Biomarker Qualification Plan: Outline of Suggested Content Elements

NOTE TO REQUESTORS: FDA is currently developing its policies for submissions under the 21 Century Cures Act (section 507)[1] and expects to issue guidance to aid in the development of submission based on a decade of reviews, input from public meetings, comments to the docket and collaborative public partnerships. In the interim the Agency has assembled this resource to help requestors. 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. For additional resources on submission content please see prior Biomarker Qualification Program submissions that we have accepted under section 507 **HERE**. Please also note that certain information contained in submissions will be made publicly available as per section 507, as described in greater detail **HERE**.

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, please contact us at CDER-BiomarkerQualificationProgram@fda.hhs.gov

I. Executive Summary

The Executive Summary should be a standalone document (i.e., separate from the rest of the Qualification Plan (QP) information). Per the section 507 transparency provisions, the Executive Summary document will be posted publicly on our Biomarker Qualification Program (BQP) website. While we expect the Executive summary and the other QP sections to have some duplicate content, the executive summary should NOT cross-reference other QP sections/material.

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 below.

A. Administrative overview:

- Requestor name, title(s) & contact information
- Alternate requestor name, title(s) & contact information
- Collaboration: name of supporting or participating organization, consortia or individuals.
- Project title
- History
    - i. Type & date of submission(s) & decision date
    - ii. Prior interactions with FDA or other regulatory agencies outside the U.S. related to this biomarker

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

iii. Describe the steps that have occurred between the Letter of Intent and this QP submission.

B. Background

Include drug development need your biomarker is intended to address.

C. Biomarker name, type, and description

If the biomarker is different from the biomarker in your LOI, please provide a description of the difference and the rationale for the change in the biomarker.

D. Context of Use (COU) statement

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

E. Measurement method

If applicable, please provide device name, with make and model if appropriate. List prior clearances or approvals such as the FDA/CMS clearance or approval with 510k or Premarket Approval (PMA), Clinical Laboratory Improvement Amendments (CLIA) numbers.

F. Drug development clinical interpretation/decision process including steps and elements of decision making process and cut-off points/limits/thresholds

An overview of the decision process in a flow diagram (decision tree) should be included.

G. Summary of analytical validation

- Completed analytical validation studies and results
  i. If FDA recognized standards are used for validation, please reference them.
  ii. For new testing, provide methods and results.
- Planned analytical validation studies and methods
  i. Purpose of proposed studies
  ii. Methods of proposed studies

H. Summary of clinical considerations in support of the biomarker's COU

- Summary of completed studies/analysis (if applicable and available)
  i. Objective
  ii. Study design
  iii. Statistical analysis
  iv. Clinical protocol
  v. Results
  vi. Risk benefit analysis
- Proposed studies/data analysis plan for biomarker qualification
  i. Objective
  ii. Study design
  iii. Statistical analysis
  iv. Clinical protocol
  v. Risk benefit analysis

II. Drug Development Need

As noted previously, 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 publicly posted.

A. Summary of current landscape

What are the current practices in this space for drug development as related to the proposed biomarker/population/drug class, etc.?

B. Description of drug development need

What are the knowledge gaps, roadblocks, challenges and limitations of the current approaches as 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)?

C. Benefits that may be realized should the biomarker development be successful

III. Biomarker Information & Interpretation

A. Biomarker name(s) and type(s) (e.g., molecular, radiographic or physiologic)

A biomarker[1] is a measurable biologic entity and is measured with a well-controlled and validated method for the specified drug development purpose. Identify what biological entities are measured and characterize the types or approaches used to measure e.g. a longitudinal measurement.

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).

Imaging biomarkers should be identified with clear specifications of imaging protocol and how a specific structure is being measured.

[1] The BEST glossary defines a biomarker as 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 an assessment of how an individual feels, functions, or survives.

Physiologic biomarkers should be identified with a clear description of what physiologic function is being tested and specific approach used to elicit the physiologic response.

B. Measurement of the biomarkers

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 analytical method to establish a standard for the biomarker measurement. Please 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[2]. Please also describe the measurement process.

C. Biomarker interpretation and utility

a. Construct of the biomarker outcomes
   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 any cut-offs, limits, and range of measurement.

b. Biomarker interpretation
   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.

[2] A complex biomarker consists of multiple independent measurements of multiple biological entities measured separately while a composite biomarker consists of multiple measurements with a single output.

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

A. COU 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 upon the information presented in the submission supporting the biomarker's COU and the recommendations made by FDA, but it should be consistent and worded identically throughout a given submission document.

Describing the COU statement early defines the type of information needed in support of qualification for the proposed approach. Only a single COU should be articulated for a given biomarker qualification submission and biomarker development effort even though your long-term goals may include multiple COUs. Recommended structures of the COU statement are as below:

BEST biomarker category to **drug development use.**

or

BEST biomarker category that action, i.e., selects or enriches or indicates or identifies purpose of intervention, i.e., severity, toxicity, susceptibility, disease progression or pharmacodynamic response of target populations, i.e., disease name/stage, patients responsive to treatment in type of study, e.g., early phase trials

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) to study interventions intended to prevent the onset of T1D.

Additional examples of COU statements are available on the Biomarker Qualification Submissions and the Qualified Biomarkers web pages.

B. COU narrative

How will the biomarker be used and provide clinical utility in drug development programs? Is this biomarker useful for development of many products across different classes of therapeutics? It 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 includes explanation of the following elements:

- What is the purpose of the biomarker for drug development based on the biomarker category?
- When is the biomarker used during drug development (stage of development)?
- How is the biomarker applied i.e. as decisional, co-decisional, enhancement or enrichment criteria?
- What is the intended population under treatment or the disease?

V. Analytical Considerations Overview

A. Summary of available analytical data as relates to this biomarker's measurement

Concise summary of currently available evidence from the literature and other preliminary/unpublished data

B. Biomarker measurement

How is the biomarker measured? Describe quality assurance (QA) and quality control (QC) process including stability of biomarker, sample preparation,

test/reference samples, sample inclusion/exclusion criteria, storage and transportation? Include scalability and throughput of the method, and a description of the specialized software if needed. If a commercial assay is used, describe what method modifications and updates may be needed for the biomarker qualification process.

C. Analytical requirements and areas of evidence needs (gaps)

Define and describe the level of analytical performance required to provide a confident decision using the biomarker. Based on currently available data, what areas of analytical measurement need to be improved to achieve analytical performance requirements? If the same biomarker(s) can be measured using different platforms e.g. newer platforms, describe analytical performance characteristics/requirements to achieve the same conclusion with the same confidence. This is important for acceptability of the biomarker(s) with a wider and future adaptation.

D. Analytical validation plan

Describe the design of the analytical validation study. Ideally measurement platform(s) and SOP should be locked down at this stage. This section should include:

- How many and what type of specimens are assayed.
- Describe replication designs for precision and reproducibility studies e.g. sensitivity, specificity, accuracy, and precision of the assay or method across day-to-day, person-to-person and site-to-site.
- Discuss clinical reference range for both completed and planned studies.
- Explain the measurement's standard error, sources of error such as interference by substances like blood and medications.
- Describe the effect of errors and limitations on the interpretation of the measurements 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 COU, and the assay or other technique used. Please justify the assay performance validation criteria used and state if any recognized 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 "Points to Consider Document: Scientific and Regulatory Considerations for the Analytical Validation of Assays Used in the Qualification of Biomarkers in Biological Matrices"; please note that all of the analytical validation topics may not be applicable to your biomarker

development effort so please include an explanation of which ones you feel are not as important and why not.

E. Additional considerations for imaging biomarkers

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

- Image acquisition, analysis, and interpretation
- Assessment of uncertainty including repeatability, reproducibility (e.g., within site, across sites, equipment model/manufacturer) and reader variability.
- Data to support proposed cut-point(s) if imaging results are not reported as a continuous variable.
- Performance characteristics including sensitivity, specificity, accuracy and agreement.
- 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.
- Algorithms used to interpret the image or data contained in the image. Please provide a full description of these algorithms including their versions and validation data or validation plan to confirm the algorithms function as intended.
- Provide the name and version of the software package(s) to be used for image acquisition and analysis.
- Description of any software or algorithm used to delineate or segment a physiological structure (i.e. a volume of an organ, a sub-section of an organ, or a size of a vein or opening etc.)
- Provide information on inter-operator and intra-operator variability.

VI. Clinical Considerations Overview

A. Natural history of disease as related to this 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;

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

B. Supportive information for Biomarker and COU: summary of current pre-clinical and clinical results supporting the biomarker's proposed COU

Compare the proposed approach with the current standard used in regulatory 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.

C. Areas of clinical evidence needs (gaps) to support the biomarker qualification

Additional considerations;

- Are there gaps when applying this biomarker that need to be filled by additional studies e.g. prospective study or meta-analysis or are alternative strategies needed to mitigate gaps and limitations?
- Is the interpretation of the evidence sufficient and reliable i.e.do we have a consensus from the community on the interpretation and reliability of the evidence?
- Is the new biomarker replacing current standards, does it supplement a standard current approach and/or is it used jointly with other elements (in conjunction with, as an endpoint or as a co-primary endpoint)?
- Is the biomarker intended for different or extended populations (new selection/inclusion/exclusions criteria)?
- Is the proposed biomarker truly novel or does it explore outside of the current paradigm, i.e., are there no comparators or other uncertainties? How will its utility in these contexts be tested and validated for this COU?

D. Benefits and risks of use of the novel biomarker: impacts for drug development, patient and public health

a. What are the potential benefits and risks of the biomarker which could include benefits/risks to individual patients in clinical trials (e.g., earlier identification of toxicity with a safety biomarker) or more general benefits and risks to drug development and regulatory decision making (e.g., a prognostic biomarker used to enrich a patient population may reduce the sample size needed to achieve statistical significance or a predictive biomarker that identifies responders early)?

b. What are the consequences of an inaccurate decision or degree of harm to the patients when the interpretation of the proposed biomarker is incorrect (i.e., the proposed approach doesn't indicate what it is thought to indicate)?

Include a brief description of potential risk mitigation strategies, should the biomarker not perform as expected. How may false positives or negatives affect the use of the biomarker in drug development? Can you suggest a way to mitigate these risks?

E. Clinical study plan and design

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

- Intervention plan with sample and data collection schedule and justification
- Subject selection criteria
- A sample study synopsis

F. Statistical analysis, performance and decision-making criteria

- Summarize the Statistical Analysis Plans (SAPs)
- Derive cut-off values
- Validate pre-specified cut-off

G. Clinical validation, expected outcomes and use case examples

This section should provide a **quantitative** description of the validity of the decisions. Describe the specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV) of the clinical decisions made using the biomarker and the certainty with which the new biomarker can be relied upon to make decisions in the proposed drug development space. How well does the biomarker perform when used as proposed in the COU and compared to the current processes giving benefits, risks and limitations? The level of evidence for clinically validation varies depending on the category of the biomarker and the COU. Please refer to the qualified biomarkers on our website.

For example, does the level of the biomarker correlate with the disease activity/stage? Or how well does it reflect the impact of a therapeutic intervention? Can the range and duration of change in the biomarker and its interpretation represent a clinically meaningful effect, impact, or outcome?

Are the conclusions or the interpretations of the measurements or readings clinically relevant and actionable? What is the level of confidence for these interpretations?

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, in a part, it is dependent 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, please 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

Please refer to the Resources for Biomarker Requestors for the mailing address and other important submission-related information. For more information about Biomarker Qualification see our program's Home Page. If you have any questions about submission procedures, please contact via email; CDER-BiomarkerQualificationProgram@fda.hhs.gov.

Useful links:

- We update guidance documents periodically. For the most recent version of a guidance, check the FDA guidance web page.
- Framework for Defining Evidentiary Criteria for Biomarker Qualification (FNIH Biomarkers Consortium Evidentiary Standards Writing Group)

- "What evidence do we need for biomarker qualification" Sci Transl Med. 2017 Nov 22;9(417); PMID: 29167393
- Database for PMA: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm
- Database for 510k: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

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. Please number the questions and respond to them one-by-one or point to the sections where your responses are described.

APPENDIX III: Confidential and Proprietary Information

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

APPENDIX IV: Detailed Technical Plans

<u>Detailed analytical measurement and validation plan</u>

A. Required environment/resources

- Site (infrastructure, access to samples and patients), personnel (staff trainings and qualifications) and equipment with performance specifications.
- Quality Assurance (QA) e.g., critical reagents and materials preparation; sample collection & transportation, sample processing and storage, sample/analyte stability, quality and analytical variables in the matrix, contaminations, cross-reactions and interferences/backgrounds)
- Quality Control (QC, e. g., equipment calibration and maintenance, references and standards, measurement reproducibility) plans and requirements.

B. Measurement methods

- Standard Operating Procedure (SOP) including testing and troubleshooting
- Algorithms and data processing protocols
- Interpretation of results

C. Analytical validation plan

- Sample inclusion and exclusion criteria
- Qualitative, semi-quantitative or quantitative analysis
- Calibration curve
- Accuracy, precision, and measurement range

- Recovery
- Reproducibility
- Selectivity and specificity
- Identification and impact of interfering substances
- Validation of the claimed measuring range (linearity, limit of detection, limit of quantitation)
- Coefficient of variation (CV)- intra/inter personnel/site
- If cut-off points are defined, the QC samples should bracket the cut-off points to define the variable at this important part of the curve.

D. 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.

E. Additional considerations for imaging biomarkers

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

- Image acquisition, analysis, and interpretation
- Assessment of uncertainty including repeatability, reproducibility (e.g., within site, across sites, equipment model/manufacturer) and reader variability.
- Data to support proposed cut-point(s) if imaging results are not reported as a continuous variable.
- Performance characteristics including sensitivity, specificity, accuracy and agreement.
- 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.
- Algorithms used to interpret the image or data contained in the image. Please provide a full description of these algorithms including their versions and validation data or validation plan to confirm the algorithms function as intended.
- Provide the name and version of the software package(s) to be used for image acquisition and analysis.

<u>Detailed clinical development and validation plan</u>

A. Objective

B. Inclusion and exclusion criteria, and demographic considerations (describe your study design in the statistical analysis plan section below)

C. Clinical data/sample collection and preparation plan

   method and timing of sample collection, inclusion/exclusion of samples, and handling of samples after the collection

D. Strength of current evidence supporting the values of the biomarker for the proposed COU

E. 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

<u>Detailed statistical analysis plan (SAP)</u>

A. Type of trial/study proposed and the rationale (e.g. RCT, historical control, cohort study, case series, registry, meta-analysis)

B. Level of evidence (highest for surrogate endpoints, lower for enrichment prognostic biomarkers)

C. Sample size calculation

D. Statistical analysis plan

   a. Decision making process including setting a cut-off value and a measurement range - accuracy, precision, and reproducibility

   b. Selectivity and specificity

   c. PPV/NPV

   d. Bias mitigation strategies

   e. Multiplicity considerations

   f. Proposed sensitivity analysis

   g. Missing data considerations and proposed analysis

   h. Causality and analysis of association