POLICY AND PROCEDURES

OFFICE OF THE CENTER DIRECTOR

Drug Development Tool Qualification Programs

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PURPOSE

- This MAPP describes general policies, responsibilities, and procedures for drug development tool (DDT) qualification programs at the Center for Drug Evaluation and Research (CDER).[1] Currently, DDT qualification programs exist for biomarkers, clinical outcome assessments (COAs), and animal models for drug development under the animal rule.[2] These programs are led by the Office of Translational Sciences (OTS), Office of New Drugs (OND), and Office of Counter-Terrorism and Emergency Coordination (OCTEC), respectively.

- This MAPP is intended to serve as a companion reference to the guidance for industry and FDA staff *Qualification Process for Drug Development Tools* (DDT qualification guidance).[3]

[1] The term *drug*, as used in this MAPP, refers to both human drugs and therapeutic biological products regulated by CDER, unless otherwise specified.

[2] See 21 CFR 314.600 for drugs and 21 CFR 601.90 for biological products.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

- This MAPP does not assign responsibilities to specific staff positions because individual roles may vary among DDT qualification programs. Review office-specific and DDT program-specific MAPPs are under development and will delineate specific staff responsibilities. These MAPPs will also describe how the relevant review offices interact with the DDT qualification programs and fulfill their responsibilities.

- This MAPP applies only to the process of DDT review outside of drug-specific regulatory applications (investigational new drug application (IND), new drug application (NDA), or biologics license application (BLA)). The qualification review process is separate from the drug application review process.

BACKGROUND

- DDT qualification programs were created by CDER as part of the FDA's Critical Path Initiative to provide a framework for development and regulatory review of scientific tools, each of which will have a well-defined context of use (COU) and is independent of a specific drug development program. DDT qualification results in public acknowledgment by the FDA that the qualified DDT can be used during drug development without a sponsor's need to request that CDER reconsider and reconfirm the suitability of the DDT for the qualified COU.

- The CDER DDT qualification review process used by the DDT qualification programs involves CDER offices for which the particular DDT may have relevance for future drug development regulatory review decisions. The qualification process allows CDER to work with submitters (e.g., public-private partnerships, industry consortia, academic collaborative groups, other government agencies, and individuals) to guide them as they develop or refine a DDT for a specific COU in drug development. In some cases, the need for a new or revised DDT may be identified by FDA staff, or the effort to develop the necessary supportive information may be led by FDA staff without a formal external submitter.

- The CDER DDT qualification process occurs in three stages as described in the DDT qualification guidance: Initiation, Consultation and Advice, and Review of Full Qualification Package (FQP).

POLICY

- Staff in each CDER DDT qualification program will follow the overall policies and procedures outlined in this MAPP and in a program-specific MAPP that describes each program's procedures, roles, and responsibilities in greater detail.

- When determining whether to review a tool for qualification, the FDA will take into account the adequacy of the information provided in the letter of intent (LOI), whether the tool is appropriate for and expected to benefit drug development, and whether adequate resources are available to form a qualification review team (QRT) at the time of an LOI submission.

- The review of DDT qualification submissions will use a multidisciplinary approach with discipline-specific reviews. These multidisciplinary reviewers form a QRT. Staff in each CDER DDT qualification program will work with appropriate CDER offices[4] to identify and assign reviewers with relevant expertise to participate on each project-specific QRT.

- When appropriate to a particular DDT and the technology related to its use, specific expertise from areas outside CDER will be sought for the DDT qualification review process.

- Each participating office will establish appropriate policies and procedures and include supervisory oversight of its assigned QRT reviewers to ensure that advice, reviews, and recommendations receive concurrence from each relevant office.

- Office and division management will enable participation of QRT reviewers by including QRT commitments as a part of the reviewer's overall workload assignment.

- DDT qualification program management will provide sufficient time for QRT members to perform their reviews and discuss review findings, advice, and recommendations with appropriate supervisors throughout the DDT qualification process.

- Offices that have reviewers participating in QRTs may choose to appoint an office liaison to each DDT qualification program.

- OTS/Translational Medicine will manage the main CDER DDT Qualification Program Web page and the intranet Web page. Staff in each DDT qualification program will manage their own Internet and intranet Web pages.

[4] For the purpose of this MAPP, *CDER offices* include OND, OTS, and OCTEC, and other relevant offices as identified by staff in the individual DDT programs.

RESPONSIBILITIES

This section highlights the general responsibilities associated with each CDER DDT program that need to be assigned and carried out by the appropriate staff. The DDT program-specific and review office-specific MAPPs will conform to this CDER MAPP and will contain more detailed information about assignment of staff and specific responsibilities.

DDT Qualification Program Oversight Staff Responsibilities Are as Follows:

- Provide procedural, policy, and scientific oversight for a DDT qualification program to promote efficiency and consistency in accordance with DDT-related guidances and MAPPs
- Coordinate the training of CDER review staff assigned to QRTs about scientific objectives and processes for DDT qualification
- Receive, from the CDER Central Document Room, DDT qualification submissions, supporting documents, and correspondence from submitters
- Triage DDT qualification submissions for appropriate CDER review process or action
- Initiate QRT formation for new DDT projects by contacting appropriate review offices through the office liaison or liaisons, if appropriate
- Oversee the qualification recommendation concurrence and clearance processes at the end of the Review stage for DDT qualification and provide all final communications to the submitters of DDT qualification projects

DDT Qualification Program Scientific Coordination Staff Responsibilities Are as Follows:

- Coordinate the scientific review of DDT qualification submissions
- Communicate with potential submitters and provide advice to enable submitters to formulate an LOI, an initial briefing package (IBP), or FQP
- Ensure that all DDT submissions are complete before distributing for review
- Work with CDER management and staff from other centers to identify scientific review issues, new opportunities for DDT collaboration, and future development efforts for the DDT qualification program

- Perform an initial assessment of the LOI, including whether:

  −The LOI is complete
  −The project has scientific merit
  −The proposed COU is acceptable for the Initiation stage

- Make recommendation for QRT formation to review the LOI, when appropriate

- Coordinate the formation of the QRT with appropriate review disciplines

- Coordinate review responsibilities across QRT review disciplines

- Advise the QRT of premeeting expectations and meeting objectives

- Provide recommendations regarding the appropriate depth and comprehensiveness in DDT qualification reviews

- Ensure coherence, clarity, and completeness for all documents generated by QRT members and documents generated jointly across QRT disciplines

- Keep DDT qualification program management and review office management informed of administrative and scientific issues for the project and coordinate meetings with review office management when the QRT needs additional guidance or when major scientific issues need to be addressed

- Determine, in conjunction with the QRT, when there is a need for a briefing of senior management in CDER

- Determine, in conjunction with the QRT, whether CDER should hold an advisory committee meeting or a public workshop or otherwise obtain input from external experts based on feedback and concurrence from all relevant CDER management

- Coordinate the development of a consolidated review package, including an executive summary, that combines all finalized discipline-specific reviews

- Coordinate the development of a draft qualification recommendation for posting on the FDA Drugs guidance Web page

Administrative Staff Responsibilities Are as Follows:

- Track and update DDT qualification program activities using the established CDER DDT tracking system/database
- Identify the person who will serve as the primary point of contact for all communications with submitters
- Identify the person who will serve as the expert for all process-related questions from submitters and review staff
- Send acknowledgment of DDT submission receipt letters to submitters
- Draft response letters for completion by the QRT and program management
- Monitor DDT qualification project progress to promote timely review of materials submitted throughout all stages of the process including, but not limited to, LOIs, briefing packages, supporting documents, and FQPs
- Follow standard CDER processes for planning and scheduling meetings, generating meeting minutes, and advising DDT submitters on submission processes
- Coordinate DDT qualification-related processes within and external to the DDT qualification program including coordination with the CDER Central Document Room
- Coordinate with the relevant CDER office directors and review staff, and with directors of other centers (if such expertise is needed) to assemble a QRT
- Coordinate the drafting of the *Federal Register* notice

Review Office Liaison Responsibility Is as Follows:

- Coordinate with review office management and aid in developing office-specific policies and procedures to support the DDT qualification programs

Qualification Review Team Member Responsibilities Are as Follows:

- Follow review office-specific MAPPs for all activities related to participation in the QRT and DDT qualification review process
- Ensure that the review recommendations and comments have concurrence and clearance from the discipline, division, and office management according to

review office procedures (e.g., that may be outlined in review office-specific MAPPs)

- Participate in meetings with other QRT members to represent the relevant review discipline issues and to discuss the qualification project; these meetings can be internal FDA meetings or meetings with submitters
- Provide timely recommendations and edits to meeting minutes and letters to the submitter
- Review the LOI and provide advice to guide the submitter in the preparation of the IBP needed to enter the Consultation and Advice stage
- Review briefing packages and other submitted materials to provide timely comments and recommendations
- Assess whether DDT development is complete to enter the Review stage
- Review the FQP and determine if the submitted data support the DDT's proposed COU
- Provide a discipline-specific written review including a recommendation as to whether the DDT should be qualified for the stated COU

PROCEDURES

Tables 1 through 3 in this section highlight the general procedures for each stage of the DDT qualification process. The DDT qualification program-specific and review office-specific MAPPs being developed will contain more detailed procedures.

Table 1. Initiation Stage

Major Steps	Accompanying Substeps
1. Potential submitter initiates communication with CDER	DDT qualification program staff: a. Provides advice and information to potential submitter to increase the probability of an adequate LOI submission b. Creates original tracking record in the electronic database; assigns DDT number c. Provides DDT number in a communication to potential submitter along with recommendations about what to include in a cover letter for all subsequent submissions and what to include in an LOI
2. Submitter submits LOI for DDT qualification to CDER	DDT qualification program staff: a. Sends submission acknowledgment communication to the submitter b. Screens the LOI to determine: i. If information is inadequate — sends communication to submitter requesting revision of the LOI ii. If information is adequate but not appropriate and beneficial to drug development, or if no reviewer resources — sends denial or postponement communication to submitter iii. If information is adequate, project is appropriate and beneficial to drug development, and reviewer resources exist — CDER forms a QRT and the DDT qualification program staff prepares a project acceptance communication that includes comments and suggestions to the submitter for topics to be addressed in the IBP

Table 2. Consultation and Advice Stage

Major Steps	Accompanying Substeps
1. CDER sends submitter a project acceptance communication requesting an IBP	CDER sends the QRT recommendation to the submitter (see Table 1, 2.b.iii.) based on QRT evaluation of the DDT LOI
2. Submitter submits DDT IBP to CDER	DDT qualification program staff: a. Updates project tracking record in the electronic database b. Sends acknowledgment communication to submitter c. Distributes IBP to QRT for review d. Schedules QRT meeting to discuss discipline-specific review of IBP e. If information in an IBP is inadequate or incomplete — sends communication to submitter to request additional information f. Schedules meeting with submitter g. Provides QRT's preliminary written advice and comments to submitter h. Attends meeting of the QRT and submitter at which the QRT and submitter discuss proposed DDT and its development plan i. Sends meeting summary and final comments after the meeting to the submitter
3. Submitter submits subsequent briefing packages or request for meeting with QRT with briefing package	a. DDT qualification program staff: i. Updates project tracking record in the electronic database ii. Sends acknowledgment communication to submitter iii. Distributes briefing package to QRT for review iv. Schedules QRT meeting to discuss discipline-specific review of briefing package v. If information in briefing package is inadequate or incomplete — sends communication to submitter to request additional information vi. Provides QRT's written advice and comments to submitter and request additional information as needed vii. If meeting occurs with submitter, sends meeting summary and final comments after the meeting b. Repeats process as necessary until DDT development is complete c. Prepares communication to submitter when DDT development is complete requesting submission of the FQP with suggestions for content and format

Table 3. Review of FQP Stage

Major Steps	Accompanying Substeps
1. DDT qualification program staff sends submitter a communication requesting submission of the FQP	DDT qualification program staff provides information to the submitter about the appropriate contents of the FQP
2. Submitter sends FQP to CDER	DDT qualification program staff: a. Updates the tracking record in the electronic database b. Sends the submission acknowledgment communication to the submitter c. Distributes the FQP to the QRT d. Determines, in conjunction with the QRT, if the FQP is adequate for QRT to begin review e. If the package is inadequate, requests additional information from the submitter f. Schedules FDA internal meetings and meetings with submitter, as needed g. Works with the QRT to coordinate reviews across review disciplines and determines the need for additional expertise
3. Internal mid-review meeting	At the internal mid-review meeting, the QRT: a. Discusses the content of the submission and identifies issues that need further consideration to support a qualification recommendation; discussion may include whether the COU needs to be modified b. Determines the need for further information from the submitter c. Reaches a tentative decision on whether, and in what format, a wider presentation and discussion are needed
4. Wider presentation and discussion (this step is optional and can occur at any point in the process)	a. The DDT qualification program staff, with input from CDER management and the QRT, determines an appropriate forum, such as: i. Regulatory briefing ii. CDER Scientific Rounds iii. Public workshop iv. Advisory committee b. The DDT qualification program staff coordinates the appropriate forum discussion according to standard CDER procedures

continued

Table 3, continued

Major Steps	Accompanying Substeps
5. Completion of review and preparation of qualification clearance package	a. QRT members forward completed discipline-specific QRT reviews with qualification recommendation to the DDT qualification program staff after office-level concurrence according to established office-specific DDT procedures.* Consult reviews will be included, if applicable. b. The DDT qualification program staff determines whether there is consensus concerning the qualification decision within the QRT. i. If the DDT is not adequately supported to receive qualification, the DDT qualification program staff prepares and sends comments and advice to the submitter regarding gaps in knowledge and how to further develop evidence supporting the DDT ii. If the DDT is adequately supported to receive qualification, the DDT qualification program staff follows the program-specific MAPP and prepares the qualification clearance package that includes: a) A comprehensive executive summary that encompasses all QRT reviews b) The draft DDT qualification recommendation for CDER clearance c) The discipline-specific QRT reviews d) The *Federal Register* notice of availability (NOA) iii. The DDT qualification program staff determines which CDER offices and FDA centers will clear the qualification clearance package
6. CDER clearance	a. The CDER qualification clearance package is sent to all applicable offices. FDA offices that contributed to the review but are not part of the clearance process are notified of impending CDER clearance and provided the executive summary and qualification recommendation. b. After the CDER office clearance process has been completed, the CDER qualification clearance package is sent to the CDER Center Director for clearance and signature. c. The CDER Center Director assesses the overall DDT and supportive evidence for qualification and is the final signatory authority for the DDT qualification recommendation. If the Center Director signs the DDT qualification recommendation, then proceed to step 7.

continued

Table 3, continued

Major Steps	Accompanying Substeps
7. Qualification recommendation made public	a. The DDT qualification program staff sends the NOA and qualification recommendation to the Regulations, Policy, and Management Staff for editing and posting on the DDT public Web page** b. At the same time, the DDT qualification program staff sends a letter informing the submitter of CDER's qualification recommendation c. The qualification recommendation is posted as a draft guidance on the FDA Drugs guidance public Web page d. Redacted qualification reviews and the executive summary are posted on the DDT public Web page
8. *Federal Register* publication of NOA announcing availability of qualification recommendation	a. A comment period begins with publication of the *Federal Register* NOA announcing the draft guidance. b. After the comment period closes, the DDT qualification program staff and the QRT review the submitted comments. Revisions to the draft guidance (i.e., the qualification recommendation) are made as necessary. c. CDER clearance of the final guidance will be obtained according to step 6. d. The *Federal Register* NOA announcing the final guidance is published.

* Offices may include OND, the Office of Biostatistics, the Office of Clinical Pharmacology, and the Office of Pharmaceutical Science.

** http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm

DISPUTE RESOLUTION

Each discipline-specific review of DDT qualification submissions will reflect the individual reviewer's interpretation of the data and represent the perspective of the reviewer's discipline. Differing opinions within a reviewer's management chain will be documented and filed with the primary reviews. When scientific disputes arise, MAPP 4151.2 Rev.1 *Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director* will be followed.

REFERENCES

1. Guidance for industry and FDA staff *Qualification Process for Drug Development Tools*

(http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)

2. Guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)

3. Draft guidance for industry *Product Development Under the Animal Rule* (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)[5]

4. MAPP 4151.2 Rev. 1 *Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director* (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm)

DEFINITIONS

- **Animal Model:** For the purpose of this MAPP, 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 for product development under the animal rule.

- **Biomarker:** A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention.[6] A biomarker can be a physiologic, pathologic, or anatomic characteristic or measurement that is thought to relate to some aspect of normal or abnormal biological function or process.

- **Clinical Outcome Assessment (COA):** A measure of how patients feel or function that can be used to determine whether or not a drug has been demonstrated to provide a treatment benefit. COAs may sometimes be called a measure or a measurement instrument. The term *instrument* refers to the means to capture data plus all the information and documentation that support its use within the intended COU. One of the distinguishing characteristics of a COA is the identification of who reports the outcome (i.e., the patient, a clinician, or another observer). COAs can also include assessments of motor, sensory, or cognitive

[5] When final, this guidance will represent the FDA's current thinking on this topic.

[6] Biomarkers Definitions Working Group, 2001, Clin Pharmacol Ther, 69:89-95.

performance that depend on patient participation in the generation of a score (e.g., 6-minute walk test or hearing test).

  - A patient-reported outcome is a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.

  - A clinician-reported outcome assessment is based on clinical observation and interpretation by a trained clinician.

  - An observer-reported outcome is assessed by observers without the need for clinical expertise.

- **Context of Use (COU):** A comprehensive statement that fully and clearly describes the way the DDT is to be used and the drug development-related purpose of the use. The COU defines the boundaries within which the available data adequately justify use of the DDT and describes all important criteria regarding the circumstances under which the DDT is qualified.

- **DDT Qualification:** A conclusion that within the stated COU, the DDT can be relied on to have a specific interpretation and application in drug development and regulatory review.

- **DDT Qualification Process:** A CDER process for regulatory review of DDT qualification submissions and for providing consultation and advice to potential DDT qualification submitters. The DDT qualification process describes process principles common to all DDT qualification programs and to specific components of the Biomarker Qualification Process, the COA Qualification Process, and the Animal Model Qualification Process.

- **DDT Qualification Program:** A CDER program that includes the DDT qualification process and the regulatory infrastructure and documentation needed to support the process. DDT qualification programs currently exist for biomarkers, COAs, and animal models for drug development under the animal rule.

- **Drug Development Tool (DDT):** A measurement or method (and associated material) that aids sponsors of investigational new drugs. DDTs include, but are not limited to, biomarkers, COAs, and animal models for drug development under the animal rule. DDTs suitable for CDER DDT qualification are a subset of all types of DDTs and should be intended for potential use over time in multiple drug development programs.

- **Full Qualification Package (FQP):** Documents submitted by the submitter that contain a complete and detailed description of the studies and analyses providing the evidence to justify qualification of the DDT for the intended COU.

- **Initial Briefing Package (IBP):** Documents that describe details about the COU and data supporting the DDT's qualification provided by the submitter after the DDT project has been accepted by CDER.

- **Letter of Intent (LOI):** Concise communication by the submitter of its intent to request the qualification of a DDT. It includes a description of the DDT and its proposed COU as well as a description of the available data intended to support the qualification for the proposed COU.

- **Qualification Recommendation:** An appended guidance to the guidance for industry and FDA staff *Qualification Process for Drug Development Tools.*

- **Qualification Review Team (QRT):** A multidisciplinary group whose members are nominated by CDER offices (and other centers as appropriate) and who have scientific expertise and regulatory knowledge related to a given DDT proposal.

- **Submitter:** Entities (e.g., public-private partnerships, industry consortia, academic collaborative groups, other government agencies, and individuals) that send DDT qualification submissions to CDER.

EFFECTIVE DATE

This MAPP is effective upon date of publication.