Guidance for Industry

Qualification Process for Drug Development Tools

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Shaniece Gathers, 301-796-2600.

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

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Clinical/Medical

Guidance for Industry

Qualification Process for Drug Development Tools

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Office of Communication
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
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
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Guidance for Industry[1]

Qualification Process for Drug Development Tools

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 qualification process for drug development tools (DDTs) intended for potential use, over time, in multiple drug development programs. DDTs include, but are not limited to, biomarkers and patient reported outcome (PRO) instruments. The guidance provides a framework for interactions between CDER and DDT submitters[2] to identify data needed to support qualification of a DDT and creates a mechanism for formal review by CDER to qualify the DDT.

Qualification is a conclusion that within the stated context of use, the results of assessment with a DDT can be relied upon to have a specific interpretation and application in drug development and regulatory decision-making.

This guidance is not intended to discuss the review of DDTs that are submitted as part of regulatory applications for a specific drug development program. Furthermore, it does not address 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.

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[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] For purposes of this guidance, *submitter* means a person, group, organization, or consortium that undertakes to collect, refine, and submit data to CDER in support of a DDT qualification using the procedures described in this guidance. If a DDT is qualified under this guidance, the qualified DDT will be made publicly available for use by sponsors of any drug or biologic investigational new drug (IND) or new drug application (NDA) or biologics license application (BLA) (see section VI). Sponsors who are developing a DDT for their own proprietary use should submit the necessary information to their IND, NDA, or BLA, rather than using the procedures described in this guidance.

II. BACKGROUND

FDA's Critical Path Initiative (CPI) recognized that the process of drug development and the availability of new therapies have not been as strongly affected by recent advances in biomedical science as might be possible. The nature of drug development has become increasingly challenging and resource intensive. One of the key areas identified by the CPI as potentially enabling advances in drug development is application of scientific advances as new tools to aid drug development. These tools may, in part, address some of these difficulties and speed the availability of new products that might also be more effective or safer with clinical characteristics that are better understood.

CDER has undertaken multiple initiatives to aid the development of new DDTs. Among these efforts is the development of a formal process, described in this guidance, that CDER will use in working with submitters of these tools to guide them as they refine the tools and rigorously evaluate them for use in the regulatory process.

If a DDT is qualified, analytically valid measurements of it can be relied upon to have a specific use and interpretable meaning in drug development. The qualification process is expected to expedite development of successful marketing applications. Once a DDT is qualified for a specific context of use, industry can use the DDT for the qualified purpose during drug development, and CDER reviewers can be confident in applying the DDT for the qualified use without the need to reconfirm the DDT's utility.

Because of the substantial work needed to achieve qualification, CDER encourages the formation of collaborative groups to undertake these tool-development programs to increase the efficiency of joint efforts and to lessen the resource burden upon any individual person or company working to gain qualification for a tool. A variety of projects undertaken by various consortia have demonstrated the usefulness of this approach. As described later in this guidance, CDER intends to make public the qualification determinations for a particular DDT, when those determinations are made in accordance with the process described in this guidance, to aid in making the tool known and available for use by all drug developers, thus maximizing the value to the public health. [3]

At the present time, CDER has seen the greatest activity towards qualification in the areas of biomarkers and PROs, and CDER staff have been identified to support these efforts. As active scientific communities emerge to undertake the work to qualify DDTs in other categories, CDER will support these efforts as well. A specific office within CDER will be assigned as the lead for each type of DDT, and will identify specific staff for oversight of the CDER qualification advice and review activities.

CDER anticipates that this guidance will encourage individuals and companies with an interest in these tools to advance their development. In providing this guidance, we expect that DDT

[3] Disclosure determinations made in connection with an IND, NDA, or BLA will be in accordance with the disclosure regulations applicable to other material in the IND, NDA, or BLA.

submitters will better understand the process through which CDER will evaluate the data for a specific context of use.

III. DRUG DEVELOPMENT TOOLS

A. Biomarkers

A ***biological marker*** or ***biomarker*** is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or biological responses to a therapeutic intervention.[4] A biomarker can define a physiologic, pathologic, or anatomic characteristic or measurement that is thought to relate to some aspect of normal or abnormal biologic function. Changes in biomarkers following treatment 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 may reduce uncertainty in drug development and evaluation by providing quantitative predictions about drug performance. There is a further description of some types of biomarkers and use in drug development in Appendix 1.

B. Patient Reported Outcome (PRO) and Other Types of Rating Scale Instruments

A patient-reported outcome (PRO) instrument is a means of capturing patient reported outcome data used to assess the impact of treatment as an objective of a clinical trial. A rating scale PRO instrument is composed of a subjective rating scale or questionnaire plus the information and documentation that support its use. Subjective rating scales, including PRO instruments, in addition to clinician or observer rating scales that measure important aspects of clinical benefit in a given population, can be used as the basis of medical product approval and labeling[5] claims if the measure is deemed to be a *well-defined and reliable*[6] assessment of the study objectives, if the findings are supported by appropriately designed *investigations,* AND if the instrument measures the concept represented by the claim. In addition to PRO tools, the Agency will also consider qualification of other clinical trial outcome measurement tools developed to support labeling claims, such as clinician rating scales and caregiver rating scales, where a respondent is requested to assign a rating to a concept using a process similar to that used for PROs.[7] Developing well-defined and reliable tools that assess important aspects of patient health status and integrating them into clinical trials can make certain trials more informative concerning the

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

[5] *Labeling* refers to the information about an FDA-approved medical product intended for the clinician to use in treating patients. See 21 CFR 201.56 and 201.57 for regulations pertaining to prescription drug (including biological drug) labeling. Section 201.56 specifically describes the need for labeling that is not false or misleading. See 21 CFR part 801 for medical device labeling. See 21 CFR 606.122 for blood and blood products for transfusion.

[6] 21 CFR 314.126.

[7] 21 CFR 314.126.

benefits and risks of treatment. Often there are no existing tools specific to the disease/condition and the clinical trial population to serve as well-defined and reliable assessments of clinical benefit.

Issues relevant to FDA review of both new and existing instruments are summarized in FDA's guidance for industry on *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf).

IV. WHAT IS QUALIFICATION?

Qualification is a conclusion that within the stated context of use, the results of assessment with a DDT can be relied upon to have a specific interpretation and application in drug development and regulatory review. Once qualified, the DDT can be used by drug developers for the qualified context in IND and NDA/BLA submissions without requesting that the relevant CDER review group reconsider and reconfirm the suitability of the DDT.

The term "context of use" is used as shorthand for a comprehensive statement that fully and clearly describes the manner and purpose of use for the DDT. The context of use statement would describe all important criteria regarding the circumstances under which the DDT is qualified. The qualified context of use defines the boundaries within which the available data adequately justify use of the DDT. The DDT may also have potential value outside these boundaries. As data from additional studies are obtained over time, submitters of DDTs will be able to continue working with the relevant Qualification Program (Biomarker Qualification Program for biomarkers or CDER-SEALD Endpoints for PRO and other rating scales) to submit additional data and expand the qualified context of use.

An additional distinction relating to biomarkers is important to bear in mind. Most biomarkers will be measured using a device of some type to perform the actual measuring procedure, such as a biochemical assay of blood samples, or counts of cells of some specific phenotype in a blood or tissue sample. In most cases, devices for 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. Review of the device and authorization for its marketing is an entirely separate process from qualification. Devices are evaluated for their ability to reliably and accurately measure the biomarker, with the device performance as the dominant factor in the marketing authorization process. However, biomarkers being considered for qualification are intended to be conceptually independent of the specific device performing the measurement. Any device that reliably and accurately measures the biomarker is expected to yield the same results. While a biomarker cannot become qualified without a reliable means to measure the biomarker, FDA clearance of a measurement device does not imply that the biomarker has been demonstrated to have a qualified use in drug development and evaluation. Data from studies designed to achieve that objective will be needed to establish qualification. Conversely, qualification of clinical biomarkers does not imply that a specific device used in the qualification process for a biomarker has automatically been reviewed for commercial use. The commercial marketing for clinical use of

the device requires submission to, and review by, CDRH. We anticipate that devices intended for use in patient management will have appropriate CDRH review.

Why is CDER Developing a Qualification Process?

DDT acceptance in the drug development and regulation process has previously been on a sponsor-by-sponsor, drug-by-drug basis. Drug sponsors seeking to use a specific DDT have typically developed only enough data to justify its use in that one case. Use in other clinical settings or with other drugs is often left undetermined, and other drug sponsors may have little ability to build upon that knowledge to more easily expand the tool's use. In addition, the case-by-case approach will often inhibit developing a DDT in the first place. It may require substantial resources and time to develop sufficient data to justify the use of a DDT for a specific purpose within a single specific drug development program. Drug sponsors may not wish to delay development of the drug to accomplish this if there is another approach to develop the drug without the DDT, or to devote such a substantial amount of resources to DDT development if they see themselves using the tool only in that single drug development program.

In contrast, 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, multiple drugs, or drug classes. Having a qualified DDT that many sponsors will be able to use will aid in advancing therapy development and evaluation in multiple cases, and can more widely benefit patients. Qualification also creates a collaborative setting where there can be advantages for multiple interested parties (individuals or companies) working together to develop a DDT for qualification. The reduction in resources for each collaborator may also allow interested parties to join a DDT development effort well in advance of being certain it will be of immediate value to them, and thus speed the DDT development so if that DDT is shown to have value in a drug development project, it will be available to them when needed.

A formal qualification process may have advantages for CDER, as well. Previously, if there were multiple sponsors interested in using a particular DDT, or one sponsor interested in using a DDT in multiple different clinical settings, there would be multiple evaluations of the data justifying 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 would be reviewed by CDER thoroughly, but only once. Subsequently, the DDT could be relied upon within the qualified context of use, largely without further detailed review. Drug sponsors of IND's, NDA's, and BLA's may choose whether to develop a DDT under an application or under the procedures described in this guidance (see footnotes 2 and 3).

V. PROCESS FOR QUALIFICATION

The CDER process for DDT qualification is a framework for interactions between CDER and DDT submitters to guide the collection of data to support a DDT's prospectively specified context of use. The qualification process consists of an initial stage of regulatory consultation and advice and a second stage of review for the qualification determination. The goal of this process is to reach a conclusion regarding the adequacy of the submitted data to support the DDT's qualification and context of use.

Early DDT development will generally occur before formally beginning the qualification process, which is intended to begin after CDER agrees that a DDT development program is likely to be worthwhile.[8] Submitters should request to begin the qualification process when they have sufficient data to support the initial submission.

The initial stage of the CDER qualification process involves consultation and advice that is intended to assess what data will be necessary for a qualification submission. This stage may involve multiple information-gathering and data assessment steps. Advancement from one step to the next is based on concurrence of the submitter and CDER. CDER will work closely with submitters to advise them on the nature and extent of evidence that should be obtained before submission of the DDT's qualification data package for regulatory review.

CDER intends to interact with DDT submitters to most effectively advance DDT development. During the consultation and advice stage, CDER-submitter interactions will largely be initiated by the DDT submitter as they develop the data and seek further discussions and advice. The qualification process enters the review stage when the data are thought to be sufficiently complete and adequate to allow for substantial review.

In the review stage, CDER will perform a full review of the complete data package and render a qualification decision. CDER review offices will participate actively in the qualification review process and weigh in on the final qualification recommendation. During this stage, CDER may initiate submitter interactions if the review raises questions for which clarifications or further information is needed.

Once a DDT is qualified for a specific use, the context of use may become modified or expanded over time as additional data are collected, submitted, and analyzed. Alternatively, if the growing body of scientific evidence no longer supports the context of use, the DDT qualification may be withdrawn.

A. Stage 1: Consultation and Advice

1. DDT Letter of Intent (LOI)

The consultation and advice stage begins with a Letter of Intent (LOI) from the submitter. The LOI is a request for an initial response from CDER concerning the potential value of a DDT. Submitters should submit this request when they have a well-identified DDT concept and evidence indicating a potential to have one or more uses in drug development. The LOI should include a short summary of the DDT, its proposed context of use, a brief overview of the available data, and a summary of the studies planned to generate data supporting potential qualification. See Appendices 2 and 3 for suggested LOI content. CDER will evaluate the LOI and make a determination on whether or not to continue with the consultation and advice stage, and communicate the decision to the

[8] The Voluntary Exploratory Data Submission (VXDS) mechanism may be valuable to submitters during early DDT development for biomarker DDTs.

submitter. If CDER declines the DDT request, a communication to the submitter will include the reasons why the decision was reached, and advice on alternative paths for DDT development and consideration.

2. DDT Briefing Package and Initial Meeting

If CDER accepts the DDT request, the submitter should then submit a briefing package. See Appendices 4 and 5 for suggested content for this initial briefing package (see section VII).

At this point a Qualification Review Team (QRT) will be created to provide ongoing advice to the DDT submitter about the evidence needed for qualification. A QRT is composed of CDER review staff from various relevant disciplines with expertise appropriate to review of the submission.

A meeting between the QRT and the submitter may include the following agenda topics:

- Thorough discussion of the submitter's goals, including context of use
- Assessment of the available data to support the objectives
- Identification of gaps in knowledge that should be addressed
- Discussion of the additional data that will be important for the submitter to obtain in support of the qualification, and the sources for that data (e.g., new studies to be designed and conducted)
- Consideration of possible alternative qualification objectives related to efficiency of filling knowledge gaps from present state of knowledge

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

3. DDT Investigation and Development

The DDT submitter then works to acquire the additional data identified during the meeting. Additional meetings between the QRT and the submitter can occur as needed during the DDT development effort to allow the QRT to provide expert advice relevant to the specific DDT proposal. During these meetings, topics of discussion and advice may include the rationale for the proposed DDT and its context of use, newly acquired data, open questions regarding the context of use that require further data collection, potential studies 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 CDER has reviewed summaries of the accumulated data and agreed that the identified critical knowledge gaps have been addressed, the process will proceed to the review stage.

B. Stage 2: Review for Qualification Decision

(1) When the submitter believes the data are sufficiently complete to support a conclusion that the DDT is qualified for a specific context of use (i.e., "fit for purpose") and CDER concurs that detailed, formal data review is warranted, the submitter should submit a formal qualification package. This submission should contain the complete and detailed description and analyses of the studies providing the evidence to justify qualification of the DDT for the requested context for use. Primary data from studies can be included as appropriate.

(2) The QRT will review the qualification package, discuss the project at internal meetings, and arrive at a QRT recommendation on the qualification decision. The QRT will interact with the submitter during the review to gain clarification about particular aspects of the qualification package or to request additional information as needed. Individual discipline reviews, as needed, and a combined executive summary review document for the qualification recommendation will be prepared by the members of the QRT. In the case of complex or controversial DDT development programs, CDER may choose to hold public discussions.

(3) The reviews will be provided to the participating CDER offices for discussion, as needed, and concurrence.

(4) If the review and decision-making process results in a CDER decision to qualify the tool, a Statement of Qualification summarizing CDER's qualification determination will be issued as a draft guidance (see section VI).

VI. PROCEDURES FOR MAKING RECOMMENDATIONS AVAILABLE

To make information about qualified DDTs available to the public, CDER intends to use the following process:

- New determinations for qualification of DDTs will be issued as draft guidance appendices to this guidance.

- The Agency will issue a notice in the *Federal Register* announcing the availability on the CDER Web site of each new draft qualification guidance. The notice will identify a comment period for each draft guidance appendix.

- Draft guidance appendices and supporting documents will be posted on the DDT Web Page.

- Comments on each draft guidance appendix will be considered in developing final guidance appendices. When statements of qualification are finalized or revised, those changes will also be announced in a *Federal Register* notice of availability. Additional information will be available through FDA's Web site and a link will be created from the *Drugs* guidance

page (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm) to facilitate public comment.

- If appropriate, the final guidance appendix will direct the public how to access the DDT at the location where it is maintained by the DDT developer.

VII. ADDRESSES FOR DDT CORRESPONDENCE AND DOCUMENTS

All qualification correspondence and documents should be submitted to the CDER Central Document Room at 5901-B Ammendale Road, Beltsville, MD 20705-1266. Please consult the Web site http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm085324 for the most recent information on how to submit physical media (e.g., CD-ROMs). The cover letter header should specify in bold print **DDT QUALIFICATION SUBMISSION**.

APPENDIX 1

BIOMARKERS: ADDITIONAL CONSIDERATIONS

As described in section III of this guidance, biomarkers are measurable characteristics that reflect physiological, pharmacological, or disease processes in animals or humans. Changes in biomarkers following treatment reflect the 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 levels of, or progress of a disease. Alterations in biomarker measurements indicate responses (favorable or unfavorable) related to an intervention. The biomarker may reflect biological processes closely related to the mechanism of action or processes substantially downstream. Biomarkers may 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, pulmonary function tests, cardiac ejection fraction).

For purposes of this guidance, biomarkers that can be applied to the process of drug development include prognostic, predictive, pharmacodynamic, and surrogate biomarkers as briefly described below. Of note, these categories are not mutually exclusive.

A *prognostic* biomarker is a baseline patient or disease characteristic that categorizes patients by degree of risk for disease occurrence or progression. A prognostic biomarker informs about the natural history of the disorder in that particular patient in the absence of a therapeutic intervention.

A *predictive* biomarker is a baseline characteristic that categorizes patients by their likelihood for response to a particular treatment. A predictive biomarker is used to identify whether a given patient is 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).

A *pharmacodynamic* (or activity) biomarker is a dynamic assessment that shows that a biological response has occurred in a patient after having received a therapeutic intervention. A pharmacodynamic biomarker may be treatment-specific or more broadly informative of disease response. Examples include blood pressure, cholesterol, HbA1C, intraocular pressure, radiographic measures, and C-reactive protein. 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 a pharmacodynamic biomarker to monitor for the desired effect in another clinical setting (e.g., blood pressure, glomerular filtration rate (GFR), serum lipids). These are often used during phase 2 studies to improve understanding of how to use the 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 has allowed a few of these biomarkers to be applied as surrogate endpoints (e.g., blood

pressure, HbA1C). Most pharmacodynamic biomarkers, however, are used to guide drug development, while clinical endpoints provide the basis for regulatory approval.

A *surrogate endpoint* is defined as a biomarker intended to substitute for a clinical efficacy endpoint. Surrogate endpoints are expected to predict clinical benefit (or harm, or lack of benefit or harm). A clinical endpoint is defined as a characteristic or variable that reflects how a patient feels, functions, or survives. Surrogate endpoints are a subset of pharmacodynamic biomarkers; it is likely that only a few biomarkers will be appropriate for use as surrogate endpoints.

Because there is 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 broad use as a surrogate endpoint. Qualification of a biomarker as a surrogate endpoint is likely to occur much less often than qualification of biomarkers for other uses.

Agency Use of Biomarkers

Biomarkers are commonly used in drug development programs, often based on accumulated experience, and many are also commonly used in clinical practice. The most common biomarkers in drug development are those used as safety assessments to identify a toxicity 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.

In some circumstances, a biomarker may identify a patient population subgroup that becomes the focus of clinical trials. These include prognostic biomarkers that identify patients with a disease risk most suitable for an efficient drug development program (e.g., sufficiently high risk of a disease-related event that avoidance of the event can be shown in a clinical trial of practical size and duration; sufficiently low risk rate 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 may identify a patient subgroup that has a greater potential for 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 where a biomarker, in the setting of a particular disease and the currently available therapies, can identify a subgroup for whom there is no available therapy and in whom clinical trials can most rapidly evaluate the potential benefit of a new therapy.

APPENDIX 2

LETTER OF INTENT TO PROPOSE BIOMARKER QUALIFICATION

The biomarker qualification Letter of Intent (LOI) should include the following information:

1. Administrative structure
   Description of the Submitter including, but not limited to Principal Investigator(s), Working Group Member(s), relevant institutions, and contact information

2. Biomarker Qualification Overview
   a. Introduction
   b. Proposed context of use
   c. High-level data description
   d. Integrated critical appraisal of the data/methods
   e. Additional data the submitter plans to obtain from ongoing or future studies
   f. Justification for the proposed context of use.

3. Overall Summaries of the following (as appropriate):
   a. Technical assay data
   b. Nonclinical biomarker data
   c. Clinical biomarker data

4. Questions for FDA

APPENDIX 3

LETTER OF INTENT TO PROPOSE PRO OR OTHER RATING SCALE QUALIFICATION

The PRO or Rating Scale Qualification Letter of Intent (LOI) 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

2. Context of use for Measure Development
   a. Concept to be measured
   b. Targeted labeling claim(s)
   c. Role of the planned measure in a clinical trial using an endpoint model that explains the targeted position of the measure among the primary and key secondary endpoints to support the targeted labeling claim(s)
   d. Targeted study population
   e. Justification for context of use

3. Literature overview of existing related rating scales or biomarkers
   a. Identification of the gap(s) in measurement
   b. Justification for development of a new rating scale or the need to make improvements to an existing measure

4. Questions for FDA

APPENDIX 4

STRUCTURE OF BIOMARKER QUALIFICATION BRIEFING DOCUMENT

The biomarker qualification briefing document should include the following sections:

Section 1: Administrative Information

This section should contain the following information:

- Cover letter
- Names of the principal investigators and working group members (if applicable)
- Any appropriate FDA forms
- Specific questions the submitter has for CDER

Section 2: Summaries

2.1 Introduction

This section should be concise. It should include a description of the disease and/or experimental setting in which the biomarker would be used, the definition of the biomarker (e.g., in the case of genomic biomarkers, whether a SNP, CNV, or differential gene expression signature) and a rationale for its use in drug development, including its context of use.

The introduction should summarize the key characteristics of the biomarker, including;

- Strengths and limitations (e.g., comparison with relevant standard methods where available, presence/absence of information on pertinent species/population).
- Whether it is a single or composite biomarker. If it is a composite biomarker, it should define its component markers and the mathematical algorithm through which these were selected.
- Objective and design of the studies supporting its use, such as prospective versus retrospective study design, study comparators and sample size.

A summary of the proposed context for intended use of the biomarker should be provided in this section. More details, including the full context of biomarker use, can be described in the next section. Suggested areas for consideration include the following:

- An assessment of expected benefits for the application of the biomarker based upon results of relevant studies, including interpretation of how the biomarker performance supports its use in the proposed context.
- Identification of unresolved issues, an explanation of why they should not be considered as barriers to qualification for the proposed context of use, and a description of plans to resolve them if applicable.

2.2 Context of Use

The structure recommended in this guidance is intended for a briefing document after sufficient supporting data have been generated. However, this structure can also be considered for submissions intended to obtain scientific advice from FDA during the consultation and advice period in which generation of the biomarker data intended to support qualification is occurring. The elements describing the context of use for a biomarker should include (i) the general area, (ii) the specific biomarker use, and (iii) the critical parameters that define when and how the biomarker should be used. The context of use can be limited to use in drug development. We expect that a biomarker proposed for qualification would facilitate drug development program(s) or drug use and offer an improvement over currently available biomarkers or safety or efficacy endpoint assessments.

A diagrammed decision tree illustrating how the biomarker would be used in the drug development process is often very helpful to clearly convey the submitter's objectives.

The proposed context of use for a biomarker should be supported by data that are available in the briefing document. If FDA identifies an inconsistency between the proposed context and the data, the Agency may request additional data during the qualification processes.

The context of use should be described according to the following categories:

General Area. Including, but not limited to nonclinical/clinical pharmacology, pharmacodynamics, efficacy, safety, disease, or toxicology.

Specific Biomarker Use(s). Biomarkers can be used for a wide range of purposes, including, but not limited to patient/clinical trial subject selection, assessment of disease state and/or prognosis, assessment of mechanism of action, dose optimization, drug-response evaluation or monitoring, efficacy maximization, and/or toxicity/adverse reaction minimization.

Critical Parameters for Context of Use. Including, but not limited to drug-specific use/drug class-specific use/use not linked to specific drugs or drug classes; disease diagnosis and phenotype definition, prognosis, or stage; sample collection; assay specifications, for example, platform type, such as microarrays or quantitative PCR for genomic biomarkers or immunoassay for proteomic biomarkers; tissue or physiological/pathological process addressed; species; demographics, including ancestry and/or geographic origin; and environmental factors.

2.3 Methodology and Results

This section should include a summary of existing nonclinical or clinical studies, including integrated analysis of the biomarker qualification studies and individual study synopses.

2.4 Knowledge Gaps and Development Plan

This section should describe the limitations of the existing information that create critical gaps in knowledge for fully justifying the biomarker qualification. Issues encountered during the studies

should be described and whether they were resolved or remain to be resolved. This section should include a description of studies proposed to obtain the additional information. If feasible, study designs should be described with moderate detail. Full study protocols are usually not necessary for the initial briefing document and meeting, but may be important for subsequent meetings. The QRT may also request study quality-related documentation for subsequent meetings. If the biomarker development program is planned as a multistep process, this should be described, with details of the initial steps and more general descriptions of the later steps if specific studies are dependent upon results of initial steps. It is helpful to provide a potential time line for the development plan, as feasible.

2.5 Measurement Methodology

This section should describe the methodology for measuring the biomarker, with sufficient detail to understand the physical devices used, specialized software needed (e.g., automated digital image analysis software), key operating characteristics of the measurement system, and general availability of the components (as compared to components possessed only by the submitter and not available to organizations outside the submitter group).

Appendix

List of references and copies of only the most important references that the submitter feels CDER reviewers may want to review.

APPENDIX 5

BRIEFING DOCUMENT TO PROPOSE RATING SCALE (PRO OR OTHER RATING SCALES) QUALIFICATION

The rating scale qualification briefing document, also known as a "Scoping Stage Summary Document," should include the following sections:

Section 1: Administrative Information

This section should contain the following information:

- Cover letter
- Names of the principal investigators and working group members (if applicable)
- Specific questions the submitter has for CDER
- Any appropriate FDA forms

Section 2: Summaries

2.1 Introduction: Proposed Plan for Rating Scale Qualification

The following topics represent areas that should be addressed for CDER review. The extent of information provided in each section will vary depending upon the development stage of the rating scale proposed for qualification.

2.1.1. Overall goals for rating scale qualification

- Identification of unmet need
- Approach to ensure public availability of rating scale after qualification

2.1.2. Concept identification

- Measurement concept
- Conceptual framework of the rating scale (hypothesized or existing)
  - Conceptual framework diagram
  - Other details (if established or drafted)
- Items
  - Stem content
  - Response options
- Recall period
- Administration
  - Timing
  - Administration mode (e.g., self-administration, interviewer administered)
  - Data collection method (e.g., paper-based, computer-assisted, telephone-based)

2.2 Context of Use

- Target patient population
  - Disease/condition severity and patient setting
  - Patient demographics
  - Language/culture groups
  - Other characteristics
- Clinical trial endpoint model
- Targeted claims (i.e., proposed claim wording)

2.3 Overview of Current Rating Scale Development Status (for existing rating scales or for rating scales already under development)

2.3.1 Development of rating scale content and documentation of content validity (summary of planned studies or completed studies)

- Concept elicitation/item generation
  - Literature input
  - Expert input
  - Patient input (focus groups, in-depth interviews)
  - Other input
- Development of rating scale
  - Response options
  - Recall period development
  - Instructions to respondent/administrator
  - Item reduction and modification
  - Confirmatory cognitive debriefing
  - Scoring algorithm development

2.3.2. Documentation of other measurement properties

- Reliability
- Construct validity
- Ability to detect change

2.3.3. Interpretation of scores

- Interpretation of individual patient change (responder definition)
- Interpretation of clinical trial results

2.3.4. Language Translation and Cultural Adaptation, if applicable

- Process for simultaneous development of versions
- Process for translation/adaptation of original version
- Process for establishing that content validity is comparable between versions

2.3.5. Data Collection

- Description of each data collection method
- Process for developing each method
- Process for establishing that content validity is comparable between versions

2.3.6. Copy of all existing final versions of rating scale (or screen shots, if applicable)
2.3.7. User manual(s)

Appendix

List of references and copies of only the most important references that the submitter feels CDER reviewers may want to review.