Biomarker Qualification Letter of Intent (LOI) 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

COMMENTS: The following information will be made publicly available as per section 507, described in greater detail HERE

Administrative Information

1. **Submission Title**:
   One sentence description of your project. See Abbreviated Biomarker Descriptions in List of FDA Qualified Biomarkers. EXAMPLES:
   - Urinary nephrotoxicity biomarkers as assessed by immunoassays
   - Total Kidney Volume (TKV) as assessed by computerized tomography (CT) scan.

2. **Requesting Organization:**
   - Name of Organization: Physical Address; Phone Number; Website address
   - Primary Point of Contact: Name; Job Title; Address if different from above; Phone Number; Email

   Alternate Point of Contact: Name; Job Title; Address if different from above; Phone Number, Email
   Supporting or participating organizations or individuals

3. **Submission Dates:**
   LOI submission date

Drug Development Need Statement

Describe the drug development need that the biomarker is intended to address, including (if applicable) the proposed benefit over currently used biomarkers for similar context of uses (COUs).

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

Biomarker Information and Interpretation

Please provide high level descriptions here and more detailed descriptions in the analytical and the clinical considerations sections.

1. **Biomarker name:** abbreviated short name for biomarker, or names if multiple, AND identify each biomarker type (molecular, histologic, radiographic, or physiologic characteristics according to BEST Glossary). For molecular biomarkers, please provide a unique molecular ID e.g. 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).

   EXAMPLES: 25 mRNA gene expression profile/signature; cardiac Troponins T (cTnT) and I (cTnI); Total Kidney Volume (TKV) (please note detection method or algorithm is not a part of the biomarker name). For more examples see the "Qualified Biomarker" column on the FDA List of Qualified Biomarkers website.

2. **Analytical methods:** name and briefly describe analytical methods used in raw measurement(s) of the biomarker(s). EXAMPLE: enzyme-linked immunosorbent assay (ELISA) with chromogenic reporters, volumetric analysis of brain magnetic resonance images (MRIs). Include all elements counted/measured/identified and indicate whether measurement is a manual read or a component of the analytic.

3. **Measurement units and limit(s) of detection:** describe if any.

4. **Biomarker interpretation and utility**
   Describe the application/conversion of the raw biomarker measurement in order for the biomarker outcomes to be used for the COU and provide the description and derivation of clinical interpretative criteria used to include:
   a. Post-analytical application/conversion of biomarker raw measure to the applied measure: briefly describe how the raw biomarker measurement is used/applied. Describe if the raw measure is used directly or if there is further processing of the raw measurement into a multi-component panel, a scoring system, or alternatively; further manipulation or transformation of the raw biomarker measurement using modeling, simulation, application of formula(e), other algorithms, or combination with other clinical information. Describe how the process is designed, including software. List the elements, inputs and output(s) of the conversion, including a description of units, if applicable.
   b. Describe rationale for post-analytical elements used as inputs in application or conversion of the raw biomarker measurement.
   c. Clinical Interpretive Criteria: describe the cut-off values, cut-points/thresholds, boundaries/limits or other comparators used in the interpretation of the biomarker measurement or its applied/converted form to draw an actionable conclusion based on the biomarker result.

Context of Use Statement (500 characters)

The proposed context of use (COU) statement is complementary to the drug development need statement. Please note that we qualify biomarkers as tools to aid in drug development. While biomarkers may be used for other purposes (e.g., to aid in clinical decision making), COUs that do not address a specified drug development use are outside the scope of the program.

The COU statement may evolve over time based on the information presented in submissions supporting the biomarker's COU and the recommendations made by FDA. However, it should be consistent and worded identically throughout the given version of the submission document. Describing the COU statement early defines the type of information needed in support of qualification for the proposed approach. Although the eventual scope of the project may span over multiple COUs, only a single COU should be initially articulated for a given biomarker qualification submission. Recommended structures of the COU statement are provide 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, e.g., severity, toxicity, susceptibility, disease progression or pharmacodynamic response of target populations, e.g., disease name/stage, patients responsive to treatment in type of study, e.g., early phase trials

EXAMPLES:

A. PD/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.

B. 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. If assistance in identification of the most appropriate biomarker category is needed, a requestor may contact the Biomarker Qualification Program at CDER-BiomarkerQualificationProgram@fda.hhs.gov.

Analytical Considerations

Please provide the following information (if applicable or available):

- General description of what aspect of the biomarker is being measured and by what method (e.g., lesion number or specific measure of organ size by imaging, serum level of an analyte, change in the biomarker level relative to a reference such as baseline).

- If this biomarker involves an index/scoring system, please provide information about the elements and weighting of the elements. Include a rational for how the index/scoring system was developed.
- Brief description of sample source, matrix (base material and any additives), stability and composition of biomarker.
- Description of pre-analytical factors and quality assurance/quality control (QA/QC) plans to preserve specimen integrity: a standard operating procedure (SOP) for sample collection including timing and location that sample will be collected from, storage *and* test/assay methodology; reference or control samples.
- Analytical validation plan: description of measurement tool and device calibrations, validation study design with statistical analysis plan (SAP) or performance data (e.g. sensitivity, specificity, accuracy, and/or precision of the assay or method).
- Once the SOP and analytical validation plan is finalized, describe how you will use this process to validate the final version of the measurement tool.
- Additional considerations for imaging biomarkers:
  - How has the method for image acquisition, analysis, and integration of the data been optimized?
  - Does data currently exist to support the proposed cut-off point(s), if imaging results are not reported as a continuous variable?
  - Provide the name and version of the software package to be used for image acquisition and analysis.
  - Description of any software or algorithm used to delineate or segment any physiological structure (i.e. a volume of an organ, a sub-section of an organ, or a size of a vein or opening etc.)
  - Describe any interpretation or transformation of the image data that will be conducted to measure, define, or represent the biomarker in question
  - Provide information on inter-operator and intra-operator variability.

Clinical Considerations

Please provide the following information (if applicable or available):

- Describe how the biomarker measurement is used to inform drug development. Please provide a decision tree to guide how the biomarker information would be used in drug development or a clinical trial.
- Describe patient population or drug development setting in which the biomarker will be used.
- Clinical validation: provide information to support biological and clinical relevance of the biomarker as applied in the COU:
  - Describe how normal or other reference values are established, provide study design(s), analytical plan, etc.
- Benefits and Risks of applying the biomarker in drug development or a clinical trial.
- Describe any current knowledge gaps, limitations and assumptions in applying the biomarker in drug development or a clinical trial.

Supporting Information

For example (if applicable or available):

- Provide underlying biological process or supporting evidence of association of the biological process with

the biomarker.

- Summary of existing preclinical or clinical data to support the biomarker in its COU (e.g., summaries of literature findings, previously conducted studies).
- Summary of any planned studies to support the biomarker and COU. How will these studies address any current knowledge gaps?
- Please describe alternative comparator, current standard(s), or approaches.

Previous Qualification Interactions and Other Approvals (if applicable)

For example:

- Letter of Support (LOS) issued for this biomarker
- Discussion in a Critical Path Innovation Meeting (CPIM)
- Previous FDA Qualification given to this biomarker with DDT Tracking Record Number
- Qualification submissions to any other regulatory agencies with submission number
- Prior or current regulatory submissions to Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH). Provide 510(k)/PMA Numbers

Attachments

This section may contain:

- Please provide a list of publications most relevant to this biomarker development proposal.

- Optional: If this biomarker development effort is part of a longer-term goal, please summarize your long-term objectives.
- Optional: If you have other supporting information you would like to provide, please submit as attachment(s).

Please note that any information provided as optional attachments will not be publicly posted.

Additional Information & Submission Information:

Please refer to the Resources for Biomarker Requestors for the mailing address and other important submission-related instructions. For more 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.