February 28, 2022

Via Docket Submission

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

Re: Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products; Draft Guidance for Industry; Availability

Docket No. FDA-2021-D-1214

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 "Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products," published on December 9, 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.

Overly Limited Scope of Guidance

Per this draft Guidance – "The 21st Century Cures Act (Cures Act), signed into law on December 13, 2016, is intended to accelerate medical product development and bring innovations faster and more efficiently to the patients who need them" – the Cures Act aims to improve all forms of medical product development. The Cures Act is not limited to drug and biologic products, as done in this draft Guidance. One critical segment of FDA-reviewed medical products is missing from the scope of this document – digital therapeutics.

In scoping out a process through this draft Guidance for using real-world data and real-world evidence to support regulatory decisions regarding the effectiveness and safety of a drug or biologic, the Agency has overlooked the use of RWD and RWE in supporting regulatory decisions regarding the effectiveness and safety of a digital therapeutic – which like drugs and biologics, are medical therapies.

Therefore, this draft Guidance should become more consistent with the language, spirit, and intent of The Cures Act by being specifically inclusive of digital therapeutics. Digital therapeutics must be treated consistently alongside other current care standards (i.e., drugs, biologics) and not be overlooked, excluded, or held to different higher standards because of the relatively recent emergence of this category of medicine.

Additionally, the following comments are provided following broader consultation with DTA members:

We encourage the FDA to consider developing guidance focused on considerations for the use of distributed networks as a source of RWD and the derived RWE when used to support regulatory decision-making. All four FDA guidances published to date focus mostly on RWD that can be accessed and analyzed by sponsors, implying that patient-level data should be the basis of the analyses and should be shared with the FDA. There is a growing body of RWD that is part of a distributed network (e.g., Sentinel, PCORnet) and the available data is analyzed locally and then combined by a central, independent-from-sponsor data coordinating center. The model of a distributed network is also being explored in a global setting. While we appreciate the Agency issuing a Guidance with a narrow scope limited to new indications for a drug already approved or to help support post-approval study requirements, we urge the Agency to broaden the scope to include new drugs and digital therapeutics.

We recognize that an evaluation of the relevance of a registry to address research questions is context-specific and that 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, best practices, and focus on the evaluation of data reliability processes used by data holders, including registry holders. The Agency could also rely upon certified third parties to oversee data holders and ensure they are meeting requirements for these core best practices since this can be resource intensive work. Data holders, including registry holders, would benefit by having the third party certify their process and could be issued with a "qualification certificate" if they met the core requirements 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 while improving the reliability of RWD, including registry data. CDRH, in its guidance "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics", described FDA's considerations in determining whether a genetic variant database is a source of valid scientific evidence that could support the clinical validity of genetic and genomic-based tests in a premarket submission. We believe that a similar approach can be taken by the Agency to determine whether a registry is a source of valid scientific evidence that could be leveraged by sponsors in support of the development of a drug.

Specific Comments

Introduction: We ask the Agency to provide more clarity on what RWE this particular guidance is relevant for, e.g:

- Is RWE used in linkages or comparisons to trial data in the scope?
- Is RWE that characterizes heterogeneity in patient population or assessment of class of products/ different MOA in the scope?

Lines 68 - 69: "Examples of non-interventional study designs include (1) observational cohort studies, in which patients are…"

- Please consider editing lines 68-69 to: "Examples of non-interventional study designs include but are not limited to…", as many other study designs can be used, especially for safety.

Lines 119 - 120: "...include ancillary protocol-specified activities or procedures (e.g., questionnaires, laboratory tests, imaging studies) that collect additional data to help address questions of…"

- Please consider adding "data acquisition using digital health technologies" to the examples provided for protocol-specified activities or procedures in the parentheses.

Lines 145 - 147: "The sponsor should provide evidence that the protocol and SAP were finalized prior to reviewing outcome data of a study and before performing the prespecified analyses."

- Because sponsors often subscribe to certain types of RWD which are "in-house" when protocol and SAP are being developed, we ask that the FDA provide examples of acceptable evidence to ensure protocol/SAP are finalized before analyses.

Lines 157 - 159: "Sponsors should describe in the study protocol all the data sources accessed when designing the study, as well as results from feasibility evaluations or exploratory analyses of those data sources."

- We ask the Agency to provide examples of essential elements to be included in the description of feasibility evaluations of other data sources being considered.

Lines 169 - 172: "Sponsors should describe patient characteristics of the source population (i.e., the population from which the study population is drawn) and the study population (i.e., the population for which analyses are conducted) and note any differences that may impact the final study findings."

- We encourage the Agency to consider adding a second statement to this bullet point to account for the spectrum of possible RWE used in regulatory decision-making, for example: "A fit-for-purpose approach based on the RWD objectives can drive the relevant descriptions of the source and study populations."

Lines 174 - 178: "To ensure transparency regarding their study design, sponsors should post their study protocols on a publicly available website, such as ClinicalTrials.gov or the web page for the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) for post-authorization studies."

- We request the addition of the ISPOR RWE portal and/or dissemination in peer-reviewed publications clearly describing methods to the list of publicly available websites. Leveraging these additional resources will continue to ensure transparency in study design.

Lines 183 - 186: "Sponsors must ensure that they are able to submit patient-level data for any RWD that have been analyzed as part of the clinical study included in a marketing application when required under 21 CFR 314.50 and 601.2."

- There can be instances where variables used in the study are derivatives of unstructured data that are difficult to submit, for instance, a response variable defined based on abstraction on physician notes or pathology reports. In such cases patient-level data may not be readily obtainable. We therefore request the Agency to recommend actions that can be taken to ensure data used is robust in such instances of derived variables.

Lines 183 - 186: “Sponsors must ensure that they are able to submit patient-level data for any RWD that have been analyzed as part of the clinical study included in a marketing application when required under 21 CFR 314.50 and 601.2.”, AND
Lines 193-195: “Sponsors should ensure that RWD and associated programming codes and algorithms submitted to FDA are documented, well-annotated, and complete, which would allow the FDA to replicate the study analysis using the same dataset and analytic approach.”

- We request that the FDA clarifies data formatting requirements by linking to the Data Standards for Drug and Biological Product Submissions Containing Real-World Data guidance when both are finalized.

Line 193: “Sponsors should ensure that RWD and associated programming codes and algorithms…”

- We recommend adding 'and data vendors or third parties' after 'Sponsors' in this line, as data vendors are applying algorithms and programming to create/derive some or all of the data elements in a given dataset to provide to the Sponsor for final analyses.

Other Sponsor Responsibilities: We encourage the FDA to add a section in Part B for Data Vendors, since they are commonly contracted by Sponsors and some of the guidance pertains to having direct access to data, transparency on data accrual and other processes under their purview

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