Biomarker Qualification Plan: Outline of Suggested Content Elements

NOTE TO REQUESTORS: FDA issued the "Qualification Process for Drug Development Tools," Guidance for Industry and FDA Staff in November 2020. This guidance describes the process for requestors interested in qualifying Drug Development Tools (DDT) and on taxonomy for biomarkers and other DDTs, as mandated by section 507 of the 21st Century Cures Act.[1] Given the changes to the process as defined in section 507, we expect to see further development of this content over time, with more experience and your input. To see prior Biomarker Qualification Program (BQP) submissions that have been accepted under section 507, go to: https://force-dsc.my.site.com/ddt/s/. Note that certain submission information will be made publicly in accordance with section 507, which is described in more detail at: https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/drug-development-tool-qualification-process-transparency-provisions.
Should you have any questions or want to provide feedback on this or other BQP resources, including the content and format of submissions and the transparency provisions under section 507,[2] contact the BQP staff at CDER-BiomarkerQualificationProgram@fda.hhs.gov.

Qualification Plan Submission Instructions:

Requestors should transmit Qualification Plan (QP) submissions through the CDER NextGen Portal and upload the following sections of the QP as separate PDF files in searchable text format:

1. Executive Summary[3]
2. Qualification Plan
   - Drug Development Need
   - Biomarker Information and Interpretation
   - Context of Use
   - Analytical Considerations Overview
   - Clinical Considerations Overview
   - Prospective Timeline, Milestones, and Dependencies
   - Transparency and Data Sharing Plans
   - Submission Information
3. Statistical Analysis Plan (SAP) with details on statistical methods
   - Requestors should submit detailed statistical methods and SAP as a standalone document that is included in their overall QP submission package. This should be

[1] Section 3011 of the 21st Century Cures Act established section 507 of the Federal Food, Drug, and Cosmetic (FD&C) Act.
[2] Drug Development Tool Qualification Process: Transparency Provisions: https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/drug-development-tool-qualification-process-transparency-provisions.
[3] Per the Section 507 transparency provisions, the Executive Summary document will be posted publicly on the CDER & CBER Drug Development Tool Qualification Project Search database.

a separate file rather than embedded within other documents, making it easy for reviewers to locate and reference during their evaluation of the requestor's QP submission.

4. Appendices (as applicable)
    - References
    - Requestor Letter of Intent (LOI) Response to Recommendations
    - Confidential and Proprietary Information
    - Detailed Analytical Plans:
        - Detailed Analytical Measurement and Validation Plan
        - Detailed Clinical Development and Validation Plan
    - Regulatory History

If the program will be submitting clinical data for the purpose of qualification of a DDT, requestors are encouraged to submit clinical data using Clinical Data Interchange Consortium (CDISC) standards to facilitate review and utilization of data. Data sharing and the capability to integrate data across trials can enhance DDT development and utilization. If requestors plan to use the DDT prior to qualification to support regulatory review for a specific Investigational New Drug (IND), New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) development program, they should prospectively discuss the approach with the appropriate CDER or CBER division.

In the event of a change in requestor during the course of this biomarker qualification project, requestors should submit a Change of Requestor communication to the BQP Team via email at CDER-BiomarkerQualificationProgram@fda.hhs.gov. This change should also be noted in the Qualification Plan submission. For additional information about the Change of Requestor process, please refer to the CDER NextGen Portal Frequently Asked Questions available at https://www.fda.gov/drugs/biomarker-qualification-program/cder-nextgen-portal-frequently-asked-questions

Table of Contents

I. Executive Summary

*[The Executive Summary should be written as a brief (~ 10 page) stand-alone document (i.e., separate from the rest of the Qualification Plan (QP) information). Per the Section 507[4] transparency provisions, the Executive Summary document will be posted **publicly** on the CDER & CBER Drug Development Tool Qualification Project Search database.[5] While we expect the Executive Summary and other sections of the QP to have some duplicate content, the Executive Summary should NOT cross-reference other QP sections/material. We expect summary-level information for the methods/results in the Executive Summary - not the complete details (which are requested later)]*

The Executive Summary must provide enough detail that a reader can clearly understand important aspects of the qualification plan. It is recommended to include the content areas outlined in Sections 1 through 8 below.

1. Administrative Overview

1. Requestor name, title(s) & contact information
2. Note: If a change of requestor has occurred since the LOI submission, please indicate this.
3. Alternate requestor name, title(s) & contact information
4. Collaboration: name of supporting or participating organization, consortia or individuals.
5. Project title

2. Background

Include the drug development need your biomarker is intended to address.

3. Biomarker Name, Type, and Description

If the biomarker is different from the biomarker described in your Letter of Intent (LOI), provide a description of the difference and the rationale for the change in the biomarker.

4. Context of Use (COU) Statement

If QP COU is different from the LOI COU, indicate the LOI COU and provide a rationale for the evolution of the COU.

[4] Section 3011 of the 21st Century Cures Act established section 507 of the Federal Food, Drug, and Cosmetic Act (FD&C) Act.

[5] CDER & CBER Drug Development Tool Qualification Project Search database enables public stakeholders to search across DDT qualification programs by stage of submission, qualification status, disease, and therapeutic area. The database is available at https://force-dsc.my.site.com/ddt/s/.

5. Measurement Method

If applicable, provide device name, with make and model if appropriate. List prior clearances or approvals such as the FDA/Center for Device and Radiological Health clearance or approval with 510k or Premarket Approval (PMA).

6. Decision Process

An overview of the decision process describing how the biomarker will be applied in the specified COU in a flow diagram (decision tree) should be included, as well as steps and elements of the decision-making process including any cut-off points/limits/thresholds.

7. Summary of Analytical Considerations

1. Summary of completed analytical validation studies and results
2. Planned analytical validation studies

8. Summary of Clinical Considerations in Support of the Biomarker's COU

1. Summary of completed studies/data analysis (if applicable)
    i. Objective
    ii. Study design
    iii. Results and conclusion
2. Summary of proposed studies/data analysis plan for biomarker qualification
    i. Objective
    ii. Study design

II. Drug Development Need

[This content section and those that follow should be submitted as a separate document from the Executive Summary above; ***only the Executive Summary document will be made publicly available****. Examples of submitted Drug Development Need applications are available in the CDER & CBER Drug Development Tool Qualification Project Database at: https://force-dsc.my.site.com/ddt/s/.]*

Include a description of why the biomarker is needed for drug development, including how its use might promote drug development in areas where there is an unmet medical need and how its use will impact regulatory decision-making. The needs assessment should describe the current drug development landscape, such as the use and limitations of available biomarkers or other drug development tools, and the added value the novel biomarker could provide to the current drug development process.

1. Summary of Current Landscape

Discuss the current practices in drug development related to the proposed biomarker, population, and drug class and the challenges and limitations associated with these current practices.

2. Description of Drug Development Need

Discuss the knowledge gaps, roadblocks, challenges, and limitations of the current approaches as they relate to the proposed tool use (e.g., availability of technology or reliability of measurement) or cost (e.g., time, monetary, patient and societal burden). Discuss how the biomarker will address the gaps identified in the drug development need.

III. Biomarker Information and Interpretation

1. Biomarker Name and Type[6]

A biomarker[7] is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, imaging, or physiologic characteristics are types of biomarkers. A biomarker is not a direct assessment of how an individual feels, functions, or survives.

Molecular biomarkers should be identified with a unique ID from UniProt (http://uniprot.org/), HUGO Gene Nomenclature Committee (http://genenames.org), Protein Data Bank (http://rcsb.org/pdb/home/home.do), or Enzyme Commission (http://enzyme.expasy.org).

Indicate whether the biomarker is a multi-component biomarker. A multi-component biomarker (MCB) is a defined combination or defined set of two or more individual biomarkers whose values, when considered together in a specified way, provide an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions.

The component measurements of a MCB could be derived from different measurement methodologies (e.g., brain imaging, EEG, genomics, cognitive, digital health technologies including cognitive measures) or combine biomarker values measured by a single assay/platform methodology (e.g., multiplex assays for proteomics, transcriptomics, genomics, or other analytes).[8]

2. Biomarker Interpretation and Utility

Describe the workflow or the system to produce the biomarker outcomes after the biomarker is measured, such as any formulas, modeling, simulations, scoring system, algorithms, programming assumptions, or other manipulations used to construct the biomarker outcomes. If multiple elements are combined, including one or more biomarker measures, explain how a composite result is constructed. Provide a rationale for inclusion of the elements and identify any gaps or limitations for the elements used in the construction.

This section may also include information on whether the biomarker results are presented as a qualitative binary or a quantitative discrete or continuous measure, and provide a rationale for

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[6] e.g., molecular, histologic, radiographic, digital, or physiologic.

[7] BEST (Biomarkers, EndpointS, and other Tools) Resource. FDA-NIH Biomarker Working Group (2016). Available at: http://www.ncbi.nlm.nih.gov/books/NBK338448/.

[8] BEST Resource: http://www.ncbi.nlm.nih.gov/books/NBK338448/.

any cut-offs, limits, and range of measurement.

Interpretation of the biomarker data to support a drug development or a clinical trial decision can be based on the measured values and other available clinical observations and supporting evidence (as defined in the COU). The interpretation of the biomarker is an integral part of the biomarker decision process.

Describe how the biomarker results are interpreted and used to support, inform, or make decisions for regulatory drug development. A decision tree or flow diagram should be included to understand how the biomarker information will be used in drug development or in a clinical trial design.

IV. Context of Use

1. Context of Use Statement

*[Describes the drug development use that is complementary to the stated drug development need **(limited to 500 characters)**.]*

The COU statement may evolve over time based on the information presented in the submission supporting the biomarker's COU and the recommendations made by FDA, but it should generally be consistent and worded identically throughout a single submission stage.

Describing the COU statement early defines the type of information needed in support of qualification for the proposed approach. A requestor may submit more than one biomarker qualification submission (i.e., LOI or QP) to allow for different contexts of use for the same biomarker; **however, each submission and development efforts should focus on a single context of use, even if the long-term goal includes multiple contexts of use**.

A COU is generally written to be consistent with the following structure:

[BEST[9] biomarker category] to [biomarker intended use in drug development]

EXAMPLES:

1. Biomarker X is a response biomarker that measures Crohn's Disease (CD) activity used as a co-primary endpoint in CD clinical trials in conjunction with an accepted assessment of patient reported symptoms.
2. Biomarker Y is a susceptibility/risk biomarker that indicates the potential for individuals to develop symptomatic Type 1 Diabetes (T1D) used as an enrichment criterion or as a stratification criterion to study interventions intended to prevent the onset of T1D.

Additional examples of COU statements are available on the CDER & CBER Drug Development Tool Qualification Project Database website. For more information about biomarker context of use, go to: https://www.fda.gov/drugs/biomarker-qualification-program/context-use.

[9] BEST (Biomarkers, EndpointS, and other Tools) Resource. FDA-NIH Biomarker Working Group (2016). Available at: http://www.ncbi.nlm.nih.gov/books/NBK338448/.

2. Context of Use Narrative

Specify how the biomarker will be used and provide clinical utility in drug development programs. Specify whether the biomarker is expected to be useful for development of many products across different classes of therapeutics. The narrative may include explanations of context or purpose and situations such as the patient population, disease, or disease stage; stage of drug development; and/or mechanism of action of the therapeutic intervention.

The narrative typically should include an explanation of the following elements:

- Purpose of the biomarker and its intended application in drug development, taking into account the specific biomarker category.
- The intended patient population and the relevant disease or disease stage for which the biomarker is applicable.
- When the biomarker will be utilized during the drug development process, specifying the stage of development at which it will be applied.
- Application of the biomarker, categorizing its use as decisional, co-decisional, enhancement, or enrichment criteria.
- Assessment of whether the biomarker is useful for the development of multiple products across various classes or mechanisms of action within therapeutic intervention.

V. Analytical Considerations Overview

Provide an overview of analytical considerations for the biomarker, including available analytical methods, pre-analytical factors, measurement techniques, analytical requirements and evidence needs, and the analytical validation plan. If FDA-recognized guidelines and standards are used for validation, reference them. For completed testing, provide protocols and results. For planned analytical validation studies provide study protocols including the purpose and design of proposed studies.

1. Available Analytical Methods and Data

- Currently available evidence from the literature and other published or unpublished data related to biomarker measurement.
- Pre-Analytical Variables including:
  - Stability of the sample
  - Sample preparation
  - Reference standard/ Quality Control Material provided by manufacture or other party; phantom for imaging studies
  - Sample inclusion/exclusion criteria
  - Validated storage and transportation conditions
- Relevant SOPs, imaging charters, or other information to consider when obtaining the biomarker, before measuring or processing it.

2. Biomarker Measurements

- The technical platform for the measurement (e.g., NGS, MRI, or immunoassay) is independent of the biomarker, but biomarker qualification requires naming at least one measurement procedure to demonstrate the utility of the biomarker measurement.
- Describe the measurement tool and method to be used to measure the biomarker. Describe the biomarker source (e.g., blood, image of skull, dermal-epidermal junction, cortical kidney tissue, etc.), and matrix (including the base material and any additives), and whether the biomarker is single concept or a complex/composite.
- Imaging biomarkers should provide clear specifications of the imaging protocol and a description of how a specific feature is being assessed or measured.
- Physiologic biomarkers should be identified with a clear description of the physiologic function being tested and the specific approach used to elicit the physiologic response.
- Scalability of the measurement method in clinical trials should be discussed.
- Describe any software needed to aid in measurement of the biomarker
- If a commercial assay is used, describe any modifications to the measurement procedure and updates needed for the biomarker qualification process.

3. Analytical Requirements and Areas of Evidence Needs

- Define and describe the level of analytical performance required to provide a confident decision using the biomarker for the proposed context of use.
- If the same biomarker(s) can be measured using different platforms (e.g., newer platforms), describe the analytical performance characteristic requirements to achieve the same conclusion with the same degree of confidence, and if all the measurements are standardized

4. Analytical Validation Plan

By the completion of the QP stage, it is expected that the measurement platform and SOP should be known and finalized. Describe the design of the analytical validation study and include the following information:

- Number and type of specimens assayed
- Description of designs for performance studies, e.g., specificity, accuracy, precision, reproducibility, limits of detection, linearity of the assay or method across different days, investigators, and sites
- Discussion of sample stability
- Clinical reference range for both completed and planned studies
- The measurement's standard error and sources of error, such as interference with substances likely found in blood and medications expected in the patient population
- Description of procedures to limit the effects of drift in the performance of the measurement procedure in the future (i.e., how the measurements will be anchored and traceable over time to the performance in the analytical validation study).
- The effect of errors and limitations on the interpretation of the measurement’s relevance to disease, disease stage, or drug intervention

The fit-for-purpose requirements for analytical validation of any measurement technology or methodology will depend on the biomarker, its context of use, and the assay or other technique used. Justify the assay performance validation criteria used and state whether any recognized guidelines and standards are used to support validation of the assay or measurement techniques. Additional background information on assay validation is available on the FDA website, such as the "Points to Consider Document: Scientific and Regulatory Considerations for the Analytical Validation of Assays Used in the Qualification of Biomarkers in Biological Matrices" and the "Bioanalytical Method Validation for Biomarkers Guidance for Industry."

5. Additional Considerations for Imaging Biomarkers

Provide a detailed understanding of how the image acquisition, analysis, and data integration processes have been optimized, including details on various aspects such as uncertainty assessment, performance characteristics, algorithms, software, and operator variability.

1. Image acquisition, analysis, and interpretation
   - Describe the process of image acquisition, analysis, and interpretation.
   - Explain how these processes have been optimized
2. Uncertainty assessment
   - Repeatability
   - Reproducibility (within site, across sites, equipment model/manufacturer)
   - Reader variability
   - Operator variability (intra and inter)
3. Cut-point(s) for non-continuous imaging results
   - Provide data to support the proposed cut-point(s) if imaging results are not reported as a continuous variable
4. Performance characteristics such as:
   - Sensitivity
   - Specificity
   - Accuracy
   - Reader Agreement
   - Bias
   - Linearity
   - Other data features
5. Device imaging performance such as:
   - Resolution
   - Field of view
   - Distortion
   - Contrast
   - Depth of penetration
   - Signal to noise ratio
   - Other relevant imaging parameters
6. Software for image acquisition and analysis
   - Provide the name and version of the software package(s) to be used for image acquisition and analysis.

7. Image interpretation
    - Provide a full description of the algorithms used to interpret the image or data contained in the image, including:
        - Software versions
        - Validation data or validation plan to confirm the software function as intended

      Describe the process of generating the final scores from the images

      Describe any software or algorithm used to delineate or segment a anatomic or pathophysiological structure(e.g., a volume of an organ, a sub-section of an organ, or cross-sectional area of a vein, etc.)

VI. Clinical Considerations Overview

1. Natural History of Disease (as it relates to biomarker and COU)

Describe the relevant aspects of the natural history of the disease and/or the disease state, and specify if the disease is acute, chronic, or recurrent as it relates to this biomarker and COU. This section may include:

- The disease etiology and causal pathways(s) in terms of agent, host, and environment.
- If known, the relationship of the biomarker to the disease (e.g., pathophysiological pathways), predictor of severity and/or clinical outcome.
- Proposed use in drug development.
- Relevant data, if any, that illustrate the relationship of the biomarker with the symptoms and disease progression or severity.

2. Supportive Information for Biomarker and COU (summary of current pre-clinical and clinical data supporting the biomarker's proposed COU)

Compare the proposed approach with the current standard used in drug development (if one exists), in clinical guidelines recommended by medical communities or with alternative approaches. A table format might be useful when comparing multiple methods.

3. Additional Clinical Evidence Needed to Support Biomarker Qualification

- Identify any gaps in the application of this biomarker that require further investigation through additional studies, such as prospective studies or meta-analyses, or if alternative strategies are necessary to address these gaps and limitations.
- Assess whether the interpretation of the evidence is sufficient and reliable.
- Clarify whether the new biomarker is intended to replace current standards, supplement existing approaches, or be used in conjunction with other elements, such as patient selection criteria, an endpoint or co-primary endpoint.
- Determine if the biomarker is designed for different or extended populations by establishing new selection, inclusion, or exclusion criteria.

4. Benefits and Risks of Use of the Novel Biomarker (impacts for drug development, patients, and public health)

- Identify the potential benefits and risks associated with the biomarker, including benefits and risks to individual patients in clinical trials, such as the earlier identification of toxicity with a safety biomarker. Additionally, consider more general benefits and risks to drug development and regulatory decision-making, such as how a prognostic biomarker used to enrich a patient population may reduce the sample size needed to achieve statistical significance or how a predictive biomarker can facilitate early identification of responders.
- Assess the consequences of an inaccurate decision stemming from incorrect interpretation of the proposed biomarker.
- Provide a brief description of potential risk mitigation strategies in the event that the biomarker does not perform as expected. Discuss how false positives or negatives could impact the use of the biomarker in drug development and suggest actionable strategies to mitigate these risks effectively.
- Identify any risks to patients related to obtaining samples or measuring the biomarker, such as additional ionizing radiation exposure for CT imaging.

5. Clinical Study Plan and Design

Clinical study and statistical analysis plans should be pre-specified in sufficient detail (refer to the appendices for technical details) and algorithms, predictors, cut-offs, etc., should be finalized at this stage. This section may include:

1. Intervention plan with sample and data collection schedule and justification
2. Subject selection criteria and demographic considerations
3. A sample study synopsis

6. Statistical Analysis, Performance, and Decision-Making Criteria

1. Summarize the Statistical Analysis Plan (SAPs)
2. Derivation of cut-off values
3. Validation of pre-specified cut-off
4. Models for analysis methods

7. Clinical Validation, Expected Outcomes, and Use Cases

This section should provide a quantitative description of the validation of the decisions made in drug development that depend on the biomarker. Describe how the specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) of the clinical decisions made using the biomarker are calculated and the certainty with which the new biomarker can be relied upon to make decisions in the proposed drug development space. Describe how you will assess how well the biomarker performs when used as proposed in the COU and compared to the current processes giving benefits, risks, and limitations. Ideally, validation should be demonstrated using an independent data set; otherwise, an explanation should be provided as to why an independent data set is not available and a rationale should be provided as to why one is not necessary. The level of evidence for clinical validation varies depending on the

category of the biomarker and the COU.

Provide details about how you will assess:

- how well the level of the biomarker correlates with the disease activity/stage;
- how well it reflects the impact of a therapeutic intervention;
- whether the range and duration of change in the biomarker and its interpretation represent a clinically meaningful effect, impact, or outcome.

VII. Prospective Timeline, Milestones, and Dependencies

This section describes a project management plan including management of resources, costs, and time.

Dependencies are other studies, tools, products, etc., upon which this qualification submission is dependent upon but are outside of the scope of this submission. For example, a qualification may depend upon receipt of data or results from clinical studies conducted by another party, or a product development to test the biomarker. If this biomarker development effort is a part of a longer-term goal, summarize your long-term objectives.

This section may also include how the studies will be funded but detailed budget breakdowns are not requested.

VIII. Transparency and Data Sharing Plans

If applicable, include ownership, commercialization objectives and patent holdings. How will the adoption of this biomarker be facilitated beyond the submitter(s), and will the protocols, reagents and specifications be shared with others?

IX. Submission Information

Refer to the Resources for Biomarker Requestors for important submission-related information. For more information about Biomarker Qualification see our program's website. If you have any questions about submission procedures, contact the BQP staff via email: CDER-BiomarkerQualificationProgram@fda.hhs.gov.

Useful links:

The FDA updates guidance documents periodically. For the most recent version of a guidance, go to the FDA guidance website.
For information regarding a proposed framework for levels of evidence required to qualify biomarkers, go to: "Framework for Defining Evidentiary Criteria for Biomarker Qualification" (FNIH Biomarkers Consortium Evidentiary Standards Writing Group).
For additional information about a proposed framework for defining the amount of evidence needed for a biomarker qualification, go to: "What evidence do we need for biomarker qualification" Sci Transl Med. 2017 Nov 22;9(417); PMID: 29167393.
To look up if an assay or biomarker method has FDA clearance or approval visit the "510(k) Premarket Notification" database, go to: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm.

X. Statistical Analysis Plan (SAP)

For any proposed studies provide detailed statistical methods and statistical analysis plan:

1. Type of trial/study proposed and the rationale (e.g., randomized controlled trial [RCT], historical control, cohort study, case series, registry, meta-analysis)
2. Statistical analysis plan
    a. Sample size calculation
    b. Decision making process including setting a cut-off value and a measurement range - accuracy, precision, and reproducibility
    c. Selectivity and specificity
    d. Positive predictive value (PPV)/ negative predictive value (NPV)
    e. Bias mitigation strategies
    f. Multiplicity considerations
    g. Proposed sensitivity analysis
    h. Missing data considerations and proposed analysis
    i. Causality and analysis of association

XI. Appendices (as applicable)

Appendix I. References

Publications/references with synopsis for each publication

Appendix II. Requestor Letter of Intent (LOI) Response to Recommendations

Response to FDA LOI comments/recommendations. Address each of the specific considerations and recommendations, and any data requests cross-referencing the numbers listed in the appendix in a separate addendum to your QP submission.

Appendix III. Confidential and Proprietary Information

If there is confidential information you wish to share with FDA but not with the public, collate it here and reference it in the QP document.

Appendix IV. Detailed Analytical Plans

I. <u>Detailed Analytical Measurement and Validation Plan</u>

1. Required environment/resources:
    a. Site (infrastructure, access to samples and patients), personnel (staff trainings and qualifications) and equipment with performance specifications.

2. Pre-Analytical Variables such as:
    a. critical reagents and materials preparation
    b. sample collection & transportation
    c. sample processing and storage
    d. sample/analyte stability
    e. quality and analytical variables in the matrix
    f. cross-reactions and interferences/backgrounds
    g. equipment calibration and maintenance
    h. references and standards
    i. measurement reproducibility
    j. plans and requirements
3. Measurement procedure:
    a. Standard Operating Procedure (SOP) including testing and troubleshooting
    b. Algorithms and data processing protocols
    c. Interpretation of results
4. Analytical validation plan:
    a. Predefined total allowable error based on the clinical needs of the device
    b. Sample inclusion and exclusion criteria
    c. Qualitative, semi-quantitative or quantitative analysis
    d. Calibration curve
    e. Accuracy, precision, and measurement range
    f. Recovery
    g. Reproducibility
    h. Selectivity and specificity
    i. Identification and impact of interfering substances
    j. Validation of the claimed measuring range (linearity, limit of detection, limit of quantitation)
5. Limitations & deficiencies of the current measurement method:

Description of assumptions and known or inherent limitation of the proposed measurement method. If available, provide possible workaround or alternative methods or techniques.

6. Additional considerations for imaging biomarkers:

How has the method for image acquisition, analysis, and integration of the data been optimized? Include discussions of:

a. Image acquisition, analysis, and interpretation

b. Assessment of uncertainty including repeatability, reproducibility (e.g., within site, across sites, equipment model/manufacturer) and reader variability.

c. Data to support proposed cut-point(s) if imaging results are not reported as a continuous variable.

d. Performance characteristics including sensitivity, specificity, accuracy, and agreement.

e. Device imaging performance characteristics such as resolution, field of view, distortion, contrast, depth of penetration, signal to noise ratio, and other imaging parameters as necessary.

f. Algorithms used to interpret the image or data contained in the image. Provide a full description of these algorithms including their versions and validation data or validation plan to confirm the algorithms function as intended.

g. Provide the name and version of the software package(s) to be used for image acquisition and analysis.

II. <u>Detailed Clinical Development and Validation Plan</u>

1. Objective
2. Study design inclusion and exclusion criteria, and demographic considerations
3. Clinical data/sample collection and preparation plan
    - Method and timing of sample collection, inclusion/exclusion of samples, and handling of samples after the collection
4. Study protocols and approvals (if available)
    - IRB approval with clinical study protocol (case report form, data monitoring, management & integrity plans)
    - HIPAA and Health Information Privacy protection plan
    - Clinical Laboratory Improvement Amendments (CLIA) waiver or certification
    - Investigational Device Exemption, if required
5. Strength of current evidence supporting the values of the biomarker for the proposed COU

Appendix VI. Regulatory History

1. Type & date of submission(s) & decision date
2. Prior interactions with FDA or other regulatory agencies outside the United States related to this biomarker
3. Describe the steps that have occurred between the Letter of Intent and this QP submission