Qualification Process for Drug Development Tools

Guidance for Industry and FDA Staff

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)

November 2020
Drug Development Tools

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Contains Nonbinding Recommendations

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

This guidance represents 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 office 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 guidance meets the Cures Act's mandate to issue final guidance on the section 507 qualification process. Specifically, this guidance represents the Center for Drug Evaluation and Research's (CDER's) and the Center for Biologics Evaluation and Research's (CBER's)[4] current thinking on implementation of section 507 of the FD&C Act with respect to describing the process for requestors[5] interested in qualifying DDTs and on taxonomy for biomarkers and other DDTs.

This guidance does not address evidentiary standards or performance criteria for purposes of DDT qualification, nor does it address qualifying medical device development tools (MDDTs) through the Center for Devices and Radiological Health (CDRH). These topics will be discussed

[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] Public Law 114-255.

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

[4] The recommendations in this guidance apply to CDER and CBER and do not include other FDA centers.

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

in other guidances and materials available on FDA's DDT programs'[6] and MDDT program's web pages, respectively.[7]

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

A. Cures Act

Building on the qualification program that CDER proposed in Critical Path reports issued in 2004 and 2006, the Cures Act amended the FD&C Act and added new section 507 to establish a statutory process for qualifying DDTs. DDTs can be used, as appropriate, to support regulatory applications, including investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs).

B. A Taxonomy for DDTs: the BEST Glossary

The Biomarkers, EndpointS, and other Tools (BEST) glossary[8] is a taxonomy for classifying and developing biomarkers and other DDT-related scientific concepts. The BEST glossary is periodically updated[9] and clarifies important definitions, captures the distinction among different types of biomarkers and DDTs, and describes some of the hierarchical relationships, connections, and dependencies among DDT terms. Unless otherwise noted, the discussion of biomarker classes or categories and types of DDTs in this guidance follows the BEST glossary

[6] See https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-ddt-qualification-programs.

[7] MDDT qualification is not a section 507 program and is administered by CDRH. For more information on MDDTs, see https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt.

[8] Section 3011(b)(3)(A) of the Cures Act states "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." FDA has identified the BEST glossary as this taxonomy.

[9] See https://www.ncbi.nlm.nih.gov/books/NBK326791/.

definitions. For examples of how the BEST[10] terminology is used in submissions or in qualified DDTs and context of use (COU) statements, see the DDT programs' web pages.[11]

C. Qualification of DDTs and COUs

DDTs are methods, materials, or measures that can aid drug development and regulatory review. Under the new section 507 of the FD&C Act, *qualification* and *qualified* mean FDA's 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.[12] A qualified DDT used within the COU may be applied to support or obtain approval or licensure (as applicable) of any drug, provided that the qualification has not been rescinded or modified.[13] For more information on how DDTs can benefit drug development, see the FDA DDT programs' web pages.[14]

The COU statement identifies the specific use of the DDT in drug development. FDA expects the content in DDT submissions to provide supporting evidence demonstrating the reliability and accuracy of the proposed DDT and its COU. For more information on the construction of a COU and details on the supporting evidence needed in submissions to demonstrate that a DDT merits qualification, see the program-specific web pages.[15] 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.

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, when scientifically appropriate for a specific application, based on agreement with the appropriate review division or office. Upon agreement with the review division, such use of a DDT within a regulatory application, however, is not considered qualified under section 507.

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

[11] For examples of biomarkers and related COU statements, see Biomarker Qualification Submissions at https://www.fda.gov/drugs/cder-biomarker-qualification-program/biomarker-qualification-submissions and List of Qualified Biomarkers at https://www.fda.gov/drugs/cder-biomarker-qualification-program/list-qualified-biomarkers. For examples of Clinical Outcome Assessment (COA) projects and related COU statements, see COA Submissions at https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/clinical-outcome-assessments-coa-qualification-submissions and Qualified COAs at https://www.fda.gov/drugs/development-approval-process-drugs/qualified-clinical-outcome-assessments-coa.

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

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

[14] See https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-ddt-qualification-programs.

[15] See the Biomarker Qualification Program (BQP) web page at https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/cder-biomarker-qualification-program; the COA Qualification Program's web page at https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/clinical-outcome-assessment-coa-qualification-program; and the Animal Model Qualification Program's web page at https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/animal-model-qualification-amqp-program.

Encouraging the identification and use of reliable DDTs can significantly facilitate the development of new, safe, and effective drugs. Qualified DDTs allow integration of innovative technology and new science and approaches to 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 shorten the duration of the study.

D. DDT Qualification Programs

There are three DDT qualification programs at FDA: biomarker, COA, and animal model. Other DDT qualification programs may be established based on scientific need and availability of resources. Section 507(e)(5) of the FD&C Act defines DDTs as including biomarkers and COAs and any other method, material, or measure that FDA determines aids drug development and regulatory review. 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.

The BQP applies to biomarkers,[16] which are defined in section 507(e)(1) 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.[17] Molecular, histologic, radiographic (imaging), and 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 BEST glossary biomarker definition.[18] FDA's BQP provides input and direction to stakeholders to aid in identifying a relevant public health need, ensuring a biomarker category is consistent with the proposed use, supporting the correct construction of the COU, and identifying the types of data or studies needed to support qualification.

The COA Qualification Program (COAQP) applies to a COA, which includes but is not limited to patient-reported outcome (PRO), observer-reported outcome (ObsRO), clinician-reported outcome (ClinRO), and performance outcome (PerfO) measures.[19] Section 507(e)(3) of the FD&C Act describes a COA as a measurement of a patient's symptoms, a patient's overall

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

[17] Qualifying a biomarker does not result in the qualification or endorsement of an exclusive technology or measurement method. If an alternative measurement method is used in drug development, equivalence may be demonstrated to the relevant review division or office 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.

[18] For the BEST glossary definition of a biomarker, see https://www.ncbi.nlm.nih.gov/books/NBK338448/.

[19] For the BEST glossary definition of a COA, see https://www.ncbi.nlm.nih.gov/books/NBK326791/.

mental state, or the effects of a disease or condition on how the patient functions. A COA may be used to determine whether a drug has demonstrated a clinical benefit. Generally, FDA will qualify 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.[20,21]

The AMQP applies only to animal models intended for use in the adequate and well-controlled animal efficacy studies that serve as substantial evidence of effectiveness for drugs developed under the regulations commonly referred to as the *Animal Rule*.[22,23] Other types of animal models, such as those used in general drug development for proof-of-concept testing or for safety testing, are not eligible for qualification through the AMQP. Section III. D of the guidance for industry *Product Development Under the Animal Rule* (October 2015) discusses the AMQP, provides helpful information on animal model development, and describes the qualification of an animal model as follows:

> Qualification of an animal model through the AMQP indicates that (1) FDA has concluded that a specific animal species, given a specific challenge agent by a specific route, produces a disease process or condition that in multiple important aspects corresponds to the human disease or condition of interest, and (2) FDA has accepted the description of the model's appropriate use in regulatory applications, including the definition of the parameters of the disease or condition that will be used as measures of quality control and quality assurance when the model is used. [24]

E. Cures Act: Promoting DDT Development, Collaboration, and Use

The Cures Act contains transparency provisions that includes information in 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

[20] See 21 CFR 314.126.

[21] Resources for information on types of COAs and appropriate COA selection are available on the program's web pages at https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/clinical-outcome-assessment-coa-qualification-program and in the BEST glossary. For information and methodologic guidance on patient-reported outcome measures and other clinical outcome assessments, see https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

[22] For additional information, see the AMQP web page at https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/animal-model-qualification-amqp-program.

[23] FDA supports the principles of the 3Rs, to reduce, refine, and replace animal testing when feasible; however, adequate and well-controlled efficacy studies conducted in animal models of the human disease or condition of interest are required for approval under the Animal Rule.

[24] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

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 FDA under section 507 of the FD&C Act after December 13, 2016. Consistent with section 507, FDA posts information on the qualification programs' web pages that includes the following:[25]

- Requestor name
- DDT qualification program (biomarker, COA, or animal model)
- DDT name or description
- COU
- Start date of the comprehensive review,[26] status (e.g., accept or not accept or qualified or not qualified), and stage (letter of intent (LOI), qualification plan (QP), or full qualification package (FQP))
- Information central to the submission, as described in the qualification submission content element outlines (for more information, see III. A. 1., Submission Content)
- For LOI or QP, the Determination Letter (accept or not accept)
- For FQP, the qualification Determination Letter and the FDA reviews
- Rescission Letter or Modification Letter, if applicable

FDA also intends to publicly post updates to submissions that significantly impact a DDT's development, which may include refinements to a DDT or COU (e.g., for a COA there may be interim submissions between the LOI and QP to ensure that the development of the COA is progressing). FDA's posting of information, in compliance with the Cures Act, that is contained in LOI, QP, and FQP submissions does not constitute an endorsement, representation, or guarantee 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 request for information that it has not posted on its web pages as part of the Cures Act transparency provisions described above, the Agency will

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

[26] For more information, see sections II. F. 2, When Does the Review Time Frame Begin? and III. A. 2, FDA Review Process.

respond in accordance with applicable law. Consistent with the Freedom of Information Act and other applicable law, the Agency will not publicly disclose information that constitutes trade secret or privileged, confidential commercial or financial information obtained from a person or an organization, nor will the Agency publicly disclose information in covered files that constitutes a clearly unwarranted invasion of personal privacy.[27]

F. General DDT Program Frequently Asked Questions

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.

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

Requestors may ask for 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 before formal submission provides advantages, including identification of a drug development need, alignment on an appropriate drug development COU, and identification of a pathway for the development of the supporting evidence for qualification. FDA recommends prospective requestors provide a draft LOI or other supporting materials to focus the requested discussion with the relevant DDT program (see section IV, Communications and Submission Process).

2. When Does the Review Time Frame Begin?

Once an LOI, a QP, or an FQP submission is deemed complete and understandable in 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 comprehensive reviews of complete LOIs, QPs, and FQPs within 3, 6, and 10 months, respectively. During the comprehensive review, FDA may ask for additional information from the requestor. The end of the review time frame is marked by issuance of a Determination Letter, which informs the requestor of the LOI or QP accept or not accept determination and, for an FQP, the qualified or not qualified DDT Committee determination.

3. What Are SMEs and How Are They Used in Submission Review?

Subject Matter Experts (SMEs) include FDA staff and can include external SMEs who have demonstrated knowledge relevant to a proposed DDT project and its COU. SMEs review submissions at each stage to identify the scientific and regulatory considerations important to a specific DDT and COU and send these scientific considerations with a recommendation to the DDT Committee.

[27] See, for example, 5 U.S.C. 552(b)(4), (b)(6); 18 U.S.C. 1905.

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

The DDT Committee, composed of CDER and CBER SMEs, scientists, and senior level medical officers 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 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.[28]

A determination to accept an LOI or 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.[29] 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. Requestors may not proceed from the LOI or QP stage to the next stage unless they receive an *accept* determination at these stages.[30]

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

Withdrawal is generally 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. Requestors may ask for a meeting with the relevant program to discuss their intention to withdraw. A project is considered withdrawn upon a program's receipt of the requestor's withdrawal memorandum, when there is a lack of progress or the requestor has been unresponsive to FDA's request for an update for a prolonged period of time. Although a project may be withdrawn, information related to that project remains publicly posted. A project that is withdrawn may be reinitiated by submitting a new LOI.

6. How Can Biomedical Research Consortia and Partnerships Contribute to DDT Qualification?

The cost, complexity, and multidisciplinary nature of many DDT qualification projects may create challenges for individual stakeholders engaging in the qualification process. FDA encourages the adoption of best practices for DDT development, which may include a collaborative setting to enhance data sharing, cooperative data generation, and application of joint expert knowledge and resources to accelerate qualification. DDT programs may refer requestors to specific consortia when the program considers that a qualification effort would benefit from a consultation or collaboration.

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

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

[30] Ibid.

III. QUALIFICATION PROCESS

A. Three Sequential Stages of Submission and Review Steps

Each DDT qualification project advances through three sequential stages of submission (LOI, QP, and then FQP) with LOI and QP progressing to the next stage (QP and FQP, respectively) upon receipt of an *accept* Determination Letter for the previous stage. At the LOI and QP stages a *not accept* determination does not allow progression to the next stage (QP or FQP, respectively) until issues have been addressed, ensuring that the requestor is well prepared to proceed to the next stage.[31] The qualification process for a project ends with FDA issuing an FQP Determination Letter for a submission with a qualified or not qualified determination. The qualification process stages and review process are described in greater detail below.

1. Submission Content

At each stage of submission, requestors should provide sufficient information to demonstrate the submission merits acceptance by FDA. The type and amount of supporting information that should be included will depend on the stage of submission. For more detailed information about the content included in each stage of submission, see the content element outlines on the DDT programs' web pages.[32]

2. FDA Review Process

For each of the three sequential stages of the qualification process (i.e., LOI, QP, and then FQP), FDA initiates a three-step review process upon receipt of each submission. First, FDA performs an initial assessment (Step 1) to ensure the submission is complete and understandable (e.g., containing all relevant content elements).[33] If the initial assessment indicates the submission is

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

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

[33] In sufficient detail specific to the stage of submission and relevant content element outline, the initial assessment evaluates the submission for clarity, consistency, and adequacy of the DDT description and its measurement approach, 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 deemed reviewable includes the content elements outlined (see footnote 32) by the specific program for the particular stage (i.e., LOI, QP, or FQP) and, where relevant, includes 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 the scientific literature, and contains the appropriate supportive information. Discussion of extraneous qualities of a DDT or extraneous measurements, 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.

not reviewable, FDA will inform the requestor of deficiencies and recommend that it is revised and resubmitted to facilitate the review process and increase the likelihood of acceptance. The advantage of getting feedback early is to allow FDA to work with the requestor in the development of a high-quality submission. Given the variation in submission content, quality, and complexity, it is not feasible to provide a review timeline for the initial assessment.

If the submission is complete, FDA issues a memorandum indicating the submission is reviewable, and it undergoes a comprehensive review (Step 2). The comprehensive review results in a list of considerations, which may include information requests, and makes a determination recommendation to the DDT Committee.

The DDT Committee (Step 3) evaluates the SME's project considerations and recommendation and makes a determination, and then the requestor is issued a Determination Letter containing the submission's status (e.g., for LOI or QP an accept or not accept status, and for the FQP a qualified or not qualified status) with considerations to help the requestor address deficiencies in its next 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.

3. Letter of Intent (Stage 1)

Submitting an LOI initiates the qualification process.[34] 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.

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. An LOI 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 achieving next steps.

4. Qualification Plan (Stage 2)

The QP submission describes available relevant data, knowledge gaps, proposed data collection plans, and analysis plans. It addresses prior recommendations expressed in the LOI Determination Letter as well as any subsequent advice provided by reviewers. Full 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.

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 QP

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

Determination Letter will include requests for data and recommendations about data needs for the FQP. Upon receipt of an accept determination for the QP, and taking into consideration the listed recommendations provided in the 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. In this case, a requestor may revise and resubmit, withdraw, or redirect the project focus with a new DDT and LOI.

5. Full Qualification Package (Stage 3)

The FQP is the comprehensive, third, 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 have been deemed sufficient. FDA conducts a comprehensive review of the FQP, which concludes with determining whether the evidentiary standards appropriate for that DDT have been met to qualify the DDT for its proposed COU or, based upon the data submitted, to qualify a DDT for a modified COU. When a not-qualified determination is made, a requestor may take into account the input from the Agency and subsequently resubmit the FQP with modifications or submit a new LOI.

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 indicating qualified or not qualified status. 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 biomedical research consortia or other expert stakeholders, of a DDT and its proposed COU as a public health priority.[35] Additionally, FDA may prioritize FQP review based on other factors,[36] including the potential impact of the DDT on drug development. Based upon these factors, an FQP that is determined to be a high or low priority may shorten or lengthen, respectively, the time frame needed for FDA's completion of an initial or comprehensive review.

B. Post-Qualification Rescission and Modification

The original requestor who obtained qualification for a DDT and COU as the project owner or primary point of contact may modify the qualified DDT by submitting a QP (not an LOI) except where prohibited by law. Modification applies only to the qualified DDT, without changes to the

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

[36] Ibid.

COU.[37] Examples include changing a panel or multicomponent biomarker and submitting longitudinal data for a COA. Early communications, before submission of a QP, may 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 for the use of intellectual property applied in a prior DDT program submission for a new qualification effort with a formal letter transferring rights or ownership to the new requestor. The written notification is similar to the process used for drug applications.[38]

FDA 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.[39] 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 rescission or modification, and the requestor or requestors affected may request a meeting to discuss the basis for the rescission or modification before its effective date. The DDT Committee intends to make determinations about whether to modify or rescind a qualified DDT based on the new information. FDA intends to maintain information on modified and rescinded DDTs and COUs and the respective Determination Letters on the DDT programs' web pages. Should a rescission or modification affect a study that is part of an IND, NDA, ANDA, or BLA, the sponsor or applicant would be notified and should request a discussion with the appropriate office or review division and the DDT program to determine what actions, if any, are needed.

IV. COMMUNICATIONS AND SUBMISSION PROCESS

A. Communications

Before and throughout the qualification process, there are opportunities for interactions between the DDT requestor and FDA. The purpose of these communications may be to identify challenges and opportunities, guide the collection of data, request input on a proposed DDT or 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 types and scheduling and

[37] Changes to a qualified COU are accomplished through submission of a new LOI.

[38] See 21 CFR 314.72.

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

submission of premeeting materials, if applicable. See the Appendix for contact information for each DDT program.

A requestor may submit a request for a teleconference or other meeting type at any time. Upon FDA notifying the requestor of receipt of a reviewable submission, an FDA project lead is identified, and all communications and exchanges of information related to the project should be directed to the project lead during the review process.

B. Submission Process

1. Electronic Portal Account Creation and Submissions

The NextGen Portal is an integrated electronic gateway for the official submission of information to FDA, project tracking, and communications to and from FDA. Requestors should create an account on the web page to initiate a DDT project.[40] Submissions are received and recorded via the requestor's account in the NextGen Portal. Consortia or other groups should be aware that within the NextGen Portal, access to an account is not generally transferrable to another individual from within the portal. Changes to account access can be made by submitting a request to the relevant DDT qualification program, which will work with the portal team to transfer access to the new account holder. Account access through the portal is limited to the individual making the initial project submission. Therefore, when projects having group sponsorship need team access, or when access by an alternate project representative is needed, advance planning on the part of the requestor can ensure such group or alternative account access is available. A requestor who needs to use an alternative approach for submissions or communications may contact the relevant program at the email address listed in the Appendix.

2. Submissions and Data Standards

Requestors may submit primary data (e.g., subject-level datasets) from studies as appropriate to their project account in the FDA portal. 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 standards[41]) when submitting these data for review.[42] Study data standards for submissions to FDA can be found at FDA's Study Data Standards web page.[43]

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[40] The FDA NextGen Portal can be accessed at https://edm.fda.gov. Additional information at this URL describes processes such as account creation, account access, and how to communicate with the program via the portal.

[41] For more information on Clinical Data Interchange Standards Consortium standards, see https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

[42] For submission and review purposes, please refer to the Study Data Standards Resources, available at https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

[43] For more information on FDA 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: These 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: An outcome that describes or reflects how an individual feels, functions, or survives (*Biomarkers, EndpointS and other Tools* (BEST) *Glossary Resource*). Assessment of a clinical outcome can be made through report by a clinician, patient, non-clinician observer, a performance-based assessment, or through other methods.

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 a patient-reported outcome (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 or not accept an LOI or a QP or to qualify or not qualify a DDT for a COU in an FQP.

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 FDA 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, scientists, senior-level medical officers 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 FDA deems summary-level data to be sufficient. 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 pages.

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.

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 the specific DDT program's web pages. 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): An FDA determination made after review of an FQP 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 the specific program's web page. Acceptance at the QP stage, including taking into consideration the listed recommendations provided in the 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 consortia, 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, includes 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, 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. Upon a determination that a submission is "not reviewable," FDA communicates this to the requestor in a memorandum with advice intended to improve the quality of the 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, for example, the accept or not accept determination by the DDT Committee for an LOI or QP submission or the qualified or not qualified determination for an FQP.

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: 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
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
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
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
PerfO	Performance Outcome
PRO	Patient-Reported Outcome
QP	Qualification Plan
SME	Subject Matter Expert
U.S.C.	United States Code

APPENDIX

CONTACT INFORMATION FOR EACH DDT PROGRAM

All submissions to any of the qualification programs must be made through the NextGen Portal for project tracking purposes and acknowledgement of receipt of a submission. Inquiries or meeting requests may be made via email to individual programs as noted below:

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

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

CDER and CBER Animal Model Qualification Program
Email: CDERAnimalModelQualification@fda.hhs.gov

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