Biomarker Qualification Letter of Intent (LOI)

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. 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, contact the BQP staff at CDER-BiomarkerQualificationProgram@fda.hhs.gov.

For information about requesting a pre-Letter of Intent (pre-LOI) meeting, please visit: https://www.fda.gov/drugs/biomarker-qualification-program/resources-biomarker-requestors.
This resource provides detailed guidance on the pre-LOI meeting process and requirements.

Should you have any questions or want to provide feedback on this or other BQP resources, including the content and format of submissions, the transparency provisions under section 507, or requesting a pre-LOI meeting, please contact the BQP staff at: CDER-BiomarkerQualificationProgram@fda.hhs.gov.

Letter of Intent (LOI) Submission Instructions:

Requesters should transmit Letter of Intent (LOI) submissions through the CDER NextGen Portal. Each submission should be accompanied by a cover letter. Requester should upload the following sections of the LOI as separate PDF files in searchable text format:

1. Executive Summary[1]
2. Letter of Intent Submission
   - Table of Contents
   - Administration Information
   - Drug Development Need Statement
   - Context of Use (COU) Statement

[1] 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.

- Biomarker Information and Interpretation
- Analytical Considerations
- Clinical Considerations
- Submission Supporting Information
- Previous Qualification Interactions and Other Approvals

3. Appendices (as applicable)
    - References and Attachments
    - Additional Information & Submission Information

If Requesters 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 Requester during the course of this biomarker qualification application, requesters should submit a Change of Requester 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 Requester 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. Table of Contents

List LOI sections, appendices and/or attachments along with the page numbers on which they begin.

II. Executive Summary

The Executive Summary should be written as a brief stand-alone document. Per the Section 507[2] transparency provisions, the Executive Summary document will be posted publicly on the CDER & CBER Drug Development Tool Qualification Project Search database. While we expect the Executive Summary and other sections of the LOI to have some duplicate content, the Executive Summary should NOT cross-reference other LOI sections/material. We expect summary-level information in the Executive Summary - not complete detail. 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

Requester name, title(s) & contact information
Submission Date
Alternate Requester name, title(s) & contact information
Collaboration: name of supporting or participating organization, consortia or individuals.
Project title

2. Background

Describe the drug development need your biomarker is intended to address. In your description, include natural history of the target disease, current therapeutic landscape, limitations of biomarkers currently used in drug development, and how your biomarker will aid in regulatory decision making. {NOTE: Add Background about disease as well as current practice/methodology. Also how the Biomarker can change or be used.}

3. Biomarker Name, Type, and Description

Provide a description of the biomarker. Indicate whether the biomarker is a multi-component biomarker.

4. Context of Use (COU)

a. Provide a Context of Use (COU) Statement. Please submit only one context of use per LOI.
b. An overview of the decision process describing how the biomarker will be applied in the specified COU.

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

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 510(k)or Premarket Approval (PMA).

6. Summary of Analytical Considerations

a. Summary of completed analytical validation studies and results
b. Planned analytical validation studies

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

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

III. Administrative Information

1. **Submission Title**:

One sentence description of your project. To 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

Important: If the primary or alternate contact name changes after submission, you must submit a support ticket to the NextGen Portal Help Desk so the system can be updated accordingly.

3. **Submission Dates:**

LOI submission date

4. **Planned Qualification Timeline, Milestones, and Dependencies**

Provide an estimated timeline outlining the key steps required for biomarker qualification, including preparation and submission of the Qualification Plan and preparation and submission of the Full Qualification Package. For each step, indicate the expected duration and projected completion dates. Identify any dependencies that may affect these steps, such as external studies, third-party datasets, or assay or tool

development occurring outside this submission. The timeline should reflect a clear and feasible sequence of activities needed to achieve qualification.

IV. 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 contexts of use (COUs). Include how the biomarker will aid regulatory decision making. It is beneficial to describe the current process or standard, problems with the current process, and how the biomarker will improve upon the current standard.

V. Context of Use Statement (500 characters)

The term 'context of use' means, with respect to a drug development tool, the circumstances under which the drug development tool is to be used in drug development and regulatory review.

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 a 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. You can visit the COU website[3],[4] to view examples of common COU deficiencies to avoid. Recommended structures of the COU statement are provide below:

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

or

[BEST biomarker category] to [action/purpose] for [target population] for use in [study type]

Provide 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.

EXAMPLES:

A. Serum glutamate dehydrogenase (GLDH) is a safety biomarker to be used in clinical trials for participants with elevated serum transaminases due to muscle injury or degeneration when Drug Induced Liver Injury is being considered. GLDH should be used in conjunction with standard hepatic injury monitoring biomarkers (e.g. alanine aminotransferase (ALT), aspartate aminotransferase,

[3] https://www.fda.gov/drugs/biomarker-qualification-program/context-use.
[4] Common COU Deficiencies to Avoid: https://www.fda.gov/media/190561/download?attachment.

gamma-glutamyl transferase (GGT), total bilirubin, and alkaline phosphatase). GLDH has not been studied in patients with pre-existing liver disease.

B. The percentage change from baseline at 24 months in total hip bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DXA) can be used as a surrogate endpoint for the assessment of investigational therapies for post-menopausal women at risk for osteoporotic fracture.

C. 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 Requester may contact the Biomarker Qualification Program at CDER-BiomarkerQualificationProgram@fda.hhs.gov.

VI. Biomarker Information and Interpretation

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 DDTs that are posted publicly on the CDER & CBER Drug Development Tool Qualification Project Search database

2. **Measurement methods:** name and briefly describe measurement 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**

   This section should provide a clear description of the biomarker, including how it is measured, its biological and clinical relevance, and how it will be interpreted and applied in the proposed context of use to support drug development.

A. Biomarker Description

(i) Clearly define the biomarker, including its full name, abbreviation(s), and the biological or physiological process it measures.

(ii) Describe the method of measurement and specify whether the biomarker is derived from imaging, laboratory testing, or another analytical approach.

(iii) Include details on measurement units, detection limits, and how the raw data are processed (e.g., direct use, transformation into scores, or classification into categories).

(iv) Note any device, assay, or platform dependencies and clarify if the biomarker has been cleared or approved for clinical use (e.g., FDA 510(k) clearance, laboratory validation).

(v) If the biomarker is a composite or multi-component biomarker, provide a complete list of all individual components.

B. Biomarker Interpretation and Utility

(i) Explain how the biomarker is expected to inform drug development in the proposed COU. This should include the relationship between biomarker values and underlying disease biology, the clinical relevance (e.g., association with disease progression, risk stratification, or prediction of treatment response), whether the biomarker serves as a prognostic, predictive, monitoring, or surrogate endpoint candidate.

(ii) Provide interpretive criteria such as cut-off values, percent change from baseline, or threshold effects that make the biomarker actionable.

(iii) Indicate if changes in the biomarker are reasonably likely to correlate with meaningful clinical outcomes (e.g., mortality, progression of organ damage, major adverse clinical events).

(iv) Highlight the advantages of using the biomarker compared to existing standards (e.g., reduced invasiveness, improved reproducibility, better alignment with real-world practice).

(v) Discuss potential limitations, confounding factors, or situations where biomarker values may be influenced by factors other than disease biology.

C. Supporting Evidence

(i) Reference clinical, epidemiological, or mechanistic evidence linking biomarker levels to patient outcomes.

(ii) Summarize guideline support or prior use in clinical research to demonstrate acceptance and relevance.

(iii) If available, cite or provide data showing responsiveness of the biomarker to interventions with known clinical benefit.

VII. Analytical Considerations

This section should describe the analytical methods used to measure the biomarker, including validation, standardization, and quality control procedures that ensure accuracy, precision, and reproducibility across studies and sites.

- Briefly describe the specific aspect of the biomarker being measured, the analytical platform or assay used, and the key measurement parameters, including units and limits of detection. (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 applicable, summarize how a composite index or scoring system is constructed, including its key elements, weighting, and supporting validation rationale or references. Identify the type of samp source and matrix used (base material and any additives) and note any collection, storage, or stability factors that may influence measurement reliability or biomarker integrity. Provide a description of pre-analytical factors and quality assurance/quality control (QA/QC) plans. This description can include information such as standard operating procedures (SOP), sample collection including timing and location, storage, test/assay methodology, and reference or control samples.
- Provide your analytical validation plan, including a description of measurement tool and device calibrations, validation study design) or performance data (e.g. sensitivity, specificity, accuracy, and/or precision of the assay or method).
- Additional considerations for imaging biomarkers:
  - Provide the method for optimizing image acquisition, analysis, and integration of the data
  - If imaging results are not reported as a continuous variable, provide data to support the proposed cut-off point(s)
  - 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.

VIII. Clinical Considerations

This section should describe how the biomarker will be used within the drug development context, including its clinical relevance, supporting evidence, and the benefits and limitations of applying it in trials. Describe how the biomarker measurement informs drug development decisions (e.g., patient selection, treatment response, efficacy evaluation).

- Describe patient population and drug development setting (early-phase, pivotal, or post-marketing trials) 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, and briefly outline any clinical studies, trial designs, or analyses used to demonstrate correlation with clinical outcomes Identify the benefits of incorporating the biomarker into clinical trials, such as improved patient stratification and address potential risks, including uncertainty in biomarker interpretation, variability across populations, or limitations in predictive value.
- Describe current gaps underlying biomarker interpretation, limitations and assumptions in applying the biomarker in drug development and how your planned studies will help address these uncertainties.

IX. Submission Supporting Information

- This section should summarize the key evidence and regulatory context supporting the biomarker's qualification. It should complement the Analytical and Clinical sections by consolidating biological rationale, relevant studies, and supporting materials that justify the biomarker's proposed context of use. Provide underlying biological process or supporting evidence of association of the biological process with the biomarker.
- Summarize key preclinical, observational, and clinical studies to support the biomarker in its COU (e.g., summaries of literature findings, previously conducted studies). Provide these supporting data in figure or table format.
- Summarize ongoing or planned studies intended to address current knowledge gaps and confirm the biomarker's performance for the proposed COU.
- Briefly describe existing biomarkers for similar purposes and explain how the proposed biomarker compares to current approaches.

X. Previous Qualification Interactions and Other Approvals (if applicable)

- List prior FDA and/or other regulatory interactions, noting any collaborative initiatives that inform or support the current qualification effort, including: Letter of Support (LOS) issued for this biomarker
- Discussion in a Critical Path Innovation Meeting (CPIM)
- Pre-LOI meeting or debrief meeting with FDA
- 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