Medical Device Development Tools

Draft Guidance for Industry, Tool Developers, and Food and Drug Administration Staff

DRAFT GUIDANCE

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U. S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Preface

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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This document provides draft guidance on a voluntary process for qualification of medical device development tools (MDDT) for use in device development and evaluation programs in the Center for Devices and Radiological Health (CDRH). CDRH believes that application of this policy will facilitate the development and timely evaluation of innovative medical devices, by providing a more efficient and predictable means for collecting the necessary information to make regulatory assessments. The purpose of this guidance is to describe the framework and process for voluntary CDRH qualification of MDDT, including definitions of applicable terms, criteria for evaluating an MDDT for a specific context of use, considerations for qualification, and the contents of a qualification submission. This guidance does not discuss the review of MDDTs submitted as part of a premarket regulatory submission for a specific medical device, nor does it address the specific evidentiary or performance expectations FDA would have for the qualification of a specific MDDT.

This draft guidance applies to both therapeutic and diagnostic devices unless otherwise specified.

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.

II. BACKGROUND

An MDDT is a scientifically validated tool – a clinical outcome assessment (e.g. patient-reported or clinician-reported rating scales), a test used to detect or measure a biomarker (e.g. assay for a chemical analyte or medical imaging method), or non-clinical assessment method or model (e.g. *in vitro*, animal or computational model) - that aids device development and regulatory evaluation. Qualification reflects CDRH's expectation that within a specified *context of use*[1], the results of an assessment that uses an MDDT can be relied upon to support device development and regulatory decision-making.

The intent of this voluntary CDRH qualification policy is to (1) enable faster, more efficient development of important life-saving and health promoting medical devices, (2) promote the development of tools to facilitate more timely device evaluation, (3) provide a mechanism to better leverage advances in regulatory science, and (4) more quickly and more clearly communicate to stakeholders about important advances in regulatory science that may be leveraged to speed device development and regulatory evaluation. We expect the qualification process to expedite development of publicly available tools which could potentially be used widely in multiple device development programs. Once an MDDT is qualified for a specific context of use, FDA's expectation is that it can be used by any medical device developer for that context of use. CDRH reviewers should accept the MDDT for the qualified context of use without the need to reconfirm the suitability of the MDDT. Importantly, the existence of a qualified MDDT does not convey a requirement that the tool must be used during the device development or regulatory evaluation process. Other scientifically valid tools or approaches may also be used.

CDRH is committed to advancing regulatory science, which provides the tools, standards, and approaches needed to evaluate the safety, effectiveness, quality, and performance of the products we regulate. Through continued advances, such as this qualification process, we are modernizing the regulatory evaluation process and reducing the time and resources needed to develop and assess new products. This promotes innovation, supports the manufacture of high quality products, and speeds the rate at which safe and effective technologies reach the market.

[1] For the purposes of this guidance, the term "context of use" refers to a key aspect of qualification -- the use parameters for which the MDDT has been validated. This use is defined in part by the device or product area in which the MDDT can be qualified, the stage of device development, and the specific role of the MDDT (for clinical uses, this includes the study population or disease characteristics). The context of use defines the boundaries within which the MDDT is qualified.

III. DEFINITION OF KEY CONCEPTS

For the purposes of this guidance, the following definitions apply:

- A **Medical Device Development Tool (MDDT)** is a scientifically validated tool - a clinical outcome assessment (e.g. patient-reported or clinician-reported rating scales), a biomarker test (e.g., assay for a chemical analyte or medical imaging method), or non-clinical assessment method or model (e.g. *in vitro*, animal or computational model) that aids device development and regulatory evaluation.

- **Qualification** is a conclusion that within a specified *context of use*, CDRH expects that the results of an assessment that uses an MDDT can be relied upon to support device development and regulatory decision-making.

- **Context of use** refers to a key aspect of qualification. This use is defined in part by the device or product area for which the MDDT is qualified, the stage of device development, and the specific role of the MDDT (for clinical uses, this includes the study population or disease characteristics, as well as specific use – diagnosis, patient selection, clinical endpoints). The context of use defines the boundaries within which the MDDT is qualified.

- A **Clinical Outcome Assessment (COA)** relies on *subjective* measures of how a patient feels or functions, and is sometimes used to determine whether or not a device demonstrates a treatment benefit. COAs include patient-reported, clinician-reported, and observer-reported outcome measures and are typically instruments composed of a scale or score. A patient-reported outcome (PRO) assessment captures the patient perspective concerning symptoms or functioning. A clinician-reported outcome assessment is based on clinical observation or interpretation by a trained clinician. An observer-reported outcome is assessed by observers without the need for clinical expertise. Examples of COA include: pain scales, quality of life or health status scores, NIH Stroke Scale. Other clinical outcomes based on subjective clinical decision-making may also be qualified as MDDTs if they may be used as a measure of treatment benefit when clearly defined. Examples include: heart failure-related hospitalization or reoperation rate.

- A **Biomarker Test (BT)** is a test or instrument (e.g. an *in vitro*/laboratory test or medical imaging method) or other *objective* measurement method used to detect or measure a biomarker. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or responses to a therapeutic intervention.[2] Examples of BT include: an instrument or method for

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

measuring blood pressure (e.g., sphygmomanometry); an instrument or method for measuring certain concentrations of serum proteins.

- A **Nonclinical Assessment Model (NAM)** is a nonclinical test method or model used in device development or evaluation that reflects device function or *in vivo* performance. A NAM could be an *in vitro* ("bench") model, animal model, or computational model and is developed to measure a parameter of interest or to substitute for another generally accepted test or measurement. Examples of NAM include: *in vitro* models to replace animal testing, the use of tissue and other material phantoms to evaluate imaging devices, electromagnetic phantoms, and validated computational models.

IV. OVERVIEW OF CDRH QUALIFICATION POLICY

Qualification reflects CDRH's expectation that within the specified context of use, the results of an assessment that uses an MDDT can be relied upon to support medical device development and regulatory decision-making. Once qualified, CDRH expects that the MDDT may be used by device developers for the qualified context of use in regulatory submissions without the need for CDRH review staff to reconsider and reconfirm the suitability of the MDDT with each submission. Medical device developers may use qualified MDDTs, but are not required to do so.

Why is CDRH developing a qualification process?

This qualification process provides a mechanism for leveraging advances in regulatory science, fostering MDDT development and adoption, and facilitating faster, more efficient device development and regulatory evaluation. This voluntary process can facilitate the scientific evaluation and assessment of a medical device by providing a more efficient and predictable means for collecting the necessary information to make regulatory assessments.

Qualification, as described in this guidance, is intended to increase efficiency in the device development process by providing some degree of generalizability for use of MDDTs across multiple medical types or clinical disorders, to advance device development and more widely benefit patients. The extent of generalization will depend on the MDDT, as well as the strength of evidence and justification for a broad proposed context of use.

Qualification also facilitates collaboration in a pre-competitive setting where multiple interested parties (individuals, companies, or organizations) may work together to develop an MDDT for qualification. This may result in a reduction in the resources expended by each individual collaborator and motivate interested parties to join an MDDT development effort, thus expediting the MDDT development and use. CDRH encourages the formation of collaborative

groups to foster MDDT development programs to increase the efficiency of tool development through joint efforts and to lessen the resource expenditure of any individual person or company. As further detailed in Section VII, we are available to discuss potential MDDT development programs with stakeholders.

A qualification process may have advantages for CDRH as well. Previously, if there was interest in using a particular MDDT for multiple products or different clinical settings, each FDA device review team would typically evaluate the data justifying the MDDT use for each product or setting separately. Instead, if an MDDT is qualified through the process described in this guidance, the relevant data supporting the tool would be reviewed thoroughly during this process, so that the MDDT could be relied upon within the qualified context of use in the future, without redundant, detailed review of the suitability of the test.

What does CDRH Qualification mean for regulatory decision-making?

The decision to qualify an MDDT means that after reviewing relevant available scientific evidence, CDRH intends to consider the MDDT a valid tool within the defined context of use and to rely on assessments using the MDDT for regulatory purposes. Qualification decisions will be made public and reflect CDRH's support for the general use of the MDDT within the specified context of use, not just for a single, specific device submission. The value to the public health will be increased as new MDDTs become widely known and available for use by multiple device developers.

A qualification decision involves a consideration of (1) the specified context of use; (2) the strength of available evidence supporting the MDDT (including tool validity, plausibility, etc); and (3) an assessment of the advantages and disadvantages of relying on assessments using the MDDT within the specified context of use.

MDDT qualification does not obviate the need for a device developer to meet existing regulatory requirements or alter the benefit-risk threshold for regulatory decision-making related to a medical device; rather, it can facilitate the scientific evaluation and assessment of a medical device by providing a more efficient and predictable means for collecting the necessary information to make regulatory assessments. The CDRH premarket review divisions maintain responsibility for evaluating new devices using information obtained using a qualified MDDT.

V. CONCEPTUAL FRAMEWORK

CDRH has defined three types of MDDTs: COAs (including patient- and clinician-reported outcomes), BTs (such as assay or medical imaging methods), and NAMs (such as *in vitro*, animal or computational models). Each type of MDDT may have a variety of potential uses relevant to CDRH's regulatory evaluation of new medical devices. MDDTs are instruments, tools or methods of measurement that address outcomes and are subject to quality issues such as

accuracy, precision, reliability, reproducibility. These quality issues may affect the usefulness of an MDDT.

The following sections provide more detail about *context of use*, distinguish this from *MDDT type*, and outline certain regulatory considerations for distributing and using qualified MDDTs.

A. Context of Use

The "context of use" refers to a key aspect of qualification. It describes the way the MDDT should be used and the purpose of the use. Once an MDDT is qualified, the context of use defines the boundaries within which the available data adequately support use of the MDDT. Context of use is defined in part by 1) the device or product area for which the MDDT is qualified, 2) the stage(s) of device development (e.g., early feasibility study, pivotal study, etc.), and 3) the specific role of the MDDT (for clinical uses this includes the study population or disease characteristics, as well as specific use – diagnosis, patient selection, clinical endpoints).

Different categories of contexts of use for an MDDT:

1. Aid in Diagnosis
   - As a definition of an adverse event (AE) within a clinical study
   - As a clinical reference standard to assist in diagnosis
2. Patient Selection[3]
   - For selection of clinical trial subjects
   - To stratify patient population by predicted risk
3. Clinical Endpoints[4]
   - As an intermediate endpoint[5]

[3] MDDTs need not be FDA cleared or approved products. However, when an MDDT test is used in a clinical trial as a companion diagnostic, in that it is essential for the safe and effective use of a corresponding developed therapeutic product, it must comply with applicable investigational use requirements. Developers may wish to see FDA's draft guidance "In Vitro Companion Diagnostic Devices" for FDA's proposed approach on this topic. (available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm262292.htm).

[4] A **clinical endpoint** is a detected symptom or measurement of a function, or any clinical characteristic or variable that reflects how a patient feels, functions, or survives, measured at a specific timepoint. Examples: mortality reports; loss of sight.

- As a surrogate endpoint[6]

4. Non-clinical Device Assessment
   - Bench or animal study methodologies which reduce test duration or minimize sample size
   - As a substitute for an evaluation typically conducted through human or animal studies
   - Reliance on *in vitro* or *in silico* studies to reduce or minimize the use of animals

The MDDT may also have potential value outside these boundaries. The MDDT may be used in device development programs for a different purpose other than the qualified context of use, subject to review and discussion with CDRH on a case-by-case basis. In addition, the qualified context of use for the MDDT may be expanded over time as additional data are obtained. If data become available that call into question the validity, appropriateness, or assessment of advantages and disadvantages of a previously qualified context of use, CDRH may modify or withdraw the qualification.

B. Tool Type

CDRH recognizes three types of MDDT, distinguished primarily by how the tool measures relevant parameters. Tools that measure clinical parameters via some subjective metric are Clinical Outcome Assessments (COA). Tools that measure clinical parameters via an objective approach (e.g., physical measurement or chemical analysis) are considered Biomarker Tests

[5] An **intermediate endpoint** is itself a clinical endpoint concerning a symptom or measure of function that is not the ultimate outcome of the disease. Improvement according to an intermediate endpoint is of value to patients even if this does not lead to reduced morbidity or mortality. An intermediate endpoint may also be a clinical endpoint measured at an earlier timepoint than has historically been accepted. A treatment effect shown by an intermediate endpoint may also be taken as reason to expect a favorable ultimate outcome; in this sense the intermediate endpoint plays the role of a surrogate. For example, exercise tolerance is sometimes used as an intermediate endpoint in trials of treatments for heart failure.

[6] A **surrogate endpoint** is a measurement used in trials as a substitute for a clinical endpoint, and is expected to reflect clinical outcomes based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. For example, blood pressure measurements are sometimes used as endpoints in trials of antihypertensive therapeutics, as a surrogate for clinical endpoints of stroke, myocardial infarction, or mortality.

(BT). Tools that measure nonclinical parameters are categorized as Nonclinical Assessment Models (NAM). These MDDT types are further detailed below.

1. Clinical Outcome Assessment

A Clinical outcome assessments (COAs) is a subjective measures of how a patient feels or functions, and is sometimes used to determine whether or not a device demonstrates a treatment benefit. COAs include patient-reported, clinician-reported, and observer-reported outcome measures and are typically instruments composed of a scale or score. A widely used example is the NIH Stroke Scale.

The reporter (i.e. clinician, patient, or other observer) of the outcome distinguishes the type of COA. 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. Patient reported outcomes (PROs)[7] are a common subtype of COA. They are a measurement of the patient's health condition based on a direct patient (i.e., study subject) report without amendment or interpretation by someone else.

A COA includes not only the measure that produces a score but also the clearly defined methods and instructions for administration of the tool, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results in the targeted patient population. COAs can measure treatment benefit directly (e.g., a PRO for pain intensity) or indirectly (e.g., a diary of rescue pain medication use for pain intensity). Qualification of a COA as an MDDT includes a review of the evidence that the proposed tool is a valid assessment for how patients feel or function in day-to-day activities.

Other clinical outcomes based on subjective clinical decision-making may also be qualified as MDDTs if they may be used to assess a treatment benefit. Examples may include hospitalization rate or reoperation rate.

CDRH intends to qualify a COA based on a determination that for a specified context of use, assessment of a clinical outcome using the COA provides *valid scientific evidence* when used in a *well-controlled investigation* (see 21 CFR 860.7).

[7] Issues relevant to FDA review of both new and existing PROs 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). Many of the issues described in that guidance are also relevant to ClinROs and ObsROs.

2. Biomarker Test

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or responses to a therapeutic intervention. A biomarker can be a physiologic, pathologic, or anatomic characteristic or measurement that relates to an aspect of normal or abnormal biologic function or process. Typically, a biomarker is measured using a test (e.g., by chemical analysis) or instrument (e.g., by sphygmomanometry). CDRH intends to consider MDDTs derived from medical imaging to be BTs, if the characteristic (e.g., tumor diameter) is objectively measured.

As with other MDDTs, CDRH intends for qualified BTs to be relied upon to support device-related regulatory decision-making for the defined context of use. BTs may be used to select patients for inclusion in a device clinical trial, to monitor treatment response, to predict or identify safety problems related to treatment with a medical device, or to identify patients who are or are not candidates for certain forms of therapy. Appropriate use of qualified BTs may increase the efficiency of the device development and evaluation process by providing reliable predictions about device performance.

Fundamentally, in order for a BT to be useful, it must be sufficiently accurate and precise. When considering BTs for qualification, the evaluation will assess both the strength of evidence supporting *the biomarker* for the specified context of use, as well as the validity of the test instrument and/or methodology to measure the biomarker. In qualifying a BT, FDA implicitly accepts the strength of evidence supporting the biomarker for the specified context of use. Subsequent BTs seeking qualification for similar contexts of use need only demonstrate the validity of the test instrument and/or methodology to measure that same biomarker.

The amount and type of new evidence needed to support qualification of a BT will depend on whether there is any test or instrument for measurement of the biomarker that is already FDA cleared or approved for clinical use through premarket review, and if so, whether the proposed context of use for the BT is consistent with the indication for use of the cleared or approved product. To qualify a BT to measure a biomarker for which there is no corresponding FDA cleared or approved device, test validity (e.g., precision and accuracy) should be demonstrated in the proposed context of use. In contrast, MDDT qualification proposals involving an FDA cleared or approved test, or involving biomarkers for which FDA has established the analytical performance criteria necessary for measurement for the specified context of use, can make use of existing data that support the analytical validity of the test, so long as the MDDT submitter is legally authorized to do so. In either case, qualification depends on meeting performance criteria for the test or instrument's accuracy, precision, etc. as an MDDT in the proposed context of use.

Importantly, the processes and criteria for qualification of a BT as an MDDT remain distinct from requirements for pre-market product review, even when the products (biomarker test for use in device development and legally marketed medical device), the objects of the product (biomarker and analyte) and inferences drawn (biology and clinical significance) are similar or identical. However, information developed for pre-market review, such as analytical validity, may be potentially relevant to qualification of a BT, even when the proposed context of use differs from the cleared or approved indication for use of the device. The MDDT submission should clearly identify the elements of BT qualification (Section VI) that are addressed using information from a premarket submission.

MDDT qualification determinations will in no way affect the regulatory or compliance status of any product intended for commercial distribution (see Section C).

3. Nonclinical Assessment Model

A nonclinical assessment model (NAM) is a nonclinical test method or model that reflects device function or *in vivo* performance and is used in device evaluation to measure a parameter of interest, or to substitute for another generally accepted test or measurement. NAM examples include *in vitro* models that replace or minimize the need for animal testing; the use of tissue and other material phantoms to evaluate imaging devices; validated computational models and the development and validation of a new animal model to evaluate a device in lieu of clinical data.

Qualified NAMs may be used to evaluate a new material property, modifications to an existing design, or a device feature historically evaluated through animal or human testing. The MDDT qualification process and standards recognition process[8] may be viewed as complementary. We anticipate that NAM qualification may be most useful for models or methods which are not yet covered by standards or guidance.

In some cases, an MDDT which is addressed in an FDA-recognized consensus standard may have already been assessed in a manner similar to the MDDT qualification process and qualification for the same context would likely not be beneficial. However, for those that have not, assessments conducted during development of the standard might contribute evidence toward MDDT qualification (e.g., round-robin testing conducted by the standards organization to assess tool validity). In addition, models proposed for different contexts of use or which necessitate different or more specific methodology than described in existing standards could also potentially be qualified through the MDDT process.

[8] Information on CDRH's standards program is available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm.

C. Regulatory Considerations and Related Recommendations

Some MDDTs may meet the definition of a device in section 201(h) of the FD&C Act and be subject to the statutory and regulatory requirements applicable to devices, such as 510(k) clearance or premarket approval. Devices intended for investigational use are exempt from most of these requirements, including clearance and approval, as long as there is compliance with applicable investigational use requirements, such as those under 21 CFR part 812. A qualified MDDT typically would be used in the research or investigation of a medical device, according to the MDDT's context of use. Such use would generally exempt a qualified MDDT that is a device from clearance, approval, and other device requirements, as long as a clinical investigation meets applicable requirements:

- If the device that is the subject of the investigation is a significant risk[9] device as defined by 812.3(m), the investigation, including use of the MDDT, is subject to all requirements of 21 CFR 812.

- If the device that is the subject of the investigation is not a significant risk device as defined by 812.3(m), the abbreviated requirements listed under 812.2(b) apply to the investigation, including the use of the MDDT.

- Investigations, including the use of the MDDT, that meet the criteria for one of the exemptions described in 812.2(c), including 812.2(c)(3), are not required to comply with part 812 with the exception of 812.119.

For qualified MDDTs that are devices that are not cleared, approved, or 510(k)-exempt, any statement that the device has been qualified by FDA should be accompanied by a disclaimer that qualification of an MDDT does not constitute FDA clearance or approval. Without such a disclaimer, the labeling could be considered misleading, which would render the device misbranded under sections 201(n) and 502(a) of the FD&C Act. If an MDDT appears to be a "device" under the FD&C Act, we will discuss these issues with you during the qualification process.

VI. CONSIDERATIONS FOR QUALIFICATION

As stated previously, CDRH's qualification decision means that CDRH expects that within the specified context of use, an MDDT can be applied in device development (to evaluate potential device designs in clinical or nonclinical settings) and that the results of an assessment that uses

[9] A determination about risk of the investigation should be made (see CDRH guidance: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf).

an MDDT can be relied upon to support regulatory decision-making (to support marketing applications and labeling modifications).

A. Considerations for CDRH Qualification

When determining whether to qualify a proposed MDDT, CDRH intends to consider the key aspects listed below. The amount and strength of evidence needed to support qualification depends largely on the defined context of use.

- *Description of MDDT*. Is the MDDT adequately described?

- *Context of use*. Is the context of use adequately and appropriately defined?

- *Strength of evidence*. Does the available scientific evidence demonstrate that the MDDT reliably and accurately measures what it is intended to measure, is scientifically plausible, and is "reasonably likely" to predict the outcome of interest?

- *Assessment of advantages and disadvantages*. Within the specified context of use and given the available strength of evidence, do the advantages of using the MDDT outweigh potential disadvantages of making decisions based on measurements obtained using the MDDT?

B. Contents of a Complete Qualification Package

1. Description of MDDT

   The qualification package should specify the MDDT type (COA, BT, or NAM), describe the measurements provided by the MDDT, and provide a descriptive summary of the MDDT principle and methodology of measurement.

2. Context of Use

   The qualification package should describe how and where the MDDT would be used within the device evaluation program. This includes 1) the device or product area in which the MDDT is proposed t be qualified, 2) the stage of device development (design evaluation, animal testing, early clinical study, pivotal clinical study to support market application, non-clinical PMA data requirement, post-market design or label changes), and 3) specific role of the MDDT (for clinical uses, this includes the study population or disease characteristics, as well as specific use – diagnosis, patient selection, clinical endpoints). For examples, please refer to section V.A.

3. Strength of Evidence

The qualification package should discuss the strength of evidence for the MDDT, and address the following areas:

- **Tool Validity.** Does the available data adequately support the validity of the measurement? Does the MDDT measure reliably and accurately? Depending on the tool type, this may include analytical, clinical, and construct validity, sensitivity, specificity, accuracy, precision, repeatability, external validity, reduction of bias, verification of the constitutive model, uncertainty quantification, numerical convergence, etc.

- **Plausibility.** Is it scientifically plausible that the measurements obtained through use of the MDDT are related to the true outcome of interest? Is there a causal path or mechanistic explanation to connect the MDDT to the outcome?

- **Extent of Prediction.** What data are available to demonstrate a predictive relationship between the MDDT and the true outcome of interest? What is the strength of that predictive relationship? Is the prediction repeatedly demonstrated in multiple studies or as a class effect? If relevant, is the conclusion (that the effect of treatment on the measurement obtained using the MDDT predicts the true effect of interest) supported by credible information?[10]

- **Capture.** Does the MDDT fully capture the aggregate effect of the intervention on the true outcome of interest? Does the MDDT account for every major effect of the intervention? Are there available data which call this into question?

The amount and strength of evidence needed to support qualification of an MDDT will vary depending on the context of use and the MDDT type. For example, an MDDT proposed for use as one component of a definition of an adverse event (AE) within a clinical study may need less data compared to a BT proposed for use measuring a primary endpoint for a pivotal study to evaluate a novel high-risk device type; the latter use may need more evidence of its validity due to the potential disadvantages of accepting an inaccurate MDDT in this context.

[10] For the purposes of this guidance, credible information includes data generated under the design control procedures of 820.30, nonclinical or animal testing, peer reviewed published literature, or other reliable information such as clinical information gathered during a trial or marketing. This definition is consistent with FDA's use of the term in Part 812.

4. Assessment of Advantages and Disadvantages

As part of the qualification determination, CDRH intends to consider an assessment of advantages and disadvantages for qualification of the MDDT. The qualification package should discuss the advantages and disadvantages of accepting the MDDT. CDRH intends to consider the following factors:

- **Assessments of Advantages of Using the MDDT:** This should take into account the following factors:
  - **The type of advantage(s).** Advantages may include: significantly accelerating the time to develop and evaluate devices; allowing for shorter or smaller clinical or nonclinical studies; allowing for safer or less invasive, easier, more convenient, or less variable measurements than the alternative; and expediting the development of a novel technology of public health importance.
  - **Magnitude of advantage.** This may include: whether there is a potential to impact multiple device development programs; whether the context of use includes life-threatening and/or serious chronic diseases or conditions or diseases/conditions where there are no or poor alternatives; or whether the MDDT is to be used for novel technology where there is no established paradigm for regulatory assessment.
  - **Likelihood of an advantage.** This is based on the strength of evidence (tool validity, plausibility, correlation/prediction, capture) in support of the MDDT, and a comparison to the available alternatives.

- **Assessments of Disadvantages of Using the MDDT:** This should take into account the following factors:
  - **Type(s) of risks.** Considering the context of use, what types of decisions might be made based on the use of an MDDT that should not have been qualified? These are considered within the context of use, including: 1) the device or product area in which the MDDT is proposed to be qualified, 2) the stage of device development (design evaluation, animal testing, early clinical study, pivotal clinical studies to support market application, post-market design changes); and 3) the specific role of the MDDT (for clinical uses, this includes the study population or disease characteristics, as well as specific use – diagnosis, patient selection, clinical endpoints).

- **Magnitude of risk.** The scope of impact of making a decision based on inaccurate conclusions from an MDDT is based on the severity of risk, a comparison of the MDDT to its alternatives, and considering the context of use.
- **Likelihood of risk.** How likely is a particular risk to occur? This could be based on the evidence in support of tool validity. For a diagnostic test, this could be the likelihood of the MDDT reporting a false positive, false negative or false estimate of predictive value.
- **Risk mitigation.** The use of mitigations may minimize the risks of relying on the MDDT. For example, alternative sources of information or confirmatory data from later timepoints may mitigate risks of decision-making based on information from an MDDT.

- **Additional Factors for Assessing Advantages and Disadvantages of Using the MDDT:** The following factors may apply:

  - **Degree of certainty.** If the advantages of using the MDDT are high, less certainty (less rigorous strength of evidence) may be acceptable to support its use. On the other hand, if the advantages are minimal or if the potential disadvantages are great, more rigorous evidence may be needed to support MDDT use.
  - **Novelty of technology.** The assessment will consider whether MDDTs facilitate development and regulatory evaluation of devices that address areas of unmet need, or that incorporate new technologies (especially first-of-a-kind) which may offer advantages that did not previously exist. Particularly where providers and patients have limited alternatives available, MDDT use may facilitate patient access and encourage innovation.

5. Consent to Public Disclosure and Use

In order to obtain FDA qualification, MDDT submitters must provide authorized consent (1) for FDA to make public sufficient information to support use of the qualified MDDT and (2) for the general public to use the MDDT and rely on data generated using the MDDT in gaining FDA clearance or approval of other devices.

VII. CDRH QUALIFICATION PROCESS

During the CDRH process for MDDT qualification the Agency and MDDT submitters interact to efficiently determine the amount and type of information needed to support qualification for a

specific tool and context of use. The qualification process consists of two stages: 1) an optional pre-qualification stage, and 2) a qualification determination stage.

Throughout the pre-qualification and qualification determination stages of review, CDRH intends to prioritize proposals for evaluation of the MDDT according to the following factors:

- Public health need met by one or more of the following:
  - Context of use includes life-threatening and/or serious chronic diseases or conditions;
  - No/poor alternatives or unmet scientific need;
  - Novel or innovative technology with no established paradigm for regulatory assessment;
  - Major efficiencies to be gained in device development and evaluation time.

- Scope of impact:
  - Potential to impact multiple device development programs;
  - Potential to impact multiple sponsors.

The number of proposals accepted for detailed CDRH involvement will depend on available resources. Where appropriate, CDRH may seek input from external individuals or groups for specific expertise, consistent with all applicable statutory and regulatory requirements, including those respecting confidentiality.

Once an MDDT is qualified for a specific use, the context of use may be modified or expanded over time in response to new data or changing science. Modification or incremental expansion of the qualified context of use over time may be undertaken through the qualification process. Alternatively, if the growing body of scientific evidence no longer supports the context of use, CDRH may withdraw the MDDT qualification.

Stage 1: Pre-Qualification (Optional)

The process for MDDT qualification can be triggered in one of 3 ways: 1) FDA identifies an area of need and/or calls for development activity in a specific area; 2) need and interest in an area is determined by individual or consortia of stakeholders (may include academia, industry, medical societies); 3) a MDDT developer chooses to pursue qualification for its tool to allow for broad use across multiple device development programs.

<u>Prioritization of Proposals</u>

Interested parties should submit a proposal including a concise overview of the qualification project, and description of the need for the MDDT (see Appendix 1). Priority proposals may be accepted for early direct FDA staff involvement.

<u>Consultation and Evidence Development</u>

The qualification review team (which may include FDA as well as external expertise, where appropriate) should interact with the submitter to identify the amount and type of data or information needed for qualification of the proposed MDDT for the context of use. CDRH intends to notify applicants of whether they have been selected for a pre-qualification meeting or teleconference with FDA staff. Additional interactions or correspondence should occur as needed during the MDDT development stage.

Stage 2: Qualification Determination

When the submitter has the data and information necessary for a complete qualification package, they may submit it to justify qualification of the MDDT for the proposed context of use (see Appendix 1). The qualification review team should interact with the submitter as needed for clarification or to request additional information. CDRH intends to hold a qualification meeting or teleconference to facilitate discussion once the package has been reviewed. In the case of complex or controversial MDDT programs, CDRH may seek external expertise or public comment.

In evaluating an MDDT for qualification, CDRH would not consider whether there may be restrictions on use of the tool stemming from patent. CDRH does not have the resources or the expertise to review patents and individual patent claims, or otherwise be involved in issues related to patent law.

Upon completion of the evaluation, CDRH intends to notify the submitter in writing of the qualification determination.

VIII. PROCEDURES FOR SUBMITTING MDDT CORRESPONDENCE AND DOCUMENTS

All MDDT correspondence and documents for CDRH should be clearly labeled as a "MDDT qualification submission," and sent to the Document Control Center (DCC).[11] Submitters should include an eCopy[12] as well.

[11] Submissions to CDRH should be sent to: U.S. Food and Drug Administration, Center for Devices and Radiological Health, Document Mail Center – WO66-G609, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002.

[12] For more information on formatting of an eCopy, please see:*http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf*. Although submission of an eCopy for an MDDT Qualification Submission is voluntary, if you choose to submit an eCopy, it should meet the technical standards outlined in Attachment 1 of the referenced guidance.

The Cover Letter should contain the following elements:

- Date:
- Subject: (in bold print) **MDDT QUALIFICATION SUBMISSION**
- MDDT Type: (in bold print)
  - **CLINICAL OUTCOME ASSESSMENT,**
  - **BIOMARKER TEST, or**
  - **NONCLINICAL ASSESSMENT MODEL**
- MDDT Tracking Record Number: (in bold print), if previously assigned
- Submission Type: (in bold print)
  - **REQUEST FOR PRELIMINARY DISCUSSION or PRE-QUALIFICATION PROPOSAL** or
  - **INTERIM CORRESPONDENCE** or
  - **QUALIFICATION PACKAGE**.
- MDDT Name(s): (in bold print): Identify the specific MDDT (by name) that is being submitted
- Context of Use: Describe the intended context of use of the MDDT (1 to 2 sentences)
- Complete submitter contact information including name(s), affiliation, mailing address, email address, phone and fax numbers

IX. PROCEDURES FOR MAKING QUALIFICATION DECISIONS AVAILABLE

To make information about qualified MDDTs available to the public, CDRH intends to use the following process:

- To allow for public comment for each new qualification determination, FDA intends to publish a draft appendix to this guidance and issue a notice of availability of new and/or revised (draft) qualification determinations. FDA expects the notice to identify a comment period for draft determinations. Once finalized, FDA intends to publish the qualification determination as an appendix to this guidance.

- CDRH expects to announce MDDT qualification determinations on an established MDDT Web page. With permission from a submitter, CDRH also intends to post new MDDTs in the process of developing evidence to support qualification, so that any parties interested in participating can contact the submitter.

- CDRH intends to provide detailed supporting documentation and information, when appropriate, on the MDDT Qualification Web page, or in some cases (e.g., for certain NAM) to capture that information in a master file for reference by multiple sponsors.

CDRH expects to make public sufficient information to support broad use of the qualified MDDT. In order for submitters to participate in this voluntary qualification process, they must agree that information about the qualified MDDT will be made publicly available for use in device development programs in the specified context of use. To this effect, as appropriate, CDRH intends to provide information for the public about how to access the MDDT.

APPENDIX 1

SAMPLE OUTLINE OF PACKAGE CONTENTS

The recommended outline below is provided as an example only for illustrative purposes and is not required. A sample package may include the following information: (1) a description of MDDT type, principle and methodology; (2) context of use; (3) amount and strength of available evidence; (4) assessment of advantages and disadvantages for qualifying the MDDT; and (5) consent to public disclosure and use.

1. Description of MDDT

- MDDT Type:
  - Clinical Outcome Assessment (COA)
  - Biomarker Test (BT)
  - Nonclinical Assessment Model (NAM)

- Description of measurements provided by the MDDT:
  - What does the MDDT measure or provide?
  - Is it intended to replace a previously accepted measurement?

- Descriptive summary of the MDDT principle and methodology of measurement

2. Context of Use

- Device or product area in which the MDDT can be qualified

- Stage of device development
  - Design evaluation
  - Animal testing
  - Early clinical study
  - Pivotal clinical study to support marketing application
  - PMA nonclinical data requirement
  - Post-market design or label changes

- Specific role of the MDDT:

  Non-clinical Device Assessment
  - Bench or animal studies methodologies which reduce test duration or minimize sample size
  - As a substitute for an evaluation typically conducted through human or animal studies

- Reliance on *in vitro* or *in silico* studies to reduce or minimize the use of animals

For clinical uses, describe the study population or disease characteristics, as well as the defined use:

- Aid in Diagnosis
  - As a definition an adverse event (AE) within a clinical study
  - As a clinical reference standard to assist in diagnosis

- Patient Selection
  - For selection of clinical trial subjects
  - To stratify patient population by predicted risk

- Clinical Endpoints
  - As an intermediate endpoint
  - As a surrogate endpoint

3. Strength of Evidence

- **Tool Validity.** Does the available data adequately support the validity of the measurement? Does the MDDT measure reliably and accurately? Depending on the tool type, this may include analytical, clinical, and construct validity, sensitivity, specificity, accuracy, precision, repeatability, external validity, reduction of bias, verification of the constitutive model, uncertainty quantification, numerical convergence, etc.

- **Plausibility.** Is it scientifically plausible that the measurements obtained through use of the MDDT are related to the true outcome of interest? Is there a causal path or mechanistic explanation to connect the MDDT to the outcome?

- **Extent of Prediction.** What data are available to demonstrate a predictive relationship between the MDDT and the true outcome of interest? What is the strength of that predictive relationship? Is the prediction repeatedly demonstrated in multiple studies or as a class effect? If relevant, is the conclusion (that the effect of treatment on the measurement obtained using the MDDT predicts the outcome of interest) supported by credible information?

- **Capture.** Does the MDDT fully capture the aggregate effect of the intervention on the true outcome of interest? Does the MDDT account for every major effect of the intervention? Are there available data which call this into question?

4. Assessment of Advantages and Disadvantages

- **Advantages of Using the MDDT:**

  - **The type of advantage(s).** Advantages may include: significantly accelerating the time to develop and evaluate devices; allowing for shorter or smaller clinical or nonclinical studies; allowing for safer or less invasive, easier, more convenient, or less variable measurements than the alternative; and expediting the development of a novel technology of public health importance.
  - **Magnitude of advantage.** This may include: whether there is a potential to impact multiple device development programs; whether the context of use includes life-threatening and/or serious chronic diseases or conditions, or diseases/conditions where there are no or poor alternatives; or the MDDT is to be used for novel technology where there is no established paradigm for regulatory assessment.
  - **Likelihood of an advantage.** Characterize the strength of evidence (tool validity, plausibility, correlation/prediction, capture) in support of the MDDT, and include a comparison to the alternatives.

- **Disadvantages of Using the MDDT:**

  - **Type(s) of risks.** Considering the context of use, what types of decisions might be made based on an inaccurate conclusion about an MDDT? These are considered within the context of use, including: 1) the device or product area in which the MDDT can be qualified, 2) the stage of device development (design evaluation, animal testing, early clinical study, pivotal clinical studies to support market application, post-market design changes); and 3) the specific role of the MDDT (for clinical uses, this includes the study population or disease characteristics, as well as specific use – diagnosis, patient selection, clinical endpoints.
  - **Magnitude of risk.** What is the scope of impact of making a decision based on inaccurate conclusions from an MDDT, including severity of risk, a comparison of the MDDT to its alternatives, and considering the context of use.
  - **Likelihood of risk.** How likely is a particular risk to occur? This could be based on the evidence in support of tool validity. For a diagnostic test, this could be the likelihood of the MDDT reporting a false positive, false negative or false estimate of predictive value.
  - **Risk mitigation.** What mitigations, if any, are proposed to be used in order to minimize the risks of relying on the MDDT? For

example, alternative sources of information or confirmatory data from later timepoints may mitigate risks of decision-making based on information from an MDDT.

- **Additional Factors:**

  - **Degree of Uncertainty.** Characterize the strength of the evidence in relation to the strength of the advantages and disadvantages of using the MDDT. If the advantages of using the MDDT are high, less certainty (less rigorous strength of evidence) may be acceptable to support its use. On the other hand, if the advantages are minimal, or if the potential disadvantages are great, more rigorous evidence may be needed to support MDDT use.
  - **Novelty of technology.** Does the MDDT facilitate development and regulatory evaluation of devices that address areas of unmet need, or that incorporate new technologies (especially first-of-a-kind) which may offer advantages that did not previously exist? Particularly where providers and patients have limited alternatives available, MDDT use may facilitate patient access and encourage innovation.

5. Consent to Public Disclosure and Use

Provide authorized consent (1) for FDA to make public sufficient information to support use of the qualified MDDT and (2) for the general public to use the MDDT and rely on data generated using the MDDT in gaining FDA clearance or approval of other devices.