February 28, 2022

Via Docket Submission

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

Re: Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

Docket No. FDA-2021-D-1146

Dear Dockets Management Staff,

On behalf of the Digital Therapeutics Alliance (DTA), we are pleased to submit the below comments related to the Food and Drug Administration's "Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products," published by the FDA on November 30, 2021.

DTA is a global non-profit trade association of industry leaders and stakeholders with the mission of broadening the understanding and adoption of digital therapeutics (DTx) into healthcare. We work across numerous geographic regions to enable expanded access to high quality, clinically evaluated digital therapeutics for patients, clinicians, and payors to improve clinical and health economic outcomes.

DTx: Delivering Clinical Interventions & Supporting Insights

This draft Guidance provides sponsors and stakeholders with considerations on how to design a registry or use an existing registry to support regulatory decision-making about a therapy's effectiveness or safety. This draft Guidance only focuses on evaluating medical therapies that are delivered using pharmaceutical products. Any mention of digital health technologies (DHT) in this draft Guidance refers to DHT products only in their supportive capacities.

Digital therapeutics – a subcategory of digital health technologies – primarily deliver clinical interventions to patients, in addition to generating and delivering real-world insights to end users and decision makers. While DTA supports the use of DTx products in this draft Guidance to directly benefit research efforts that assess the effectiveness or safety of drugs and biologic products, it is important for this Guidance to be amended to ensure that DTx-generated insights will also be used to validate the effectiveness and safety of therapies delivered by digital therapeutics themselves.

Data generated from DTx products will be increasingly incorporated into registries for the purpose of researching and reporting on therapy safety and effectiveness outcomes, so it is necessary for FDA to expand the scope of this Guidance to recognize that DTx-generated data streams will be used to report on the real-world impacts of drug, biologic, and DTx therapies.

The following comments are provided following broader consultation with DTA members:

Registry Development

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. The Agency could also establish certified third parties to oversee data holders and ensure they are meeting requirements for these core best practices. Any data holder, including registry holders, could then apply to this third-party and ask that their processes be evaluated.

If the data holder/registry owner meets the core requirements, a "qualification certificate" could be issued which could be renewed on an annual basis. We believe having clearly articulated core requirements and a process for certification of the data repository would greatly enhance trust in these data sources, bring efficiencies to development and maintenance of these data repositories, and at the same time improve the reliability of RWD, including registry data.

Specific Comments

Lines 109 - 110: "Supporting, in appropriate clinical circumstances, inferences about safety and effectiveness in the context of:"

- We request additional examples of what the Agency considers "appropriate clinical circumstances."
- We recommend the Agency add a third contextual sub-bullet under the bullet point in lines 109 - 110: "- Bridging clinical outcomes to an underrepresented sub-population or alternative standard-of-care."

Lines 209 - 210: "Patient demographic factors, including date of birth, gender, race and ethnicity, height, weight, smoking status, alcohol use, and recreational drug use"

- We suggest adding geography to this bullet (i.e., state/region if in the United States, country if global).

Lines 235 - 236: "Specific clinical events (e.g., heart attack, stroke, hospitalization, death) of interest and date of occurrence"

- We suggest adding the following phrase to the bullet point: "specific clinical events (i.e., heart attack, stroke, hospitalization, death) or other AEs of interest and date of occurrence"

Lines 296-297: "Factors that FDA considers when assessing the reliability of registry data include how the data were collected (data accrual)."

- We ask the Agency to elaborate on what characteristics of data accrual/collection need to be evaluated to ensure reliability of a registry.

Lines 405 - 406: "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"

- We recommend the FDA amend lines 405-406 with the following language to account for potential selection bias even after accurate matching: "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."
- Two key methods, deterministic and probabilistic, are used for linkage. We also encourage the FDA to provide examples of how these two methods were used with a specific focus on how these methods can impact the reliability of the registry data.

Thank you for the opportunity to provide commentary on this process. We look forward to ongoing conversations regarding this and other related efforts.

Sincerely,
Megan Coder, PharmD, MBA
Chief Policy Officer