February 14, 2020

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

Re: Docket No. FDA–2020-D-0529: FDA Draft Guidance, Qualification Process for Drug Development Tools.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance, Qualification Process for Drug Development Tools.

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's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO commends the Agency for the development of the Draft Guidance on Qualification Process for Drug Development Tools (DDTs) as required by the 21st Century Cures Act. BIO believes that the Draft Guidance provides a useful framework for how new DDTs can be developed and used as well as the process for qualification of such tools, information that will be essential to Sponsors looking to qualify a DDT. BIO has included in this letter several recommendations for FDA's consideration as the Guidance is finalized.

I. BIO Requests Flexibility in Timelines for DDT Qualification and Discussions around DDT in the Context of a Development Program

The Draft Guidance provides a new submission process for engagement with FDA and target timelines for a three-stage, sequential, review process: the letter of intent (LOI), the qualification plan (QP), and the full qualification package (FQP). FDA has proposed that the LOI will be reviewed within three months; the QP reviewed within six months; and the FQP reviewed within 10 months of issuing the reviewable memorandum. While the Draft Guidance recognizes that FDA may prioritize and accelerate the FQP, the six-month timeline for reviewing the QP (Stage 2) is relatively long. BIO request that FDA ensure DDT review timelines are flexible. We also suggest that the Guidance consider including details on potential flexibility around qualification reviews, such as stepped review of qualification packages or "rolling submissions", which can expedite review processes and speed the time to full qualification.

Additionally, while we appreciate that the DDT qualification process is a voluntary pathway that stakeholders can take outside the context of an IND, we believe that similar transparency and timelines would be helpful for sponsors seeking to develop a DDT within

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the context of a drug development program. Further, we note that certain drug development programs (e.g., rare disease and oncology, among others) can have accelerated plans where the Phase I study could serve as the registrational study or evidence for registration. Discussions of DDT in the context of a development program may in some instances become rate limiting for these accelerated plans.

II. BIO requests the FDA to Clearly Identify the Meeting Types that Should be Used for DDT Discussions

For discussions around DDTs that are product related, BIO requests that the Agency provide further guidance on which types of meetings a sponsor should use to engage in technical discussions with the Agency in the context of the IND process. Additionally, BIO also requests that FDA consider a flexible approach in communications between FDA and the sponsor to better accommodate accelerated development timelines.

III. BIO Requests Additional Detail Regarding when a Qualified DTT may be Rescinded or Modified

The Draft Guidance clearly indicates that CDER or CBER DDT programs may modify or rescind a qualified DDT and/or COU based on new information that calls into question the basis for such qualification. BIO cautions FDA from rescinding or modifying DDTs that have already been qualified as modifying or rescinding a qualified DDTs as the required elements for supporting evidence for qualification and the significant amount of documentation required may be a high burden for a sponsor to consider if there is risk that the qualified DTT and/or COU can be revoked or rescinded. Further, it poses an additional challenge for sponsors who have elected to utilize a primary or secondary endpoint based on a qualified DDT and/or COU that may later be modified or rescinded. To this end, BIO requests that FDA provide additional detail in the Draft Guidance regarding how these situations will be addressed with minimal impact to an ongoing clinical trial. Additionally, BIO requests that the FDA carefully consider rescinding or modifying a qualified DDT and the potential impact to an ongoing clinical trial that is using a qualified DDT and/or COU that is modified or rescinded before the trial is complete, or before the product is FDA approved. Without an understanding of the potential risk associated with using a qualified DDT and/or COU as a primary or secondary endpoint Sponsors may elect not to employ these important new tools intended to aid drug development and regulatory review.

IV. BIO Requests that the Guidance Clearly Indicate how CDRH Regulation Aligns with the DDTs Process in the Context of DDTs

BIO understands that evidentiary standards or performance criteria for purposes of DDT qualification and qualifying medical device development tools are out of scope of the current Guidance. However, it would be helpful if the Guidance explicitly mentioned DDTs that meet the definition of a medical device or other devices that do not meet the definition of medical device but are used as tools during drug development and how CDRH regulation is expected to align with the DDT construct described in the Guidance. We note that this has often been a source of concern within Industry and providing information on this topic would allow for increased clarity. Specifically, it would be helpful if FDA discussed in the Guidance how to determine and/or confirm if a DDT meets the definition of a medical device that CDRH intends to regulate, how the device development and submission process aligns with the DDT Qualification Process, how to most appropriately utilize an investigational device (for

both significant risk and non-significant risk devices), and how to coordinate regulatory activities between CDRH and CDER/CBER.

VII. Additional Information on Use of External Experts
BIO appreciates that FDA references the use of external subject matter experts to review QPs and FQPs through the use of cooperative agreements. BIO supports the FDA's use of subject matter experts and believes that the use of such experts could help provide expertise to the FDA where specific expertise may be limited. BIO requests that FDA include additional detail in the Draft Guidance regarding the process by which external subject matter expertise will be engaged.

VIII. Additional Information on Prioritization of Review
BIO notes that the Draft Guidance indicates that "FQP review may be prioritized based on factors that include, as applicable, the following: (1) the severity, rarity, or prevalence of the disease or condition targeted by the DDT and the availability or lack of alternative treatments for such disease or condition and (2) the identification, by FDA or by biomedical research consortia or other expert stakeholders, of a DDT and its proposed COU as a public health priority. Additionally, FDA may prioritize FQP review based on other factors determined appropriate, and FDA intends to consider the potential impact the DDT will make on drug development." BIO requests that FDA provide additional detail in the Draft Guidance regarding what other factors FDA will consider when making determinations regarding prioritization of the review of DDTs as well as activities FDA will undertake to support transparency around DDT review prioritization. BIO also requests that FDA provide additional detail regarding how prioritization may impact the timelines outlined in the Draft Guidance.

Finally, given the global nature of drug development and use of such tools in global clinical trials and global filings, it would be helpful to include formal options to have parallel/joint qualification procedures with European Medicines Agency (EMA). BIO also requests that reference to digital biomarker (included in footnote 17) be placed within the main body of the comment letter. BIO appreciates this opportunity to submit comments regarding FDA's Draft Guidance, Qualification Process for Drug Development Tools. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
Danielle Friend, Ph.D.
Senior Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Entire Guidance		BIO requests that FDA clarify in the Guidance how the "Fit for Purpose Initiative," another pathway for regulatory acceptance of DDTs in drug development programs, relates to the timelines and processes outlined in this guidance.
II. BACKGROUND		
A. DDT Qualification Programs		
Line 101-103	In this section FDA indicates that "*COAQP applies to COAs, which FD&C Act section 507 defines as a measurement of a patient's symptoms and overall mental state or the effects of a disease or condition on how the patient functions, and it includes patient-reported outcomes (PROs).*"	BIO requests the following edit: "COAQP applies to COAs, which FD&C Act section 507 defines as a measurement of a patient's symptoms and overall mental state or the effects of a disease or condition on how the patient functions, and it includes patient-reported outcomes (PROs), **clinician-reported outcomes (Clin-ROs), observational and performance reported outcomes.**"
Line 106-108	In this section FDA indicates "*Generally, FDA will consider qualifying a COA if it is well-defined and reliably assesses a targeted concept for a specified COU when used in adequate and well-controlled investigation*" We suggest that it could be useful to elaborate on what is meant by adequate, or to refer to the	BIO requests the following edit: "*Generally, FDA will consider qualifying a COA if it is well-defined and reliably assesses a targeted concept for a specified COU when used in adequate and well-controlled investigation*. ***This includes including choice of control, method of patient assignment to treatment (e.g., randomization), adequate measures to minimize bias (e.g., blinding), well-defined and***

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	discussion in the December 2019 draft guidance "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products".	***reliable assessment of individuals' response (i.e., efficacy endpoint), and adequate analysis of the clinical investigation's results to assess the effects of the drug (i.e., statistical methods)."***
Line 119-121	In this section FDA indicates that "*An animal model is defined as a specific combination of an animal species, challenge agent, and route of exposure that produces a disease process or pathological condition that, in multiple important aspects, corresponds to the human disease or condition of interest;*" one could produce a disease process that does not reflect the behavioral characteristics of the disease.	BIO requests the following edit: *An animal model is defined as a specific combination of an animal species, challenge agent, and route of exposure that produces* ***and/or reflects*** *a disease process or pathological condition that, in multiple important aspects, corresponds to the human disease or condition of interest*"
B. 21st Century Cures Act		
C. General DDT Program Concepts		
Lines 193-195; also see footnote 36	In this section FDA indicates that "*Drug developers or other interested parties should consult the DDT programs' web pages to learn about program considerations and recommendations related to a specific qualification project or to learn more about program resources available to DDT developers*" and includes a footnote which references several websites for the DDT Program (e.g. BQP, COAQP, AMQP). The information contained in these webpages can be quite useful. As web pages are uncontrolled documents and hyperlinks may change more frequently that the guidance is updated.	BIO requests that the FDA highlight some of the key information included in the referenced website in the final version of the guidance.
1. How Do Requesters Determine Their Readiness to Initiate the Qualification Process		
Lines 197 - 205	In this section FDA provides information to Sponsors regarding "*How Do Requestors Determine Their*	BIO request that FDA include general criteria that are appropriate across all programs within the guidance for

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	Readiness to Initiate the Qualification Process"; however, the information provided only indicates that requestors may request a meeting with the relevant DDT qualification program at any time to discuss the qualification pathway. The Draft Guidance does not provide basic metrics for when to initiate the process. Engaging in a meeting with FDA requires preparation and can be time consuming for all parties involved. It would be beneficial for FDA to provide some clarity and/or generic metrics regarding readiness to initiate the qualification process before requestors contact FDA to request a meeting. Additionally, it is unclear during which phase of drug development a requestor should submit a DDT referencing a COU for a specific new investigational drug (i.e., should the Pre-IND or IND precede the LOI?)	when a requestor is nearing the threshold for initiating the qualification process. BIO requests that the FDA provide more clarity regarding when during development FDA recommends requestors engage with the Agency. E request that FDA also provide more clarity around what type of meeting is most appropriate for discussions regarding the qualification pathway of a DDT and COU.
2. When Does the Review Time Frame Begin?		
Lines 209 - 211	In this section FDA indicates that "*Once a submission is deemed complete after an initial assessment, FDA will issue the requestor a reviewable memorandum marking the date that the comprehensive review starts and the review time frame begins*;" however, It is unclear what constitutes a complete submission at each of the stages of review.	BIO requests that FDA provide additional detail within the guidance on what constitutes a complete submission at each of the stages of review.
3. What Does an Accept or Not Accept Determination Mean and How is it Made?		
4. What does It Mean to Withdraw from a DDT Program?		
5. What are Subject Matter Experts and How Are They Used in Submission Review?		
6. How can Biomedical Research Consortia and Partnerships Contribute to DDT Qualification?		
D. A Taxonomy for DDTs: the BEST Glossary		
IV. QUALIFICATION PROCESS		

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A. Three Sequential Stages and Review		
1. FDA Review Process		
Lines 293 - 295	In this section FDA indicates that "*If the initial assessment indicates important missing elements, FDA may send the requestor a not reviewable memorandum with advice intended to improve the quality of the submission;*" however a "not reviewable memorandum" is not defined, while a "reviewable memorandum" is defined in the glossary of the draft guidance.	BIO requests that FDA provide a definition of a "not reviewable memorandum" in the glossary of the Draft Guidance. Alternatively, BIO requests the following edit: Change to "If the initial assessment indicates important missing elements, FDA may send the requestor ~~a not reviewable memorandum~~ **a notice or memorandum that the submission is not reviewable in the current state** with advice intended to improve the quality of the submission."
2. Letter of Intent (Stage 1)		
Lines 314-320	In this section the FDA indicates that "*The LOI is a concise document that describes the DDT, a relevant drug development need, and a proposed COU*."	BIO requests that the FDA consider including the following reference to demonstrate what is meant by 'concise' and what should be included in a LOI.[1,2,3]
3. Qualification Plan (Stage 2)		
Lines 333-341	In this section FDA indicates that "*The QP submission describes available relevant data, knowledge gaps, data collection, and the analysis plan*"	BIO requests that FDA consider including the following reference to demonstrate what should be included in the Qualification Plan.[4, 5,6]

[1] FDA Document on the Letter of Intent to Propose a COA Qualification.
[2] FDA Document on the Letter of Intent for Animal Model Qualification Submissions.
[3] FDA Document on the Letter of Intent for Biomarker Qualification.
[4] FDA Document on COA Qualification Plan.
[5] FDA Initial Briefing Package Outline for Animal Model Qualification.
[6] FDA Document on Biomarker Qualification Package.

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Lines 338 – 344	In this section FDA indicates that "*The relevant DDT qualification program will review the QP for completeness, and if all needed information is contained in the submission to allow a comprehensive review, FDA will issue the requestor a reviewable memorandum, thereby initiating the time frame for the QP review.*" It is unclear what the timeline is to conduct the completeness review and notify sponsors if missing information is identified.	BIO requests that FDA clarify in the Draft Guidance when sponsors will be informed after the initial review for "completeness" if missing information is identified. Ideally, FDA would contact sponsors to address any gaps in information within the first 1-2 weeks after the QP is received to prevent any delays in the development program. BIO requests that FDA indicate in the Draft Guidance the timeline for reviewing the QP for completeness.
4. Full Qualification Package (Stage 3)		
Lines 356-358	In this Section the FDA indicates that "*The FQP includes detailed descriptions of all studies, analyses, and results related to the DDT and its COU as described in FDA's response to a requestor's QP.*"	BIO suggests that FDA include the following reference to demonstrate what should be included in the FQP.[7] BIO encourages FDA to consider the time and amount of resources that may be needed to develop the FQP given the required elements that FDA includes in the Draft Guidance.
B. Post-Qualification Modification and Rescission		
Lines 403-405	In this section FDA indicates that "*CDER or CBER DDT programs may decide to modify or rescind a qualified DDT and/or COU, based on new information that calls into question the basis for such qualification or other regulatory and scientific considerations indicating that the DDT is not appropriate for its COU.*"	BIO requests that FDA provide additional detail regarding the potential impact to an ongoing clinical trial that is using a qualified DDT and/or COU if the qualified DDT and/or COU were to be modified or rescinded by FDA before the trial is complete. BIO requests that the FDA provide additional information regarding how FDA would approach such a situation. We also suggest that the

[7] FDA Document on a COA Full Qualification Package.

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	Because clinical trials can often take several years to complete, additional information should be included in the Guidance pertaining to the potential impact to an ongoing clinical trial that has selected a primary or secondary endpoint based on a qualified DDT and/or COU and the qualified DDT and/or COU is subsequently modified or rescinded during the clinical trial.	Guidance include examples or sample criteria as to when FDA may choose to rescind the qualification.
V. HOW TO COMMUNICATE AND SUBMIT A DOCUMENT		
A. What Are the Processes for Submitting to a DDT Program?		
1. Electronic Portal Account Creation and Submission		
A. Submission and Data Standards		
Lines 451-453	In this section the FDA indicates that "Requestors are strongly encouraged to use relevant data standards (e.g., Clinical Data Interchange Standards Consortium (CDISC) standards) when submitting these data for review."	As there are relevant data standards other than the CDISC Standard, BIO requests that FDA also refer to other data standards beyond CDISC.
GLOSSARY		
A. Definitions		
B. Acronyms and Abbreviations		
APPENDIX A		