Biotechnology Innovation Organization

February 5, 2019

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

**Re: Docket No. FDA-2018-N-4000: Framework for a Real-World Evidence Program**

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments to the Framework for a Real-World Evidence Program.

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.

This important and anticipated Framework is well written and provides Sponsors and the community important information on FDA's vision for advancing the use of Real-World Evidence (RWE). Below, we provide general comments and recommendations on the Framework. Additional detailed comments have also been included at the end of this document:

- BIO is committed to increasing public learning and understanding of FDA's perspectives on the acceptance of RWE to support regulatory decision-making. We applaud FDA for the work done in engaging external stakeholders, in particular through the workshops developed in collaboration with the Duke Margolis Center for Health Policy. We note that the Framework currently does not lay out plans for future workshops or external stakeholder engagement and education, nor does it set forth how the Agency plans to share experiences and learnings from its demonstration projects and other stakeholder engagements. BIO encourages FDA to consider more detailed plans on how it intends to engage with external stakeholders in order to educate the community at large. Publicly sharing the learnings by the FDA, industry Sponsors, academics and other relevant groups, would allow the community to advance the generation and use of credible RWE for regulatory decision-making. For example, FDA could hold public educational workshops during which the Agency, Sponsors and other stakeholders, as appropriate, could share the results and learnings of demonstration projects, pilot studies, and other relevant activities on the use of RWE for regulatory decision making.

- The Framework implies, but nowhere explicitly states, that RWE in the appropriate regulatory context of use can be used to help to satisfy or be sufficient to meet the

1201 Maryland Avenue SW
Suite 900
Washington DC 20024
202.962.9200 P
202.488.6306 F
bio.org

"substantial evidence" requirement. The concept of "adequate and well controlled investigations" is also not discussed. BIO encourages FDA to affirm that studies using RWE — in the appropriate regulatory context-of-use — may help satisfy or be sufficient to meet the 'substantial evidence' requirement under 505(D) of the FDCA when two-or-more RCTs are not necessary or feasible and may be considered 'adequate and well controlled'. Formally documenting this approach, already employed by FDA in certain circumstances, will make it clear that the Agency considers the totality of the evidence and the context of the specific scenario when making regulatory decisions.

- BIO recognizes the importance of validating methodology used in the generation of evidence for regulatory decision-making. However, a traditional randomized control trial will differ in material ways from RWE generation approaches, including observational studies. As such, the term "replication" should be avoided when referring to comparisons between RWE and traditional RCTs. BIO believes that "consistency in outcomes" may be a more appropriate way to describe the desired finding of these efforts.

- The Framework emphasizes the importance ensuring that relevant and appropriate endpoints are captured in the RWD sources under consideration. BIO welcomes this mention of endpoints and would suggest FDA considers developing guidance on RWD endpoints and how to best establish the association between real world endpoints and traditional clinical trial endpoints.

- The Framework recognizes the importance of developing data standards and methods to maximize the utility of RWD and states FDA is "active in developing data standards for regulatory use and will continue to expand its work in this area. FDA will consider data standards along with the other critical aspects of the RWE Program" (pages 13-14). However, the Framework does not describe how FDA plans to expand its efforts in this area. BIO suggests FDA elaborate on its objectives and workplan for continued efforts to develop data standards for regulatory use and requests opportunities to discuss how industry can assist with this work.

- In regard to data quality and standards, although Sponsors have final responsibility for documenting the characteristics of the data used to generate RWE, data source owners (e.g., RWD originators, data collectors, and aggregators) can play a critical role in facilitating this process.[1] They can enhance data quality and reliability through improved documentation on, e.g., data provenance, cleaning processes, algorithmic transformations, and linking methods. BIO suggests that the FDA consider the important role data source owners can play in enhancing trust and credibility in RWD.

- BIO recommends the Agency clarify whether data standards related to the submission of RWD are likely to become mandatory in a fashion similar to CDISC. Unlike clinical trials, Sponsors often do not own the data sources and have limited, if any, ability to impact data standards. Examples are registries, claims data and electronic medical records.

[1] Duke-Margolis RWE Collaborative white paper, Characterizing RWD Quality and Relevance for Regulatory Purposes (Oct. 1, 2018)

- The Framework notes that future guidance will address considerations for the use of real-world data from other countries (pages 16-17). However, it does not indicate if guidance will address and supporting guidances should also address the use of foreign literature and data used to support ex-US approvals. This is particularly relevant for reducing regulatory burden for drugs with established safety and efficacy profiles in literature (e.g., off label standard of care, approved by other regulatory health authorities, particularly those where FDA has an MOU based on that country's regulatory structure, such as those where there is a MRA for GMP acceptance). For example, FDA could draw from existing guidance documents such as "FDA Acceptance of Foreign Clinical Studies Not Conducted Under and IND Frequently Asked Questions."

- Lastly, BIO appreciates the amount of work FDA is undertaking as part of its implementation of the RWE program. However, it is unclear from the Framework the specific timelines FDA might be considering for the development of the suggested draft guidances, some of which will be iterative. Given the breadth of the work laid out in the Framework, BIO encourages FDA to communicate specific timing and/or prioritization for the development and release of draft guidances. BIO suggests the Agency consider providing an updated Framework document with the suggestions discussed in this document, or alternatively, provide regular updates on the priorities, progress, and timelines of the efforts listed under Program Items in the Framework. BIO welcomes the opportunity to partner with the Agency in providing information or resources throughout the guidance development process.

BIO welcomes this opportunity to submit comments on the Framework for a Real-World Evidence Program. We provide additional specific, detailed comments to improve the clarity of the Framework 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 |
|---|---|---|
| **Introduction (pages 3-4)** | | |
| **General** | The Framework should provide an understanding of FDA's use of the terms "reliability and relevance" and "quality", especially as they relate to one another or to other, associated terms, in the drug and biologics context. | BIO suggests FDA consider explaining in future guidance documents how these terms are defined and applied in the drug and biologics context and seek to harmonize the use of such terms within the Framework. |
| **Definitions of Real-World Data and Real-World Evidence (pages 4-7)** | | |
| **Page 6** | The Framework acknowledges that data may be retrospective or prospective and that appropriate methods will differ between these. However, the case when studies have both a retrospective and prospective component is not addressed. | BIO suggests that FDA considers providing additional clarity in this or future guidance documents, regarding studies that are both retrospective and prospective (e.g., how far in the past can/should the baseline be?). |
| **Page 5** | The Framework states that "Under FDA's RWE Program, evidence from traditional clinical trials will not be considered RWE". BIO is concerned that this statement is overly broad and may preclude data collected in traditional clinical trials from ever being used in RWE. This interpretation could preclude, for example, the use of data collected for a placebo control group in a traditional clinical trial as a synthetic control group for a RWE study. | BIO suggests that FDA modify this statement as follows: "Under FDA's RWE Program, traditional clinical trials will not be considered RWE, though some of the data collected in such trials may be used in RWE studies (e.g., data from traditional clinical trial placebo group could be used as a historical control group in future RWE studies)". |
| **Supporting FDA's Regulatory Decisions of Effectiveness (pages 9-11)** | | |
| **Page 9** | The Framework list only one specific example of RWE use in support of product approval. | We would encourage the FDA to, as part of its program, consider publishing on its website a list of product approvals that relied on RWE to support efficacy/effectiveness claims. This feature would enhance information and knowledge sharing |

| SECTION | ISSUE | PROPOSED CHANGE |
|---|---|---|
| | | |
| **Pages 11 - 12** | Using rigorous design and statistical methods to replicate randomized trial results with observational studies is *one* way to study characteristics of observational studies. BIO believes that randomization is not the only suitable method to reduce bias and that non-randomized observational data may generate RWE acceptable for regulatory decision-making regarding treatment effectiveness. Discussing, evaluating, and aligning on methodologies should be also part of the FDA's process when considering new guidance. | A wide body of methodological approaches relating to causal inference in observational studies exists (as an example, please see the partial list below). Furthermore, there is emerging consensus regarding methodological standards and good procedural practices for observational studies of treatment effectiveness and safety. In addition to following pharmacoepidemiologic study design principles, there are statistical methods available, including multivariable regression, propensity score analysis, marginal structural models, and instrumental variable analysis, to adjust for potential confounding and support causal interpretation of effect estimates. These methods have been used and accepted to support regulatory decisions based on observational safety studies, which also have the potential for bias and confounding due to non-random treatment assignment.<br><br>BIO encourages FDA to convene a public workshop focused on methodologies for observational studies and their applications to different study designs incorporating RWD.<br><br>*Rubin DR. Estimating causal effects of treatments in randomized and nonrandomized studies. J Educ Psychol 1974; 66:688–701*<br><br>*D'Agostino, R. B. (1998), Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Statist. Med., 17: 2265-2281*<br><br>*Rubin, D. (2005). Causal Inference Using Potential Outcomes. Journal of* |

| SECTION | ISSUE | PROPOSED CHANGE |
|---|---|---|
| | | *the American Statistical Association, 100(469), pp.322-331.*<br><br>*Robins, J., Hernán, M. and Brumback, B. (2000). Marginal Structural Models and Causal Inference in Epidemiology. Epidemiology, 11(5), pp.550-560.*<br><br>*Baiocchi, M., Cheng, J. and Small, D. (2014). Instrumental variable methods for causal inference. Statistics in Medicine, 33(13), pp.2297-2340* |
| **Using Trials or Studies with RWD/RWE for Effectiveness Decisions (pages 13-14)** | | |
| **Page 13** | The introductory paragraph states that "FDA's RWE Program will evaluate the potential use of RWE to support changes to labeling about drug product effectiveness, including adding or modifying an indication, such as a change in dose, dose regimen, or route of administration; adding a new population; or adding comparative effectiveness or safety information."<br><br>BIO welcomes the scope of the work described. However, it is unclear if FDA is considering including the use of RWE for new diseases/conditions. Furthermore, the description of potential label changes does not explicitly reference new endpoints, including outcomes of importance to patients (e.g., as reflected in PROs), or new claims (e.g., symptom control). | BIO suggest FDA clarify explicitly in future guidance that "adding or modifying an indication" encompasses the possibility of adding diseases/conditions, endpoints, and claims. |
| **Page 13** | The Framework is silent on whether any of the proposed guidance documents will address how | FDA should consider providing guidance on whether if/how different kinds of label expansions/revisions might |

| SECTION | ISSUE | PROPOSED CHANGE |
|---|---|---|
| | different labeling decisions (e.g., new indication, new population, comparative claim) could interact with RWD quality considerations and study design/methods considerations to help Sponsors match data sources and study approaches to particular regulatory contexts. See "Considerations for Generating RWE Fit for Regulatory Purposes" (Figure), p. 10, of the Duke-Margolis Center for Health Policy's *A Framework for Regulatory Use of Real-World Evidence* (Sept. 13, 2017, https://healthpolicy.duke.edu/sites/default/files/atoms/files/rwe_white_paper_2017.09.06.pdf). | interact with RWD quality considerations and study design/methods considerations when evaluating submissions including RWE. FDA should also acknowledge that such considerations must be made in the context of the specific regulatory question at hand as well as the already available evidence related to the proposed label change. These decisions must be made on a case by case basis. BIO recommends FDA collaborate with Sponsors to align on understanding on "Fit for Purpose". Early engagement between the Agency and Sponsors can identify examples for use (e.g., based on disease prevalence, study type) in guidance development. |
| **Page 13** | The Framework lays out three aspects of considerations regarding the use of RWE/RWD for regulatory effectiveness decision making:<br>"1. Whether the RWD are fit for use<br>2. Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question<br>3. Whether the study conduct meets FDA regulatory requirements (e.g., for study monitoring and data collection)" | BIO recommends that FDA consider a 4th aspect on whether the statistical methods applied meet required rigor and validity for making scientific conclusions.<br><br>This would address a number of critical issues, including: the role and requirement of pre-specification of analysis plans; appropriateness of methodology for analyzing different levels of data (subject level, group level, study level, etc.); appropriateness of methodology to mitigate risk of data dredging; appropriateness of methodology to handle data duplications across data sources; and appropriateness of methodology to integrate data from different sources (among multiple RWE sources or between RCT and RWE) with population difference accounted for. |
| **Assessing Fitness of RWD for Use in Regulatory Decisions (page 14-19)** | | |

| SECTION | ISSUE | PROPOSED CHANGE |
|---|---|---|
| **Page 17** | The Framework stated that FDA will address the use of registries as part of future guidance on data reliability and relevance. There are existing international efforts to improve and harmonize registry data quality and governance to support drug development and regulatory decision-making, for example, disease-specific workshops with registry owners, patient groups, and industry under the auspices of the EMA Initiative for Patient Registries (which also includes an EMA paper on registries currently out for public comment). | As part of its guidance development, BIO encourages FDA to liaise with EMA to understand the latter's work with registry owners/developers and industry to improve registry data quality and utility. BIO also suggests that the recommendations for data standards for a registry be aligned with these work streams. |
| **Page 18** | The Framework discusses data linking to enrich data depth but does not speak to the separate issue of data pooling – i.e., combining datasets with similar data fields but unique patients to increase statistical power or diversity, among other purposes. | BIO suggests FDA consider a flexible approach to handling data missingness (including systemic gaps), linkages, and pooling. Future guidance should encourage Sponsors to choose the most scientifically appropriate methods to address the issue at hand (e.g., missing data, data gaps, linkage, pooling, data overlap). Rather than prescribe the use of specific methods for specific circumstances, BIO recommend that future guidance suggest that Sponsors transparently describe in detail the methods they have chosen and justify their choice. |
| **Page 18** | FDA will explore strategies for filling gaps in data that may be difficult to obtain from currently used EHRs and medical claims data, including exploring the use of mobile technologies, electronic patient reported outcome tools, wearables, and biosensors. | BIO welcomes FDA's intent to explore and assess other methods to collect relevant RWD and we appreciate the FDA bringing up the challenges associated with connecting various data sources. |
| **Potential for Study Designs Using RWD to Support Effectiveness (pages 19-22)** | | |

| SECTION | ISSUE | PROPOSED CHANGE |
|---|---|---|
| **Page 19** | If a hybrid trial has both traditional and pragmatic clinical trial elements, then the primary analysis would be a combined analysis of both elements. | BIO suggests that FDA consider including in future guidance document criteria to define when a hybrid design could lead to a label expansion. |
| **Page 21** | The Framework states "In the context of retrospective observational studies using RWD, FDA will focus on critical questions such as the following:<br>1. What are the characteristics of the data (e.g., contain data on a relevant endpoint, consistency in documentation, lack of missing data) that improve the chance of a valid result? (…)" | BIO welcomes FDA's commitment to assess and provide guidance on data characteristics to improve the chance of a valid result. BIO encourages FDA to consider providing more guidance on monitoring and data assurance measures a study Sponsor should undertake to ensure acceptable quality of RWD. |
| **Pages 21-22** | FDA will consider policies to prevent practices impacting transparency | BIO agrees with the call for transparency, e.g. implemented via a registration of observational studies similar to ClinicalTrials.gov. BIO notes, however, that RWD datasets often have unique features that distinguish them from traditional clinical trial datasets, and which may require some flexibility in how and when changes to the analysis plan are implemented. BIO encourages the FDA to explore, as part of the RWE program, what types of changes to pre-specified analysis plan may be acceptable and define how these should be documented. |
| **Page 22** | FDA will consider "expert" and "stakeholder" recommendations, e.g., joint ISPOR-ISPE recommendations on good procedural practices for treatment effectiveness studies, including transparency and reproducibility, when developing guidance and policies to guard against data dredging and selective publication of only favorable results from observational studies. | BIO applauds the FDA for considering externally developed recommendations (and the referenced ISPOR-ISPE recommendations reflect good scientific practice).<br><br>BIO looks forward to working with FDA to identify policies and practices to improve the transparency of observational studies, including mechanisms for study registration and results publication. |

| SECTION | ISSUE | PROPOSED CHANGE |
|---|---|---|
| | | |
| **Data Standards — Appropriate Data Standards for Integration and Submission to FDA (pages 24-26)** | | |
| **Page 25** | The Framework discusses data standards but does not provide data submission requirements. | In addition to data standards, BIO recommends that FDA address the data submission requirements for different settings of using RWE/RWD to support regulatory decision making. For example, sometimes the Sponsor does not own the database and it is owned by a disease registry or foundation. Another example is when the Sponsor uses data that is part of FDA's Sentinel initiative. BIO welcomes the opportunity to work with the Agency and provide additional feedback on this issue. |
| **Page 25** | The Framework only appears to cover the evaluation of final analytic datasets or datasets at the point of a common data model (CDM). | Data curation/harmonization/normalization are critical processes that occur upstream from a CDM or analytic dataset. We encourage the FDA to develop future guidance that specifically addresses the critical processes mentioned above, as these directly impact all aspects of RWD used for research. Curation processes for RWD are often not systematic within or across data streams, not transparent and/or proprietary and cannot be reproduced. We recommend that FDA's future guidance distinguish between pre vs. post-CDM (or final dataset) processes & evaluation/criteria.<br><br>In addition, the program should develop guidance on required documentation of critical steps of analytic dataset creation. |
| **Stakeholder Engagement (pages 26-27)** | | |
| **General** | BIO believes it is critical for FDA to further gain experience with novel technology and approaches to use RWD and related topics. Nevertheless, BIO | BIO believes it is important for the Framework to articulate how drug Sponsors can participate in demonstration projects and bring knowledge on RWE |

| SECTION | ISSUE | PROPOSED CHANGE |
|---|---|---|
| | believes there is currently a lack of industry Sponsor participation in many of the demonstration projects. | and/or other new technologies that could be beneficial for the Agency. |
| **Page 26** | As consistency of RWE acceptance and alignment across FDA review divisions has been a concern, Framework statements about senior leadership input, centralized internal guidance mechanism, and "shared learning and consistency in applying the Framework" are positive. However, beyond the consultation services of the cross-functional RWE Subcommittee, it will be important for FDA to ensure that reviewers keep abreast of innovations in RWD and RWE generation (e.g., evolving study designs and methods). | BIO encourages the FDA to consider opportunities for formal continuing education on RWE across FDA, or the use of external experts on RWE when necessary. |
| **Page 26** | The Framework is silent on whether any guidance will address the practicalities of Agency-Sponsor interactions (e.g., how existing meeting structure applies to RWE, frequency and timing of communications/meetings during RWE study planning and execution, what documentation should be submitted and when), | BIO suggest FDA address practical issues concerning RWE-specific Agency-Sponsor interactions and RWD submissions in future guidance. |