July 8, 2019

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

Re: Docket No. FDA-2019-D-1263: Submitting Documents Using Real-World Data and Real-World Evidence to the Food and Drug Administration for Drugs and Biologics

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments to the Draft Guidance on Submitting Documents Using Real-World Data and Real-World Evidence to the Food and Drug Administration for Drugs and Biologics.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

BIO welcomes this procedural draft guidance from FDA. We believe this document establishes a simple and reliable mechanism for identifying submissions with Real World Data (RWD), and that this procedural step is an important one in the implementation of this new area of regulatory science and policy at FDA. We hope that FDA uses the checklist provided in the Appendix as a tool to connect intention to action. Specifically, FDA leadership has established a foundation of receptivity to data sources like RWD, but this intention to embrace innovation may be delayed or impeded by practical implementation challenges or lack of experience with RWD at the review division level. BIO encourages efforts to understand resources needed across FDA's review divisions, in particular as they learn to assess novel data sources and applications of such data.

BIO encourages the Agency consider how Real World Evidence (RWE) or RWD tracking efforts could be utilized by the Agency to generate publicly available information (e.g., public summaries[1]), as this information will benefit sponsors, researchers, as well as the Agency in advancing use of RWD for regulatory decision-making. For example, FDA could periodically publish aggregate, deidentified data on the number of RWE submissions made, context-of-use, study design, data type, and therapeutic area. Similar metrics have been made available to track the implementation of the Breakthrough Therapies Program and have been found generally helpful by the research community.

[1] For example, a table linked to https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

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The draft guidance also describes submitting documents containing RWD/E in submissions that are either INDs, NDAs, and BLAs. In addition, the Agency encourages that Sponsors request early feedback in the form of Type B or C meetings if a Sponsor is considering the use of RWD/E in an IND, NDA, or BLA. Therefore, we suggest that the FDA consider internal tracking of pre-submission feedback (i.e., Type B and C meetings) that may be related to the regulatory use of RWD/E, since these meetings provide context on Agency's acceptance/denial for the use of RWD/E within an IND, NDA or BLA.

Furthermore, in order to better promote the collection and utilization of RWD/E for regulatory purposes, BIO recommends the Agency include, in this, or future guidance:

(i) a description of FDA's process to determine whether the Agency agrees/disagrees with the Sponsor's classification of RWD/E as included in the cover letter accompanying a submission;
(ii) information on whether and how RWD/E was used to inform the regulatory decision;
(iii) additional recommendations on the most appropriate mechanism for seeking FDA feedback pertaining to RWD/E;
(iv) additional examples to those in Section III of the draft guidance which provide information on regulatory submissions that could include RWD and/or RWE and which ones the Agency intends to track or not. The RWD/E examples provided should be expanded to provide additional clarity on when to flag a submission that is used for supporting a regulatory approval or satisfy a post approval study. This would help ensure accuracy in achieving the stated objectives and better inform the use of RWD/E; and
(v) consider a common data structure and electronic data submission system. As there is currently no standard format for submitting RWD/E to the Agency, we recommend that the Agency work with industry and other relevant stakeholders to develop a common data structure for these submissions. Additionally, given that submissions containing RWD/E may include large datasets that cannot be submitted electronically due to FDA server restrictions, we recommend that the Agency address these capacity concerns regarding its technological infrastructure and logistics around the accessibility of these datasets to FDA reviewers.

Lastly, BIO suggests that FDA consider expanding the guidance to address inter-center harmonization on submission and use of RWE, in general, between Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) and the Center for Devices and Radiological Health (CDRH). Namely, this draft guidance has been developed and issued by CDER and CBER only, while the final guidance issued August 2017 titled "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" covers CBER and CDRH. Neither the latter nor this draft guidance contain recommendations on how to indicate submitting RWD/E to CDRH, which could lead to inconsistency in tracking and informing the RWE program on medical device and combination product submissions containing RWE in support of regulatory decisions regarding safety and/or effectiveness. Furthermore, as FDA receives tracking information and develops best practices to inform the program, BIO encourages the Agency to share learnings and best practices (i.e., process and content via MAPPs) with other regulators (e.g., EMA, PMDA) to enable early harmonization and convergence.

BIO appreciates this opportunity to submit comments on the Draft Guidance on Submitting Documents Using Real-World Data and Real-World Evidence to the Food and Drug Administration for Drugs and Biologics. We provide additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Sesquile Ramon, Ph.D.
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
General	In the cover letter, "the study design using RWE" section is confusing. In particular, it is unclear if sponsors are to identify the study design used to generate RWE or if they are to identify the study design(s) that measures a product's efficacy and safety and upon which the RWE is relevant	BIO suggest FDA provide additional clarity
Lines 27-39	BIO believes the definition of RWD would benefit from additional clarity, in particular around what would be considered "routinely collected" and does not indicate whether data collection needs to be part of common clinical practice.	BIO recommends that FDA further clarify and elaborate on the definition of RWD and provide additional examples. BIO suggests that the Agency clarify the meaning of "routinely collected" in this context and indicate whether or not data collection needs to be part of common clinical practice. BIO suggests the following edit sourced from the Framework for FDA's Real-World Evidence Program: "**Section 505F(b) of the FD&C Act defines RWE as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials" (21 U.S.C. 355g(b))[1].** For the purposes of this guidance, FDA defines RWD and RWE as follows (…)" 1- The definition of RWE provided by section 3022 of the Cures Act was subsequently revised by a technical amendment in Section 901 of the FDA Reauthorization Act of 2017 (Public law 115-52).

SECTION	ISSUE	PROPOSED CHANGE
II. BACKGROUND		
III. EXAMPLE SUBMISSIONS USING RWD AND/OR RWE		
Line 84	Natural history studies typically can serve multiple purposes, including as an external control in rare diseases. The wording suggests that only the natural history studies for the purpose of clinical outcome assessment or biomarker is excluded.	BIO suggested edits: "New protocols for single arm trials that use RWE as an external control, **including natural history studies, or as a complimentary data source for the treatment arm**"
IV. IDENTIFYING RWE SUBMITTED AS PART OF A REGULATORY SUBMISSION		
Lines 109-112	We support the Agency's efforts to standardize data collection format and we encourage the Agency to develop distinct terms that could be used not just for tracking, but to generate summaries and aid in database searches. In addition, as written, this recommendation appears to allow variability in the manner RWD/E in regulatory submissions could be identified and reported, leading to information bias.	To ensure accurate tracking of RWD/E in regulatory submissions and to help emphasize the importance/regulatory acceptability to using RWD/E in an IND, NDA or BLA, BIO recommends that FDA consider editing the guidance so that a table or check box for RWD/E is incorporated into required fields for the sponsor to complete within the submission application (e.g., Form FDA 1571). BIO believes that this would help to standardize submissions (i.e., decrease variability in characterizing whether and what kinds of RWD/E are included in a submission), increase accuracy of RWD/E use and reduce information bias.
Lines 118-120	This section states: "To provide evidence in support of the effectiveness or safety for a new product approval (e.g., collecting information about effectiveness or safety outcomes from an RWD source in a randomized clinical trial)" For a new product approval, the use of RWE to support safety is separated from information on the use of RWE to support effectiveness. The Draft Guidance states.	BIO recommends that for a new product approval, the use of RWE to support safety is separated from information on the use of RWE to support effectiveness (i.e., sponsors should be asked to indicate if the RWE is submitted for (a) effectiveness purposes, (b) safety purposes, or (c) both.)

SECTION	ISSUE	PROPOSED CHANGE
Lines 106-157	In Section IV, "IDENTIFYING RWE SUBMITTED AS PART OF A REGULATORY SUBMISSION," the draft guidance does not recommend that sponsors include in their cover letter a justification for the choices of the purpose of using RWE as part of the submission, the study design using RWE, and the RWD sources used to generate RWE. Furthermore, the table in "APPENDIX: SAMPLE PRESENTATION TO INCLUDE IN COVER LETTER FOR SUBMISSIONS INCLUDING REAL-WORLD EVIDENCE" (lines 150-157) does not contain a category which allows sponsors/applicants to include a brief summary of the methodology used for collection and use of RWE. This information would be critical in assessing whether the RWE would be used to inform a regulatory decision.	BIO suggests that the Agency edit Section IV to ask sponsors to provide a rationale for using RWE as part of the submission, the choice of RWD source(s) selected, and the choice of study design used to generate the RWE. Alternatively, the FDA should indicate if and in which section of the application this rationale should be included. Additionally, BIO requests that FDA make corresponding edits to the sample presentation table in the Appendix.
A. Purpose of Using RWE as Part of the Regulatory Submission		
Line 128	Adding safety information, as well as updating safety information to the label, is also a common and important use for RWE'	BIO suggested edits: Changing "adding" to "**adding/updating**".
B. Study Design Using RWE		
C. RWD Source(s) Used to Generate RWE		
Lines 147	Mobile technologies should be considered	As the use of mobile technologies is expanding, we would recommend that a separate bullet point be created to proactively call out use of this technology.
APPENDIX: SAMPLE PRESENTATION TO INCLUDE IN COVER LETTER FOR SUBMISSIONS INCLUDING REAL-WORLD EVIDENCE		

SECTION	ISSUE	PROPOSED CHANGE
Table, Section Purpose(s) of using RWE as part of the submission	Adding safety information, as well as updating safety information to the label, is also a common and important use for RWE.	BIO suggested edits: "~~**add**~~ **adding/updating** safety information.
Line 153-154	The standardization of the checklist will aid in tracking and metrics reporting as well as support development of lessons learned. The guidance notes that use of the table is "is provided as an example of how sponsors or applicants can identify in the cover letter", variation can limit the ease of collection of information.	BIO suggested edits: "This table **the recommended format** ~~**is provided as an example**~~ of how sponsors or applicants can identify in the cover letter accompanying the submission that the submission contains real-world data (RWD) or real-world evidence (RWE)."