
Guidance for Industry and FDA Staff

Qualification Process for Drug Development Tools

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

**January 2014
Procedural**

Guidance for Industry and FDA Staff

Qualification Process for Drug Development Tools

*Additional copies are available from:
Office of Communication
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
Hillandale Building
10001 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
<http://www.fda.gov/cder/guidance/index.htm>*

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

**January 2014
Procedural**

TABLE OF CONTENTS

I. INTRODUCTION.....	1
II. BACKGROUND AND GENERAL CONCEPT	2
III. DRUG DEVELOPMENT TOOLS.....	3
A. Biomarkers.....	3
B. Clinical Outcome Assessments	4
C. Animal Models	5
IV. QUALIFICATION—DEFINITION	6
V. QUALIFICATION PROCESS	7
VI. PROCEDURES FOR MAKING RECOMMENDATIONS PUBLIC	10
VII. PROCEDURES FOR SUBMITTING CORRESPONDENCE AND DOCUMENTS.....	10
APPENDIX 1: Qualification Process	12
APPENDIX 2: Biomarkers — Additional Considerations	14
APPENDIX 3: Letter of Intent to Propose Biomarker Qualification	24
APPENDIX 4: Biomarker Qualification Initial Briefing Package	25
APPENDIX 5: Letter of Intent to Propose COA Qualification	27
APPENDIX 6: COA Qualification Initial Briefing Package	28
APPENDIX 7: Animal Models: Additional Considerations.....	31

Guidance for Industry¹ Qualification Process for Drug Development Tools

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance describes the process for qualifying drug² development tools intended for potential use, over time, in multiple drug development programs. *Drug development tools* (DDTs) are methods, materials, or measures that aid drug development. DDTs include, but are not limited to, biomarkers, clinical outcome assessments (COAs), and animal models for drug development under the Animal Rule.³ This guidance provides a framework for interactions between the Center for Drug Evaluation and Research (CDER) and the entity proposing the DDT for qualification (the submitter). It also explains the kinds of data that should be submitted to support qualification of a DDT and creates a mechanism for CDER's formal review of the data to ultimately qualify the DDT. For purposes of this guidance, a *submitter* is a person, group, organization (including the federal government), or consortium that takes responsibility for and initiates a DDT qualification proposal using the procedures described in this guidance.

Qualification does not pertain to the process for review of DDTs that are submitted as part of regulatory applications for a specific drug development program. Furthermore, this guidance does not address the evidentiary standards or performance requirements needed for purposes of qualification.

FDA's guidance documents, including this guidance, 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.

¹ This guidance has been prepared by the Qualification Process Working Group in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration..

² The term *drug* as used in this guidance refers to both human drugs and therapeutic biologics regulated by CDER unless otherwise specified.

³ See 21 CFR 314.600 for drugs and 21 CFR 601.90 for biologics products.

II. BACKGROUND AND GENERAL CONCEPT

In 2004, FDA's Critical Path Initiative (CPI)⁴ recognized that the process of drug development and the availability of new therapies were not fully benefitting from the many advances in biomedical science. In addition, drug development had become increasingly challenging and resource intensive. An important area identified by the CPI as potentially enabling significant progress in drug development was applying those scientific advances as new tools to aid the development process. Such tools could speed the availability of new products that may be more safe and effective.

In response, CDER has undertaken multiple initiatives to support the development of new DDTs. Among these efforts has been the creation of a formal qualification process, described in this guidance, that CDER can use when working with submitters of DDTs to guide development as submitters refine the tools and rigorously evaluates them for use in the regulatory process.

The DDT qualification process described in this guidance is intended to expedite development of publicly available DDTs that can be widely employed. Drug developers can use a DDT that has been qualified within a specific context of use (COU)⁵ for the qualified purpose during drug development as long as:

- The study is conducted properly (e.g., all procedures and protocols specified in the COU are followed).
- The DDT is used for the qualified purpose.
- At the time of qualification, there is no new information that conflicts with the basis for qualification.

Once a DDT has been qualified, CDER reviewers can feel confident of the application of the DDT within the qualified COU and not have to re-confirm the DDT's utility.

FDA has seen significant interest in the qualification of biomarkers, COAs, and animal models for drug development under the Animal Rule. CDER has identified staff to support these efforts and designated a specific CDER office to lead the development of each type of DDT. This office identifies a point of contact for DDT developers and staff who oversee qualification advice and review activities. Consultation with staff from other FDA centers and offices⁶ occurs when appropriate. As active scientific communities emerge to undertake the work to develop other types of DDTs, CDER may establish qualification programs for these efforts.

⁴ See FDA's Critical Path Initiative, available at <http://www.fda.gov/scienceresearch/specialtopics/criticalpathinitiative/default.htm>

⁵ The COU is a complete and precise statement that describes the appropriate use of the DDT and how the qualified DDT is applied in drug development and regulatory review. The COU statement would describe all important criteria regarding the circumstances under which the DDT is qualified.

⁶ The Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiologic Health (CDRH), Office of Counterterrorism and Emerging Threats (OCET) in the Office of the Commissioner (OC).

Contains Nonbinding Recommendations

CDER expects this guidance to provide information to individuals, the federal government, and companies with an interest in these tools to advance DDT development. In providing this guidance, CDER expects that DDT submitters will better understand the process through which CDER will evaluate the data for a specific COU.

Because substantial effort is involved in achieving qualification, CDER encourages the formation of collaborative groups to work jointly to increase the efficiency of DDT development. A variety of projects have been undertaken by various consortia that have demonstrated the usefulness of this approach. Nevertheless, CDER will consider DDT proposals from individual persons or companies, as well as from collaborative groups.

In summary, the DDT qualification process will enable CDER to advise DDT developers and provide concurrence for the DDT use that is not limited to a single, specific drug development program. CDER believes that making DDTs widely known and available for use by drug developers will contribute to drug innovation, thus supporting public health. Consequently, CDER intends to make public the DDT qualification and the COU statement when those determinations are made in accordance with the process described in this guidance.

DDT qualification is not necessary for use of a DDT within an individual drug development program, and use of a DDT within such a program does not automatically qualify the DDT for the general COU. Drug developers who are interested chiefly in acceptance of a particular DDT within an individual drug program should continue to plan for the use of a new (or new use of an existing) DDT as part of their discussions with CDER about the specific investigational new drug application (IND), new drug application (NDA), or biologics license application (BLA) of interest. In addition, unless otherwise specified in the publicly available qualification recommendation, CDER qualification of a DDT does not imply that the DDT is automatically regarded as qualified for use in medical product development programs outside of CDER.

III. DRUG DEVELOPMENT TOOLS

DDTs can take a variety of forms. The following sections describe the types of DDTs, (biomarkers, clinical outcome assessments, and animal models) for which qualification programs have been established.

A. Biomarkers

A *biological marker* or *biomarker* is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention.⁷ A biomarker can be a physiologic, pathologic, or anatomic characteristic or measurement that is thought to relate to some aspect of normal or abnormal biologic function or process. Biomarkers measured in patients before treatment can be used to select patients for inclusion in a clinical trial. Changes in biomarkers following treatment may predict or identify safety problems related to a candidate drug, or reveal a pharmacological activity expected to predict an eventual benefit from treatment. Biomarkers can help reduce

⁷ Biomarkers Definitions Working Group (2001). *Clinical Pharmacology and Therapeutics*, 69, p. 89–95.

uncertainty in drug development and evaluation by providing quantifiable predictions about drug performance and they can contribute to dose selection. A *composite biomarker* consists of several individual biomarkers that are combined in a stated algorithm to reach a single interpretive readout. Appendix 2 contains a more detailed description of some types of biomarkers that are in use in drug development.⁸

B. Clinical Outcome Assessments

Clinical outcome assessments (COAs) measure a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions. COAs can be used to determine whether or not a drug has been demonstrated to provide treatment benefit. Treatment benefit can also be defined in terms of a safety benefit compared to other treatments in the same COU. COA qualification is based on a review of the evidence to support the conclusion that the COA is a *well-defined and reliable assessment*⁹ of a targeted concept(s) in a specified COU in *adequate and well-controlled investigations*.¹⁰

A COA is composed of a measure that produces a score together with clearly defined methods and instructions for administering the COA and assessing response; a standard format for data collection; and well-documented methods for scoring, analysis, and interpretation of results in the targeted patient population. COAs can provide direct or indirect evidence of treatment benefit. For COAs that provide indirect evidence of treatment benefit, qualification also includes a review of the evidence that the COA is adequately related to how patients feel or function in daily life. One of the distinguishing characteristics of COAs is who is doing the reporting of the outcome (i.e., the patient, a clinician, or another observer). COAs can also include assessments of motor, sensory, or cognitive 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 (PRO) is a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of the patient's symptoms or functioning without amendment or interpretation of the patient's response by a clinician or anyone else. A clinician-reported outcome (ClinRO) assessment is based on clinical observation and interpretation by a trained clinician. An observer-reported outcome (ObsRO) is assessed by observers without the need for clinical expertise.

Issues relevant to FDA review of new and existing PROs are summarized in FDA's guidance for industry, *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.¹¹ Many of the issues described in that guidance are also relevant to other types of COAs.

⁸ See also the draft guidance, *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Product*, issued in December 2012. Once finalized, this guidance will represent FDA's thinking on this topic. FDA guidances are available on its guidance webpage, which can be accessed at: <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁹ See 21 CFR 314.126.

¹⁰ See 21 CFR 314.126.

¹¹ FDA guidances are available on its guidance webpage, which can be accessed at: <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

This DDT guidance describes a process for qualifying COAs when they are ultimately intended for use as primary or secondary endpoints in a clinical trial for purposes of supporting medical product approval and labeling claims. Often, there are no existing tools specific to the disease or condition and the clinical trial population to serve as well-defined and reliable assessments to support demonstration of treatment benefit.

C. Animal Models

For the purpose of this guidance, an *animal model* is defined as a specific combination of an animal species, challenge agent,¹² 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.

The Animal Model Qualification (AMQ) program¹³ applies specifically 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 Animal Rule.¹⁴ The selection of an appropriate animal model is critical for the approval or licensure of these products. Other types of animal models, such as those used for proof-of-concept testing or for safety testing are not eligible for qualification.

Qualification of an animal model through the AMQ program is voluntary (i.e., not required for product approval or licensure under the Animal Rule). The AMQ program is intended to respond to the need for publicly available animal models. The qualification process supports the development of these animal models, each of which potentially can be used for efficacy testing in development programs for multiple investigational drugs for the same targeted disease or condition. Such animal models are considered to be product-independent.

For qualification, the natural history model should be analogous to the human disease; that is the disease process or pathologic condition in a given species of animal corresponds in multiple important aspects to the human disease or condition of interest. In addition, the human and animal disease or condition should share the same, or very similar, pathogenic or toxic mechanisms. In the animal model, the *challenge agent* is the material used to induce the disease or condition in the animal; the *etiologic agent* causes the disease or condition in humans. The two agents should be the same; if not, the submitter should provide a strong justification. Additional information that may be helpful for the qualification of animal models is provided in Appendix 7.¹⁵ FDA endorses the principles of replacement, reduction, and refinement¹⁶ of the

¹² The term *challenge agent* refers to the material used to induce the disease or condition in the animal.

¹³ FDA's Animal Model Qualification program is being developed by CDER in collaboration with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

¹⁴ See 21 CFR 314.600 for drugs; 21 CFR 601.90 for biological products.

¹⁵ FDA has also developed guidance to support the use of animal models to study diseases and conditions under the Animal Rule. See FDA's guidance web page at to make sure you have the most recent version of the guidance: <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

use of animals in biomedical research and encourages submitters to take this into consideration in their development plans.

IV. QUALIFICATION—DEFINITION

Qualification is 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. The COU describes the way the DDT is to be used and the purpose of the use. A complete COU *statement* should describe fully the circumstances under which the DDT is qualified and the boundaries within which the available data adequately support use of the DDT. Once a DDT has been qualified for a specific COU in drug development, it can be used to produce analytically valid measurements that can be relied on to have a specific use and interpretable meaning. The DDT can be used by drug developers for the qualified context in IND, NDA, and BLA submissions without the relevant CDER review group reconsidering and reconfirming the suitability of the DDT. Drug developers can use qualified DDTs, but are not required to do so.

The DDT may have other potential value. For example, subject to review and discussion with CDER staff, a DDT may be used in IND programs for a purpose outside of the qualified COU. In addition, as data from additional studies with the DDT are obtained over time, these data could be used as part of a new DDT submission to support expansion of the qualified COU.

In the past, DDT acceptance in the drug development and regulation process was initiated on a sponsor- and drug-specific basis. Sponsors seeking to use a specific DDT typically developed only enough data to support its use in a specific case. Use in a different clinical setting or with other drugs would generally be left undetermined. Other drug sponsors or other parties would have little ability to build on that knowledge to expand the tool's use to additional settings.

Qualification as envisioned in this guidance is intended to provide some degree of generalizability for use of the tool, such as use across multiple clinical disorders, drugs, or drug classes. The extent of generalization will depend on the specific DDT. Having a qualified DDT available to sponsors will help advance therapy development and evaluation in multiple cases and can more widely benefit patients.

Qualification facilitates a collaborative setting where multiple interested parties may work together to develop a DDT for qualification. This approach brings certain advantages, including reducing committed resources for individual collaborators. This in turn may encourage interested parties to join a DDT development effort despite uncertainties as to the DDT's immediate utility.

A formal qualification process also creates advantages for FDA. Previously, if multiple sponsors were interested in using a particular DDT, or one sponsor was interested in using a DDT in multiple different clinical settings, FDA staff would have to perform multiple evaluations of the data to justify the DDT use on a case-by-case basis. If instead, a formal qualification is achieved under the principles described in this guidance, the relevant data will need to be reviewed only

¹⁶ Russell, WMS and RL Burch, 1992, *The Principles of Humane Experimental Technique*, Potters Bar, UK: Universities Federation for Animal Welfare (Original work published 1959).

once. Subsequently, the DDT could be relied on within the qualified COU, largely without further detailed review.

V. QUALIFICATION PROCESS

The process for DDT qualification provides a framework for interactions between CDER and DDT submitters to guide the collection of data to support a DDT's prospectively specified COU. The qualification process consists of three stages: (1) an initiation stage, (2) a consultation and advice stage, and (3) a review stage for the qualification determination. The appropriate review offices will participate in the entire qualification process for the DDT (see Appendix 1). The goal of the process is to reach a determination about the adequacy of the submitted data to support DDT qualification within a COU. CDER intends to interact actively with DDT submitters to advance DDT development.

If a DDT is qualified for a specific use, the COU may be modified or expanded over time as additional data are collected, submitted, and analyzed. Modification or incremental expansion of the qualified COU over time may be undertaken by the original DDT submitter or any other submitter working in the field. Alternatively, if the growing body of scientific evidence no longer supports the COU, the DDT qualification may be withdrawn.

Following is a detailed description of the process for qualifying a DDT.

Stage 1: Initiation

1. Initiation Request

A submitter interested in having a DDT considered for qualification should first contact CDER and request a DDT tracking number (see section VII for details). Once received, CDER's designated point of contact for the DDT will assign the DDT tracking number in the electronic database and provide the submitter with the number, as well as any additional details (if necessary) for submission of a letter of intent (LOI).

2. DDT Letter of Intent

The LOI is a concise document requesting an initial consultation with CDER concerning the potential value of a DDT. Submitters should send the LOI (see section VII for details) when they have a well-identified DDT concept. The LOI should include a short description of the DDT, its proposed COU, and a rationale to support qualification (see Appendices 3, 5, and 7 for suggested LOI content). After receipt of an LOI, CDER will evaluate the LOI and make a determination on whether or not to begin the consultation and advice stage. This determination will be made based on the scientific merit of the proposal as well as the availability of CDER resources to perform the review. CDER will review and communicate the decision to the submitter. If CDER declines the DDT request, a communication to the submitter will include the reasons for the decision and any advice on alternative paths for DDT development and consideration.

Stage 2: Consultation and Advice

Contains Nonbinding Recommendations

1. Initial DDT Briefing Package and Meeting with the Submitter

If the qualification review team (QRT) accepts the DDT request, the appropriate qualification program will advise the submitter to submit an initial briefing package (IBP). See Appendices 4, 6, and 7 for the suggested content of this IBP and section VII for cover letter contents.

At this point, a QRT composed of staff from CDER and other relevant centers and disciplines with expertise appropriate to reviewing the submissions will provide ongoing advice to the DDT submitter about the evidence needed for qualification. After the submission of the IBP, a meeting between the QRT and the submitter may occur with the following possible agenda topics:

- Thorough discussion of the submitter's goals, including COU
- Assessment of the available data to support the objectives
- Identification of gaps in knowledge that should be addressed
- Discussion of any additional data that will be needed to support the qualification and the sources of that data (e.g., new studies to be designed and conducted)
- Possible discussion of adopting a step-wise qualification approach, when there are appropriate intermediate COU assessments that could be supported with less extensive new information than necessary for the ultimate desired COU

If there is an alignment of goals for DDT development following the QRT evaluation and advice, the consultation and advice stage will continue. Should the goals for the DDT change so that it is no longer appropriate for CDER or the submitter to continue the consultation process, this stage can be terminated by either party.

2. Further DDT Development and Consultation

The DDT submitter should work to acquire the additional data identified during the meeting or in correspondence with the QRT. Additional meetings between the QRT and the submitter can occur as needed during the DDT development effort to enable the QRT to provide expert advice relevant to the specific DDT proposal. During these meetings, discussions and advice should focus on the rationale for the proposed DDT and its COU, newly acquired data, questions about the COU that require further data, potential studies and methods to obtain that data, and identification of other gaps in the existing information that should be addressed before proceeding to the review stage of the qualification process.

When the QRT has reviewed summaries of the accumulated data and agrees with the submitter that the identified critical knowledge gaps have been addressed, the process will proceed to the review stage.

Stage 3: Review of Full Qualification Package

1. When the QRT and the submitter agree that the consultation and advice phase is complete, the submitter should provide a full qualification package (FQP). This

Contains Nonbinding Recommendations

- submission should contain a complete and detailed description of the studies and analyses providing the evidence to justify qualification of the DDT for the intended COU. In most cases, submission of primary data from studies will be expected. The submitter should also provide a statement acknowledging that a summary of the information in the qualification package will be made public on FDA's DDT qualification Web page (see Section VI).
2. The qualification process enters the review stage when CDER determines that the data in the FQP are sufficiently complete for review. The submitter will be notified when the review stage starts.
 3. The QRT will review the FQP, discuss the project at internal meetings, and arrive at a QRT qualification recommendation. The QRT will interact with the submitter during the review if clarification is needed about particular aspects of the qualification package or to request additional information. Individual discipline reviews and a combined executive summary review document for the qualification recommendation will be prepared by members of the QRT. In the case of complex or controversial DDT development programs, the QRT may choose to hold public discussions (e.g., workshops, conferences, or other forms of public forums).
 4. The discipline reviews will be provided to the participating FDA centers/offices for further discussion and concurrence.
 5. If the review and decision-making process results in a CDER recommendation to qualify the DDT, a statement of qualification summarizing the qualification recommendation will be posted on FDA's Guidance Web page (see section VI). Although the submitter will have proposed a specific COU, the COU that receives qualification will be determined by what is supported by the submitted data.

VI. PROCEDURES FOR MAKING RECOMMENDATIONS PUBLIC

When submitters enter the qualification process, they agree that the qualified DDT will be made publicly available for use in drug development programs in the specified COU. CDER qualification of a DDT will not displace intellectual property, copyrights, or ownership rights.

To make information about DDT qualification recommendations available to the public, CDER intends to use the following process:

1. A letter regarding the qualification recommendation will be sent to the submitter.
2. New DDT qualification recommendations will be developed and posted on the Internet on FDA's guidances Web page in the section titled Qualified Drug Development Tools.
3. A link to the qualification recommendations will also be posted on the DDT qualification programs Web page. The DDT qualification programs Web page will also contain supporting documentation (DDT reviews and Executive Summary) for DDT qualification recommendations.
4. Newly posted draft and final qualification recommendations will be announced in the New/Revised/Withdrawn list, which is posted on the FDA Drugs guidance page.
5. FDA will issue a notice in the *Federal Register* announcing the availability of new and/or revised (draft) qualification recommendations and final qualification recommendations and identifying a comment period for the draft recommendations.
6. Comments received on draft DDT qualification recommendations will be considered carefully when developing final qualification recommendations.
7. The qualification recommendations will be revised as new scientific information becomes available to ensure that the most up-to-date DDT information is available to the public, as appropriate.

VII. PROCEDURES FOR SUBMITTING CORRESPONDENCE AND DOCUMENTS

All DDT correspondence and documents submitted to FDA should be transferred to either a compact disc (CD) or optical disc storage media format (e.g., DVD) and accompanied by a paper copy cover letter (see cover letter elements below). The cover letter should also be included in the electronic media. The paper copy cover letter and electronic media should be submitted to CDER's Central Document Room at 5901-B Ammendale Road, Beltsville, MD 20705-1266. Primary data from the studies can be submitted as appropriate. Submitters are strongly encouraged to consider the use of relevant data standards (e.g., Clinical Data Interchange Standards Consortium (CDISC)) when submitting these data for review.¹⁷

¹⁷ For submission and review purposes, these electronic data should conform to the requirements described in the *Study Data Specifications* document <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM312964.pdf>.

Contains Nonbinding Recommendations

The cover letter should contain the following elements:

1. Date:
2. Subject: (in bold print) DDT QUALIFICATION SUBMISSION
3. DDT Type: (in bold print), (i.e., BIOMARKER, CLINICAL OUTCOME ASSESSMENT, or ANIMAL MODEL)
4. DDT Tracking Record Number: (in bold print), if previously assigned
5. Submission Type: (in bold print) (INITIATION or LETTER OF INTENT or INITIAL BRIEFING PACKAGE or CORRESPONDENCE or SUPPORTING DOCUMENT FOR CONSULTATION AND ADVICE STAGE or FULL QUALIFICATION PACKAGE.)
6. DDT Name(s): (in bold print): Identify the specific DDT (by name) that is being submitted
7. COU: Describe the intended use of the DDT (1 to 2 sentences)
8. Complete submitter contact information including name(s), affiliation, mailing address, email address, phone and fax numbers

- Physical Media

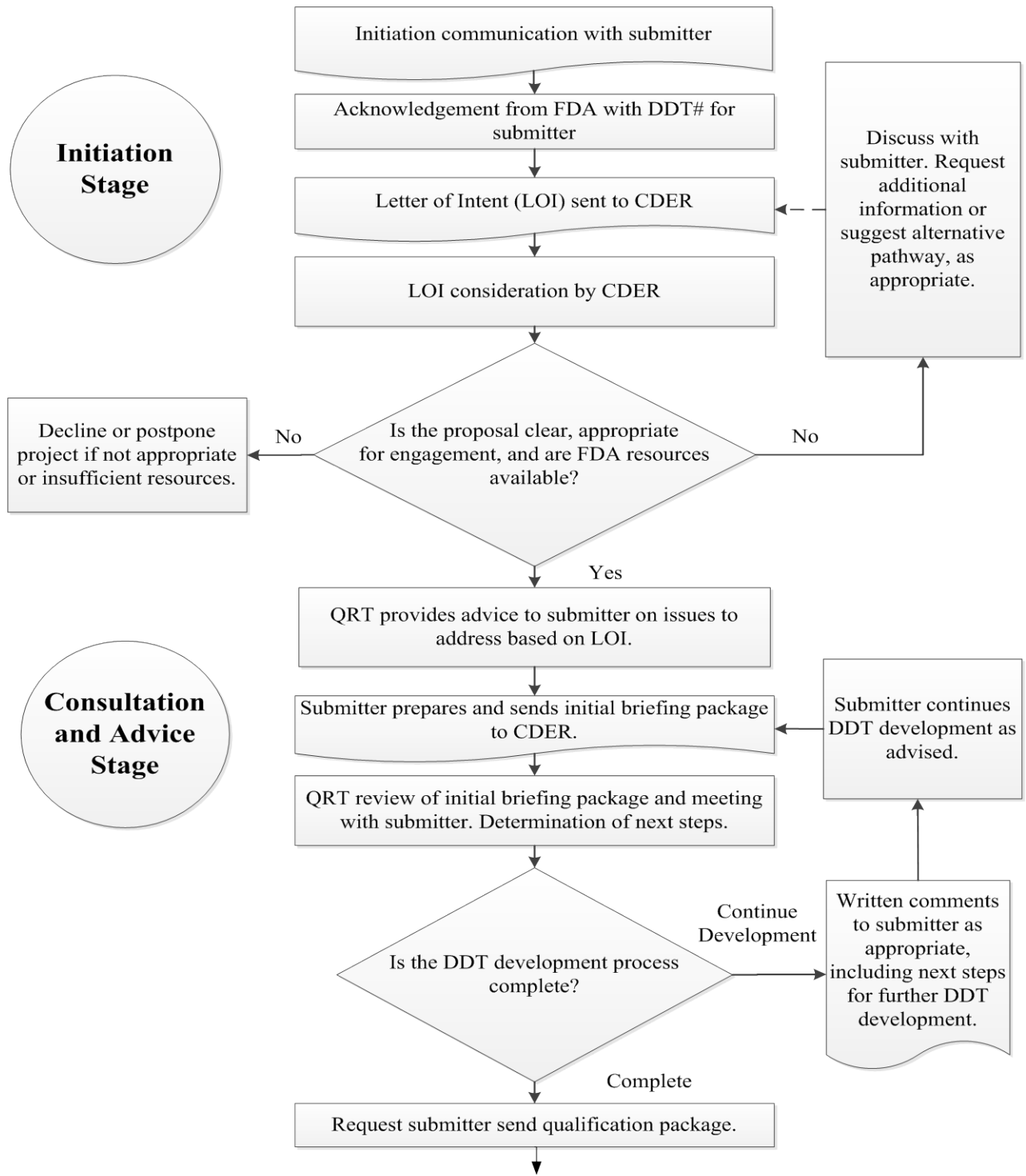
For the most recent information on submitting physical media (e.g., CD-ROMs), see <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissions/Requirements/ElectronicSubmissions/UCM163567.pdf>.

- Data Standards

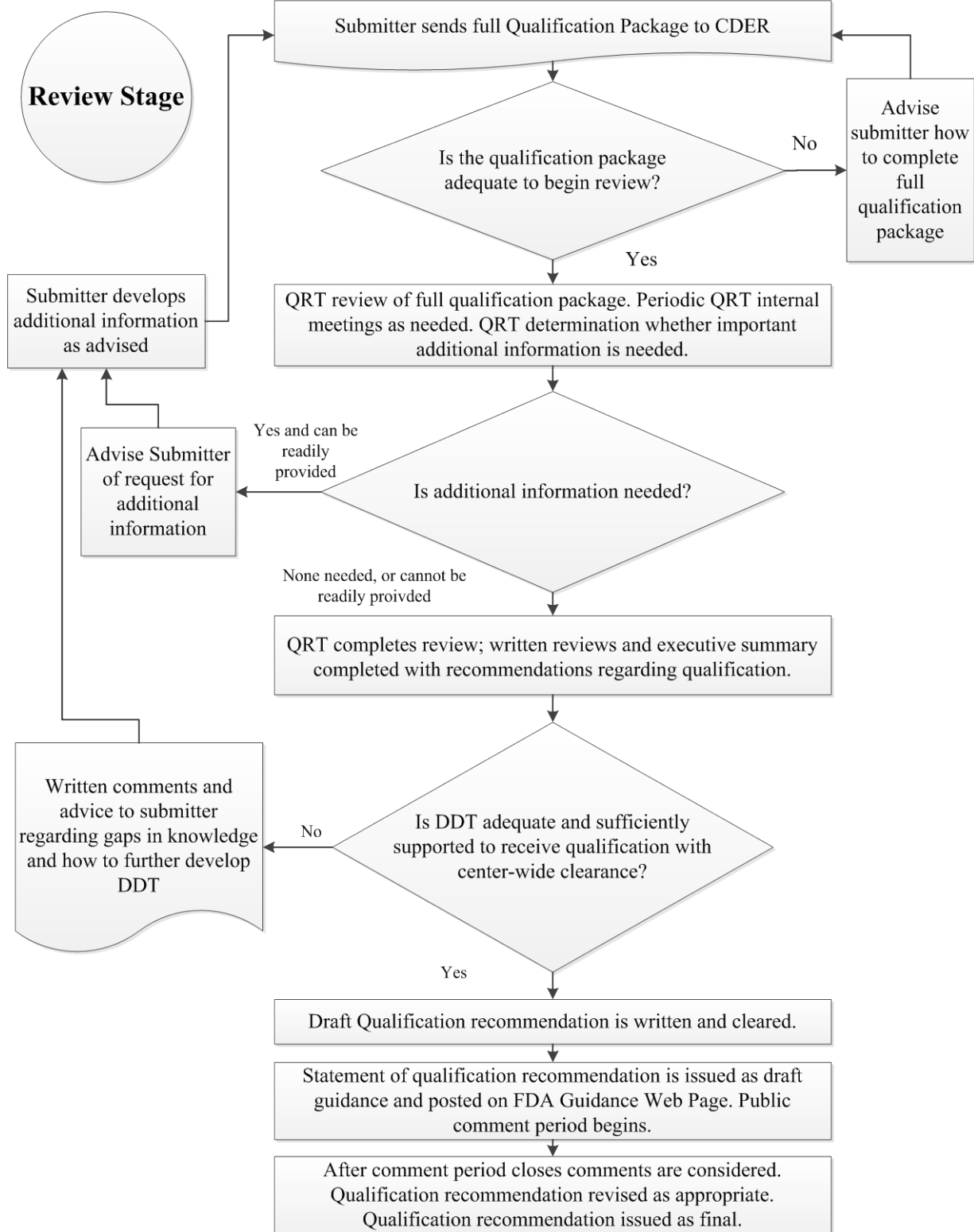
CDER strongly encourages submitters to consider the use of data standards, starting as early as possible in the product development lifecycle, so that they are incorporated into the design, conduct, and analysis of studies. Study data standards for submissions to CDER can be found at the following location:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

APPENDIX 1: QUALIFICATION PROCESS



Contains Nonbinding Recommendations



APPENDIX 2: BIOMARKERS — ADDITIONAL CONSIDERATIONS

As described in section III of this guidance, biomarkers are measures that can help characterize baseline state, a disease process, or a response to a treatment. Thus, they can reflect physiological states, pharmacological responses, or disease characteristics or processes in animals or humans. Changes in biomarkers following treatment reflect a biological response to the product and may predict or identify safety problems related to a drug candidate or reveal a pharmacological activity expected to predict an eventual benefit from treatment.

Biomarkers include measurements that suggest the etiology of, susceptibility to, activity of, or progress of a disease. Alterations in biomarker measurements can indicate responses (favorable or unfavorable) to an intervention. The biomarker may reflect biological processes closely related to the mechanism of disease or processes substantially downstream from the primary disease processes. Biomarkers can be used to assess many different types of biological characteristics or parameters, including genetic composition, receptor expression patterns, radiographic or other imaging-based measurements, blood composition measurements (e.g., serum enzyme levels, prostate specific antigen), electrocardiographic parameters, or organ function (e.g., creatinine clearance, cardiac ejection fraction).

For purposes of this guidance, biomarkers that can be used in the process of drug development and considered for qualification include, diagnostic, prognostic, predictive, and pharmacodynamic biomarkers, as briefly described below. Of note, these categories are not mutually exclusive; that is, a biomarker could fit into more than one category. What follows are illustrative descriptors; they are not meant to suggest that biomarkers in these categories intended to be used in a specific therapeutic product development program must be qualified through the CDER Biomarker Qualification Program.

A *diagnostic* biomarker is a disease characteristic that categorizes a person by the presence or absence of a specific physiological or pathophysiological state or disease.

A *prognostic* biomarker is a baseline characteristic that categorizes patients by degree of risk for disease occurrence or progression of a specific aspect of a disease. A prognostic biomarker informs about the natural history of the disorder in that particular patient in the absence of a therapeutic intervention. It can be used as an *enrichment strategy*¹⁸ to select patients likely to have clinical events of interest or to progress rapidly.

A *predictive* biomarker is a baseline characteristic that categorizes patients by their likelihood of response to a particular treatment relative to no treatment. A predictive biomarker can be used as an enrichment strategy to identify a subpopulation likely to respond to a treatment intervention in a particular way. It may predict a favorable response or an unfavorable response (i.e., adverse event).

¹⁸ See also the draft guidance, *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Product*, issued in December 2012. Once finalized, this guidance will represent FDA's thinking on this topic.

Contains Nonbinding Recommendations

A *pharmacodynamic* (or activity) biomarker is one for which a change in the biomarker shows that a biological response has occurred in a patient who has received a therapeutic intervention and for which the magnitude of the change is considered pertinent to the response. A pharmacodynamic biomarker may be treatment-specific or more broadly informative of disease response. Examples include:

- blood pressure
- cholesterol
- hemoglobinA1c (HbA1C)
- intraocular pressure
- radiographic measures

The specific clinical setting can determine how the biomarker is used and interpreted. A biomarker that might be monitored as a safety assessment to warn of toxicity in one setting might be used to monitor for the desired effect in another clinical setting (e.g., blood pressure, glomerular filtration rate, serum lipids). These biomarkers are often used during phase 2 studies to improve understanding of how to use a drug and guide selections of dose or regimen for testing in phase 3 studies. After extensive experience, sufficient knowledge of a particular clinical disorder and the biomarker's role in the disorder may accumulate to allow a few of these biomarkers to be used as surrogate endpoints (e.g., blood pressure, LDL cholesterol, HbA1C). Most pharmacodynamic biomarkers, however, are used to guide drug development and not as a basis for regulatory approval.

Because of the substantial risk of adversely affecting the public health if a biomarker is falsely accepted as a surrogate endpoint, robust scientific evidence is needed to justify qualification of a biomarker for use as a surrogate endpoint. There have been numerous biomarkers that represented plausible surrogate endpoints (e.g. reduced rate of ventricular premature beats following a heart attack, cardiac output in congestive heart failure, increased HDL cholesterol in patients with coronary artery disease). However, when tested in outcome trials, these biomarkers have failed to predict the expected clinical benefit. It has generally not been clear whether this represented an erroneous expectation of a relationship of the biomarker to the outcome or an unrecognized *off-target* effect of the drug. Qualification of a biomarker as a surrogate endpoint will inevitably occur far less frequently than qualification of a biomarker for other uses.

Using Biomarkers in Drug Development Programs

Biomarkers are commonly used in drug development programs, often based on accumulated experience, and many are also commonly used in clinical practice. Biomarkers are commonly used in drug development as safety assessments to identify a toxic response in a patient, often before it becomes clinically evident (e.g., electrolytes, liver enzymes, renal function measures, muscle enzymes). Measures of physiologic state or function are also frequently used in drug development (e.g., blood pressure, ejection fraction, GFR). Similar measures are often used to evaluate candidate drugs in animal toxicology studies. As already noted, biomarkers can also be used for patient selection for clinical study enrollment or for stratification of patients during study randomization.

In some circumstances, a biomarker may identify a patient subpopulation that becomes the focus of clinical trials. These *prognostic biomarkers* can identify patients with a disease risk most

Contains Nonbinding Recommendations

suitable for an efficient drug development program (e.g., sufficiently high risk of a disease-related event such that reduction of the rate of the event can be shown in a clinical trial of practical size and duration; sufficiently low risk of a disease-related event to allow time for the drug to have an effect on the pathologic process before an event occurs). In other circumstances, a *predictive biomarker* can identify a patient subgroup that has a higher likelihood of benefit from the mechanism of action of the specific drug or a lower risk of an identified adverse effect of the drug. There are also cases when a biomarker, in the setting of a particular disease and the currently available therapies, can identify a subgroup for which there is no available therapy and in whom clinical trials can most rapidly evaluate the potential benefit of a new therapy.

In some cases, measurement of a biomarker will require administration of a drug product. For example measurement of an imaging biomarker may require administration of an imaging drug. Qualification of the biomarker is distinct from marketing approval of the imaging drug. When the imaging drug is already approved and the biomarker use falls within the imaging drug's approved use, biomarker qualification efforts can proceed without need of an IND for the imaging drug. When the imaging drug is not already approved, the clinical studies supporting biomarker development will need to be performed under an IND.

Drug sponsors who choose to use a qualified biomarker may decide to use within their IND/NDA/BLA the same assays or methods that were used by the submitter to arrive at qualification, or they may choose to use an alternate assay. When planning to use a qualified biomarker, drug sponsors should identify within their IND/NDA/BLA which methodology or assay is proposed for use. If the methodology or assay is the same as was used to generate the data to support the qualification, no further information on the method or assay is needed. If a sponsor chooses an alternate assay or method the sponsor should provide the review division, via submission to the particular IND/NDA/BLA, information to support the conclusion that the alternate method or assay is similar to those that are known to support the qualified COU. This will most easily be accomplished when a comparison of performance on appropriate test samples is carried out with the new assay and the assay used in qualifying the biomarker. If that comparison can be adequately evaluated, the drug sponsor will not have to obtain additional evidence.

Qualified Biomarkers in the Context of Regulated Diagnostics

Most biomarkers (and some COAs) will be measured using a device to perform the actual measuring procedure. Examples include a biochemical assay of blood samples; a way to count cells of some specific phenotype in a blood or tissue sample; a pressure measuring device to measure blood pressure or intraocular pressure; imaging instrumentation or activity monitors. The analytical performance of the device will be considered during the evaluation of the DDT for qualification. In most cases, devices for clinical evaluation will have been (or will need to be) reviewed by FDA to be commercially marketed if they are to be used in management of patients in clinical practice.¹⁹

¹⁹ See also the draft guidance, *In Vitro Companion Diagnostic Devices*, issued in July 2011. Once finalized, this guidance will represent FDA's thinking on this topic.

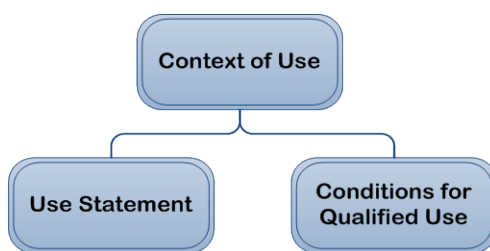
Contains Nonbinding Recommendations

Review of the device and authorization for its marketing is an entirely separate process from qualification. Devices for marketing approval are evaluated by CDRH/CBER to assess their ability to reliably and accurately measure the biomarker and assess whether the device provides clinically useful information when used as intended. DDTs being considered for qualification, however, are intended to be conceptually independent of the specific device performing the measurement. Multiple devices that reliably and accurately measure a qualified DDT are expected to yield the same results. Thus, although a DDT cannot become qualified without a reliable means of measuring it, FDA clearance of a measurement device does not imply that what it measures has been demonstrated to have a qualified use in drug development and evaluation. Data from studies designed to show that a DDT has a clear role in drug development will be requested from submitters to establish qualification. Conversely, qualification of a DDT does not imply that a specific device used in the qualification process has automatically been reviewed for commercial use. The commercial marketing for clinical use of the device requires submission to, and review by, CDRH/CBER. Qualification of any DDT by CDER does not create an indication for any medical device and does not allow for approved marketing of such a device for the qualified use.

Context of Use Statement in the Biomarker Qualification Process

This section provides guiding principles for formulating a **COU** statement for biomarkers being proposed for qualification through CDER's Biomarker Qualification Program (BQP). As illustrated in Figure 1, a COU statement contains a concise biomarker **use statement** and a comprehensive description of conditions for the biomarker to be used in the qualified setting, termed the **conditions for qualified use**.

Figure 1. Appropriately Constructed Context of Use



- **Use statement.** The use statement should be concise and include the name and identity of the biomarker(s) and purpose for use in drug development.
- **Conditions for qualified use.** The conditions for qualified use should contain a comprehensive description of conditions for the biomarker to be used in the qualified setting.

Some of the elements that should be captured in formulating a clear and comprehensive COU statement are provided in Table 1 (see below).

Elements of the COU statement, in particular the conditions for qualified use, may not be fully determined when the letter of intent (LOI) is submitted. Nonetheless, submitters should make the COU statement as comprehensive and clear as possible at the time of initiating interactions

Contains Nonbinding Recommendations

with the BQP. Submitters should begin to consider major parameters that might constitute conditions for qualified use in a final (qualified) COU when formulating their initial COU statement for the LOI. Elements of the COU statement that will need further determination, as knowledge about the biomarker develops, should be identified early in the qualification process. The COU statement generally is refined and clarified during the consultation and advice stage of the biomarker qualification process through discussions between submitters and CDER. A well-developed COU statement can greatly streamline these interactions in the consultation and advice stage of the qualification process. The biomarker QRT's understanding of the intended COU is of utmost importance in guiding discussions between FDA reviewers and submitters on what evidence is needed to support biomarker qualification.

Table 1. Elements of the COU Statement for Biomarker Qualification*

	Elements of COU statement	Examples	Notes
1	Identity of the biomarker	<ul style="list-style-type: none"> - Specific type of radiologic exam with specific imaging modalities (e.g., MRI, PET, Doppler) - Specific substance/analyte in physiologic fluid - Specific genomic biomarker 	<p>The term <i>biomarker</i> may refer to a single biomarker with a single, specific COU, or to a <i>composite biomarker</i> that is made up of several individual biomarkers combined in a stated algorithm to reach a single interpretation.</p> <p>A <i>COU</i> applies to the composite biomarker as a unified entity. Individual components of the composite biomarker do not have separate COUs unless they are intended for use as stand-alone biomarkers.</p>
2	Aspect of the biomarker that is measured and the form in which it is used for biological interpretation	<ul style="list-style-type: none"> - Specific aspect of radiologic findings such as lesion number, volume, diameter, area, perimeter or other characteristics (e.g., tumor volume). - A specific measure of organ size - Serum level of an analyte; possibly also specified in relation to time (e.g., at a specific time, steady-state, AUC, post-treatment minus pre-treatment) - Used in graded measurement form or after threshold categorization (e.g., change relative to a reference such as baseline, historical control, or normal range, or X-fold change) 	<p>Certain biomarkers may require explicit temporal statements such as the window of measurement time if applicable.</p> <p>Specify the mode(s) of measurement when applicable (e.g., MRI, PET, and ultrasound).</p> <p>Specific physiologic fluid/tissue or site of sampling may need to be noted (e.g., plasma, serum, urine, saliva, sweat, cerebral spinal fluid (CSF)).</p>

Contains Nonbinding Recommendations

	Elements of COU <i>statement</i>	Examples	Notes
3	Species and characteristics of animal or subjects studied	<ul style="list-style-type: none"> - Animal species or range of species - For each species, important characteristics (e.g., strain, age, sex, disease model, healthy) - Human and important characteristics (e.g., age, race/ethnicity, sex, disease, healthy, genotype, disease phenotype) 	<p>Provide the relevant details needed to understand the target species, group of species, or patients for which biomarker qualification is sought.</p> <p>Certain qualified biomarkers may apply specifically to a sub-set of individuals or strain of the species studied. If so, this sub-set or strain should be specified in the COU statement.</p>
4	Purpose of use in drug development	<ul style="list-style-type: none"> - Demonstration of absence of toxicity (nonclinical or clinical). - Demonstration of organ toxicity without performing extensive histopathology (nonclinical biomarkers) - Evaluation of exposure-response - Use in clinical study subject enrollment or randomization (e.g., diagnostic, enrichment, stratification) 	<p>A general description of this element will usually be a part (explicit or implicit) of the use statement component of the COU statement. In addition, a more precise description may be included in the conditions for qualified use section.</p> <p>For many biomarkers, this will be the biological interpretation of the biomarker measurement, and that interpretation is then applied to make the decision described for element #6.</p>

Contains Nonbinding Recommendations

	Elements of COU <i>statement</i>	Examples	Notes
5	Drug development circumstances for applying the biomarker	<p>- Nonclinical:</p> <ul style="list-style-type: none"> • determination of “no observable adverse effect level” (NOAEL) for a specific toxicity when prior toxicology studies did not identify a NOAEL with adequate precision; • selection of the best drug candidate among several drug candidates based upon a specific toxicity; • demonstration of activity of the drug on the disease pathophysiology (via an animal disease model) <p>- Clinical :</p> <ul style="list-style-type: none"> • selection of doses to take into phase 3 study (i.e., apply biomarker in dose finding studies intended to predict efficacy); • ensuring patient safety in dose escalation safety studies; • demonstration of activity of the drug on the disease pathophysiology (i.e., clinical proof-of-concept studies) 	Describe the situation in drug development when application of the biomarker improves the drug development process. This might be a description of a type of problem that arises in drug development and for which the biomarker enables making a decision.

Contains Nonbinding Recommendations

	Elements of COU <i>statement</i>	Examples	Notes
6	Interpretation and decision/action based on biomarker	<ul style="list-style-type: none"> - Biomarker levels above N indicate cellular injury in [organ X]. The NOAEL level is below the exposure in which the signal was observed and should be used in determining starting doses in clinical studies - Biomarker levels above N indicate a physiologic response has occurred, and the drug compound can be advanced for development - The absence of biomarker levels above N indicated no significant organ injury has occurred, and the drug candidate(s) with this profile can be advanced for further development - The absence of biomarker levels above N indicate no significant organ injury has occurred, and dosing may continue in such patients - Patients with biomarker levels greater than N are expected to have an endpoint event rate of approximately Y or greater and should be enrolled in the clinical study - Patients with the biomarker positive for the presence of Z have at least a N-fold greater risk of an adverse response to drugs acting via mechanism of action Y and should not be enrolled in clinical studies (or, if the biomarker is a response biomarker, such patients should have dosing discontinued). 	<p>This element of the COU statement defines the interpretation that is drawn from measurement of the qualified biomarker and the effect of that interpretation on the drug development program.</p> <p>For composite biomarkers, the algorithm used to combine components leads to a single interpretation, and that single interpretation is applied to decision-making and has an effect on the drug development program.</p> <p>For some biomarkers, the decision (drug development action) cannot easily be separated from the description of the purpose and circumstances of use or the interpretation of the biomarker, and two or more of these elements would be combined in phrasing the appropriate condition of use (i.e., there may not be separate statements for each of these elements in all cases).</p>

* Table 1 is a guide to the elements of COU statement but should not be the format for submission of the COU statement. A COU statement can be formatted in paragraph form, or as a use statement plus conditions for qualified use as a list.

Not all elements in the table are relevant for every biomarker. In addition, the COU statement does not need to have all the elements in the same order as the table. The elements listed in Table 1 should be incorporated on an as-needed basis for the respective COU statement. This list of elements is also not intended to be exhaustive. Some biomarkers have other elements, such as drug classes/categories (e.g., drugs that activate a specific receptor or that cause toxicity by a given mechanism) that may need to be included as part of the COU statement to ensure clarity. Submitters should include these as needed.

Important Considerations in Constructing a COU Statement

The **initial COU statement** is written as the use statement plus the conditions for qualified use (see figure 1) for which the submitter proposes they have or will obtain the evidence to support. The COU will be refined as additional knowledge accumulates. The proposed COU statement can be modified during the consultation and advice stage based on the evidence.

The **use statement** will likely include the identity of the biomarker (or analyte), the general information provided by the biomarker and/or the overall utility in drug development. Some examples of the biomarker use statement are:

[Biomarker A] is a measure of non-clinical skeletal muscle toxicity for use in non-clinical safety assessments of drugs.

[Biomarker B] is a surrogate marker for clinical benefit of drugs used to treat [disease Y] for use as a basis for new drug approval.

[Biomarker C] is a prognostic marker of disease progression in patients with [disease Z] for use as an enrichment factor in [disease Z] treatment studies.

Some biomarkers may have multiple applications in a drug development program that relate to a single purpose of use that is not exclusively specific to any one of the applications. In this case, the decision or impact on the drug development program may be best conveyed with examples of the different specific applications.

The **conditions of qualified use** should describe how, in what animals or subjects, and in what kinds of studies, the biomarker will be applied in the future to be within the qualified COU and not how the biomarker was studied to support qualification. For example:

The COU should **not** say “evidence to support the biomarker qualification came from dog toxicology studies of up to 7 days of exposure.” Rather, it could say “[Biomarker X] can be used in dog toxicology studies of up to 7 days exposure” (if 7 days is the limit of qualification that was determined during the review stage).

Mode of measurement as part of the COU statement: The biomarker used in the qualified setting may be dependent upon the specific modality and method used for its measurement. These specifics will need to be adequately identified in the qualified conditions of use. For example:

A specific plasma protein as a biomarker would have been measured with one or more specific assay methods to provide the data reviewed during qualification. The information on qualified conditions of use should identify which assays were used and are known to provide accurate and precise measurements at the time of qualification. The information may provide the important performance parameters or any other assay-related information that will assist users of the biomarker in evaluating whether an alternate assay is also adequate for the biomarker measurement.

An imaging biomarker is obtained using one or more imaging modalities (e.g., MRI, CT, ultrasound), and quantitative measurements assessed using specific methods (e.g., specific software packages). The information on qualified conditions of use should

Contains Nonbinding Recommendations

identify which modalities and measurement methods are known to be adequate, and where possible, performance characteristics that enable an assessment of any future modality or software package as an alternative.

CDER strongly recommends that a decision-tree diagram be included. The statement of COU is often greatly clarified by including an explicit decision-tree diagram that illustrates the application of the biomarker(s) in the COU and includes the actions that would be taken based on the biomarker results.

APPENDIX 3: LETTER OF INTENT TO PROPOSE BIOMARKER QUALIFICATION

The biomarker qualification letter of intent (LOI) should be accompanied by a cover letter (see section VII) and should include the following information:

1. Administrative structure

Description of the submitter including, but not limited to, principal investigator(s), working group member(s), institutions, and contact information not contained within the cover letter

2. Biomarker qualification overview

- a. Introduction
- b. Clear identification of the biomarker and a brief description of how it is measured
- c. Proposed COU (see Appendix 4)
- d. High-level description (1 to 2 pages in length) of the important current knowledge related to the COU. This description should provide a data overview that supports the use of the biomarker for the proposed COU.
- e. A brief overview of the data the submitter plans to obtain from ongoing or future studies to further support the biomarker for the proposed use
- f. Indication of whether there are plans to submit the biomarker to other regulatory agencies for qualification

3. Process-related questions for CDER (provision of scientific questions may be deferred to submission of the initial briefing package)

APPENDIX 4: BIOMARKER QUALIFICATION INITIAL BRIEFING PACKAGE

The biomarker qualification initial briefing package (IBP) should include the following sections. As is the case for all submissions to the Biomarker Qualification Program, a cover letter (refer to section VII) should also be included.

1. Introduction and overview

This should include a concise description of the disease and/or experimental setting in which the biomarker would be used, a description of the biomarker and the rationale for its use in drug development as intended in the proposed COU.

The introduction should briefly summarize important characteristics and knowledge of the biomarker, including;

- Strengths and limitations (e.g., comparison with relevant standard methods when available, presence/absence of information on pertinent species/population)
- Whether it is a single or composite biomarker. If a composite biomarker, identify its components, the rationale or method through which these were selected and the algorithm for how the components are combined into a unified composite biomarker.
- Objective and design of the existing studies supporting its use, such as prospective versus retrospective study design, cohort study versus case-control study, study comparators, if applicable, and sample size
- An assessment of expected benefits arising from the use of the biomarker
- Identification of unresolved issues and a brief description of plans to resolve them

2. Proposed COU statement in the biomarker qualification process

3. Current knowledge regarding the biomarker and support for the proposed use

An overall discussion should include an integrated analysis of the existing relevant study results, including interpretation of how the biomarker performance supports its use in the proposed context.

This discussion should be followed by identification of specific issues regarding the biomarker and the evidence currently available. Study synopses of existing studies (nonclinical or clinical as appropriate) and summary data result tables/figures should be provided. Submitters should refrain from simply providing statements of conclusions from the existing studies. Features of the studies important for assessing the relevance of the study to the proposed COU for the biomarker should be described. The document should distinguish between existing studies that are known only from a published report in a journal and those where the original protocol and primary data are available to the submitter. Inconsistencies between studies in important findings, if any, should be discussed.

Important study aspects may include details of how the biomarker was measured in the studies (as compared to how proposed for qualification), what the observed or expected variability is, and how the potential for variability (e.g., intra- patient and inter- patient) was addressed. If

Contains Nonbinding Recommendations

multiple methods or devices were used in prior studies, or are proposed for future use, variability introduced by the use of different methods should be discussed.

Study-quality documentation is usually not essential for the initial briefing document, but may be useful for submission of the qualification package.

4. Knowledge gaps and development plan

This section should describe the limitations of the existing information that create important gaps in the knowledge needed to fully support the biomarker qualification. Issues encountered during the studies should be described and whether they were resolved or remain to be resolved should be clearly stated. The studies that are proposed to obtain the additional information should be described, clearly indicating what issues the studies are intended to address. Important features of the design of proposed studies should be described, as feasible. Full study protocols are usually not necessary for the initial briefing document and meeting, but may be important for subsequent meetings. If the biomarker development program is planned as a multistep process, details of the immediate next steps and more general descriptions of the later steps should be described. It is helpful to provide a potential time line for the development plan, as feasible.

5. Measurement methodology

This section should describe the methodology for measuring the biomarker, with sufficient detail to provide an understanding of the physical devices used, specialized software needed (e.g., automated digital image analysis software), critical operating characteristics of the measurement system, and general availability of the components of the measuring system (versus components available only to the submitter and not available to outside organizations).

6. Specific questions for CDER

This section should include any questions for CDER, with sufficient detail and context of the respective questions to enable the QRT to provide meaningful responses.

Appendix

List of references.

It is helpful to include copies of the selected references the submitter regards as most pertinent to the submission. Copies of a large number of references should generally not be included.

APPENDIX 5: LETTER OF INTENT TO PROPOSE COA QUALIFICATION

The clinical outcome assessment (COA) letter of intent (LOI) is a concise document that should be accompanied by a cover letter (refer to section VII) and should include the following information:

1. Administrative structure

Description of the submitter including, but not limited to, principal investigator(s), working group member(s), institutions, and contact information not contained within the cover letter.

2. Concept(s) of interest (COI) for meaningful treatment benefit

- a. A description of the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., presence/severity of symptoms, limitations in performance of daily activities)
- b. Targeted labeling or promotional claim(s) based on the COA to be developed (i.e., proposed wording)

3. COU for COA qualification

- a. Targeted study population including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, comorbidities, language/culture groups)
- b. Targeted study design and statistical analysis plan (includes the role of the planned COA in future drug development clinical trials, including the planned set of primary and secondary endpoints with hierarchy, if appropriate)
- c. Applicable study settings for future clinical trials
 - i. Geographic location with language/culture groups
 - ii. Other study setting specifics (e.g., inpatient versus outpatient)

4. COA type

- a. PRO, ClinRO, ObsRO or performance measure
- b. General description of proposed or existing measure

5. Need for the qualified COA

- a. Overview of existing related outcome assessments
- b. Identification of the gap(s) in measurement

6. Indication of whether the Submitter plans to submit the COA to other regulatory agencies for qualification

7. Process-related questions for CDER (provision of scientific questions may be deferred to submission of the briefing package)

APPENDIX 6: COA QUALIFICATION INITIAL BRIEFING PACKAGE

The COA qualification initial briefing package (IBP) should be accompanied by a cover letter (refer to section VII) and should include the following sections:

Section 1: Proposed Plan for COA Qualification

The following areas should be addressed for CDER review. The extent of information provided in each section will vary depending upon the evidence currently available to address each issue.

1.1 Introduction and overview

This should include a concise description of the disease and the clinical trial setting in which the COA would be used, the limitations of existing assessments, a brief description of the existing or planned COA, and the rationale for use in drug development.

1.2 COI for meaningful treatment benefit

- Describe the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., the specific symptom presence or severity or limitations in performance or daily activities relevant in the targeted COU)
- Identify targeted labeling or promotional claims based on the COA (i.e., proposed claim wording)

1.3 COU

- Identify the targeted study population, including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, language/culture groups)
- Identify the targeted study design. Most commonly the COA will be used to assess the change (compared to a control) induced by a medical treatment.
- Identify the targeted study objectives and endpoint positioning (i.e., planned set of primary and secondary endpoints with hierarchy). Usually, the COA will serve as a primary or secondary study endpoint.

1.4 Critical details of the measure to the degree known

- Reporter, if applicable
- Item content or description of the measure
- Mode of administration
- Data collection method

1.5 Overview of current COA development status (for existing measures or for measures already under development)

1.6 Description of the involvement of external expertise, including scientific communities or other international regulatory agencies, if applicable

Section 2: Summaries of Planned Studies or Completed Studies

- 2.1 Evidence of content validity (i.e., documentation that the COA measures the COI in the COU)
 - Development of the measure
 - Literature input
 - Expert input
 - Reporter input (e.g., for PRO measures, concept elicitation, focus groups, or in-depth qualitative interviews to generate items, select response options, recall period, and finalize item content)
 - Other input
 - Justification for scoring algorithm (e.g., for multi-item COAs, the rationale and algorithm for how the items and domains are combined into a single score)
 - For COAs with multiple versions, process for establishing that content validity is comparable between versions (e.g., COAs with multiple administration modes or methods)
- 2.2 Cross-sectional evaluation of measurement properties
 - Score reliability (including test-retest or inter-rater reliability)
 - Construct validity (comparison with other measures, e.g., patient and clinician global assessments)
- 2.3 Longitudinal evaluation of measurement properties
 - Longitudinal construct validity
 - Ability to detect change
- 2.4 Longitudinal evaluation to provide guidelines for interpretation of trial results
 - Evaluation of individual patient change (e.g., responder definition(s))
- 2.5 Language translation and cultural adaptation, if applicable
 - Process for simultaneous development of versions in multiple languages or cultures
 - Process for translation/adaptation of original version
 - Evidence that content validity is similar for versions in multiple languages
- 2.6 User manual, as available
 - Summary of current experience and known measurement properties in the targeted context of use
 - Administration procedures
 - Training materials
 - Scoring and interpretation procedures
 - Copy of all versions of the COA (or screen shots, if applicable)
- 2.7 Appendices (may include)
 - List of references and copies of only the most important references that the submitter feels CDER reviewers may want to review
 - Study documents (e.g., protocols, analysis plan, interview guide, data collection form(s))

Contains Nonbinding Recommendations

Note: The link to appendices should be embedded in the relevant summaries.

Section 3: Questions

Specific questions for CDER

APPENDIX 7: ANIMAL MODELS: ADDITIONAL CONSIDERATIONS

The discussions in this appendix are focused on study conduct and the limitations of qualification.

For more information on the letter of intent (LOI), the initial briefing package (IBP), and other resources, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284078.htm>

Study Conduct

There are no regulations that specifically address data quality and integrity issues for studies conducted for purposes of animal model qualification. Qualification is a regulatory recommendation; thus, these studies should be conducted in a manner that ensures data quality and integrity. FDA considers the Good Laboratory Practice of Nonclinical Laboratory Studies regulations²⁰ (GLP) to be a well-established and relevant system for ensuring data quality and integrity; therefore, FDA recommends the use of GLP, to the extent practicable, for the model defining natural history studies.²¹ Submitters should also identify aspects of the studies anticipated to be challenging and propose methods for adapting the studies to ensure the quality and integrity of the resulting data. Submitters should provide this information to FDA for concurrence on the data quality and integrity plan before the studies are initiated. The studies submitted for qualification will be subject to inspection by FDA to verify the quality and integrity of the data.

Submitters should contact the Animal Model Qualification program (AnimalModelQualification@fda.hhs.gov) for further discussions regarding study conduct practices.

Limitations of Qualification

A qualified animal model does not guarantee that the model will be found acceptable under the second criterion of the Animal Rule as “a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans.” The regulatory decision to allow the use of a single species will be made on a case-by-case basis.

²⁰ See 21 CFR 58.

²¹ The *model defining natural history studies* are the animal studies that establish the ranges of values of key parameters of the disease or condition that will be specified in the COU for the qualified model and will be used as measures of quality control and quality assurance when the model is replicated.

Contains Nonbinding Recommendations

The qualification process is intended to expedite development of publicly available animal models that can be used in multiple drug development programs. Drug developers can use a qualified animal model as long as:

- The study is conducted properly (e.g., all procedures and protocols specified in the COU are followed and the data are verifiable).
- The DDT is used for the qualified purpose (e.g., same animal species, same challenge strain, untreated animals within the quality control limits specified in the COU).
- At the time of qualification, there is no new information that conflicts with the basis for qualification.