rare disease. If finalized, the Agency would neither incorporate Congressional desire to utilize RWE, nor embrace the spirit of initiatives like the "Operation Warp Speed" pilot for rare disease drug development announced by CBER Director Peter Marks.

Given that the Congressional direction to issue this guidance is over six years old, and that the advancement of RWE has been supported through multiple cycles of PDUFA funding, we expect that FDA's views on how RWE may support drug development would be significantly more mature. Rather, the guidance focuses on the challenges associated with externally controlled designs and RWE without providing actionable recommendations to sponsors to support successful therapeutic product development. We do not believe that such a focus fulfills the legislative intent of the provisions of the 21st Century Cures Act [Public Law No. 114-255] that FDA cites as an impetus for issuing this guidance.[1]

For instance, Lines 83-85 of the draft guidance state the following (emphasis added):

> *"In many situations, however, the **likelihood of credibly demonstrating the effectiveness of a drug of interest with an external control is low**, and sponsors should choose a more suitable design, **regardless of the prevalence of disease**."*

Footnote 17 highlights another concerning limitation (emphasis added):

> *"Scenarios that would not be suitable for externally controlled trials include when the natural history of the disease of interest is not understood sufficiently or **when the disease course is considered well-understood but is variable.**"*

The Agency has a history of engaging with individual product sponsors on a case-by-case basis. FDA has embraced the use of external controls, including those utilizing RWE, to support the demonstration of efficacy in several approved products, such as Skysona[2], Myozyme[3], Carbaglu[4], and Ceptrotin[5]. CAR T-cell therapies, with their potentially paradigm-altering modalities, have also relied heavily on RWE to demonstrate effectiveness. The experience of sponsors is that the Agency has been more accepting of registry data, RWE, and historical external controls than this guidance suggests.

It is important to note that some of the disparities in clinical trial participation and lack of representation in clinical data used by the Agency to inform regulatory decisions stem from logistical barriers to participation research (such as lack of transportation and financial burden, interference with work and

[1] Through Section 3022 of 21st Century Cures [Public Law No. 114-255], Congress required FDA to establish a program to evaluate the potential use of RWE and develop a framework to implement the RWE program and defined RWE broadly as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials." While the 21st Century Cures provision was limited to the use of RWE to support the approval of new indications of previously approved drugs and post-approval study requirements, the FDA Reauthorization Act of 2017 [Public Law No. 115-52] included FDA's PDUFA VI commitment to consider the use of RWE for the evaluation of a drug's effectiveness. In PDUFA VII, which was adopted as part of the FDA User Fee Reauthorization Act of 2022 [Public Law No. 117-180], FDA committed to establishing the "Advancing Real-World Evidence Program" to identify approaches for generating RWE that meet regulatory requirements in support of labeling for effectiveness.

[2] https://www.fda.gov/media/162098/download

[3] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125141s0000_Myozyme_MedR.pdf

[4] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022562s000sumr.pdf

[5] http://wayback.archive-it.org/7993/20170723031357/https://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/Appr

ovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM074084.pdf

family responsibilities, and out-of-pocket expenses). Greater utilization of RWE, such as RWE derived from registries, has the potential to facilitate the inclusion of more representative patient populations to reflect the risks and benefits of products more accurately.

Considering the clear Congressional direction for the use of RWE and interest of CBER leadership in advancing the development of products for unmet needs and rare indications, we respectfully request that FDA issue a new draft of this guidance that provides clear recommendations regarding how external controls, including those utilizing RWE, can be used to support product development, and recommendations on the collection, analysis, and submission of control data that would best support regulatory approval particularly when traditional trial design is unethical or unfeasible. This revised guidance could therefore help ensure that externally controlled trials are used scientifically, rigorously, and transparently, with appropriate consideration for potential biases and other limitations. It will also reduce the burden on both sponsors and the Agency to have a clear set of recommendations rather than only case-by-case interactions.

We also urge the Agency to consider the anticipated treatment effect and the innate differences between CGT and small molecule space when considering data sources for external controls in this guidance. We also ask that the Agency provide references in the guidance to areas where the considerations may be applied differently to CGT products or products with durable treatment effects.

We applaud the involvement of CDER, CBER, and OCE in drafting this guidance and encourage FDA to maintain this alignment in future iterations of the guidance. There currently needs to be more consistency between Centers and various review divisions regarding how externally controlled trials, including those that leverage RWE and registry information, can support CGT product development. We are encouraged by the collaboration that this guidance document reflects and urge the Agency to take active strides toward revising and implementing the final version across product categories.

Thank you for your consideration of these comments. If you have any questions about the Society's comment, please do not hesitate to contact Margarita Valdez Martínez, Director of Policy and Advocacy, at mvaldez@asgct.org.

Sincerely,

David M. Barrett, JD
Chief Executive Officer