OBJECTIVE

This White Paper provides the BIO membership ("BIO") perspective regarding the use of real-world evidence (RWE) and the underlying real-world data (RWD) for inclusion within the label of an approved product, including the addition of new indications for already approved products. RWE can provide additional types of clinical information that informs decision-makers and speeds access of medical products to patients. This paper is not intended to be an all-inclusive position paper, and cited papers should be consulted for more detailed technical guidance.

SCOPE

This document is focused on the policy aspects of RWE in a specific regulatory context—considerations of label expansion for an approved product.

Examples of “label expansion” referenced in this paper include the addition of a new indication and efficacy claims for an already approved product, addition of age-groups and target populations not included within the original application, addition of drug dosing and administration information, safety revisions, patient-preference data, and additional health-outcomes results such as re-hospitalization rates.

This paper is primarily concerned with the printed label as defined by 21 U.S.C. § 321(m), including the following items: prescribing information, package insert; professional labeling; direction circular; and package circular.

Manufacturer communication of information not in the printed label, but consistent with FDA-required labeling and based on RWE, is not directly within the scope of this policy paper. However, many of the points discussed within this paper also apply to the communication of such information.

Importantly, this paper is not intended to be a comprehensive review of the technical considerations concerning issues such as RWD quality and RWE study designs. These technical aspects are discussed thoroughly in other papers and are incorporated herein by reference and citation.
I. INTRODUCTION

This White Paper aims to capture the perspective of BIO Membership ("BIO") regarding the use of real-world evidence (RWE) and the underlying real-world data (RWD) for changes to the label of an approved product, including for the support of a new label indication or population for an already approved product. While RWE has potential uses in a variety of regulatory contexts, BIO members identified label expansion as a priority issue that can benefit from greater regulatory clarity. This topic is timely; activities to further RWE use, including the issuance of draft guidance and a regulatory framework, are explicitly listed as FDA deliverables under the 21st Century Cures Act and Prescription Drug User Fee Act (PDUFA) VI. We expect that many of the points addressed within the discussion below should also be relevant in developing a broader framework for integrating RWE in regulatory decision-making.

BIO has captured the positions within this paper to both communicate the perspectives of industry, and to inform policy makers regarding future use of RWE. Looking forward, BIO Members are open to partnering with the FDA and relevant stakeholders to better communicate industry’s capabilities regarding RWE.

BIO believes that RWE studies can augment insights gained from traditional randomized clinical trials (RCTs) about the effectiveness of therapeutics. This application of RWE builds on the long-standing FDA use of RWD in safety assessments, including Sentinel. RCT designs and their associated statistical models have evolved over the past century to control for most known sources of bias and confounding when making statistical inferences about the efficacy of tested interventions. By contrast, RWE reflects how patients are treated in routine clinical practice and how they take their medicines in everyday use (i.e., the real world).

RWE studies can provide meaningful insights about the therapeutic impact of a product in the real-world population that will be exposed, across variables that may not be included in RCTs—for example, the performance of a therapeutic intervention as a function of age, underlying conditions/co-morbidities, real-world medication-taking behaviors, quality of life improvements, or in comparison to other available therapies not studied in RCTs. The external generalizability contributed by RWE can be used to understand the risks and benefits to the range of populations and patients who use the therapeutic, to target new patient populations, account for regional and global variations in health-care practice, and provide further information than that afforded by RCTs alone.

RWE can also provide critical insights in cases where RCTs are unethical or impractical. For example, in rare disease, pediatrics, and other limited populations, RWE studies can mitigate challenges often faced by RCTs such as ethical constraints or limited trial enrollment, providing historical controls where appropriate control populations do not exist or are not feasible.

While traditional RCTs will remain important, the number and size of those trials might be reduced with growing acceptance of new research approaches including RWE. RWE provides additional context and greater external generalizability to the benefit-risk regulatory assessment. The use of RWE—introduced by this broader generalizability—may allow for improved regulatory decision making as evidence may become more readily available.

BIO Members believe that RWE studies, including high quality observational studies, that are conducted in accordance with best practices articulated by expert groups, such as International Society for Pharmacoeconomics and Outcomes Research/International Society for Pharmacoepidemiology (ISPOR/ISPE), may be sufficient to inform specific regulatory decision-making for label expansion without the need for additional RCTs. Decisions about an individual regulatory question are made on a case by case basis, and the totality of the evidence must be considered. Depending on the specific details of any given situation, the additional evidence provided by a high-quality observational study may be sufficient to answer the question at hand. Although some recently published
thought papers suggest that observational studies are not yet appropriate for label expansion. BIO believes that the necessary tools are actively being developed and in some specific contexts are already sufficient to generate meaningful evidence and should form the basis of future FDA guidances.

This position is informed by several considerations:

- First, the Federal Food Drug and Cosmetics Act (FFDCA) and related regulations allow sponsors to use RWE in meeting the “substantial evidence” requirement that a drug is effective for each of its intended uses.

- Second, RWD quality—including data derived from both primary and secondary data sources—can be assessed satisfactorily using existing strategies, including those described through expert workgroups and publication, to determine suitability for regulatory decision making.

- Third, RWE studies, including interventional and observational studies, may be designed to provide sufficient evidence to demonstrate effectiveness to support label expansion in an already-approved drug. Industry has built on its substantial experience and expertise in conducting clinical studies and is already applying these principles to the design and execution of RWE studies and outcome analysis. In several instances, FDA has already relied upon RWE in regulatory-decision making.

In order to encourage utilization of RWE in drug development and research, FDA, industry, and other stakeholders should collaborate jointly to design a workable approach for use of RWE in regulatory decision-making. Specifically, the FDA should continue to clarify how it will review RWE studies for use in potential label expansion decisions, including aspects such as data quality standards, expectations for study protocols, statistical analysis plans and reporting, and recommended best practices for study design and analyses. At the same time, FDA and industry should work together to further illustrate application of RWE through the use of case examples to facilitate incorporation of RWE in product labels. Finally, the Agency should leverage its growing experience in reviewing RWE for regulatory decision-making and build on existing recommendations for the conduct and reporting of observational research studies and pragmatic clinical trials.
II. CURRENT REGULATIONS ALLOW REAL-WORLD EVIDENCE TO BE USED FOR LABEL EXPANSION

BIO believes the use of RWE for the purpose of label expansion is authorized under current regulations. Under Sec. 505(D) of the FFDCA, sponsors are required to demonstrate product effectiveness by providing “substantial evidence” that a drug is effective for each of its intended uses. This substantial evidence is to be provided by adequate and well-controlled trials and other confirmatory evidence. In defining “substantial evidence,” FDA was agnostic on particular details including data sourcing, study design, specific statistical methodologies, and statistical significance, so long as the sponsor describes key characteristics of study design, conduct, and analysis. FDA is required to exercise its scientific judgment to determine the types, quality, and quantity of evidence and information an applicant is required to provide for a particular drug to meet the regulatory standards; FDA has historically demonstrated flexibility in doing so. In fact, in April 2019, FDA expanded the use of an approved oncology treatment to include males based on real-world data from EHRs as additional supportive data.

A well-designed observational study may meet the substantial evidence standard for label expansion under the FFDCA. FDA has already relied on RWE—such as case series and historical controls—for the basis of approval in rare disease populations and oncology. In these situations, randomized studies were infeasible, and the natural history of the disease was well- understood. Real-world studies could also inform label expansion decisions for products treating more prevalent conditions as industry and the FDA become more familiar with the quality of available data and application of analytical best practices in regulatory contexts.

In addition to outlining the circumstances where FDA may consider RWE to support label expansion, BIO would welcome a commitment by FDA to ensure review teams include members with expertise in the use of RWD. Mechanisms should be put in place to ensure that the review process of RWE is considered and applied consistently across review divisions.

III. INDUSTRY IS DEVELOPING STRATEGIES AND BEST-PRACTICES TO ASSESS THE QUALITY OF RWD—INCLUDING BOTH PRIMARY AND SECONDARY DATA SOURCES

BIO members agree that use of RWD to support label expansion relies on the data being of sufficient quality, depth, and relevance such that FDA can be assured of the external validity of study conclusions and that the regulatory standards of safety and efficacy are met. To this end, BIO members are adopting published and discussed best-practices to collect quality RWD, whether the data are derived from primary sources or originate from secondary sources such as electronic health records (EHRs) or payment/claims data. For instance, BIO members are developing approaches to address shortcomings within collected data sets, improve upon the design and methods of data collection and structure, and increase the completeness and richness of variables captured. As technology evolves and the public’s participation in generating data (user-generated content) increases, there will likely be a continual need for re-assessment and adaptation in how all of these data can be accessed and analyzed to ensure quality.

While BIO members are not always in control of RWD generation, we recognize that sponsors should prioritize datasets that adhere to several best practices, including the following:

- **Dataset generation should use accepted procedures and outcome measures**, including use of validated endpoint ascertainment, to help identify and/or minimize bias in parameter measurement. Transparency in data linkage methods and validations thereof are also an important element to assess if RWD are fit for purpose, given the data utilized for RWE links multiple files/sources at the patient level.

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18 FDAMA §115.
19 Sponsors are required under §314.126 to submit adequate statements and protocols to FDA that addresses how bias, patient selection, and comparisons will be addressed in the study design and analytical plan. [https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm635276.htm](https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm635276.htm)
20 Label expansion for NovoSeven RT, a product that is used to treat Hemophilia. The Hemostasis and Thrombosis Research Society registry data was used as evidence supporting the products’ expansion of indication in Acquired Hemophilia [https://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM056054.pdf](https://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM056054.pdf)
21 FDA expands approval of Blincyto for treatment of a type of leukemia in patients who have a certain risk factor for relapse [https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm603151.htm](https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm603151.htm)
22 **“Primary Data”** refers to RWD sets generated via prospective observational or pragmatic studies through a moderated process. **“Secondary Data”** refers to RWD generated for purposes other than research. Terminology is not intended to reflect a hierarchy of data types. [https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm625228.htm](https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm625228.htm)

Data management and data control processes are in place to ensure provenance of data following transfer and storage, that is, a process of quality controls is applied to prevent introduction of errors during creation of the research or analytic datasets. Documentation of methods, protocols, terminologies, and specifications for the collection, exchange, storage, and retrieval of information should exist to ensure transparency and high data quality.

Data accuracy is assessed during data collection by processes incorporating checks for the correctness of data types, ranges and values, and consistencies between independent values that measure similar attributes.

Sponsors must assess the limitations due to missing, unmeasured or unavailable covariate data. Sponsors should employ strategies to address missing data elements, which could include sensitivity analyses, natural language processing tools to extract information from unstructured notes, machine learning approaches, or additional prospective studies and data generation. Data collection protocols, reports, and manuscripts should include a description of the limitations of the data, how such limitations were addressed, and the potential impact on validity of the conclusions.

Data collected should be relevant to the question of interest. The representativeness of the subset of patients contributing to the final analyses should be described relative to the complete sample. For example, sponsors should aim to have an understanding of patient referral patterns to evaluate whether patients in a particular health system are typical of patients with that particular condition. Reasons for patients being excluded from analyses should be described.

IV. REAL-WORLD STUDIES, INCLUDING OBSERVATIONAL AND INTERVENTIONAL STUDIES, CAN BE DESIGNED TO SUPPORT LABEL EXPANSION OF AN APPROVED PRODUCT

BIO recognizes that study design and methods used to generate RWE should be guided by the research, clinical, and regulatory questions the sponsor seeks to answer.

BIO believes that observational or interventional real-world studies are appropriate in many instances to support label expansion. Several factors help determine whether an observational or interventional real-world study can support reliable inferences from the study results, including, for example:

- Biological plausibility of the study hypothesis (i.e., availability of pre-clinical and clinical data supporting the mechanism of action (MOA), dosing/toxicity, and the expected clinical benefit);
- Degree to which the natural history of disease is understood;
- Acceptance of the predictive or prognostic biomarkers being measured;
- The clinical endpoints are relevant, observed, and captured in RWD;
- The observed treatment effect is supported by rigorous causal inference analysis specifying relationships between treatment, other key variables, and the outcome.

BIO members are exploring study designs and data analysis methods to convert data into evidence that can support regulatory decision-making. Several recognized guidelines and established best practices support the credibility of research conducted in real-world settings. For example, two recent published reviews demonstrate a high degree of consensus among 13 guidelines and sets of recommendations from experts in academia, professional societies, industry, a non-governmental institute, U.S. governmental agencies, and a network coordinated by the EMA. These current practices include:

- Hypothesis(es) generation should occur at the outset of study design.
- Use of pre-specified statistical analysis plans that address the specific study hypotheses and objectives and explain the details of the primary and any secondary analyses. The plan should be included in the protocol and, at a minimum, include details on the statistical models and tests, sample size estimation, significance level and power of the study, handling of missing values, subgroup analyses and the assessment of effect modification, and method of confounding adjustment and sensitivity analyses. Operational definitions of exposures, covariates, and outcomes should also be delineated.
Consideration and incorporation of several different sensitivity analyses when appropriate to test potential drivers of study outcomes (i.e., differences in baseline characteristics, treatment changes midstream or missing data). Sensitivity analyses may also be used to determine the impact of various study decisions relating to design, exposure definition and outcome definition, and of deficiencies in the data source(s) selected. Such analyses can be very helpful in determining the potential impact of varying assumptions (e.g., changing cut-points for categorical variables, limiting or expanding case or outcome definitions, changing definitions of current exposure) on study results, and can facilitate better interpretation of study results in light of significant uncertainty. It is important for sponsors to provide their own interpretation of the impact of any sensitivity analyses on study conclusions.

Transparency in methods and analyses conducted to enable others to reproduce study results will increase confidence in study findings by testing the robustness of results under different study design.\textsuperscript{28,29} Protocols and analysis plans should be finalized prior to data analysis, and deviations from protocols should be noted in final reports.

Finally, BIO recognizes that specific conditions and study outcomes can further increase confidence in the validity of real-world study results as credible evidence in demonstrating a potential causal treatment effect.\textsuperscript{30} These conditions include, for example:

- Large, clinically meaningful effect size, and evidence of a dose-response gradient, where applicable;
- Use of bias analyses as appropriate to assess impact of confounding and other potential sources of bias on effectiveness estimates;
- The treatment effect (similar direction and magnitude) should be consistent with the scientific understanding and therapeutic response, and consistent across available databases and data types, patient populations, geographic regions, healthcare systems, and/or time periods; and
- The results are robust toward variations in the analysis assumptions and sensitivity.

\section*{V. REGULATORY CHALLENGES AND RECOMMENDATIONS IN RWE USE IN LABEL EXPANSION}

BIO believes that further industry investment in RWE requires the development of a scientifically robust and FDA-endorsed framework that provides clarity and confidence that these studies will be used—and how they will be used—in regulatory decision-making. To that end:

- BIO encourages FDA to affirm that RWE studies—in the appropriate regulatory context-of-use—may help satisfy or be sufficient to meet the “substantial evidence” requirement under 505(D) of the FFDCA when two or more RCTs are not necessary or feasible.
- Sponsors and FDA should set up enhanced, structured opportunities to pilot the use of RWE in regulatory submissions. The development of regulatory use cases demonstrating how RWE can provide appropriate evidence for regulatory decisions related to label expansion, including the approval of a new indication or patient population for certain clinical questions and contexts, will be critical for advances to be made. Sponsors are hesitant to propose RWE in their submissions when regulatory requirements are unclear or applied inconsistently. Likewise, increased industry experience will support sound regulatory requirements. A clearly defined process for engaging FDA and contemplating pilots/use cases would likely incentivize greater industry engagement.
- BIO members believe industry, FDA, and other stakeholders should work together to augment the agency’s internal expertise and familiarity with data and methods used to generate real-world evidence for the purpose of effectiveness evaluations. FDA should consider how to best utilize external experts when necessary to enhance FDA’s internal expertise.
- BIO members encourage the FDA to describe when it will accept RWE generated from secondary data sources and identify when RWE might be appropriate and fit for purpose for evaluating effectiveness in support of label expansions. When fit for purpose, secondary data can provide valuable insights into a product’s effectiveness profile in the real-world setting.

\textsuperscript{29} See Ref. 6
\textsuperscript{30} See Ref. 27 and Ref. 29, 2016; Morton SC et al. 2016; See also Bradford Hill’s criteria of strength of association and biological gradient
Where possible, access to publicly funded data and data from national data/research networks should be available to medical researchers and drug developers. Access to these data (while ensuring patient privacy and data security) is especially important to achieve FDA’s vision of a “learning healthcare system” with research embedded in real-world clinical practice.31

In addition to ongoing initiatives to expand the application of RWE in regulatory decision-making, BIO members support collaboration efforts to develop a more robust learning healthcare system. This includes improving data quality through longitudinal integration across datasets, robust data curation, and structured data collection. In the long-term, stakeholders should collaborate to ensure greater harmonization across EHRs and similar data sets to facilitate the collection and analysis of appropriate RWD.

VI. CONCLUSION

As described in this document, BIO believes that well-designed and appropriately conducted observational and interventional RWE studies should be accepted as supporting or providing sufficient evidence for the purpose of label expansion for an approved product. BIO recognizes that data quality and study design underline the integrity of an RWE study outcome and believe that tools and best practices have matured so that RWE can be impactful in regulatory decision making. Industry is presently exploring tools and gaining expertise to ensure that RWD meet the necessary quality standards for regulatory decision making.

Looking forward, enhanced FDA expertise and the development of a transparent approach for the use of RWE in regulatory decision making would further bolster industry commitment to these studies. For example, a better understanding of FDA’s standards, improving relevant expertise within the FDA, and partnering with industry to develop additional RWE use-case studies will inform industry on how to best utilize RWD and design RWE studies to better meet regulator expectations. BIO members are developing expertise using RWD and are actively partnering to further refine best practices.

We look forward to discussing this further with FDA and industry colleagues and moving real-world studies into mainstream regulatory processes.

VII. ACKNOWLEDGEMENTS

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