

# Qualification of Medical Device Development Tools

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

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For questions regarding this document, contact [MDDT@fda.hhs.gov](mailto:MDDT@fda.hhs.gov).



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

# **Preface**

## **Public Comment**

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

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### I. Introduction

This document provides guidance on a voluntary program for qualification of medical device development tools (MDDT) for use in evaluating devices subject to regulation by Center for Devices and Radiological Health (CDRH). CDRH believes that this policy will facilitate the development and timely evaluation of medical devices, by providing a more efficient and predictable means for collecting the necessary information to support regulatory submissions and associated decision-making.

The purpose of this guidance is to describe the framework and process for voluntary proposal and qualification of an 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 package. For purposes of this guidance, a submitter is a person, group, consortium, or organization (including the federal government) that takes responsibility for and initiates the MDDT qualification process using the procedures described in this guidance.

This guidance does not discuss the review of tools that are submitted in individual premarket regulatory submissions for use with a particular medical device nor does it address the specific evidentiary or performance expectations for the qualification of an individual MDDT submission.

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. Overview**

### **A. What is an MDDT & MDDT qualification?**

An MDDT is a method, material, or measurement used to assess the effectiveness, safety, or performance of a medical device. An MDDT is scientifically validated and can be qualified for use in device evaluation and to support regulatory decision-making. Examples of MDDTs are clinical outcome assessments, assessments of biomarkers, and non-clinical assessment methods or models. The use of a qualified MDDT by a product sponsor is voluntary.

Qualification<sup>1</sup> reflects CDRH's expectation that, within a specified context of use (statement that describes the conditions and boundaries within which the MDDT has been qualified for use), the results of an assessment that uses an MDDT can be relied upon in device evaluation and to support regulatory decision-making. In brief, qualification is a voluntary process to establish the scientific rigor associated with an MDDT for a specific use in supporting regulatory decision-making.

The intent of this voluntary CDRH MDDT program is to promote the development and use of tools to streamline device development and regulatory evaluation. Once an MDDT is qualified for a specific context of use, CDRH encourages developers to make their qualified MDDTs publicly available, which can include under a licensing arrangement, so that they can be used by any medical device sponsor for that context of use. CDRH reviewers should accept the MDDT for the qualified context of use without the need to reconfirm the suitability and utility of the MDDT when used in a CDRH regulatory submission. CDRH review divisions maintain the responsibility for evaluating regulatory submissions using information obtained from a qualified MDDT.

The process for MDDT qualification can be initiated in one of three 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, patient groups); or 3) MDDT developer pursues qualification to foster broad use of the tool, potentially across multiple device development programs.

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. Moreover, the qualification of one tool type (e.g., patient

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<sup>1</sup> The qualification definition in this guidance is consistent with the BEST definition. *See* BEST (Biomarkers, EndpointS, and other Tools) Resource; Glossary, <http://www.ncbi.nlm.nih.gov/books/NBK338448/>.

reported outcome measure for quality of life post-surgical procedure) does not prohibit the qualification of a similar tool with the same context of use by a different tool developer.

Decisions qualifying tools reflect CDRH's support for the use of the MDDT within the specified context of use. The availability of qualified MDDTs that can be utilized by many sponsors will aid in streamlining device development and regulatory evaluation. Once an MDDT is qualified, this may contribute to its acceptance and use by multiple device developers across multiple medical device development programs, which would increase impact on public health. To advance these goals, FDA only intends to qualify tools where FDA can make public certain high-level information about the existence of the qualified tool and its potential utility. FDA will not make public any proprietary information without permission from the tool developer. These issues are discussed in more detail in Section VI below.

## **B. Why is a qualification program beneficial?**

Qualification, as described in this guidance is intended to increase predictability in device evaluation and regulatory decision-making by making it clear to prospective sponsors that FDA accepts assessments from an MDDT in support of demonstrating safety, effectiveness, or performance of a medical device, without need to reconfirm suitability and utility of the MDDT, when used within the qualified context of use. Qualification also improves efficiency in the regulatory process because a qualified MDDT can be used by multiple sponsors across multiple medical device development programs.

Furthermore, the qualification program provides a mechanism for leveraging advances in regulatory science. Advancements in regulatory science help to bridge the gap between research and development of medical devices and the delivery of high quality, safe, and effective devices to patients. CDRH is committed to advancing regulatory science,<sup>2</sup> 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 program, we are modernizing the regulatory evaluation process and reducing the time and resources needed to develop and assess new medical products. This promotes innovation, supports the manufacture of high quality products, and speeds the rate at which safe and effective medical technologies are made accessible to patients.

Qualification also facilitates MDDT development and adoption, including through collaboration in a non-competitive setting, where multiple interested parties (individuals/stakeholders, companies/consortia, or organizations) may work together and pool resources to expedite development, validation and use of an MDDT. CDRH encourages the formation of consortia or other collaborations 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

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<sup>2</sup> Regulatory Science in FDA's Center for Devices and Radiological Health: A Vital Framework for Protecting and Promoting Public Health available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM274162.pdf>

or company. As further detailed in this guidance, stakeholders who wish to discuss developing an MDDT for potential qualification should contact FDA.

The qualification program also presents advantages for CDRH pertaining to review resources. Historically, if there was interest in using a particular tool to generate evidence in support of regulatory decisions, such as a patient reported outcome measure, then each FDA device review team evaluated the data justifying the tool use for each product or use separately. With this new program, the review of the tool and its relevant data, takes place outside of the review of the individual regulatory submission and will be reviewed during the MDDT qualification process. Once qualified, the tool can then be relied upon by FDA staff within the context of use, without further detailed review of the suitability of the MDDT. Sponsors can find instructions for using a particular qualified MDDT in the publicly available qualification summary documentation.

### C. How could MDDTs be used in device evaluation and regulatory decision-making?

MDDTs can be used in demonstrating safety, effectiveness, or device performance and to support regulatory decision-making, by facilitating the efficient provision of supporting evidence in non-clinical or clinical settings. MDDTs may have a variety of roles in a device clinical study such as patient selection, study population enrichment, monitoring treatment response, predicting or identifying safety problems related to treatment with a medical device or identifying patients who are or are not candidates for certain forms of therapy. In addition, MDDTs may be used in a variety of ways to collect, evaluate, and/or predict bench or *in vivo* performance. Appropriate use of qualified MDDTs may increase the efficiency of the device development and evaluation process by providing reliable predictions about device performance or identifying patients more likely to respond to treatment or experience disease progression in the near future. Some examples of the specific roles for MDDTs in device development include:

- For selection of clinical study subjects;
- To stratify patient population by predicted risk;
- For study population enrichment;
- For an intermediate endpoint;<sup>3,5</sup>
- For a surrogate endpoint;<sup>4,5</sup>

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<sup>3</sup> 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.

<sup>4</sup> 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.

<sup>5</sup> Use of **intermediate or surrogate endpoints** may allow for smaller trials or shorter follow-up, or be easier to measure than traditional clinical outcomes of a disease or condition. Optimal conditions for using intermediate or

- For a definition of an adverse event (AE) or symptoms of disease;
- To reduce test duration or minimize sample size, e.g., using as a computational model;
- To replace an evaluation typically conducted in human studies;
- To reduce or minimize the use of animals, e.g., using a simulation;
- For developing post-market surveillance methodologies such as:
  - 1) Patient Reported Outcomes (PROs) for approved devices; and 2) methods or models capturing real world outcomes.

### III. Definition of Key Concepts

For the purposes of this guidance, the following definitions apply and are consistent with the recent Biomarkers, Endpoints, and other Tools (BEST) resource<sup>6</sup>. This section includes brief definitions followed by examples and other explanatory information about the terms.

- **A Medical Device Development Tool (MDDT)** is a method, material, or measurement used to assess the effectiveness, safety, or performance of a medical device. An MDDT is scientifically validated and can be qualified for use in device evaluation and to support regulatory decision-making within a specified context of use.

MDDTs can be a clinical outcome assessment (COA) (e.g., patient-reported or clinician-reported outcome rating scales), a biomarker test (BT) (e.g., assay for a chemical analyte or medical imaging method), or a non-clinical assessment model (NAM) (e.g. *in vitro* method, animal or computational model), used in device evaluation and to support regulatory decision-making.

- **Context of Use (COU)** is a statement that fully and clearly describes the way the MDDT is to be used and the medical product development-related purpose of the use.
- **Qualification** is a conclusion, based on FDA review that within the stated context of use, a medical product development tool can be relied upon to have a specific interpretation and application in medical product development and regulatory review.

Hence, qualification reflects CDRH's expectation that within a specified context of use (statement that describes the conditions and boundaries within which the MDDT has been qualified for use), the results of an assessment that uses an MDDT can be relied upon in device evaluation and to support regulatory decision-making.

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surrogate endpoints include when the traditional endpoint is a rarely occurring event or delayed in its presentation (as in certain chronic diseases); when measurement of the endpoint is invasive, uncomfortable, costly, or easily confounded; or when the treatment effect is small, and therefore would require trials of impractical size in order to meet statistical significance.

<sup>6</sup> See BEST Resource *supra* note 1.



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CDRH recognizes three types of MDDTs, distinguished primarily by how the tool measures relevant parameters: Clinical Outcome Assessments (COAs), Biomarker Tests (BTs), and Non-clinical Assessment Models (NAMs). The following definitions are consistent with the BEST Resource:

1. A **Clinical Outcome Assessment (COA)** can be made through report by a clinician, a patient, a non-clinician observer or through a performance-based assessment.

COAs include patient-reported, clinician-reported, and observer-reported outcome measures and are typically instruments that include a scale or score. A COA includes not only the measure that produces a score, but also the clearly defined methods and instructions for administering 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 or indirectly (e.g., a diary of rescue pain therapy used for pain intensity).

The four common types of COAs are patient-reported outcome (PRO) measures, clinician-reported outcome (ClinRO) measures, observer-reported outcome (ObsRO) measures, and performance outcome (PerfO) measures. Other COAs used as a measure of patient benefit or safety may be qualified as MDDTs.

- **Patient-reported outcome (PRO) measures<sup>7</sup>**: A PRO is a measurement based on a report that comes from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's report by a clinician or anyone else. A PRO can be measured by self-report or by interview, provided that the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient (e.g., pain severity or nausea) can only be measured by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others. An example includes quality of life or health status scores, for example, the EXAcerbations of Chronic Pulmonary Disease Tool – Patient Reported Outcome (EXACCT-PRO).
- **Observer reported outcome (ObsRO) measures**: An ObsRO measure does not include medical judgment or interpretation. Generally, ObsROs are reported by a parent, caregiver, or someone who observes the patient in daily life. For patients who cannot respond for themselves (e.g., infants or cognitively impaired), we encourage observer reports that include only those events or behaviors that can be observed. As an example, observers cannot validly report an infant's pain intensity, (a symptom) but can report infant behavior thought to be caused by pain (e.g., crying). For example, in the assessment of a child's functioning in the classroom, the teacher is the most appropriate observer. Examples of ObsROs include a parent report of a child's vomiting episodes or a report of wincing thought to be the result of pain in patients who are unable to report for

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<sup>7</sup> "Guidance for Industry and FDA Staff: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims," December 2009, available at: <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>

themselves.

- **Clinician-reported outcome (ClinRO) measures:** A ClinRO is based on a report that comes from a trained health-care professional after observation of a patient’s activities with a health condition. A ClinRO measure involves a clinical judgment or interpretation of the observable signs, behaviors, or other physical manifestations thought to be related to a disease or condition. ClinRO measures cannot directly assess symptoms that are known only to the patient (e.g., pain intensity).
- **Performance outcome (PerfO) measures:** A PerfO is a measurement based on a task(s) performed by a patient according to instructions that is administered by a health care professional. Performance outcomes require patient cooperation and motivation. These include measures of gait speed (e.g., timed 25 foot walk test), memory recall, or other cognitive testing (e.g., digit symbol substitution test).

Other clinical outcomes based on 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.

2. A **Biomarker Test (BT)** is a test or instrument used to detect or measure a biomarker.

A **biomarker** is a defined characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or responses to a therapeutic intervention. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives.

Categories of biomarkers include:

- susceptibility/risk biomarker;<sup>8</sup>
- diagnostic biomarker;<sup>9</sup>
- monitoring biomarker;<sup>10</sup>
- prognostic biomarker;<sup>11</sup>
- predictive biomarker;<sup>12</sup>
- pharmacodynamic/response biomarker;<sup>13</sup> and
- safety biomarker.<sup>14</sup>

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<sup>8</sup> <https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/susceptibility-risk-biomarker/>

<sup>9</sup> <https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/diagnostic-biomarker/>

<sup>10</sup> <https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/monitoring-biomarker/>

<sup>11</sup> <https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/prognostic-biomarker/>

<sup>12</sup> <https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/predictive-biomarker/>

<sup>13</sup> <https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/pharmacodynamic-response-biomarker/>

<sup>14</sup> <https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/safety-biomarker/>

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

CDRH also intends to consider MDDTs derived from medical imaging to be BTs, if the characteristic (e.g., tumor diameter) is objectively measured.

Reliable measurement of biomarkers can help reduce uncertainty in device development and evaluation by providing quantifiable predictions about device performance. BTs used to measure biomarkers in patients before treatment can be used to select patients for inclusion in a clinical trial. BTs used to detect changes in biomarkers following treatment may predict or identify safety problems related to a therapeutic device or reveal the response to an intervention expected to predict clinical benefit from treatment.

A **Non-clinical Assessment Model (NAM)** is a non-clinical test model or method that measures or predicts device function or *in vivo* device performance.

A NAM could be an *in vitro* (“bench”) model, an *ex vivo model*, animal model, or computational model, and is developed to measure or predict a parameter of interest. Examples of NAM include: *in vitro* models to replace animal testing, tissue and other material phantoms to evaluate imaging or other devices, and physics-, chemical- or biological- based computational models.

Qualified NAMs may be used to evaluate a new material property, modifications to an existing design, or a device feature historically evaluated through other bench, animal or human testing.

## **IV. CDRH Qualification Decision Framework**

When determining whether to qualify a proposed MDDT, CDRH will consider the following:

- *MDDT description.* Is the MDDT adequately described?
- *Context of use.* Is the proposed context of use adequately and appropriately defined?
- *Public Health Impact.* Would the scope and use of the tool have a broad public health impact?
- *Strength of evidence.* Does the available scientific evidence demonstrate that the MDDT reliably and accurately measures what is intended, 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 outweigh potential disadvantages of making decisions based on measurements obtained using the MDDT? Of particular importance are regulatory, public health, and/or clinical impact.

## **A. Qualified Context of Use**

The Context of Use (COU) is a key aspect of qualification. It describes the way the MDDT should be used, the purpose of MDDT, and the conditions under which the MDDT is qualified. Once an MDDT is qualified, the context of use defines the boundaries within which the available data adequately support use of the MDDT.

The COU should describe the specific role of the MDDT in device development. A complete COU should include:

- 1) The tool or product area in which the MDDT is proposed to be qualified;
- 2) The specific output/measure from the MDDT;
- 3) The role of the MDDT in regulatory evaluation (e.g., for use in clinical studies, this includes the study population or disease characteristics, as well as specific use – diagnosis, patient selection, study endpoints); and
- 4) The phase(s) of medical device development in which tool measurements can be used (e.g., design evaluation, animal testing, early clinical study, pivotal clinical studies to support market application, post-market study, or changes, etc.).

The COU defines the boundaries within which the available evidence adequately support use of the MDDT. The amount and strength of evidence needed to support qualification depends largely on the defined COU. The COU should describe all of the criteria under which the MDDT is qualified. A qualified context of use may include any limits on the extent of prediction.

Once an MDDT is qualified, the COU may be modified or expanded in response to new data or changing science. Tool developers that would like FDA to consider changes to the COU for the qualified MDDT should submit a new MDDT qualification package. Because the COU is central to the appropriate use of the MDDT, we recommend that the COU be conveyed prominently when a tool developer offers its MDDT to other device developers.

## **B. Evidence to Support Qualification**

The amount and strength of evidence needed to support qualification of an MDDT will vary depending on the COU and the tool type. For example, an MDDT proposed for use as one component of measuring an adverse event in a clinical study may need less data than a biomarker test tool proposed for measuring a primary endpoint in a pivotal study for a novel high-risk device. The latter use may need more evidence of its validity due to the potential disadvantages of accepting an inaccurate MDDT for this COU.

Submitters should explain how the strength of evidence for use of the MDDT is adequate to support the proposed COU. Evidence may include performance characteristics of the tool that would affect the usefulness of an MDDT, such as:

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- **Tool Validity and other Performance Characteristics:** This evidence should demonstrate that the tool provides accurate and precise measurements. Sufficient data should be provided to adequately describe performance characteristics of the tool. Depending on the tool type, this evidence may include analytical, clinical, construct validity, external validity, reduction of bias, verification of the constitutive model, uncertainty quantification, numerical convergence, etc. Submitters can refer to resources such as Clinical and Laboratory Standards Institute (CLSI)<sup>15</sup> documents for more information about validation.
- **Predictive Ability:** This evidence should describe the degree to which the tool measurement is related to the outcome of interest. This should include evidence on the strength of that predictive relationship and that the prediction is repeatedly demonstrated in multiple studies or as a class effect.
- **Extent of Prediction - Capture:** The evidence should show the tool's ability to capture the aggregate effect on the true outcome of interest. The available data should account for every major effect of the medical device that is intended for the extent of prediction.

The type of evidence needed will vary depending on the tool type and COU and may include (but is not limited to) as appropriate:

- design verification;
- simulation results from computational models;
- bench performance data (including full test reports and protocols);
- animal performance data (including full test reports and protocols);
- clinical data (including full test reports, protocols, and all appropriate (pre-specified) statistical analyses to demonstrate the relationship between the tool and the COU);
- human factors testing; and/or
- literature articles (the full text article, a summary and a description of how the article supports qualification).

For COAs, CDRH will review the evidence that supports that the proposed tool is a valid assessment for how a patient feels or functions in day-to-day activities.

For BTs, it is important to note that a biomarker test being considered for qualification is conceptually independent of the biomarker (e.g. sphygmomanometer vs. blood pressure). A biomarker, however, cannot be qualified without a reliable means to measure it. In assessing BTs for qualification, CDRH will evaluate both the strength of evidence supporting the biomarker for the specified COU, as well as the performance characteristics of the test(s) used to provide the biomarker data. Test validity (e.g., precision and accuracy) should be demonstrated for the proposed COU.<sup>16</sup>

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<sup>15</sup> <http://clsi.org/>

<sup>16</sup> The amount and type of new evidence needed to support qualification of a BT may also depend in part on whether there is any test or instrument for measurement of the biomarker that is already FDA cleared or approved for clinical

When CDRH qualifies a BT, this means we also accept the strength of evidence supporting the biomarker for the specified COU. Subsequent BTs seeking qualification for similar COU need only demonstrate performance characteristics of the test(s) to measure that same biomarker.

For NAMs, CDRH will review the evidence that the proposed tool is an adequate substitution for another accepted test or measurement or is otherwise a valid assessment of the device function or prediction of *in vivo* device performance.

## **C. Assessment of Advantages and Disadvantages of Qualification**

Qualification will depend on whether the probable advantages outweigh the probable disadvantages of making decisions based on measurements obtained using the MDDT. CDRH intends to place emphasis on regulatory, public health, and/or clinical impact.

When assessing advantages and disadvantage, CDRH intends to consider the following factors:

- **Assessments of 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 non-clinical 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(s).** This may include: whether there is a potential to impact multiple device development programs; whether the COU includes life-threatening and/or serious chronic diseases or conditions, diseases/conditions where there are no or poor alternatives, or underserved populations such as pediatrics; 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 in support of the MDDT, and a comparison to the available alternatives.

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use through premarket review, and if so, whether the proposed COU 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 performance characteristics (e.g., precision and accuracy) should be demonstrated for the proposed COU. 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 COU, 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 as an MDDT for the proposed COU.

- **Assessments of Disadvantages of Using the MDDT:**
  - **Type of disadvantage(s).** Considering the COU, what types of decisions might be made based on the use of an MDDT that should not have been qualified? For example, the disadvantage of using a COA with poor external validity may be lesser if it is used during early device design versus a pivotal clinical study.
  - **Magnitude of disadvantage.** The scope of impact of making a decision based on inaccurate conclusions from a MDDT is based on the severity of risk, a comparison of the MDDT to its alternatives, and considering the COU.
  - **Likelihood of disadvantage.** How likely is a particular risk to occur? This could be based on the evidence in support of tool validity. For example, for a BT, this could be the likelihood of the MDDT reporting a false positive, false negative or false estimate of predictive value.
  - **Mitigation of disadvantage(s).** The use of mitigations may minimize the risks of relying on the MDDT. For example, alternative complementary sources of information or confirmatory data from later time points may mitigate risks of decision-making based on information from an MDDT.
  
- **Additional Factors for Assessing Advantages and Disadvantages of Using the MDDT:**
  - **Degree of certainty.** If the advantages of using the MDDT are high, and disadvantages are minimal, 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 qualification.
  - **Novelty of technology.** The assessment will consider whether the MDDT facilitates 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.

It is important to emphasize that the assessment of advantages and disadvantages does not refer to assessing the accuracy, precision, predictive ability, or extent of prediction of the tool. Rather, this assessment will involve determining whether the advantages outweigh the disadvantages of using the tool in the course of developing and/or evaluating a medical device. While the accuracy, precision, predictive ability, and extent of prediction may contribute to the advantages or disadvantages, this will not be the sole means of assessment.

## **D. Regulatory Considerations and Related Recommendations**

Some MDDTs may meet the definition of a device in section 201(h) of the FD&C Act. Whether an MDDT is a medical device under section 201(h) of the FD&C Act will often depend on how it is intended to be used. For example, if the MDDT product is only for use in device development/ evaluation and is not for use in diagnosing or treating patients or study subjects, it is unlikely it would be a device. On the other hand, if the MDDT is intended for use in diagnosing or treating, or aiding in the diagnosis or treatment of subjects in a clinical study, it would likely be a device. A product intended for use in diagnosing or treating, or aiding in the diagnosis or treatment of patients in clinical settings outside clinical studies would likely be a device, but would not be an MDDT. Some MDDTs may have both device uses as well as non-device uses.

### MDDT use in Clinical Studies

Devices intended for use in clinical investigations are exempt from most requirements applicable to devices, including premarket clearance or approval, as long as the investigation complies with applicable requirements, such as those under 21 CFR part 812, or is exempt from such requirements.<sup>17</sup> As MDDTs would typically be used in the research or investigation of a medical device, MDDTs that are devices would typically be exempt from clearance, approval, and other device requirements, as long as the clinical investigation is compliant.

The use of an MDDT in a medical device clinical study does not change the IDE requirements for a given investigation (see 21 CFR part 812). 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 development and regulatory evaluation of a medical device by providing a more efficient and predictable means for collecting the necessary information to make regulatory assessments.

### Qualification of an MDDT versus Clearance or Approval of a Medical Device

FDA qualification of an MDDT is different from FDA clearance or approval of a medical device. The type of evidence needed to support MDDT qualification is not the type of evidence that is needed to support marketing authorization for a medical device. As described in section IV.B, FDA intends to evaluate tool validity, predictive ability, and extent of prediction-capture when making qualification determinations; for clearance or approval, FDA evaluates whether the device is substantially equivalent or has a reasonable assurance of safety and effectiveness. As a result, using a qualified MDDT for clinical treatment or diagnosis of a patient when the product is not cleared or approved could cause unexpected harm to patients.

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<sup>17</sup> If the device that is the subject of the investigation is significant risk, as defined at 21 CFR 812.3(m), the investigation, including use of the MDDT, is subject to all requirements in 21 CFR part 812. If the device that is the subject of the investigation is not a significant risk device, the abbreviated requirements listed under 21 CFR 812.2(b) apply to the investigation, including the use of the MDDT. Investigations, including the use of an MDDT, that meet the criteria for one of the exemptions described at 21 CFR 812.2(c), including 812.2(c)(3), are not required to comply with part 812 with the exception of section 812.119.



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Use of such tests for clinical diagnostic purposes may mislead healthcare providers and cause serious adverse health consequences to patients, who are not aware they are being diagnosed or treated based on results of tests with research or investigational products. To avoid confusing or misleading healthcare providers or patients, we recommend that tool developers make clear to users that qualification does not constitute FDA clearance or approval of the product as a medical device. For example, prominent statements that a tool developer makes in MDDT labeling and promotional materials regarding the qualification of its product by FDA as an MDDT could be accompanied by language clarifying that the qualification of an MDDT does not constitute FDA clearance or approval. As another example, an MDDT developer could prominently convey that the qualified COU only applies to the use of the product in device development or evaluation, and that the tool has not been cleared or approved by FDA. In addition, to avoid labeling that is misleading, manufacturers of MDDTs that are also legally marketed medical devices should separate FDA-regulated labeling from materials used for the product as an MDDT.

Tool developers may see different ways to address these concerns and are encouraged to discuss other approaches with the FDA review team when proposing its MDDT.

### MDDT qualification as compared to consensus standards and device-specific FDA guidance

The MDDT qualification program is not meant to replace the consensus standard development and recognition process<sup>18</sup> or FDA's issuance of device-specific guidance documents. FDA views the MDDT qualification program as a complementary program for evaluating and recognizing tools that are useful for medical device evaluation and to support regulatory decision-making.

Consensus standards are typically technical methods. For methods and approaches that are mature and that the community recognizes as standard, consensus standard recognition may be a more appropriate pathway.

Device-specific guidance documents typically outline FDA's recommendations regarding the range of different types of assessments for one product area, whereas an MDDT can focus on one assessment or measurement approach, potentially useful across a range of different products.

## **V. CDRH Qualification Process**

The voluntary qualification process consists of several phases, which are described below.<sup>19</sup>

### **A. Proposal Phase**

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<sup>18</sup> MDDT Program available at

<https://www.fda.gov/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/>

<sup>19</sup> *Id.*

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The goal of the proposal phase is to determine if the MDDT is suitable for qualification through the MDDT program. The number of proposals accepted will depend on available FDA resources.

1. Those interested in seeking qualification should begin by submitting a proposal. A complete proposal package should include the following:

### **MDDT Description**

- The category of the development tool (COA, BT, NAM) with appropriate explanation.
- A statement declaring if the product (proposed development tool) is a cleared or approved medical device.
- A proposed Context of Use with an explanation of how the development tool will be used by device sponsors within that Context of Use (i.e., what is the tool intended to measure or assess?).
- A description of the development tool with sufficient detail for CDRH to understand the development tool.
- A description of how the development tool achieves the specified measure. This could include schematics, photos, figures, and engineering drawings, as appropriate.

### **Justification**

- A description of how the tool will meet a public health need.
  - A description of the readiness of the development tool. If a tool is not fully developed, a development timeline should be included.
  - A brief overview of the proposed evidence plan to qualify the development tool, including a timeline.
  - Those interested in seeking qualification should meet with FDA via FDA's Q-Submission Program.<sup>20</sup>
2. CDRH plans to review proposals and prioritize those with stronger potential to meet a public health need. Each of the following would weigh in favor of the tool potentially meeting a public health need:

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<sup>20</sup> <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf>

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- Context of Use includes life-threatening and/or serious diseases or conditions, or underserved populations such as pediatrics;
  - Context of Use includes novel or innovative technology with no established paradigm for regulatory assessment;
  - No/poor alternatives or unmet scientific need;
  - Major efficiencies to be gained in device development and evaluation time;
  - Use of the development tool allows for safer or less invasive, easier, more convenient, or less variable measurements than the alternative; or
  - Potential to impact multiple device development programs and/or multiple sponsors.
3. For proposals that potentially meet a public health need, CDRH plans to determine acceptance based on:
- **Proposed Context of Use:** Does available information support the tool principle/method of measurement for the proposed Context of Use? Is the Context of Use feasible and beneficial to meet a public health need?
  - **Prioritization:** Does CDRH have appropriate resources to review the tool based on potential impact of meeting the identified public health need? Is the expected timeline for the submitter to file a qualification package appropriate to meet the public health need?
  - **Tool readiness:** Does the tool exist in prototype or final form?
4. CDRH intends to notify submitters of its decision regarding proposal acceptance in writing approximately 60 days from receipt of the proposal. For proposals that are accepted, CDRH intends to recommend a suitable next phase (incubator, pre-qualification, or qualification) for the submission. For those proposals not accepted, CDRH plans to also provide the factor(s) contributing to this decision.

## **B. Incubator Phase (Optional)**

In certain instances CDRH may accept tools with a high potential public health impact that are not fully developed. The goal of the incubator phase is for CDRH to work with submitters to foster the development of tools that have potential to significantly improve public health. CDRH's ability to participate in the incubator phase may be limited by available resources.

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1. CDRH will invite suitable submitters to participate in the incubator phase in the proposal decision letter.
2. Submitters can engage CDRH by submitting an incubator inquiry package (IIP). The IIP should consist of similar content to the proposal package, and should include an updated tool development plan including a timeline, list of questions for CDRH, and any additional information to provide for a productive discussion:
3. CDRH intends to provide feedback to the submitters' questions in order to aid in the development of the tool. At the end of each interaction, CDRH may also recommend whether the tool is ready to advance to pre-qualification or qualification phase.

### **C. Pre-Qualification Phase (Optional)**

The goal of the pre-qualification phase is for CDRH to provide feedback on the plan to collect evidence to support qualification of the tool.

1. Submitters should provide a pre-qualification package, (PQP) which includes similar content to the proposal, with additional detail so that CDRH can fully understand the tool and the proposed COU.

The PQP should include a complete plan for gathering the necessary evidence to support tool qualification. The evidence plan should include detailed protocols of all studies and tests to be completed to support qualification. When appropriate, a statistical analysis plan should also be included. While summary data of already collected evidence may be provided to support the final evidence plan, full test reports and data are not reviewed at the pre-qualification phase.

2. CDRH then conducts expert review of the tool description, proposed COU, and evidence plan, and provides feedback addressing any potential studies or protocol modifications that could improve the evidence plan. Finally, the tool advances to the qualification phase when a tool submitter has demonstrated that the evidence plan submitted appears adequate to support the proposed COU.

### **D. Qualification Phase**

The goal of the qualification phase is to determine whether, for a specific COU, the tool is qualified based on the evidence and justifications provided (refer to Section IV for factors which CDRH will consider in deciding whether to qualify an MDDT).

1. Submitters should provide a complete qualification package (see Appendix 1 for a sample outline of a Qualification Package). In brief, the package should include:
  - a. all descriptive elements and protocols as described in the proposal and pre-qualification sections;

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- b. statement if the tool has been previously submitted to the MDDT Program or through the Drug Development Tool Program;<sup>21</sup>
- c. MDDT description;
- d. all of the evidence needed to support qualification;
- e. discussion of how the strength of evidence supports qualification;
- f. assessment of advantages and disadvantages for tool use.

The package should also include the following, to facilitate proper use of the MDDT:

- information for how to contact the tool developer in order to access the tool and
  - information about how sponsors can use the data from use of the tool in a clinical trial for a regulatory submission.
2. CDRH plans to review the qualification package based on the decision framework described in Section IV. CDRH intends to qualify the MDDT if the tool is adequately described, the proposed COU is appropriately defined, the strength of evidence supports use of the MDDT within the proposed COU, and the probable advantages of using a tool outweigh the probable disadvantages for the proposed Context of Use. Once CDRH has determined whether or not to qualify a tool, CDRH intends to notify the submitter in writing of the decision.
  3. CDRH intends to make public certain high-level information about tools that are qualified, as described in Section VI.

## **E. Potential Changes to Qualification Status**

After an MDDT is qualified, its developer may wish to modify or expand its COU in response to new data or changing science. Modification or incremental expansion of the qualified COU over time may be undertaken through the qualification program. There may also be situations where the bases upon which an MDDT was qualified has changed, CDRH may re-evaluate the qualification decision.

## **VI. Communication to Public of FDA Qualification Decisions**

Once an MDDT is qualified for a specific COU, FDA intends to accept its use by any medical device sponsor for that COU. The intent of the voluntary FDA MDDT program is to promote the development and widespread use of tools to streamline device development and regulatory evaluation. These goals would best be served by making certain high-level information about such tools public, so that device sponsors other than the tool developer would be aware of the existence and potential utility of qualified tools. Thus FDA only intends to qualify tools where

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<sup>21</sup> <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/>

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FDA can make such information public. Specifically, FDA intends to publicly disclose a summary of evidence and basis of qualification (SEBQ) if FDA qualifies the tool. An SEBQ includes:

- a brief description of the tool and its principle of operation;
- the qualified context of use;
- a general summary of the evidence to support qualification and a discussion of the strength of that evidence;
- a brief assessment of the advantages and disadvantages of using the MDDT for its qualified context of use; and
- information on how a device developer can contact the tool developer so that it may access the tool.

Any tool submitter with questions about the content and detail FDA intends to provide in an SEBQ should raise those with FDA during the proposal phase. Before publicly disclosing any of a tool developer's proprietary information, FDA will obtain written permission from the tool developer.

Nothing about the MDDT program is intended to place limitations or requirements on MDDT licensing or fees, or the degree of access to intellectual property associated with an MDDT that a tool developer may give to a device sponsor.

## **APPENDIX 1**

### **SAMPLE OUTLINE OF QUALIFICATION PACKAGE CONTENTS**

The recommended outline below is provided as an example only for illustrative purposes and is not required. Refer to Section IV for details. A sample qualification package should include the following information:

1. Administrative Information:
  - a. Tool Name
  - b. Tool Type, including,
    - COA (Clinical Outcome Assessment),
    - NAM (Non-clinical Assessment Model), and
    - BT (Biomarker Test).
  - c. Submission Package Phase:
    - Proposal;
    - Incubator;
    - Pre-qualification; and
    - Qualification.
  - d. MDDT Tracking Number (if known).
  - e. Statement regarding whether the tool has been previously submitted to the MDDT Program or to the Drug Development Tool Program.
  - f. Statement regarding whether the product (proposed tool) is a cleared or approved medical device.
2. MDDT Description:
  - a. Measurements Provided,
  - b. tool Principle and Method of Measurement, and
  - c. description of Tool Readiness.
3. Context of Use:
  - a. The tool or product area;
  - b. the specific output/measure from the MDDT;
  - c. the role of the MDDT in regulatory evaluation; and
  - d. the phase of tool development.
4. Evidence to Support Qualification, including (as appropriate):
  - a. Design Verification;
  - b. Computer Simulations;
  - c. Bench Performance Data;
  - d. Animal Performance Data;
  - e. Clinical Performance Data;
  - f. Human Factors Testing; and
  - g. Literature References.

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5. Discussion of the Evidence Strength to Support Qualification:
  - a. Tool Validity and other Performance Characteristics (e.g., Accuracy and Precision, etc)
  - b. Predictive Ability; and
  - c. Extent of Prediction (Capture).
  
6. Assessment of Advantages and Disadvantages for Tool Use:
  - a. Advantages of Tool Use for Public Health;
  - b. Disadvantages of Tool Use for Public Health;
  - c. Degree of Certainty of Tool Use; and
  - d. Novelty of Tool Technology that Impacts Public Health.
  
7. Proposed Materials for Tool Use:
  - a. Truthfulness Statement;<sup>22</sup>
  - b. Version of Qualified Tool;
  - c. Documentation of Changes to Qualified Tool Version (as appropriate);
  - d. Context of Use Statement;
  - e. Instructions Manual; and
  - f. Validation (control and calibration) Procedures.

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<sup>22</sup> All tool submitters should include a statement certifying that all information submitted is truthful and that no material fact has been omitted.