



February 28, 2022

Dockets Management Staff
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Comments for Docket No. FDA-2021-D-1146: Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on this guidance document. ASGCT is a nonprofit professional membership organization comprised of more than 4,800 scientists, physicians, clinicians, 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 its efforts to produce this guidance to further clarify the agency's thinking with regards to how it effectuates Section 505F of the Federal Food Drug and Cosmetic Act (added by 21st Century Cures Act). This guidance reflects and responds to the immense interest of gene therapy product sponsors, academic researchers, and interested patient groups and data analytics firms, currently engaged in bringing the next generation of durable treatments that address the underlying causes of disease.

ASGCT supports the use of real-world data (RWD) as a source of robust evidence to inform regulatory decision-making throughout a product's lifecycle.¹ While the agency has a history of engaging with individual product sponsors on a case-by-case basis on how to use registry data to support product development, we believe that clear and more transparent standards will increase the utilization of such data and reduce burden on sponsors, data owners, and the agency. In addition, 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 stems from logistical barriers to participation in research (such as lack of transportation and financial burden, interference with work/family responsibilities, and out-of-pocket expenses). Greater utilization of RWD, such as RWD derived from registries, has the potential to facilitate the inclusion of more representative patient populations to more

¹ While outside the scope of this guidance, ASGCT encourages coordination between FDA and CMS when designing, requiring, or utilizing registry data. For instance, when CMS proposed coverage with evidence development for CAR-T therapy in 2019, the CMS proposed data requirements for a registry were not consistent with the FDA post-market study data requirements. The use of registries that span a product lifecycle or used to support product development has great potential, but only if there is alignment between the major federal agencies that have the greatest impact on patient access to new therapies.

accurately reflect the risks and benefits of products.

We appreciate the involvement of CDER, CBER, and the OCE in drafting this guidance. There is currently a lack of alignment between Centers and various review divisions regarding how RWE and registry information can be used to support CGT product development. We are encouraged by the collaboration this guidance documents reflects and urge the agency to take active strides towards implementing the final version across product categories.

The use of real-world evidence (RWE) is especially important for CGTs with durable treatment effects. For instance, CAR T-cell therapies, with their potentially paradigm-altering modalities, have relied heavily on RWE to demonstrate effectiveness. CGT trials are expected to have large treatment effects, and therefore, the experience of ASGCT member CGT sponsors is that the agency has been more accepting of registry data, RWE, and historical external controls. We urge the agency to continue to take anticipated treatment effect into consideration as well as the innate differences between CGT and small molecule space when implementing the standards outlined 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 effect.

We also encourage the agency to consider additional transparency about the data the agency has access to outside of individual product sponsor applications. Currently, individual sponsors report entering into contracts to obtain patient level data to provide to the FDA, later discovering that the agency already has access to such data. Streamlining knowledge about the agency’s access can reduce the use of agency resources and encourage convergence around data FDA has audited and inspected.

We recognize that an evaluation of how relevant a given registry is to address a specific research question is context-specific and a sponsor should conduct such an evaluation for every planned study. There are, however, elements of data reliability (e.g. process of data collection, audit trail of accessed data and changes made, processes for tracking data completeness, and loss to follow-up) that could be evaluated regardless of a specific research question or study design. We would recommend that the FDA consider establishing a process that would establish metrics and focus on the evaluation of data reliability processes used by data holders, including registry holders.

In addition to these comments the society respectfully requests that the following line edits to the guidance also be considered.

Lines	Comment/Issue	Proposed Change
II. BACKGROUND		
90-93, 109-115	<i>“Registries have the potential to support medical product development, and registry data can ultimately be used, when appropriate, to inform the design and support the conduct of either interventional</i>	<i>“Registries have the potential to support medical product development, and registry data can ultimately be used, when appropriate, to inform the design and support the</i>

	<p><i>studies (clinical trials) or non-interventional (observational) studies. Examples of such uses include, but are not limited to: ...</i></p> <ul style="list-style-type: none"> • <i>Supporting, in appropriate clinical circumstances, inferences about safety and effectiveness in the context of: <ul style="list-style-type: none"> – <i>A non-interventional study evaluating a drug received during routine medical practice and captured by the registry</i> – <i>An externally controlled trial including registry data as an external control arm</i> </i> <p>Comment: Gene and cell therapy trials, especially for rare diseases, are often small due to safety considerations, limited patient populations, and large treatment effects. Therefore, it is important to consider how registry data can be utilized to better understand these products in the context of broader populations and current clinical care.</p> <p>In addition to this third contextual sub-bullet, ASGCT recommends the Agency provide examples of what factors the Agency will consider when assessing “appropriate clinical circumstances” as described on line 109.</p>	<p><i>conduct of either interventional studies (clinical trials) or non-interventional (observational) studies. Examples of such uses include, but are not limited to: ...</i></p> <ul style="list-style-type: none"> • <i>Supporting, in appropriate clinical circumstances, inferences about safety and effectiveness in the context of: <ul style="list-style-type: none"> – <i>A non-interventional study evaluating a drug received during routine medical practice and captured by the registry</i> – <i>An externally controlled trial including registry data as an external control arm</i> – <i>Bridging clinical outcomes to an underrepresented sub-population or alternative standard-of-care</i> </i>
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III. DISCUSSION

A. Using Registry Data to Support Regulatory Decisions

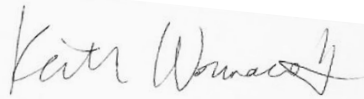
<p>144-154</p>	<p><i>“Registries can have limitations for use in a regulatory context. For example, existing registries may focus on one disease, with limited information on comorbid conditions, even after linkage to other data sources. In addition, the enrolled patients may not be representative of the target population of interest due to challenges related to patient recruitment and retention. For example, patients with more severe disease may be more likely to be enrolled in a registry compared to patients with milder</i></p>	
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	<p>disease; or enrolled patients might have different self-care practices, socioeconomic backgrounds, or levels of supportive care versus the entire population of interest. These issues can potentially introduce bias into analyses that make use of registry data. Additional potential limitations of registries involve issues with data heterogeneity (e.g., different clinical characteristics across various populations) and variation in approaches used to address data quality.”</p> <p>Comment: ASGCT appreciates that registries can contain bias by their design. The society respectfully suggests that in addition to the comments on lines 156-164 which address the agency’s preferred use of registries and design considerations for new registries, the agency include its current thinking on how sponsors can manage bias when utilizing data from existing registries, especially for products under development to address unmet medical needs.</p>	
B. Relevance of Registry Data		
205-210	<p>“The following are non-exhaustive examples of potential data to include in a registry:</p> <ul style="list-style-type: none"> • Demographic and clinical information: <ul style="list-style-type: none"> – Patient demographic factors, including date of birth, gender, race and ethnicity, height, weight, smoking status, alcohol use, and recreational drug use” <p>Comment: ASGCT suggests adding patient geographic location to this bullet, i.e., state/region if in the United States, country if outside the United States to control for both bias and geographic disparities.</p>	<p>“The following are non-exhaustive examples of potential data to include in a registry:</p> <ul style="list-style-type: none"> • Demographic and clinical information: <ul style="list-style-type: none"> – Patient demographic factors, including date of birth, gender, race and ethnicity, geographic location, height, weight, smoking status, alcohol use, and recreational drug use”
205, 233-236	<p>“The following are non-exhaustive examples of potential data to include in a registry: ...</p> <ul style="list-style-type: none"> • Health-related outcome information: <ul style="list-style-type: none"> – Specific clinical events (e.g., heart attack, stroke, 	<p>“The following are non-exhaustive examples of potential data to include in a registry: ...</p> <ul style="list-style-type: none"> • Health-related outcome information:

	hospitalization, death) of interest and date of occurrence”	– Specific clinical events (e.g., heart attack, stroke, hospitalization, death, or other adverse events) of interest and date of occurrence”
C. Reliability of Registry Data		
296-299	<p>“Factors that FDA considers when assessing the reliable of registry data include how the data were collected (data accrual). FDA also considers whether the registry personnel and processes in place during data collection and analysis provide adequate assurance that errors are minimized and that data integrity is sufficient.”</p> <p>Comment: ASGCT requests that the Agency elaborate on which characteristics of data accrual (collection) the agency considers when evaluating the reliability of a registry.</p>	
D. Considerations When Linking a Registry to Another Registry or Another Data System		
398-400, 405-406	<p>“The appropriateness of using additional data sources also depends on how the sponsor intends to use the linked data and the ability to obtain similar data for all patients. For example, for each potential data source, the sponsor should consider whether:</p> <ul style="list-style-type: none"> • The data can be accurately matched to patients in the registry and whether linking records between the two (or more) databases can be performed accurately” <p>Comment: ASGCT recommends FDA amend lines 405-406 to account for potential selection bias even after accurate matching. Furthermore, two key methods (deterministic and probabilistic) are used for linkage. We encourage the FDA to provide examples of how these two methods should be used with a specific focus on how these methods can impact the reliability of the registry data.</p>	<p>“The appropriateness of using additional data sources also depends on how the sponsor intends to use the linked data and the ability to obtain similar data for all patients. For example, for each potential data source, the sponsor should consider whether:</p> <ul style="list-style-type: none"> • The data can be accurately matched to patients in the registry and whether linking records between the two (or more) databases can be performed accurately, and whether the linked patients are a representative subset of patients to meet the research objectives”

Thank you for consideration of these comments. Please do not hesitate to let ASGCT know if you have questions.

Sincerely,



Keith Wonnacott, PhD
Chair, ASGCT Regulatory Affairs Committee