Qualification Process for Drug Development Tools

Guidance for Industry and FDA Staff

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Chris Leptak at 301-796-0017, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2019
Drug Development Tools

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
and the Center for Biologics Evaluation and Research (CBER)

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Qualification Process for Drug Development Tools Guidance for Industry and FDA Staff[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

Section 3011 of the 21st Century Cures Act (Cures Act)[2] added new section 507, Qualification of Drug[3] Development Tools (DDTs), to the Federal Food, Drug, and Cosmetic Act (FD&C Act). This draft guidance meets the Cures Act's mandate to issue guidance on this section-507 qualification process and related Prescription Drug User Fee Act (PDUFA) VI[4] commitments; the draft guidance of the same name issued January 7, 2014, is withdrawn.[5] Specifically, once finalized, this guidance will represent the Center for Drug Evaluation and Research's (CDER's) and the Center for Biologics Evaluation and Research's (CBER's)[6] current thinking on taxonomy for biomarkers and other DDTs, and on implementation of section 507 of the FD&C Act with respect to the processes for requestors[7] interested in qualifying DDTs.

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[1] This guidance has been prepared by the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] Pub. L. 114-255.

[3] The term *drug* refers to both human drugs and biological products unless otherwise specified.

[4] Under FDA Reauthorization Act of 2017 (FDARA, Public Law 115-52).

[5] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[6] Reference to *FDA* or *the Agency* in this guidance means CDER and CBER and does not include other FDA Centers.

[7] Under section 507, a requestor means "an entity or entities, including a drug sponsor or a biomedical research consortium seeking to qualify a DDT for a proposed context of use." CDER and CBER recognize the important contributions of academia, patient advocacy groups, and other stakeholder communities as requestors and as supporters of DDT development efforts.

This guidance does not address evidentiary standards or performance criteria for purposes of DDT qualification, nor does it address qualifying medical device development tools (MDDT) through the Center for Devices and Radiological Health (CDRH). These topics will be discussed in guidances and in other materials available on FDA's DDT program and MDDT program web pages, respectively.[8]

Section 507 of the FD&C Act defines DDTs as including biomarkers, clinical outcome assessments (COAs), and any other method, material, or measure that FDA determines aids drug development and regulatory review.[9] FDA has determined that animal models evaluated under the Animal Model Qualification Program (AMQP) aid drug development and regulatory review for purposes of section 507.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

DDTs are methods, materials, or measures that can aid drug development and regulatory review.[10] Under new section 507 of the FD&C Act, *qualification* and *qualified* mean a determination that a DDT and its proposed context of use (COU) can be relied upon to have a specific interpretation and application in drug development and regulatory review.[11] A qualified DDT used within the COU may be used to support or obtain approval or licensure (as applicable) of any drug or biological product, provided the qualification has not been rescinded or modified.[12] For more information on how DDTs can benefit drug development, see the CDER and CBER DDT program web pages.[13]

Seeking qualification of a DDT for a specified COU is voluntary. DDTs that have not been qualified or that are qualified for a different COU may still be used in regulatory applications,

[8] For more information on MDDT, see https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt.

[9] FD&C Act section 507(e)(5).

[10] FD&C Act section 507(e)(5).

[11] FD&C Act section 507(e)(7).

[12] FD&C Act section 507(b)(2).

[13] For more information on CDER's and CBER's DDT programs, see https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-ddts and https://www.fda.gov/drugs/drug-development-tool-qualification-programs/drug-development-tool-qualification-process-transparency-provisions.

when scientifically appropriate for a specific application, based on agreement with the appropriate review division or office before the Agency reviews an application. Such a DDT is not, however, considered qualified, a status that would support using that DDT within its COU without having to seek prior agreement with a review division or office on the acceptability of that DDT for that use.

The COU statement identifies the specific use of the DDT in drug development. FDA expects the content in DDT submissions to provide support for the proposed DDT and proposed COU. For more information and details on the program-specific construction of a COU, see the respective web pages for the Biomarker Qualification Program (BQP), the COA Qualification Program (COAQP), or the Animal Model Qualification Program (AMQP). The DDT and its COU may evolve over the course of a qualification effort and are directly related to the information provided in qualification submissions.

Encouraging the identification and use of reliable DDTs can significantly advance the development of new, safe, and effective drugs. Qualified DDTs allow integration of innovative technology and approaches to conditions or diseases that may create opportunities in new areas of drug development as knowledge of disease and pathogenesis advances. For example, using a DDT to enrich a study population with individuals exhibiting certain characteristics may help to reduce the size of the study population and may shorten the duration of the study. Qualifying a DDT is a stepwise process; if at any stage a DDT is determined to be not accepted or not qualified, a requestor may take into account the input from the Agency and subsequently resubmit.

A. DDT Qualification Programs

There are three DDT qualification programs at FDA: biomarker, COA, and animal model.

BQP applies to biomarkers, which are defined in section 507 of the FD&C Act as characteristics (such as a physiologic, pathologic, or anatomic characteristic or measurement) that are objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention.[14,15] Molecular, histologic, radiographic (imaging), or physiologic characteristics are examples of types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives, as noted in the Biomarkers, EndpointS and other Tools (BEST) glossary.[16]

[14] The term biomarkers includes those used as surrogate endpoints; FD&C Act section 507(e)(1).

[15] Qualifying a biomarker does not result in the qualification or endorsement of a specific measurement method. If an alternative measurement method is used in drug development, equivalence may be demonstrated to the relevant review division(s) or office(s) such that the alternative method has the same or similar performance characteristics to the method used for the qualification. A sponsor interested in pursuing the development of a specific biomarker test for marketing as a device should consult the appropriate center at FDA (CDRH or CBER) that is responsible for review of the test.

[16] For more information on the BEST glossary, see: https://www.ncbi.nlm.nih.gov/books/NBK326791/.

The BQP's goals are to work with stakeholders through providing input and direction to support identifying and developing new biomarkers, to provide a process and framework for qualifying biomarkers used in regulatory decision making, and to qualify a biomarker for a specific COU that addresses clearly stated drug development needs.[17,18]

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).[19] The BEST glossary further describes a COA as a DDT that describes or reflects how a patient feels, functions, or survives.[20]

A COA may be used to determine whether a drug has demonstrated a clinical benefit. 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 investigations.[21] A qualified COA may be used in clinical trials within the qualified COU for purposes of supporting new drug development, regulatory review, and labeling.[22]

AMQP applies only to animal models intended for use in the adequate and well-controlled efficacy studies that serve as substantial evidence of effectiveness for drugs developed under the regulations commonly known as the Animal Rule.[23,24,25] Qualifying an animal model does not guarantee that it will be appropriate for all drugs or biologics under development. Other types of

[17] Although biomarkers may be digitally measured, digital biomarkers are not DDTs that are recognized by CDER or CBER as a separate class of biomarker. See the BEST glossary for definitions of classes and types of biomarkers.

[18] For the BQP website, see https://www.fda.gov/drugs/drug-development-tool-qualification-programs/cder-biomarker-qualification-program; also see the List of Qualified Biomarkers page: https://www.fda.gov/drugs/cder-biomarker-qualification-program/list-qualified-biomarkers.

[19] FD&C Act section 507(e)(3).

[20] For more information on the BEST glossary, see: https://www.ncbi.nlm.nih.gov/books/NBK326791/.

[21] See 21 CFR 314.126.

[22] Resources for information on types of COAs and appropriate selection are available on the program's website and in the BEST glossary. For information on patient-reported outcome measures, consult the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

[23] See the AMQP webpage, https://www.fda.gov/drugs/drug-development-tool-qualification-programs/animal-model-qualification-program.

[24] See 21 CFR 314.600-650 for drugs and 21 CFR 601.90-95 for biological products.

[25] FDA has determined that the animal models covered by the program would aid drug development and regulatory review for purposes of section 507 of the FD&C Act (see section 507(e)(5)).

animal models, such as those used for proof-of-concept testing or for safety testing, are not eligible for qualification under the CDER/CBER program.[26]

An animal model is defined as a specific combination of an animal species, challenge agent,[27] 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.[28] For an animal model to be qualified, the animal model requestor should demonstrate that (1) the natural history of the disease or condition in the animal model is comparable to the human disease; (2) the disease process or pathologic condition in a given species of animal corresponds in multiple important aspects to the human disease; and (3) the animal disease or condition shares the same, or very similar, pathogenic or toxic mechanisms as the human disease or condition of interest. Additional information that may be helpful for qualifying animal models (e.g., essential elements of an animal model, principles of study design) is provided in the guidance for industry *Product Development Under the Animal Rule*.[29]

B. 21st Century Cures Act

Building on the qualification program that CDER established in 2004 under FDA's Critical Path Initiative,[30] the Cures Act amended the FD&C Act and added new section 507 to establish a process for qualifying DDTs that can be used, as appropriate, to support regulatory applications, including investigational new drugs (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs), in CDER and CBER. Although the qualification process for DDTs is voluntary, requestors who seek DDT qualification must follow the three-stage process as described in the Cures Act.[31] This process consists of sequential stages of submission: the letter of intent (LOI), the qualification plan (QP), and the full qualification package (FQP). These stages are discussed in section III of this guidance. FDA makes a determination upon concluding the review at each stage and issues the requestor a Determination Letter indicating the status of the submission.

[26] While we have concluded animal studies are required under the Animal Rule, we encourage sponsors to consult with us on nonanimal testing methods they believe may be suitable, adequate, validated, and feasible. We are willing to consider if alternative methods could be assessed for equivalency to an animal test method.

[27] The term *challenge agent* refers to the chemical, biological, radiological, or nuclear substance used to induce the disease or condition in the animal.

[28] See the guidance for industry: *Product Development Under the Animal Rule* (October 2015).

[29] We update guidances periodically. For the most recent version of the guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[30] For more information on FDA's Critical Path Initiative, see https://www.fda.gov/science-research/science-and-research-special-topics/critical-path-initiative.

[31] FD&C Act section 507(a)(1).

The Cures Act includes transparency provisions that apply to information that includes the qualification submissions and FDA's Determination Letters in response to such submissions. The Cures Act codified a statutory process for DDT qualification and added transparency provisions that help promote an understanding of how to develop DDTs for qualification, support a shared learning environment for developing best practices, provide information about the availability of qualified DDTs, and provide opportunities for information sharing and collaborative DDT development. These transparency provisions apply to qualification submissions sent to CDER and CBER under FD&C Act section 507 after December 13, 2016. Consistent with section 507, FDA posts information on the qualification program web pages that includes the following:[32]

- Requestor name
- DDT qualification program (e.g., biomarker, COA, or animal model)
- DDT name or description
- COU
- Start date of the comprehensive review,[33] status (accept or not accept or qualified or not qualified), and stage (LOI, QP, or FQP)
- Information central to the submission, as described in the qualification submission content element outlines[34]
- For LOI or QP, a Determination Letter (accept or not accept)
- For FQP, in addition to the qualification Determination Letter, the FDA summary reviews
- Rescission or modification letter, if applicable

[32] For more information on CDER and CBER's transparency provisions for qualification submissions, see: https://www.fda.gov/drugs/drug-development-tool-qualification-programs/drug-development-tool-qualification-process-transparency-provisions.

[33] This date coincides with the date of issuance of the reviewable memorandum, which the FDA issues after completing the initial assessment that ensures the submission is complete and comprehensible.

[34] For qualification submission content element outlines see https://www.fda.gov/drugs/cder-biomarker-qualification-program/resources-biomarker-requestors (Qualification Stages & Submissions), https://www.fda.gov/drugs/drug-development-tool-qualification-programs/clinical-outcome-assessments-qualification-program-resources-stage (COA Qualification Program Stages and Submissions), https://www.fda.gov/drugs/drug-development-tool-qualification-programs/animal-model-qualification-program.

FDA also intends to publicly post updates to submissions that significantly impact the DDT's development. The FDA posting of information, in compliance with the Cures Act, that is contained in LOI, QP, and FQP submissions does not constitute an endorsement or a representation, guarantee, or warranty about the accuracy, completeness, currency, or suitability of the information contained in materials submitted by external parties.

If FDA receives a Freedom of Information Act (FOIA) request for information that it has not posted on its website as part of the Cures Act transparency provisions described above, the agency would respond in accordance with applicable law. Consistent with FOIA, and as it has done for many years, the agency would not publicly disclose information that constitutes trade secrets or commercial or financial information obtained from a person that is privileged or confidential, nor would the agency publicly disclose information in covered files that constitutes a clearly unwarranted invasion of personal privacy.[35]

C. General DDT Program Concepts

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.[36]

1. How Do Requestors Determine Their Readiness to Initiate the Qualification Process?

Requestors may request a meeting with the relevant DDT qualification program at any time to discuss the qualification pathway for their specific DDT and COU. Early interaction with FDA provides advantages, including identification of drug development need and alignment on an appropriate and clinically relevant COU. Because there are program-specific considerations about these early interactions, FDA encourages requestors to contact the relevant DDT program (see section IV).

2. When Does the Review Time Frame Begin?

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. FDA aims to complete its reviews of complete LOIs, QPs, and FQPs within 3, 6, and 10 months, respectively. At the end of the review a Determination Letter informs the requestor of the accept or not accept determination.

[35] See, e.g., 5 U.S.C. 552(b)(4), (b)(6); 18 U.S.C. 1905.

[36] For the DDT Programs' web sites see BQP: https://www.fda.gov/drugs/drug-development-tool-qualification-programs/cder-biomarker-qualification-program or
COAQP: https://www.fda.gov/drugs/drug-development-tool-qualification-programs/clinical-outcome-assessments-coa-qualification-submissions or
AMQP: https://www.fda.gov/drugs/drug-development-tool-qualification-programs/animal-model-qualification-program.

3. What Does an Accept or Not Accept Determination Mean and How Is It Made?

The DDT Committee, composed of CDER and CBER subject matter experts, senior-level medical officers, scientists, executives, and their designees, makes the determination to accept or not accept a submission into the relevant program based on several factors, including the scientific merit of the submission, the ability of the DDT and the COU to address a specified drug development need, the availability of information and resources that support the proposed qualification effort, and, if appropriate, demonstration that the DDT is feasible and practical in a clinical trial context.[37]

A determination to accept an LOI or a QP submission indicates that the requestor may proceed to the next stage, the QP or FQP, respectively, provided the requestor addresses the recommendations and comments in the Determination Letter.[38] A determination not to accept an LOI or QP submission is not a final determination, as a requestor may address information requests or recommendations from a prior Determination Letter and resubmit an updated LOI or QP submission. You may not proceed from the LOI or QP stage to the next stage unless you receive an accept determination at these stages.[39]

4. What Does It Mean to Withdraw from a DDT Program?

Withdrawal is an action taken at the requestor's discretion, at any point in the process, to remove a project from further consideration by a DDT program. A requestor may request a meeting with the relevant program to discuss intentions and to submit a memorandum giving notice of the intent to withdraw. The project is considered withdrawn upon receipt of the requestor's withdrawal memorandum. Although a project may be withdrawn, information related to that project remains publicly posted. A withdrawn project is reinitiated by submitting a new LOI.

5. What Are Subject Matter Experts and How Are They Used in Submission Review?

Subject matter experts (SMEs) include FDA staff and external SMEs who have demonstrated knowledge relevant to a project's proposed DDT and COU. For purposes of review, non-FDA SMEs may be engaged to review QPs and FQPs through use of cooperative agreements, grants, or other appropriate mechanisms. SMEs participate in reviewing submissions at each stage of the review process to identify the scientific and regulatory considerations important to a specific DDT and COU. This review results in a list of considerations and includes SME and program recommendations to the DDT Committee.

[37] See FD&C Act section 507(a)(2)(B).

[38] See FD&C Act section 507(a)(1).

[39] See FD&C Act section 507(a)(1).

252 *6. How Can Biomedical Research Consortia and Partnerships Contribute to DDT*
253 *Qualification?*
254
255 The cost, complexity, and multidisciplinary nature of many DDT qualification projects may
256 create challenges for individual stakeholders engaging in the qualification process. CDER and
257 CBER encourage the adoption of best practices for DDT development, which may include a
258 collaborative setting to enhance data sharing, cooperative data generation, and application of
259 joint expert knowledge and resources. Collaboration and knowledge-sharing can accelerate and
260 aid achievement of critical milestones toward qualification. Contact information for ongoing
261 DDT qualification projects is publicly available on the DDT programs' web pages. DDT
262 programs may refer requestors to specific consortia when the program believes that a
263 qualification effort would benefit from a consultation or collaboration.
264
265 **D. A Taxonomy for DDTs: the BEST Glossary**
266
267 The BEST glossary is a taxonomy for classifying and developing biomarkers and other DDT-
268 related scientific concepts. The BEST glossary is periodically updated through an ongoing
269 public process and clarifies important definitions, captures the distinction among different types
270 of DDTs, and describes some of the hierarchical relationships, connections, and dependencies
271 among DDT terms.[40] Unless otherwise noted, the discussion of biomarker classes or categories
272 and types of DDTs in this guidance follows the BEST glossary definitions. For examples of how
273 the BEST terminology is used in submissions or in qualified DDTs and COUs, see the DDT
274 programs' web pages.
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276
277 **III. QUALIFICATION PROCESS**
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279 **A. Three Sequential Stages and Review**
280
281 Each DDT qualification project advances through three sequential stages (LOI, QP, and FQP)
282 with LOI and QP progressing to the next stage (QP and FQP, respectively) upon receipt of an
283 *accept* Determination Letter for the previous stage. At the LOI and QP stages a *not accept*
284 determination does not allow progression to the next stage (QP or FQP) until issues have been
285 addressed, which ensures the requestor is well prepared to proceed to the next stage.[41] The
286 qualification process ends with FDA issuing an FQP Determination Letter for a submission with
287 a qualified or not qualified determination.
288

[40] Section 3011(b)(3)(A) of the 21st Century Cures Act, "For purposes of informing guidance under this subsection, the Secretary shall, in consultation with biomedical research consortia and other interested parties through a collaborative public process, establish a taxonomy for the classification of biomarkers (and related scientific concepts) for use in drug development."

[41] See FD&C Act section 507(a)(1).

1. FDA Review Process

Upon receiving a submission, FDA initiates a three-step review. First, FDA performs an initial assessment (Step 1) to ensure the submission is complete, thereby allowing a full review of the submission.[42] 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. The initial assessment adds efficiency to the process by informing requestors early of potential deficiencies and providing them with an opportunity to make revisions and resubmit in a timely manner. The advantage of giving feedback early is to work with the requestor to develop a high-quality submission, thereby improving the likelihood of acceptance and enabling more focused recommendations toward DDT development. If considered to be clear and complete, a submission undergoes a comprehensive review (Step 2). The comprehensive review ends with the reviewers compiling a list of considerations, which may include data requests, and making a recommendation to the DDT Committee. The DDT Committee (Step 3) evaluates the considerations and recommendation and makes the accept or not accept (LOI, QP) or qualified or not qualified (FQP) determination as is relevant to the submission.

For more information, requestors may consult the DDT programs' respective web pages and communicate with the appropriate program to ensure that their submissions contain the appropriate content elements, are complete, and adequately address the scientific considerations associated with the DDT and COU. Timelines between the end of one stage and the beginning of the next in any given project are largely under the requestor's control and will vary.

2. Letter of Intent (Stage 1)

Submitting an LOI initiates the qualification process.[43] The LOI is a concise document that describes the DDT, a relevant drug development need, and a proposed COU. The LOI should provide a scientific rationale to support the DDT and its COU. If additional information is needed to address any of these components, FDA may return the LOI submission to the requestor for revision and resubmission. If the LOI submission is complete, FDA will issue a reviewable memorandum to the requestor, thereby initiating the comprehensive review and the time frame for the LOI review.

FDA aims to complete the LOI review within 3 months of issuing the reviewable memorandum. The LOI review concludes when FDA issues the requestor an LOI Determination Letter. Acceptance of any submission is based on factors that include scientific merit. An LOI

[42] The initial assessment includes an assessment of the DDT description and measurement method, the description of the drug development need, the COU, relevance and strength of supporting data, and project priority in terms of the public health need. A submission that is deemed reviewable includes the content elements outlined by the specific program for the particular stage (i.e., LOI, QP, or FQP) and, where relevant, may include clearly identified responses to the DDT program's prior recommendations or data requests. Characteristics of a reviewable submission include that it is clearly and concisely written, is well-organized, is adequately supported throughout by in-text citations to scientific literature, and contains the appropriate supportive information. Discussion of extraneous qualities of a DDT, its measurement, inclusion of additional COUs or other content that is outside the specific qualification effort, even when positive, will detract from the quality of a qualification submission.

[43] FD&C Act section 507(a)(1)(A)(i).

Determination Letter indicates whether the project is accepted into the relevant DDT qualification program and includes recommendations, considerations, and requests for information to advise the requestor about next steps. A project is considered formally accepted into the relevant DDT program upon FDA's issuing an accept Determination Letter at the LOI stage.

3. Qualification Plan (Stage 2)

The QP is the second stage of the DDT qualification process. The QP submission describes available relevant data, knowledge gaps, data collection, and the analysis plan. It addresses prior recommendations expressed in the LOI Determination Letter as well as any subsequent advice provided by reviewers. Study protocols and analytic plans should be included as needed and appropriate, with an estimated time frame for completing data collection, data analysis, and reporting. 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.

FDA aims to complete the QP review within 6 months of issuing the reviewable memorandum. The QP review concludes when FDA issues the requestor a QP Determination Letter. The Determination Letter will include requests for data and recommendations regarding data needs for the FQP. Upon an accept determination for the QP, and taking into consideration the listed recommendations provided in the FDA QP Determination Letter, requestors can construct *a specific actionable plan* that includes the types of supporting data, studies, and FQP content that they need to execute to prepare for the FQP submission. If a QP is not accepted, the project has not successfully completed the second stage of the qualification process, so a requestor may revise and resubmit, withdraw, or redirect the project focus with a new DDT and LOI.

4. Full Qualification Package (Stage 3)

The FQP is the third, all-inclusive, and final stage of submission in the qualification process, ending with a qualification determination. 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. Evidence supporting qualification should include full study protocols and reports, statistical or quantitative analysis plans, summary data, statistical program files for the main analyses, and subject-level data unless summary-level data are deemed sufficient. As in the prior stages, upon submission there is an initial assessment, during which FDA assesses the FQP for completeness, which includes verifying that the requestor clearly addressed all prior recommendations and comments. If the assessment determines there are missing elements, FDA intends to issue the requestor a not-reviewable memorandum describing the information that is needed. If the submission is considered complete, then FDA will send the requestor a reviewable memorandum. Once the submission is deemed reviewable, FDA conducts a comprehensive review of the FQP, which concludes with determining whether to qualify the proposed DDT for its proposed COU or, based upon the data submitted, to qualify a DDT for a modified COU.

FDA aims to complete the FQP review within 10 months of issuing the reviewable memorandum. The FQP review concludes when FDA issues the requestor a qualification Determination Letter.

As described in section 507 of the FD&C Act, 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.[44] Additionally, FDA may prioritize FQP review based on other factors determined appropriate,[45] and FDA intends to consider the potential impact the DDT will make on drug development.

B. Post-Qualification Modification and Rescission

A requestor who obtained qualification for a DDT and COU, as the project owner or point of contact, may modify the qualified DDT by submitting a QP (not an LOI). Modification applies only to the qualified DDT without changes to the COU. Examples include simplifying an animal model, changing a panel or multicomponent biomarker, and submitting longitudinal data for a COA. Early communications, before submission of a QP, help guide the requestor's modification effort.

A person, or organization, who is not the original requestor may propose modification to a qualified DDT or its COU by submitting a new LOI. The new LOI should provide the rationale for the change and supporting data for the proposed modification. The original qualification effort may remain qualified with the modification represented as an additional qualification, or it may be determined that the original qualified DDT and COU may be subsumed into one modified DDT and COU. Such a determination will be indicated in the Determination Letter. Alternatively, the original requestor may transfer his or her ownership or interest in a project to another individual for modification of a qualified DDT or the use of intellectual property in a prior DDT program submission for a new qualification effort with a formal letter from the original requestor naming the new project owner and including a description of the project being transferred. The written notification is similar to the process used for drug applications.[46]

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.[47] When a DDT program initiates a rescission or modification, the DDT program intends to provide a written summary of the basis for making such a modification or rescission, and the requestor involved may request a meeting to discuss the basis for the rescission or modification before its

[44] FD&C Act section 507(a)(2)(C).

[45] Id.

[46] See 21 CFR 314.72.

[47] FD&C Act section 507(b)(3).

effective date. The DDT Committee intends to make determinations, based on the new information, about the status of a qualified DDT. Information on modified and rescinded DDTs and COUs and the respective Determination Letters will be maintained on the DDT programs' web pages.

IV. HOW TO COMMUNICATE AND SUBMIT A DOCUMENT

Throughout the qualification process, there are opportunities for interactions between the DDT requestor and CDER and/or CBER. The purpose of these communications may be to identify challenges and opportunities, guide the collection of data, request input on a proposed COU, identify the level of detail appropriate for a given stage of submission, or obtain clarification on considerations and recommendations. Requestors should contact the appropriate qualification program for additional information on meeting type and scheduling and submission of pre-meeting materials, if applicable. See Appendix A for contact information for each DDT program.

A requestor may submit a request for a teleconference or other meeting type at any time. Once an FDA project lead has been identified for the project, all communications and exchanges of information related to the project should be directed to that project lead to facilitate the review process.

A. What Are the Processes for Submitting to a DDT Program?

1. Electronic Portal Account Creation and Submissions:

The NextGen Portal is the website where a requestor for a DDT project may create an account for submissions to and communications with a DDT qualification program.[48] The portal is an integrated electronic gateway for the official submission of information to FDA, for project tracking and through which the account holder may request and receive FDA communications. Consortia or other groups should be aware that within the NextGen Portal, ownership of an account is not generally transferrable to another individual from within the portal. As a result, projects having group sponsorship may need to consider making their own arrangement for account access or transfer as appropriate. A requestor who needs to use an alternative approach for submissions or communications may contact the relevant program at the email address listed in Appendix A.

[48] The FDA NextGen Portal can be accessed at https://edm.fda.gov. There is additional information for requestors at this URL describing processes such as account creation, account access, and how to communicate with the program via the portal.

B. Submissions and Data Standards

Requestors may submit primary data from studies as appropriate. The DDT programs strongly encourage requestors to use data standards, starting as early as possible in the conduct of studies in support of drug development, so that they are incorporated into the design, conduct, and analysis of studies. Requestors are strongly encouraged to use relevant data standards (e.g., Clinical Data Interchange Standards Consortium (CDISC) standards[49]) when submitting these data for review.[50] Study data standards for submissions to FDA can be found at FDA's Study Data Standards web page.[51]

[49] For more information on CDISC standards, see: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

[50] For submission and review purposes, please refer to the *Study Data Specifications* document https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

[51] For more information on CDER and CBER study data submission, see https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber.

GLOSSARY

A. Definitions

Accept or not accept: The terms are used at two points in the submission-review process for both the LOI and QP stages and describe: (1) the recommendation made by the SMEs in coordination with the relevant qualification program, based upon factors that include scientific merit, in conjunction with listing any considerations relevant to the qualification effort and (2) the determination made by the DDT Committee in response to such recommendation as it relates to a qualification submission.

Animal model: 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.

Biomarker: A characteristic (e.g., a physiologic, pathologic, or anatomic characteristic or measurement) that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention, and includes a surrogate endpoint (FD&C Act section 507(e)(1)).

Biomedical research consortia: Collaborative groups that may take the form of public-private partnerships and may include government agencies, institutions of higher education (as defined in section 101(a) of the Higher Education Act of 1965), patient advocacy groups, industry representatives, clinical and scientific experts, and other relevant entities and individuals (FD&C Act, section 507(e)(2)).

Clinical outcome assessment (COA): A measurement of a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions. These measurements include ClinRO, ObsRO, PerfO as well as PRO (FD&C Act, section 507(e)(3)).

Comprehensive review: The detailed review of a submission, the start of which is the issuance of the reviewable memorandum that begins the review time frame. The product of the comprehensive review is a thorough evaluation of the submission, a set of considerations and requests for data, and a recommendation to the DDT Committee (LOI and QP: accept or not accept; FQP: qualify or not qualify).

Content elements: The content elements relevant to a program's DDT type, specific stage (LOI, QP, or FQP), and other supporting information are available upon request to the program or on the specific DDT program's web page.

Context of use (COU): The circumstances under which the DDT is to be used in drug development and regulatory review (FD&C Act, section 507(e)(4)). See the specific program's web page for more information on the content and structure of a COU.

Determination: A decision made at the conclusion of the review of a submission about whether to accept an LOI or a QP or to qualify or not qualify a DDT for a COU.

Drug development tool (DDT): A biomarker, COA, or any other method, material, or measure determined to aid drug development and regulatory review (FD&C Act, section 507(e)(5)). Animal models developed to be used for product development under the Animal Rule have been determined by CDER and CBER to be DDTs under section 507 of the FD&C Act.

Drug Development Tool Committee: The DDT Committee is composed of CDER and CBER subject matter experts, senior-level medical officers, scientists, executives, and their designees. The DDT Committee evaluates the SME and program considerations and recommendation and decides to accept or not accept (LOI and QP stages) or to qualify or not to qualify (FQP stage) a DDT qualification submission.

Full qualification package (FQP): The final stage in the series of three sequential qualification submissions. The FQP describes in detail all studies, analyses, and results related to the DDT and its COU. Evidence in support of qualification should include full study protocols and reports, summary data, statistical program files for the main analyses, and subject-level data unless CDER and/or CBER deem summary-level data to be sufficient. If FDA determines that additional information is needed, the FQP submission may be returned to the requestor. Content elements are FQP-specific and are available upon request to the program or available on a specific DDT program's (BQP, COAQP, or AMQP) web page.

Initial assessment: An administrative evaluation of a submission's completeness, scientific content, and overall quality that determines whether the submission is reviewable and eligible for a Comprehensive Review. A submission that is deemed reviewable includes the content elements outlined by the specific program for the particular stage (i.e., LOI, QP, or FQP) and, when relevant, may include clearly identified responses to the DDT program's prior recommendations or data requests. Characteristics of a reviewable submission include that it is clearly and concisely written, is well-organized, is adequately supported throughout by in-text citations to scientific literature, and contains the appropriate supportive information. Discussion of extraneous qualities of a DDT, its measurement, inclusion of additional COUs, or other content that is outside the specific qualification effort, even when positive, will detract from the quality of a qualification submission.

Letter of Intent (LOI): The first stage in the series of three sequential qualification submissions. Submission of the LOI initiates the qualification process for a DDT and its proposed COU. Content elements are LOI-specific and are available upon request to the program or posted on a specific DDT program's web page. An accept determination at this stage accepts a project into the relevant DDT program.

Patient-reported outcome (PRO): A measurement based on a report from a patient regarding the state of the patient's health condition without amendment or interpretation of the patient's report by a clinician or any other person (FD&C Act, section 507(e)(6)).

Qualification (and qualified): A CDER or CBER determination that a DDT and its proposed COU can be relied upon to have a specific interpretation and application in drug development and regulatory review (FD&C Act, section 507(e)(7)).

Qualification Plan (QP): The second stage in the series of three sequential qualification submissions. It describes available data, knowledge gaps, and the data-collection plan and summarizes available evidence to support qualification. Content elements are QP-specific and are available upon request to the program or posted on a specific program's web page. Acceptance at the QP stage, including taking into consideration the listed recommendations provided in the FDA QP Determination Letter, gives requestors the information needed to construct *a specific actionable plan* that includes the types of supporting data, studies, and FQP content that they need to execute to prepare for the FQP submission.

Requestor: An entity or entities, including a drug sponsor or a biomedical research consortium, seeking to qualify a DDT for a proposed context of use (FD&C Act, section 507(e)(8)).

Review Time frames: The time taken to review a submission once FDA has deemed it reviewable and a memorandum notifying the requestor of receipt of a reviewable submission has been sent to the requestor. For LOI, QP, and FQP submissions, the time frames are targeted to be completed within 3, 6, and 10 months, respectively, from the date on the reviewable memorandum.

Reviewable: A term used to denote that a submission is ready for FDA to begin the Comprehensive Review. A submission FDA deems reviewable includes the content elements outlined by the specific program for the particular stage (i.e., LOI, QP, or FQP) and, where relevant, may include clearly identified responses to the DDT program's prior recommendations or data requests. Characteristics of a reviewable submission include that it is clearly and concisely written, is well-organized, is adequately supported throughout by in-text citations to scientific literature, and contains the appropriate supportive information. Discussion of extraneous qualities of a DDT, its measurement, inclusion of additional COUs or other content that is outside the specific qualification effort, even when positive, will detract from the quality of a qualification submission.

Reviewable memorandum: A memorandum issued to the requestor indicating that the submission is reviewable and the date the memorandum is issued is the Reviewable Date (i.e., the date that the Comprehensive Review and time frame begins).

Status: Refers to the accept or not accept determination by the DDT Committee for an LOI or a QP submission.

Subject matter expert (SME): A member of FDA staff or an external expert who has demonstrated knowledge in clinical, scientific, pharmacologic, statistical, engineering, and/or other technical disciplines relevant to a project's proposed DDT and COU. SMEs are used in the review of submissions to identify the scientific and regulatory considerations important to a specific DDT and COU.

Surrogate endpoint (SE): A marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is not itself a direct measurement of clinical benefit but is known to predict clinical benefit and could be used to support traditional approval of a drug or

biological product or is reasonably likely to predict clinical benefit and could be used to support the accelerated approval (FD&C Act, section 507(e)(9)).

Time frame(s): See Review Time frame above.

Withdrawal: An action taken at the requestor's discretion during the qualification process and before qualification to remove the DDT from further consideration by a DDT program.

B. Acronyms and Abbreviations

AMQP	Animal Model Qualification Program
ANDA	Abbreviated New Drug Application
BEST	Biomarkers, EndpointS and other Tools (glossary)
BLA	Biologics License Application
BQP	Biomarker Qualification Program
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
COA	Clinical Outcome Assessment
COAQP	COA Qualification Program
COU	Context of Use
ClinRO	Clinician-Reported Outcome
DDT	Drug Development Tool
FDA	U.S. Food and Drug Administration
FDARA	FDA Reauthorization Act of 2017
FD&C Act	Federal Food, Drug, and Cosmetic Act
FQP	Full Qualification Package
IND	Investigational New Drug Application
LOI	Letter Of Intent
MDDT	Medical device development tool
NDA	New Drug Application
ObsRO	Observer-Reported Outcome
PDUFA VI	Prescription Drug User Fee Act VI
PerfO	Performance Outcome
PRO	Patient-Reported Outcome
QP	Qualification Plan
SME	Subject Matter Expert
U.S.C.	United States Code

APPENDIX A

HOW CAN A REQUESTOR COMMUNICATE WITH A DDT PROGRAM?

Contact information for each DDT program is provided here:

CDER Biomarker Qualification Program
Email: CDER-BiomarkerQualificationProgram@fda.hhs.gov

CDER Clinical Outcome Assessments Qualification Program
Email: COADDTQualification@fda.hhs.gov

CDER and CBER Animal Models Qualification Program
Email: AnimalModelQualification@fda.hhs.gov

CBER DDT Qualification Programs (includes Biologics Biomarkers and Clinical Outcome Assessments)
Email: CBER-DDTQualificationProgram@fda.hhs.gov