Framework for Defining Evidentiary Criteria for Biomarker Qualification

Final Version

Evidentiary Criteria Writing Group

Revised 10/20/16

Table of Contents

Background and Scope of this Framework

The aim of this document is to create alignment among scientific stakeholders including FDA, NIH, industry, academia, patient groups and the non-profit sector regarding a proposed framework for levels of evidence required to qualify biomarkers[1]. Specifically, this document aims to enhance the clarity, predictability, and harmonization of the process by developing a general framework to assist the development of biomarkers for qualification, to improve upon the quality of submissions to the FDA, and to clarify the evidentiary criteria needed to support the biomarker's Context Of Use (COU). In addition, the framework will enable a consistent, comprehensive set of parameters/components to address during qualification with a semi-quantitative output to frame a consistent interaction between biomarker developers and FDA.

Of note, this document focuses on evidentiary criteria to support the regulatory acceptance of biomarker use in drug development programs. The evidentiary criteria to support biomarkers as part of diagnostic tests regulated by CDRH and CBER are outside the scope of this document. In addition, drug development uses of biomarkers that do not require regulatory approval are outside the scope of this effort, although concepts discussed may be useful in that context.

The document introduces a general framework for proposed evidentiary criteria for qualification that is intended to be broadly applicable across all categories of biomarkers and contexts of use (COUs). Since each category of biomarker and COU has unique factors to consider as part of the development process, it is proposed that modules be created to address these more specific issues. The second part of this document specifically focuses on the first such "module", describing evidentiary considerations in the qualification of biomarkers used in determinations of clinical drug safety assessments. These considerations are further tested and illustrated in three accompanying case studies of markers that have been or could be proposed for use in drug safety assessments.

It is anticipated that this document will support FDA in the development of relevant Guidance(s) for Evidentiary Criteria (EC) in biomarker qualification.

Relevant background information influencing the development of this document and the proposed framework:

- Although the FDA biomarker qualification pathway has made continued progress, there remains a lack of clarity regarding levels of evidence and degree of biological understanding with respect to biomarkers and their use in clinical trials and drug development programs. Progress in this area has been hampered by the lack of clear, predictable, and specific regulatory criteria for the evidence required to qualify new markers.
- Although this framework primarily focuses on biomarkers qualified for regulatory use across multiple drug development programs via the FDA's Biomarker Qualification

---

[1] For the purposes of this framework, "biomarker" refers to both single entities and multiple entities (panels).

Program (BQP), the framework should also help harmonize biomarker development considerations as part of drug-specific development programs.

- While the regulatory acceptance of biomarkers in preclinical studies can have great value for drug development programs, the focus for this initial framework is on regulatory acceptance of biomarkers for clinical applications. It is recognized, however, that:
    - Availability of preclinical data (feasible for some, but not all, clinical studies) could be an important part of the evidence to inform scientific understanding and prior performance metrics in support of a clinical biomarker's regulatory acceptance.
    - In general, availability of preclinical evidence could be considered a plus, but absence of it should not automatically lead to a negative assessment (i.e., biomarkers may not be functionally conserved between non-humans and humans). For questions difficult to address in humans alone (e.g., limitations of access to organ tissue) where there is conservation of biomarker function across species, non-clinical supportive evidence may serve to bridge the knowledge gap.
    - Even in the absence of clinical translation, development of more sensitive and specific preclinical biomarkers for assessment of organ toxicity to inform first-in-human studies may be of great regulatory importance.

The General Framework: (Applicable to All Biomarker Types)

Background

Biomarker Categories

The FDA/NIH Leadership Council identified harmonization of biomarker-related terms as a priority to facilitate improved communication and shared understanding of terms related to biomarker development and utility among stakeholder groups (regulatory, scientific, business, and health care providers). An interagency biomarker working group was formed in 2015 and has developed an initial draft of a biomarker glossary of terms. The first release of this glossary, the BEST (Biomarkers, EndpointS, and other Tools) resource was published on January 28, 2016 and is located on the National Library of Medicine website (http://www.ncbi.nlm.nih.gov/books/NBK326791/). The glossary is intended to be a living document that can be updated and amended over time. The categories of biomarkers described as part of this effort will be of benefit in the discussion and development of COUs and will help to inform the accompanying levels of evidence.

A biomarker 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, radiographic, or physiologic characteristics are

types of biomarkers. Generally, a biomarker is not a direct assessment of how an individual feels, functions, or survives. Categories of biomarkers include:

- <u>Susceptibility/Risk biomarker</u> – A biomarker that indicates the potential for developing a disease or medical condition or sensitivity to an exposure in an individual without clinically apparent disease or medical condition.
- <u>Diagnostic biomarker</u> – A biomarker used to identify individuals with the disease or condition of interest or to define a subset of the disease.
- <u>Monitoring biomarker</u> – A biomarker measured serially and used to detect a change in the degree or extent of disease. Monitoring biomarkers may also be used to indicate toxicity or assess safety, or to provide evidence of exposure, including exposures to medical products.
- <u>Prognostic biomarker</u> – A biomarker used to identify likelihood of a clinical event, disease recurrence or progression.
- <u>Predictive biomarker</u> – A biomarker used to identify individuals who are more likely than similar patients without the biomarker to experience a favorable or unfavorable effect from a specific intervention or exposure.
- <u>Pharmacodynamic/Response biomarker</u> – A biomarker used to show that a biological response has occurred in an individual who has received an intervention or exposure.
- <u>Safety biomarker</u> – A biomarker used to indicate the presence or extent of toxicity related to an intervention or exposure.
- <u>Surrogate endpoint</u> – An endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

Milestones in the Development of an Evidence Framework for Biomarker Qualification

- The need for evidentiary criteria for biomarkers has been clear since the 1999 FDA/NIH workshop on biomarkers (NIH Definitions Working Group. Biomarkers and surrogate endpoints in clinical research: definitions and conceptual model. In Biomarkers and Surrogate Endpoints: Clinical research and Applications. [ed. Downing GL] 1-9 [Elsevier, Amsterdam, 2000]), and reinforced ever since release of the original [FDA Critical Path publication in 2004](.).
- The history of biomarker qualification begins even earlier with classic statistical theory on surrogate endpoints (Prentice, 1989). Boissel et al (1992) elaborates the criteria that biomarkers must meet to be considered valid surrogates, but these criteria do not include benefits (efficiency) or identify issues that relate to risk of failure. The ICH E9 Guidance, (1998) includes a brief paragraph on overall statistical guidance mentioning key issues, but does not discuss evidentiary requirements. Lesko & Atkinson (2001) outlines the concepts of biomarker and surrogate endpoint validity. Wagner (2002) introduces the term qualification and distinguishes the separate needs for assay validation and qualification, based on different evidentiary requirements. A "pre-Critical

Path" FDA perspective discusses the consequences of failure (Katz, 2004). Lee et al. (2006) elaborates fit-for-purpose method validation and, for successful biomarker measurement, differentiates it from the evidentiary standards surrounding biomarker use. More recent work by Kakkis et al. (2015) describes a framework for qualifying biomarkers as primary endpoints in rare diseases.

- While other aspects of the biomarker qualification process have been steadily developed and implemented since the FDA Critical Path publication in 2004, progress on EC development has been intermittent given the complexity of defining a generalized framework that is applicable across multiple disease areas, types of biomarkers, and COUs.

- Assessment of the amount of evidence needed for biomarker qualification cannot currently be provided as an absolute relationship and is instead related to many factors, some of which are not easily quantified. Thus, our framework and others in the past have taken a semi-quantitative approach. One salient, initial, semi-quantitative effort to develop EC, Williams et al. (2006), presents a framework that aims to "*qualify biomarkers in terms of cost effectiveness using a set of principles that enable the evaluation of biomarkers even with incomplete knowledge.*" This approach applies "tolerability of risk" to supportive evidence and concludes that biomarker qualification essentially rests on the principle that the value of incremental benefits provided by the true results of the biomarker must exceed the incremental costs (defined as societal harm) of the false results with the biomarker. The article lays out a very useful conceptual way of thinking about evidence, but one that is of limited specificity and in particular limited practicality given the difficulty of measuring "costs" defined as societal harm.

- An article by Altar et al. (2008), based on a PhRMA/FDA workshop, provides the first "evidence map" with categorical descriptions of different types of scientific evidence required for different levels of risk, but is overly complex and does not adequately account for COU.

- An IOM study in 2010 emphasizes the importance of COU as part of a three-part framework that includes analytical validation, qualification, and utilization components. However, it does not address specific decision processes or specific evaluation criteria.

- Amur et al (2015a) and (2015b) note the (established) difference between biomarker development within drug-specific development programs and the biomarker qualification pathway described in the FDA's Drug Development Tools Guidance (January, 2014) and emphasizes importance of COU described in conjunction with definitions of biomarkers types and uses. The manuscripts also describe general and statistical considerations for different categories of biomarkers and discuss the need for risk-based evaluation of evidentiary standards. They do not define risk-based evidentiary criteria, however.

- A symposium co-sponsored by the University of Maryland CERSI/FDA/Critical Path Institute (August 2015) further laid out issues associated with establishing EC. In particular, this meeting offered the first real exploration of EC for enrichment and safety biomarkers through specific (some hypothetical) case studies and discussion of relevant

statistical considerations. The meeting was not intended to organize the discussion into a proposed framework.

- A [Brookings Institute meeting in October 2015](#) titled "Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration" proposed a draft set of biomarker-related definitions to improve communication of complex scientific concepts. Although the meeting discussed general challenges associated with biomarker development, it did not specifically address EC.
- A National Biomarker Development Alliance (NBDA) [workshop](#) titled "Collaboratively Building a Foundation for FDA Biomarker Qualification" (December 2015) developed case studies for four disease areas (clinical nephrotoxicity, Alzheimer's disease, Glioblastoma multiforme, and prostate cancer) with proposed COUs.
- A workshop co-sponsored by the Biomarkers Consortium and FDA, "Biomarker Qualification Workshop: Framework for Defining Evidentiary Criteria" was held on April 14 and 15, 2016. An earlier version of this framework document was distributed prior to the workshop, along with 3 case studies: kidney injury, liver injury and vascular injury.

This document synthesizes key elements of the above efforts to propose an overarching framework for EC. In particular it applies some of the Williams et. al. (2006) concepts of risk and benefit to specific considerations driven by COU, and uses these to help define an "evidence map" that incorporates some of the takeaways from the recent workshops listed above.

The Proposed Framework

Underlying Assumptions

The operating assumption of this document is that, while the COU is critical for determining the specific EC required for regulatory qualification of a biomarker for use in drug development programs, there are other key concepts that can be generalized and applied as part of a standardized framework. Future framework documents are in preparation focusing on Analytical Validation and Statistical Considerations, and will be available at a later date.

Although not a specific part of the EC framework, the identification and characterization of the biomarker of interest is essential to a successful biomarker qualification effort and frequently occurs in parallel with the development of the COU. Broadly speaking, biomarker identification includes the biomarker's description and source material (e.g., plasma, urine, CT scan); analytical validation of the method by which the biomarker is assessed or quantified requires assessment of the method's performance characteristics.

It is expected that an EC framework will benefit the biomarker qualification process by:

1) Providing biomarker developers and FDA with increased clarity, predictability, and consistency across biomarker development programs. Ultimately, a standardized framework will help guide collaborative discussion and decision-making, especially during the "Consultation and Advice" (C&A) step of the biomarker qualification process. During C&A, the

COU continues to be refined through collaborative discussion between FDA and the biomarker developer and the level and types of evidence required are also being defined.

2) Increasing the quality of biomarker qualification submissions and their reviews by demonstrating in specific terms the level of evidence required (including the quality of the data) to support a given COU.

General EC Framework Components

The EC framework is a five-component process that involves: 1) describing the drug development need, 2) defining the COU (i.e., how the biomarker will be used in a drug development context), 3) considering potential benefits should the biomarker project be successful (e.g., improved sensitivity or selectivity), 4) considering risks associated with the intended use of the biomarker in a drug development program (i.e., frequency and consequence of false negatives or false positives), and 5) determining the EC to support the COU based on the Benefit and Risk (Figure 1).

The submitter is expected to provide a clear and objective explanation of the anticipated benefits, the reasonable risks, and the risk mitigation strategies proposed for use of the biomarker within the proposed COU. The sponsor's evaluation is critical for communicating how the overall balance of benefits, risks, and risk mitigation efforts may impact the expected level of EC that would be reasonably required to support qualification.
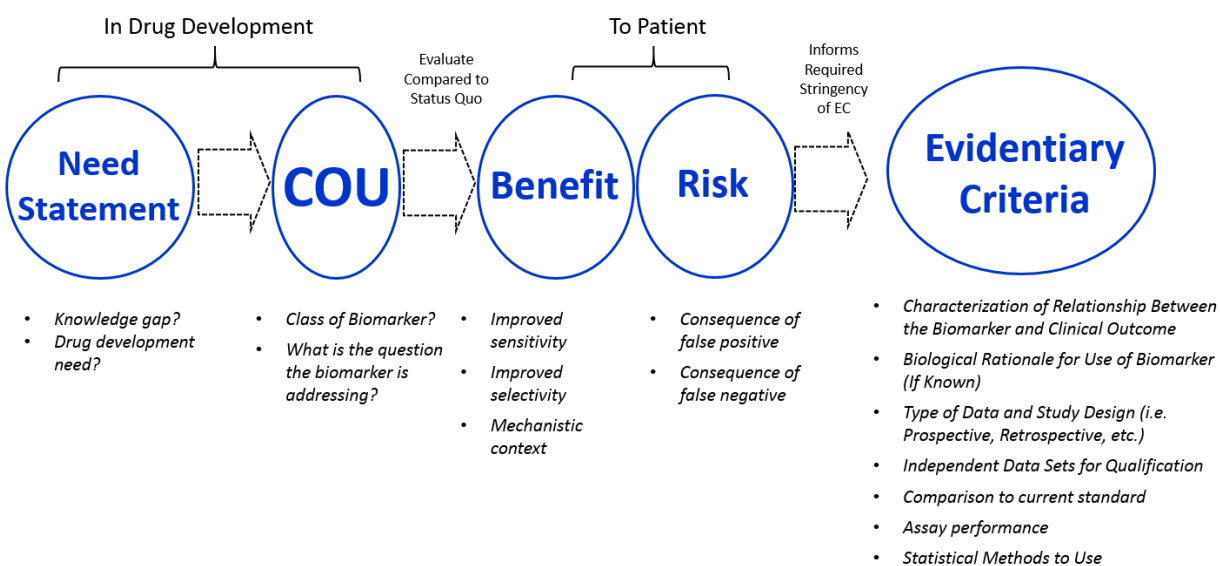
Figure 1–The Proposed Five-Component Process

The process for defining this framework first involves describing the need that the biomarker is intended to address. For a biomarker developer and FDA to commit resources for a given project, the need must reflect a meaningful area of study that has 1) direct relevance to drug

development and 2) the potential to impact a broader number of programs. Next, the biomarker developer proposes a COU for a biomarker qualification submission with the help of specified COU elements. Once the COU is identified, the Benefit and Risk is determined within the broader context of the impact on patients (e.g., the role of the proposed biomarker in drug development, the severity of the disease or condition, availability of other tools to advance drug development in that disease or condition). Finally, the level of evidentiary criteria required for use of the biomarker in a well-defined COU is directly linked to the Benefit and Risk.

There may be unknowns, assumptions, and limited data upon which decision-making for EC must rely, and tolerance for uncertainty in Benefit and Risk considerations may differ between a biomarker's need statement and intended COU. Therefore, open discussion between FDA and the biomarker developer regarding available evidence, evidence that may be collected, and residual uncertainty contributes to achieving an aligned decision about the overall biomarker development plan. The biomarker development plan should be designed to yield sufficient evidence (i.e., if the studies are successful) to support a favorable Benefit and Risk relative to the need statement for use of the biomarker within a well-defined COU.

The final component in the EC framework is determining the level of evidence required to support the biomarker qualification COU. Ultimately, a body of evidence (i.e., correlative science) needs to be defined to support the COU. Although this step is directly linked to the risk of making an incorrect decision when using the biomarker in its given COU, it also is informed by the benefit associated with the availability of a biomarker for that particular COU relative to the need statement. For example, FDA may be willing to accept a lower level of evidence if a biomarker and its COU are addressing an unmet medical need (e.g., the biomarker is used to select patients for enrollment into a clinical trial for a life-threatening disease with no available treatment).

Refinement of the COU

Based on prior biomarker qualification projects, the COU will likely evolve over time as understanding of the biomarker matures, goals are more clearly articulated, and data are collected, assessed, and interpreted. This activity is a dynamic process that involves substantial interaction between the biomarker developer and the FDA. The refinement of the COU takes into account not only what data are available but also what information can be generated by or is accessible to the biomarker developer. Therefore, the process described above may be iterative if the evidence is not sufficient to support the COU. For example, if less evidence than expected becomes available, one could modify the COU. This "looping back" to a revised COU might prompt collection of other sources of evidence to support the modified COU, or "looping back" to prompt additional studies to fill gaps in the evidence grid to support the initial COU.

The current framework is intended to support constructive discussions between biomarker developers or potential submitters to the biomarker qualification program and regulators that allow for refinements of the COU as the data mature (Figure 2). The iterative nature of biomarker development and this proposed framework builds in flexibility, allowing for a COU

with more narrow scope (i.e., a limited COU) when appropriate, that may serve to catalyze further research contributions from stakeholders. For example, such a limited COU could be quite reasonable upon completing the evaluation of compelling and extensive new learning phase data. As additional information improves scientific understanding, expansion and refinement of the biomarker's COU may occur over time.
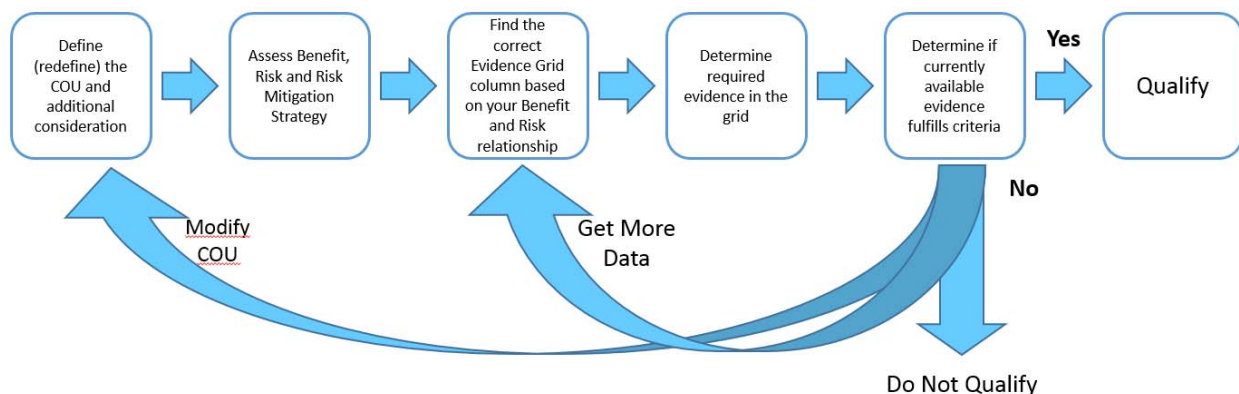
Figure 2 – Workflow and Decision Process Summary

Individual Components of the EC Framework

Need Statement

The need statement is a concise and coherent description of the knowledge gap or drug development need (e.g., improved safety monitoring) that the program is planning to address. The need statement is also known as a problem statement, statement of need, or needs assessment. It presents facts and evidence that drive the COU relative to drug development as well as the evaluation of the risk and benefit relative to the intended patient population. Therefore, the need statement ultimately informs the level of evidentiary standards for the qualification plan.

Generally speaking, we need reliable biomarkers that can reduce uncertainty and support decision making in the drug development process. The level of this need, however, will vary based on the current landscape, such as the reliability of currently used biomarkers and the level of improvement new biomarkers might provide to the patients and drug development process. As such, the need statement may include:

- the nature and extent of the need, the drug development issue the biomarker addresses and the target population;
- major challenge(s) and unique aspects of these challenges that the project addresses;
- reasons and causes for the need being addressed.

Context of Use

The COU is a statement that fully and clearly describes the way the medical product development tool is to be used and the medical product development-related purpose of the use. The COU is critical for the biomarker qualification submission and is based in large part of on the need statement that the biomarker is intended to address. FDA has identified considerations related to a biomarker's COU, including the concise use statement and the comprehensive description of conditions for use in the qualified setting (see Appendix 1). Therefore, this document is focused only on those factors that are important for establishing the value and utility of the biomarker and that influence the Benefit and Risk assessment relative to the need statement and determination of EC for biomarker qualification.

Many of the elements of the COU may not be defined or may only be described in general terms during the initial development of a biomarker. Through collaborative discussions with FDA, especially during Consultation and Advice, these COU elements become further defined over the course of the biomarker development program. Additional examples of COU elements are provided in **Appendix 1** of this document.

Considerations for Drafting a COU

When a biomarker developer begins the process of defining a COU, there are a number of questions that should be considered to aid in the clear articulation of the COU and to promote a common understanding of the intended use of the biomarker in drug development. Careful definition of COU should aid in the design of feasible and efficient biomarker development plans. Although these questions may not apply to all biomarkers or COUs, they may be helpful in determining the COU for a biomarker submission (and the process shown in Figure 2). These considerations are intended to be elaborated before the COU is defined, but can be re-addressed as new information becomes available. These considerations are not the COU statement, which follows, but rather, are intended to frame the process and the discussions.

- What is the analyte(s) of interest? Is it a genetic, protein, cellular, metabolomic, microscopic, or imaging marker?
- What is the analytic method used for detection of the analyte?
- Will the biomarker be used in a well-defined, small population or a more heterogeneous, larger population? What is the severity of the disease? Are there other drug development tools available?
- Will the biomarker be used alone or in addition to other accepted biomarkers to inform about something previously undetectable or not adequately detectable, or to delineate a previously unknown pathology, disease mechanisms or pharmacological effect?
    - What value does the novel marker add to currently accepted biomarkers?
    - Is it proposed to be used as a standalone biomarker to inform an observation or characteristic formerly unknown or undetectable in a patient ?
    - What is the regulatory status of other biomarkers in use or planned for use in concert with the novel biomarker?

- How will the biomarker be used in drug development or clinical trials (type of biomarker as defined by BEST)?
  - Will the biomarker be used to assess overall safety or one component of safety? Will the biomarker be used with other measures that overlap, partially overlap or have no overlap in information or use?
  - Will the biomarker be used as a surrogate endpoint? If yes, what clinical outcome is the biomarker believed to be reasonably likely to predict?
  - Will use of the biomarker be limited to use in clinical trial enrichment (i.e., as a patient enrichment, risk stratification, prognostic or predictive biomarker)? Will it be used alone or with other tools for enrichment? Or is it proposed as a response biomarker to facilitate dose selection for future trials (e.g., to measure a pharmacodynamic effect)? Will it be used alone or with other tools?
  - Are there well-established biomarker(s) with overlapping or partially overlapping COUs? What history informs its longevity or recognition within the scientific community? (e.g., FDA review center use, historical acceptance)
- Will there be supportive animal/nonclinical data?
  - The more directly applicable, supportive nonclinical data are supplied during drug development to demonstrate utility and to guide the details of clinical use, the lower the requirements might be for clinical qualification data.
- How limited or broad is the claim?
  - For example, if the biomarker is a safety biomarker, is the biomarker claim one that claims overall safety of the subject, safety of an organ, or safety of a part of a functional unit of an organ? The broader the claim, the higher the EC need to be.

COU Statement

The COU statement is a concise description of how a biomarker is intended to be used in drug development. It is comprised of two main elements:

- What category of biomarker is proposed and what information content would it provide? Examples of categories (as described in BEST) include:
  - Susceptibility/Risk biomarker
  - Diagnostic biomarker
  - Monitoring biomarker
  - Prognostic biomarker
  - Predictive biomarker
  - Pharmacodynamic/Response biomarker
  - Safety biomarker
- What question is the biomarker intended to address ("What is the biomarker's specific fit-for-purpose use?")? Examples of a biomarker's role in drug development or clinical trials include:
  - Defining inclusion/exclusion criteria for clinical trial enrollment
  - Altering treatment allocation

- Cessation of a patient's participation in a clinical trial
- Adaptation of the clinical trial design
- Establishing proof of concept
- Supporting clinical dose selection for first in human studies
- Supporting clinical dose selection for Phase 3 studies
- Serving to enrich clinical trial for an event or population of interest
- Evaluating treatment response (e.g., pharmacodynamic effect)
- Supporting regulatory acceptability of a surrogate endpoint for accelerated approval
- Supporting regulatory acceptability of a surrogate endpoint for traditional approval

Conditions for using the qualified biomarker in an IND drug development program

Data to support the optimal application of a biomarker may be needed to address numerous variables such as reasonable clinical study duration for reliable utility of the biomarker; when sample collection should be specified with respect to test article administration; defining any likely considerations within a given study population for biomarker alterations that may not involve test article administration; the value of a targeted gene sequence alteration in predicting susceptibility, or outcome; etc. Animal study data that demonstrate the added value and utility of the biomarker that are generated using the same drug under development may be critical to defining the COU in a manner that will improve the Benefit and Risk assessment relative to the need statement. For additional details, please see Appendix 1.

Assessment of Benefits and Risks

The relationship of Benefits and Risks, given that the COU is related to the biomarker's value to drug development or clinical trials, is assessed from the perspective of patients. In the regulatory context, there are three potential areas of interest: 1) the ability of a clinical trial to yield interpretable results, 2) impact on patients enrolled in a clinical trial, and 3) impact on patients from a public health point of view should a product be approved or denied approval based, in full or in part, on biomarker information.

A Benefit and Risk analysis results from a balanced assessment of the risks associated with an erroneous result and the potential benefits of qualifying a new biomarker. The assessment of both benefits and risks should be made for a biomarker within its proposed COU and relative to the need statement. For example, if the COU is limited to a serious or life-threatening disease without available treatment options, and the biomarker is believed to promote efficiency in drug development or clinical trial design, or improve success of the drug development program, these factors should be included in the Benefit and Risk analysis. Hence the risk determination includes evaluating the priority or uniqueness of the proposed biomarker's information within the overall determination of patient safety and efficacy.

Benefit and Risk takes the need statement, results from the COU assessment, and the applicable considerations discussed above into account. For example, in a population with a

poor prognosis, the current practice may be that patients do not receive a sufficient therapeutic dose of an investigational drug to mitigate an adverse outcome. Thus, the "cost of doing nothing" is high: patients will not be able to get effective treatment. In this context, even a high risk of negative consequences when failing may be acceptable, especially if the toxicity is reversible once detected. While precise quantification of Benefits and Risks is not feasible or practical, a data-driven semi-quantitative assessment that encompasses all of the relevant components of the relationship between benefit and risk is generally sufficient for decision-making. Note that the type, quality, and amount of data required will be linked to the Benefit and Risk through the EC grid relative to the need statement. Thus a candidate marker with a high negative consequence if incorrect and low improvement over current standard[2] would require a more extensive data package than a candidate with low negative consequence of failure and high benefit.

The Benefit and Risk assessment links the COU to the evidence needed: 1) defining the COU, 2) translating the COU with the aid of a Benefit and Risk assessment and the need statement, and 3) determining level of EC within an evidence map to support qualification. To have a favorable Benefit and Risk, the biomarker development plan should be designed to yield a level of evidence that is sufficient to: 1) mitigate the risks associated with using the biomarker within its well-defined COU and 2) provide assurance that use of the biomarker in this COU will confer its anticipated benefit. For all risks identified, appropriate risk mitigation strategies should be discussed as well as how potential benefits impact the overall favorability and level of evidence for qualification. The following questions should be considered by biomarker developers as these questions will define the level of EC needed to support the biomarker's COU relative to the need statement.

1) What is the potential consequence or harm if the biomarker's performance is not aligned with expectations based on the COU? At what point would the benefit-risk profile no longer be favorable?
    a. If the biomarker has a role in assessing patient safety, is the novel biomarker information supportive when taken into account with other standard measure information or is the information provided by the novel biomarker completely unique?
    b. Are there mechanisms to mitigate risk to enhance benefit to the patient?
    c. Consequences of both a false positive and a false negative result should be discussed. For example, a false negative result for a novel safety biomarker may be considered to increase risk of patient harm, while a false positive result for the same safety biomarker may jeopardize the successful development of a

---

[2] Here and throughout this document we use the term "current standard" to reflect ongoing efforts to improve upon drug development paradigms in response to increased scientific understanding and thus the currently accepted "measurements" for a given outcome. For some areas, "current standards" have been accepted for long periods of time and are sometimes referred to as "gold standards". Unfortunately, use of "gold standard" implies never changing, so we believe "current standard" more accurately reflects the desire to improve upon the status quo when data and scientific investigation warrant such a change.

promising new drug with significant societal benefits. Conversely, a false negative result for a pharmacodynamic/response biomarker may jeopardize drug development progression, while a false positive for a pharmacodynamic/response biomarker may be perceived to increase risk of patient harm by prolonging test agent exposure and needlessly increasing chances for potential adverse effects while depriving a patient of an alternative effective therapy.

2) What is the severity of the disease or condition? What are the unmet needs of the population defined in the COU? What are the risks for mortality and morbidity in the absence of treatment? For example:
   a. How well defined are the potential risks of use of the biomarker, and might they be mitigated? If the risk occurs, is it reversible?
   b. What is the level of patient tolerance for risk (within the COU)?
   c. Do the potential benefits of use of the biomarker outweigh the risks of using a biomarker that underperforms? How much uncertainty is tolerable given the severity of disease?

3) What is the relative perceived benefit of the new biomarker vs. the current standard?
   a. What is the availability of other tools that can be used to advance drug development in that disease or condition (i.e., is the biomarker filling an unmet need)?
   b. Are there factors about biomarkers currently being used as part of the status quo that may warrant the development and use of a new biomarker? For example, compared to the status quo, does the biomarker in its proposed COU improve patient comfort or convenience (e.g., the patient needs to return for sample collection less frequently, or the matrix within which the biomarker is found has changed to a sample type that is less painful to collect)?
   c. When used in its proposed COU, does the biomarker improve the efficiency of the clinical trial (e.g., reduce the number of patients required, reduce the timeline)?
   d. The magnitude and probability of benefit should also be considered when weighing the benefits of the biomarker with the risk of erroneous results. For example, predictive biomarkers can be used to identify individuals who are likely to experience a favorable or unfavorable effect from a specific intervention or exposure. However, the benefit of this biomarker may be experienced only by a small number of patients in the target population. It is also possible that different patient subgroups are likely to experience different levels of the same benefit. Whether or not these subgroups can be identified is an important factor that will inform the level of risk associated with this benefit.

4) What is the relative overall perceived incremental risk vs. benefit of the new biomarker vs. the current standard?

5) When in the drug development lifecycle is the biomarker intended to be used? For example, a biomarker with an early exploratory COU may require a lower level of evidence to mitigate potential risks than a biomarker with a Phase 3 study COU intended to support drug approval.

6) What is the scope of the biomarker COU in terms of impacting drug development and regulatory review? Will the focus be restricted to just clinical trial design elements or will there be impact on drug labeling including indicated patient population, drug dosing, warnings/precautions, etc.?

Linking the Benefit and Risk to the Level of Evidence: Evidentiary Categories of Benefit and Risk

The EC Framework contains a spectrum of Benefit and Risk outcomes (i.e., unfavorable to favorable). Recognizing that not all data/information will fit perfectly into any standard category, it will be important to assess all elements of potential risks and benefits associated with the biomarker's COU relative to the need statement in order to make an informed assessment as to where on the continuum the biomarker best fits. Ultimately, for each of the types of data needed to support a biomarker's COU, an understanding of Benefit and Risk relative to the need statement helps to refine the level of evidence needed. Thus, the degree of risk depends on the impact on decision-making in drug development and the risk to patients enrolled in the trials.

Favorable Benefit and Risk. An example of favorable Benefit and Risk that would require a minimal level of evidence, is a biomarker that is used for stratification of patients to ensure equal distribution of biomarker positive and biomarker negative individuals in the different arms of a clinical trial. If the biomarker does not perform as expected, the loss consists of the resources spent on the biomarker assay and would not influence the trial outcome or patient safety. But even stratification has its own spectrum of Benefit and Risk outcomes. In the setting of hypothesis testing for a targeted therapy, if the biomarker's clinical utility is not supported or the trial design is not appropriate to the biomarker's use, the trial results may not be interpretable or an incorrect conclusion could be drawn from the data. As such, in these circumstances the Benefit and Risk may be less favorable, requiring a higher level of evidence.

Intermediate Benefit and Risk. An example of intermediate Benefit and Risk that would require a moderate level of evidence, is a biomarker that is used to enrich clinical trials so that the trials are more likely to have a favorable clinical outcome or more likely to experience a clinical event of interest. If the biomarker does not perform as expected, then it might result in a failed trial. Depending on the enrichment strategy employed, the Benefit and Risk may not be impacted even if the biomarker's role is not supported; or, the Benefit and Risk may be intermediate if the biomarker's unsupported role results in patients being misdirected from standard of care. Another intermediate Benefit and Risk example in the continuum is a safety biomarker used to monitor a specific organ injury used in addition to the traditional safety biomarkers.

Challenging Benefit and Risk. An example of an even more challenging Benefit and Risk (potential for high benefit while accompanied by high risk) is a biomarker used as surrogate endpoint, which would require a high level of EC. If the biomarker is not truly a surrogate endpoint in terms of predicting clinical benefit, the results of the clinical trial would be invalid and inappropriate approval decisions would be made. This would lead to potentially ineffective drugs being marketed or patients being denied access to effective therapy. Yet another example of a high risk COU is a safety biomarker intended to replace the current standard to identify organ toxicity. In both of these examples, a high level of evidence would be needed to support the biomarker's COU.

Evidentiary Criteria

The evidence maps in this framework are inspired by, but are considerably less complex than, the map used by Altar et al. (2008). The level of need and choices made in the COU section determine the overall relative level of benefit and risk. The overall level of Benefit and Risk determined as a result of the need statement and COU, in turn determines the level of evidence needed to evaluate the biomarker for qualification.

Assay validation[3]:

The characterization and validation of biomarker assay performance is a fundamentally important aspect of biomarker qualification. Biases introduced in the conduct or interpretation of the assay will affect the biomarker's accuracy and thus its evaluation as a useful Drug Development Tool (DDT). In this section the scientific and regulatory considerations for the validation of soluble biomarker assays used in the qualification of DDTs. The topics to be discussed include the optimization of pre-analytical factors, core assay performance expectations, and setting minimally acceptable assay performance criteria.

Biofluid-based Biomarker Assay Validation Considerations

In order to develop assay considerations, several key assumptions regarding the nature and use of assays for qualification of soluble biomarkers measured in biological matrices were made and are outlined below.

1. The validation expectations for biomarker qualification assays are not identical to the expectations outlined for PK or toxicokinetic assays.
2. The performance characteristics of biomarker qualification assays are in line with the COU and ultimately the clinical application of the biomarker in drug development.

---

[3] The text in this section is derived from the efforts of the Biomarker Assay Collaborative Evidentiary Considerations Writing Group that was convened following the symposium co-sponsored by the University of Maryland CERSI/FDA/Critical Path Institute in August, 2015. A more robust discussion of the issues summarized herein is being developed by the Working Group, and a white paper on Analytical Validation Considerations is in preparation.

3. Biomarker qualification assays are not sufficient for, and are not intended to be used as, *de facto* substitutes for an IVD or for approvals or clearances by the CDRH, or assumed to be directly applicable in clinical practice.

4. Although an FDA approved or cleared assay is not required to support a biomarker qualification effort, adequate assay performance and validation is essential for a biomarker's qualification.

As outlined in the draft PK bioanalytical guidance (FDA, 2013), basic bioanalytical parameters already exist that should be considered when developing an assay for the qualification of biomarkers. Not all parameters will be important or even necessary for every assay, but each should be considered based on the biomarker COU. Good scientific judgment must be used, while keeping the COU in mind at all times. Different platforms will have different requirements for the assessment of performance criteria and may have other considerations beyond this minimal list, or may not include some members of this list. If a parameter is not addressed, a justification should be formulated for why it was excluded.

In considering setting the performance and rigor of criteria required for biomarker assay validation, it is essential to understand the purpose and clinical requirement of that assay as they relate to the biomarker's COU. Early in the exploration of a biomarker's utility, a simple and minimally validated assay may be sufficient to generate useful data. However, when qualifying a biomarker, a fit for purpose validated assay will be needed to provide sufficiently robust data for confirmatory and clinical study sample analysis.

Validation is establishing that the performance of a test, tool, or instrument is acceptable for its intended purpose. Elements of validation include but are not limited to analytical validation and clinical validation. It describes in mathematical and quantifiable terms the performance characteristics of an assay. At a fundamental level, the validation of a biomarker assay used for qualification should include the assessment of **Precision, Accuracy, Limit of Detection, Limit of Quantitation, Specificity, Linearity and Range, Ruggedness and Robustness**.

Pre-Analytical

Pre-analytical covers all actions taken with the sample until the actual analysis of the biological specimen. Pre-analytical variables that affect the integrity of the biological specimens, and later the results of analyses include specimen collection, processing, storage, shipment, and handling. Pre-analytical variables can introduce inconsistency in to assay results, either systematically or randomly, resulting in lack of reproducibility. Not only must these factors be taken into consideration early in the assay development phase well prior to the full validation of the assay, but they must be established and remain consistent between the validation samples and the qualification samples.

Assay Validation Acceptance Criteria

Establishing assay acceptance criteria is likely the most difficult exercise for a biomarker assay validation. Unlike the predefined performance criteria established for PK assays, the acceptable performance criteria for biomarker assays are dependent upon individual biomarker's physiological behavior, which is similar to the validation approach used for IVD methods.

As discussed by Lee *et al.* (2006), the fit-for-purpose status of a biomarker method is deemed acceptable if the assay is capable of discriminating changes that are statistically significant from the intra- and inter-subject variation associated with the biomarker. If the assay is not capable of such discrimination, either the assay lacks the appropriate analytical attributes or the biomarker is not suitable for the proposed purpose. For example, an assay with 40% total error determined during validation may be adequate for statistically detecting a desired treatment effect in a clinical trial for a certain acceptable sample size, but this same assay may not be suitable for a clinical trial involving a different study population that has much greater physiological variability.

An assay's performance characteristics are considered to be acceptable if (1) appropriate assay characterization practices are applied (evaluation of assay precision, accuracy, limit of detection, limit of quantitation, specificity, linearity and range, ruggedness and robustness), and (2) the assay can distinguish biomarker changes that are outside of the normal variability. Of course, it is desirable to have an assay that over performs, such that if additional analytical error is introduced into the assay, the biomarker's performance will not suffer.

Imaging-based Biomarker Assay Validation Expectations for Qualification

Similar to biofluid-based biomarker assays, imaging biomarkers hold tremendous potential for utility in informed decision making for drug development. Clinical imaging biomarkers have been successfully qualified with both EMA (e.g., hippocampal volume in Alzheimer's disease; Total Kidney Volume in polycystic kidney disease) and FDA (e.g., Total Kidney Volume in polycystic kidney disease). At the same time, general definition and agreement upon the performance requirements are needed to enable efficient advancement and expansion in the number of qualified imaging biomarkers. The expectations for imaging biomarkers assay validation will be addressed following the alignment and acceptance of expectations around biofluid-based biomarker assay validation.

Scientific understanding:

- Understanding of the biological rationale or plausibility and specificity of the biomarker– the degree to which the initiating disease or adverse events trigger subsequent steps in a biological pathway and the role of the biomarker in that causal or outcome pathway.
- Understanding of the molecular mechanism(s) underlying the alteration in the level of the biomarker.
- Understanding the link of the proposed biomarker to the currently accepted clinical outcome measure.

Biological Performance:

- Consistency of the correlation between biomarker change and clinical outcome, disease progression, drug toxicity, drug exposure, with the currently accepted biomarker. Consistency is measured using repeated studies with a given compound by one or multiple testers, across studies with mechanistically different compounds, and across different species.
- Presence of a dose response and temporal relationship to the magnitude of the biomarker response and outcome.
- Specificity of the biomarker response.

Types and amount of data/samples required:

As noted in the map, the evidence acceptable for satisfying evidentiary criteria in some cases may be partially or entirely composed of retrospective, literature, or other "real world" types of evidence. The level of evidence required to qualify the marker can be described according to the following variables:

- Evidence type: clinical, non-clinical, modeling, or literature review.
    - Longevity of use, acceptance by scientific or medical practice community
    - FDA prior acceptance of use of the biomarker in one or more development programs.
- Clinical study type (decreasing power of evidence from top to bottom):
    - Systematic Review
    - Prospective Randomized Controlled Trial
    - Retrospective Randomized Controlled Trial
    - Cohort Study
    - Case/Control Study
- Study Characteristics
    - Randomized/not randomized
    - Controlled/not controlled
    - Blinded/unblinded
    - Objectives (primary/secondary/exploratory)
    - Observational
    - Longitudinal
    - Multi-site/single site
    - Compliance to data collection
- Size of cohort(s) *[Note: this is directly related to statistical power]*

Statistical considerations[4]

Production of a Statistical Framework Document is ongoing and this document will be available at a later date. The following excerpt from the Statistics Document highlights those points that are specific to the statistical issues brought up by the Statistical Considerations Working Group in the context of the overall framework document.

The statistical approaches appropriate for addressing the key elements of the framework will differ depending on the type of biomarker measurement(s) and the COU. For some biomarkers, a large and often confusing body of evidence will have already been accumulated relating the biomarker to various biological characteristics or clinical outcomes. It is essential to incorporate a statistical approach as early in the process as possible and review existing evidence carefully to determine comparability across study characteristics and how variations in those characteristics across studies might affect key associations between the biomarker and clinical outcomes of interest.

Biomarker measurement methods, patient populations, treatment settings (drugs or other therapeutic interventions), and endpoints examined might all differ between data sets. Claims regarding presence or absence of associations between the biomarker and clinical outcomes made in prior studies should also be critically examined to determine whether the claims are supported by appropriate statistical analyses, with particular attention to the possibility of false positive or negative findings. False positive findings are readily generated by extensive data exploration when there is no accounting for multiple testing. In contrast, for small studies that have not been designed to have sufficient statistical power to detect differences in biomarker values between groups or other associations between the biomarker and the clinical endpoint of interest, statistically non-significant results are frequently inappropriately interpreted as negative findings. These are all important considerations in assessing the credibility and relevance of prior claims made about a biomarker.

Data gaps will be identified in the evidence needed to support an intended COU statement after initial review. Sometimes additional evidence can be gained through access to raw, unprocessed data or images from prior studies. With full access to raw data, it may be possible to select data from specifically defined subsets of subjects consistent with the preliminary COU and to re-process the data in a uniform way to facilitate pooled data analyses across existing data sets, or alternatively to apply alternate algorithms for comparison.

Similarly, for biospecimen-based laboratory biomarkers, availability of biospecimens may permit analyses of biomarkers using alternative assays methods. New biomarker data

---

[4] The text in this section is derived from the efforts of a cross-sector Statistical Considerations Working Group that was convened following the symposium co-sponsored by the University of Maryland CERSI/FDA/Critical -Path Institute in August, 2015.)

generated from biospecimens may be used to evaluate the impact of particular assay methods on measured biomarker values and on the strength of their associations with clinical outcomes.

Sometimes the only way to acquire the necessary data to support a biomarker for qualification is to launch a prospective clinical study. Prospective studies are usually time- and resource-intensive, so if they are necessary, careful planning is essential to ensure that they will yield evidence that will permit definitive evaluation of the qualification COU statement. A useful approach to understand the level of evidence associated with clinical trial data has been described previously (Hayes et.al., 1996) and updated to take into account new approaches to some retrospective analyses (Simon, 2009). This grading system provides a set of characteristics that allow ranking of the significance of a particular clinical result. Thus, the system provides a clear guideline for the most rigorous statistical approaches and limits to those approaches that may provide support for qualification, but do not stand on their own.

Aspects of biomarker quantification methods (assay, analysis algorithm, normalization, etc.) must be established and explored with statistical analyses. Quantification approaches that relate statistical analyses to relevant clinical outcomes include covariate adjusted values, change in biomarker value from baseline, or various combinations of multiple measurements of the same or different biomarkers (e.g., construction of a multi-biomarker classifier or risk score). For many biomarkers and disease processes that are continuous in nature, it is preferable to express measures quantitatively when establishing the relationship of the biomarker to outcome. For clinical decision making purposes, quantitative biomarkers will often need to be dichotomized and an appropriate verification of proposed cutpoints will be required.

The most clinically relevant outcome measure must also be selected. Sometimes a currently accepted clinical outcome measure will not be available, in which case a standard with known limitations, or possibly multiple competing standards, may be used to define the outcome. In any case, it is preferred that the biomarker relationship to the clinical correlate be repeated in an independent dataset from the initial training set.

Once a relationship between a biomarker and a clinical outcome of interest has been established, several cutpoints on a continuous biomarker may be considered for decision making to select those most relevant for defined settings. Subjects indicated by the biomarker as being "at risk" with each different cutpoint are compared to the primary clinical outcome. The primary outcome may be one of the following types: 1) a binary event outcome (e.g., organ failure), 2) time to event outcome (e.g., time to diagnosis with a disease) or 3) a quantitative or continuous clinical outcome (e.g., change in a numerical biomarker of disease progression). The list below shows statistical analyses that may be helpful for these three different types of clinical outcomes:

1. Binary Event Outcome
   - ROC curves
   - Proportion with event at different thresholds
   - Sensitivity/Specificity, Positive Predictive Value/Negative Predictive Value

2. Time to Event Outcome
   - Cox Regression – Outcome is time to current standard event
   - Kaplan-Meier curves
3. Quantitative / Continuous Outcome
   - Mean (SD) decline in biomarker positive group compared to total group (with CIs)
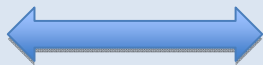   - Proportion above a critical threshold

The level of evidence needed to qualify a biomarker depends on the benefit and risk of using the biomarker in its intended COU relative to the need statement. The totality of this relationship may be reflected in the choice of a cutpoint (i.e., selecting one that maximizes sensitivity versus one that maximizes sensitivity and specificity).

Evidentiary Criteria Level Assessment Map

Our current inability to specifically quantitate benefit, risk or value of individual data sources prevents a direct, strictly-quantitative link from benefit and risk to the amount of evidence needed to qualify a biomarker. However, it is generally agreed that we can categorize benefits, risks and evidence into broad semi-quantitative groups. Until regulatory science is sufficiently advanced to provide this direct link, we have proposed the use of categorical descriptions for what constitutes a high and minimal evidentiary criteria. In order to provide initial context, we have suggested example categorical descriptions of expectations for several areas that have been discussed in this document (Table 1).

It is important to note that the evidentiary criteria for qualification are dependent on the COU. For a broad COU, the criteria for each area may be in the high criteria range. Alternatively, a biomarker that is used in more limited way (e.g., a biomarker that is used for stratification of patients to ensure equal distribution of biomarker positive and biomarker negative individuals in the different arms of a clinical trial) could be fulfilled with a minimal level of evidence. Clearly, the criteria will be modified as more data becomes available, the field advances as a whole and/or as the COU is refined during the biomarker qualification process.

Table 1. Guide for assessing categorical evidentiary criteria

Criterion	High		Minimal
(1) Assay[1]	Regulatory Clearance or Approval for Marketing as a Diagnostic		"Fit-for-purpose" Validation with acceptable performance characteristics
(2a) Scientific Understanding[2]	Causal biological links Established between the disease, the intervention and the biomarker		Gaps in causal links and/or analyte identity

(3) Biological Performance Expectations[3]	Low potential for false result	⟷	Improved performance over current state: [e.g. current standard if available]
(4a) Type of clinical data or sample source: Prospective study	Focused, randomized appropriately powered trial and confirmatory study	⟷	Narrow subgroup of intended population, small or exploratory trial with multiple measures and lack of correction for multiple comparisons
(4b) Type of clinical data or sample source: Retrospective study	Large population, well controlled combined/meta analysis or multiple studies independently confirming results	⟷	Existing retrospective analysis with confirmatory existing studies
(5a)[4] Statistical evidence of the relationship of the biomarker to clinical outcomes	Conclusive across multiple studies	⟷	Evidence in the literature
(5b) Statistical evidence on the usefulness of the biomarker threshold for decision making	Significantly better than current standard (could be in combination with the current standard)	⟷	Similar or slightly better than current standard

Note 1: Assay validation study plan described briefly. Critical attributes of the assay validation data sets address the proposed acceptance criteria for: a) analyte stability, b) assay linearity, c) precision, d) accuracy, e) sensitivity, d) specificity, e) spike-recovery, f) interference, etc

Note 2: The scientific and biological underpinnings of the biomarkers can be summarized

Note 3: In relevant animal and human studies conducted with test agents the performance attributes and weaknesses discovered can be summarized

Note 4: May include adjustments for covariates or patient factors and may differ by subgroups.

In order to consistently present the extent of evidence for any biomarker submission, a standard visual representation is provided illustrating the level of evidence required for regulatory qualification. This grid shown in Table 2 helps provide a focused view of the most important criteria needed for decision making and regulatory discussion/advice. A submitter's assertions for each criterion as to how the current state of evidence supporting a biomarker qualification compares to a reasonable requirement expected of a submitter, can be communicated using this map.

Initially, the level of evidence described in the column titled "Requirement based on the COU" would be suggested by the submitter for review. The level of evidence then could be modified during the initial advice and consultation stage with the FDA. After this discussion with the FDA, it is expected that the level of evidence agreed upon between the submitter and the FDA would remain the same until a qualification decision is made or the COU is changed This evidence map is intended to be used for gaining alignment between submitters and FDA reviewers at several key milestones as new evidence emerges: 1) for initial discussions to align expectations; 2) at purposeful interim progress updates to ensure that evidence expectations have been met before proceeding further; and 3) upon completion to support the qualification outcome. It also can be used internally by the submitter to track the current level of evidence of the biomarker relative to the intended level of evidence to meet the qualification claim.

Table 2. Evidentiary Criteria Grid

[This grid is envisioned as a tool to be filled out by the sponsor and used in discussions between the sponsor and the agency. The text under "Based on COU" will change depending on the biomarker program. The criterion detail rows will be added or modified based on the sponsor and agency expectations for the program.]

Criterion	Above	Based on the COU	Below
(1) Assay[1]		"Fit-for-purpose" Validation with acceptable performance characteristics	
Analytical validation			
(2) Scientific Understanding[2]		Gaps in causal links and/or analyte identity	
Biological rationale or plausibility (strength of understanding of the causal link between a disease, biomarker, and an outcome)			
Understanding of molecular mechanisms regulating the level of the biomarker (both pathologic physiologic and pharmacologic)			
Understanding the link of BM to the current standard			
(3) Biological Performance Expectations[3]		Improved performance over current state: [e.g., current standard if available]	

Sensitivity to detect change compared to the current standard (if available)			
Consistency of response across species and mechanistically distinct interventions			
Presence of dose response			
Specificity of BM response			
(4) Types of data and samples proposed to establish qualification		Appropriate study and analysis with confirmatory study results.	
Prospective Study			
Retrospective Study			
Additional considerations to Types of data and samples proposed to establish qualification	What clinical research study strategy is proposed: randomized, non-randomized? controlled or uncontrolled clinical study? How many test agents? How many subjects? Multi-site/ single site? Blinded/ Unblinded? Primary and Secondary Objectives?		
(5) Statistical considerations[4]		Similar to or better than current standard if available	
Relationship of the biomarker to clinical outcomes			
Usefulness of the biomarker threshold for decision making			
Additional aspects of statistical considerations	Key attributes of the proposed statistical analysis plan: 1) pre-specify biomarker thresholds to consider, 2) propose analyses to test biomarker thresholds, 3) establish standards for evaluation of analysis results, 4) design and power any new studies needed to fill gaps in evidence.		

Note 1: The assay validation study plan is described briefly. Critical attributes of the assay validation data sets address the proposed acceptance criteria for: a) analyte stability, b) assay linearity, c) precision, d) accuracy, e) sensitivity, d) specificity, e) spike-recovery, f) interference, etc.
Note 2: The scientific and biological underpinnings of the biomarkers can be summarized
Note 3: In relevant animal and human studies conducted with test agents the performance attributes and weaknesses discovered can be summarized
Note 4: May include adjustments for covariates or patient factors.

Summary of Evidentiary Criteria Level Assessment

Summarize the assessed level of validation of the analyte assays for each of the biomarkers proposed.

Summarize the assessed strength of the underlying biological rationale for the proposed use and strength of causal linkage of the biomarker response pathways to outcome.

Summarize data analyses generated for each of the proposed biomarkers using published studies in animals, and humans. Comment on evidence for dose-exposure-response characteristics, and sensitivity and specificity relative to known conventional biomarkers where possible. Describe known performance limitations.

Clinical Safety Module: Specific Framework Applicable to Clinical Safety Biomarkers

Background

The specific framework for safety biomarkers described herein was discussed and revised during a two-day workshop open to the entire biomedical research and development community and co-sponsored by the FDA and the FNIH Biomarkers Consortium in April, 2016. The process follows the general outline above but contains specific questions and considerations in the COU, benefit, risk, and evidence sections that are specifically relevant for qualifying and supporting the regulatory acceptance of clinical safety markers.

The Need Statement

For a biomarker developer and FDA to commit resources for a given project, the need must reflect a meaningful area of study that has a direct relevance to drug development and the potential to impact a broader number of programs.

Context of Use

Considerations for defining the Context of Use before drafting a COU Statement

When a biomarker developer begins the process of defining a COU for a single or panel of safety biomarkers for use in a clinical trial or drug development context, there are a number of questions to ask that will help refine more precisely how, when, and why the biomarkers are intended to be used, once they are considered qualified by regulatory authorities:

A. ***What is the claim of additional beneficial utility of the safety biomarker in drug development over the current state? Will the biomarker be used in addition to other accepted conventional safety biomarkers, or will it be used alone and relied upon to fill a gap and inform about something previously undetectable by serological or other conventional specimen testing (short of biopsy)?:***
   o Does it add value to currently used safety biomarkers by improving overall sensitivity and detecting safety concerns earlier, at lower doses, or in a higher percentage of subjects? (if yes, may be considered lower risk, and require lower evidentiary standards)
   o Does it enhance specificity assessment when used with current conventional biomarkers? (if yes, may be considered lower risk, and require lower evidentiary standards)
   o If it is expected to outperform currently used conventional safety biomarkers with known limitations, could those limitations in a clinical trial impact patient well-being? (if yes, may be considered lower risk, and require lower evidentiary standards)

- o Will it be used to replace and substitute for an existing safety test when data supports an improved benefit over current practices? (if yes, may be considered higher risk, and require higher evidentiary standards)
- o Will it be used as a standalone biomarker and be relied upon to inform something formerly unknown or undetectable about a patient?(if yes, may be considered higher risk, and require even higher evidentiary standards)
- o Will it provide "mode-of-toxicity" information not possible from other conventional biomarkers? (if yes, may be considered lower risk, and require lower evidentiary standards)
- o Will it be used to predict which patients may be more susceptible or more resistant to continued dosing? (if yes, may be considered higher risk, and require higher evidentiary standards)

B. **What will be the purpose of the biomarker, and what interpretations, decisions, and actions are intended to be made based on the safety biomarker data?**
- o Will the biomarker make clinical trial conduct more efficient by ensuring monitorability of a certain target organ's safety and enable the conduct of a clinical trial protocol?
- o Will the biomarker be used to monitor clinical trial subjects in real time so that dosing of a particular subject could be interrupted or modified sooner?
- o Will the biomarker be used to monitor clinical trial subjects in real time to enable a dose cohort to be interrupted sooner?
- o Will the absence of a significant change in the biomarker support continued dosing or dose escalation?
- o Is the biomarker proposed to be measured in samples after completion of a clinical study of limited duration to facilitate and support safe dose selection decisions for subsequent trials?
- o Will the biomarker be used to help adjudicate whether an ambiguous conventional safety signal is associated with drug candidate administration?
- o Will the biomarker be used to provide mechanistic information and help determine if prior safety concerns in a drug class exist with a drug candidate?

C. **What are the characteristics of the subjects intended to be studied? The more variables in the population in which the biomarker is to be relied upon, the broader the evidence that would be required to support its use. On the other hand, the benefit potential would be lower for normal healthy subjects as compared to patients with life threatening disease, who would be administered a test agent with remaining safety concerns.**
- o Will the biomarker be limited to use in a normal healthy volunteer population? (if yes, lower evidentiary standards/ but also lower benefit potential)
- o Will the biomarker be used in patients with disease; and if so, what is the specific cohort or subset of patients? (if yes, medium evidentiary standards/ medium benefit potential)

o If targeted for use in patients, can exclusion criteria be defined logically in order to limit risk using considerations based on the target organ of interest and biological knowledge of the biomarker? (if yes, medium evidentiary standards/ medium benefit potential)
o Will the biomarker be used in a broader patient population with numerous potentially serious underlying disease(s)? (if yes, high evidentiary standards/ high benefit potential)

D. **_Will supportive animal/ nonclinical studies and biomarker data be generated with the test agent under development in advance of clinical studies proposed using the safety biomarker? The more directly applicable supportive nonclinical data to be supplied during drug development, that demonstrates utility and guides the details of clinical use, the lower the requirements may be for clinical qualification data._**
o Will the nonclinical studies demonstrate monitorability, define the expected onset of the biomarker alterations after initiation of dosing with the test article, and provide confidence in optimizing the design of the clinical study sample collection?
o Will the nonclinical studies define the characteristics of the target organ safety concern, especially regarding reversibility and therapeutic or safety margins of the drug candidate?

E. **_What is the identity and source of the biomarker(s) and what is the analytical platform?_**
o Are the biomarkers proteins, biochemicals, nucleic acids, a non-invasive image?
o Is the biomarker expected to inform the safety of an entire organ or select anatomical regions?
o Is the biomarker a single analyte or is it a panel of analytes? Will each of the analytes being considered for qualification become an integral member of a composite panel?
o Is the assay platform widely commercially available with reference standards similarly available for each analyte?
o Is extensive sample processing required before the biomarker can be analyzed?

F. **_Is there a currently established accepted biomarker in the clinic that could be deployed in a clinical qualification strategy? Or is there a biomarker with known limitations available in the clinic?_**
o Is there a currently accepted marker based on histopathology that has been applied in animal toxicology studies, but that cannot be practically applied in a clinical qualification study strategy?
o Are standard of care therapeutic agents available in clinical practice that are known to reproducibly result in clinical toxicities to the target organ of interest?
o Are the proposed safety biomarkers known to be similarly associated with flare-ups and therapeutic mitigations of certain natural diseases seen in humans that share histopathologic manifestations seen following drug toxicities in animals?

Drafting the COU Statement

The COU statement is concise description of how, when, and why a biomarker is to be used in a drug development program or clinical trial upon a favorable qualification consideration by regulatory authorities. It is comprised of a few main elements:

- the identity and source of the safety biomarker
- the advantage(s) of use with (or in place of) conventional safety biomarkers
- the breadth of subjects and/or patients intended for its use
- the intention of leveraging nonclinical data to support clinical trial use
- the clinical trial decisions expected to be impacted

Hypothetical example 1: *A new plasma protein safety biomarker X may be used together with amylase and lipase in healthy volunteers and in patients with no risk factors for accelerated pancreatic diseases as a more sensitive and earlier biomarker to monitor for drug-induced pancreatic acinar cell injury in early clinical trials. X will be used in clinical trials of limited duration when such injury has been demonstrated to be monitorable and reversible in animal studies of similar duration conducted with the same test agent. Applying this biomarker in initial single and multiple dose clinical studies would enable or restrict planned dose escalation studies, or drive decisions to interrupt or continue dosing.*

Hypothetical example 2: *A new plasma microRNA biomarker Y may be used together with ALT in any clinical phase trial subject presenting with a significant elevation in this conventional biomarker to inform the mechanism of such transaminase elevation. Applying biomarker Y only to such selected samples would inform the mechanism of injury and assist with adjudication decisions regarding whether or not observed transaminase elevations are specifically drug-induced or may be associated instead with natural fluctuation in underlying liver disease(s).*

Hypothetical example 3: *Endogenous plasma biochemicals A, B, C, and Z may be used together as a 4-plex panel to generate a single algorithm-based score in normal healthy volunteer subjects to inform potential for a dose-related increase in pulmonary phospholipidosis. A, B, C, Z will be used in clinical trials when pulmonary phospholipidosis has been demonstrated to be monitorable and reversible in animal studies of similar duration conducted with the same test agent. Applying this biomarker in multiple dose clinical studies could assist understanding of human relevance, and enable or restrict dose escalation decisions.*

Benefit and Risk Assessment

By following the steps and answering the questions above, the reviewer defines the context for the following **Benefit and Risk Assessment**:

1) What is the perceived consequence of harm if the safety biomarker in question were to fail; what happens if we are wrong - mild injury, severe injury, death; the inappropriate disruption of clinical trial progression?

    a. What is the risk of a false negative result?
    b. What is the risk of a false positive result?
    c. What are the risk mitigation strategies?

2) What is the perceived consequence of harm if the safety biomarker is not qualified, and clinical program development timelines are not accelerated as a result, the negative impact on drug development could be high since, if the severity of untreated disease progression in an intended patient population is high, then the added risk of a false negative safety biomarker is minimal, while the benefit could be high. Conversely when the new safety biomarker is intended for use in normal healthy volunteers who receive no benefit from a drug candidate, then any risk of a false negative safety biomarker result could represent a decrease in quality of life. Is the intended patient population for the proposed new safety biomarker limited for use only in patients with severe debilitating diseases or is the safety biomarker intended for broader use in clinical trials including normal healthy subjects?

2) What is the relative perceived benefit of the new biomarker vs. the status quo? (e.g., the biomarker allows for safer, less invasive in vivo safety testing in *x* patients, or dramatically increases the sensitivity with which adverse events may be detected, resulting in saving compounds for continued development in an area of high unmet medical need).

3) What is the relative overall perceived incremental benefit vs. risk of the new safety biomarker vs. the status quo?

Evidence Map

The variables described in the general approach above are herein specifically adapted to the context of safety biomarkers:

1) Assay validation:

- Analytical validation parameters of the assay platform (and of appropriate sample processing and storage procedures) used for measuring the biomarker – reliability, reproducibility, analytical sensitivity, spike recovery, analytical interference, analytical specificity, sources of variability, cross-site standardization.

2) Scientific understanding:

- Biological rationale or plausibility, and specificity – degree to which the following are understood: a) the initiating drug-induced adverse events in an organ or tissue that, b) trigger subsequent steps in a biological damage response pathway and, c) link to the role of the safety biomarker in that adverse outcome pathway.

- Understanding of the molecular mechanism(s) underlying regulation of the level of the biomarker, both those molecular regulatory mechanisms associated with organ injury driving relevant biomarker changes, as well as those molecular mechanisms which may similarly regulate the biomarker but may represent nonspecific mechanisms not associated with drug-induced tissue injury.
- Understanding the link of the safety biomarker to the observed currently accepted histopathology. (e.g., leakage from necrotic tissue, involvement during stages of tissue regeneration, proliferation, vacuolation, etc.).

3) Performance:

- Sensitivity of the biomarker to respond to true toxicants in accordance with the currently accepted histopathologic outcome.
- Consistency of correlation of the biomarker change to the specific organ toxicity seen across mechanistically different toxicants, and across different species.
- Presence of a dose response and temporal relationship to the magnitude of the biomarker response and injury severity.
- Specificity of the biomarker response only to the claimed organ toxicity, and NOT to toxicities in other tissues, nor to pharmacologic changes without toxicity in the target organ.

4) Types and amount of data/samples required:

- Evidence type: clinical, non-clinical, modeling, or literature review.
- Clinical study type (decreasing power of evidence from top to bottom):
    - Systematic Review
    - Prospective Randomized Controlled Trial
    - Retrospective Randomized Controlled Trial
    - Cohort Study
    - Case/Control Study
- Study Characteristics
    - Randomized/not randomized
    - Controlled/not controlled
    - Blinded/unblended
    - Objectives (primary/secondary/exploratory)
    - Observational?
    - Longitudinal?
    - Multi-site/single site
    - Compliance to data collection?
- Size of cohort(s) *[Note: this is directly related to statistical power]*

5) Statistical Considerations

(NOTE: Production of a Statistical Framework Document is ongoing and this document will be available at a later date. The excerpt from the Statistics Document contained in the general framework for evidentiary criteria above highlights those points that are specific to the statistical issues brought up by the Statistical Considerations Working Group.)

Evidentiary Criteria Level Assessment Map

Criterion	Above	Based on the COU	Below
(1) Assay[1]		"Fit-for-purpose" Validation with acceptable performance characteristics	
Analytical validation			
(2) Scientific Understanding[2]		Gaps in causal links and/or analyte identity	
Biological rationale or plausibility (strength of understanding of the causal link between a disease, biomarker, and an outcome)			
Understanding of molecular mechanisms regulating the level of the biomarker (both pathologic physiologic and pharmacologic)			
Understanding the link of BM to the current standard			
(3) Biological Performance Expectations[3]		Improved performance over current state: [e.g., current standard if available]	
Sensitivity to detect change compared to the current standard (if available)			
Consistency of response across species and mechanistically distinct interventions			
Presence of dose response			
Specificity of BM response			
(4) Types of data and samples proposed to establish qualification		Appropriate study and analysis with confirmatory study results.	
Prospective Study			

Retrospective Study			
Additional considerations to Types of data and samples proposed to establish qualification	What clinical research study strategy is proposed: randomized, non-randomized? controlled or uncontrolled clinical study? How many test agents? How many subjects? Multi-site/ single site? Blinded/ Unblinded? Primary and Secondary Objectives?		
(5) Statistical considerations[4]		Similar to or better than current standard if available	
Relationship of the biomarker to clinical outcomes			
Usefulness of the biomarker threshold for decision making			
Additional aspects of statistical considerations	Key attributes of the proposed statistical analysis plan: 1) pre-specify biomarker thresholds to consider, 2) propose analyses to test biomarker thresholds, 3) establish standards for evaluation of analysis results, 4) design and power any new studies needed to fill gaps in evidence.		

Note 1: The assay validation study plan is described briefly. Critical attributes of the assay validation data sets address the proposed acceptance criteria for: a) analyte stability, b) assay linearity, c) precision, d) accuracy, e) sensitivity, d) specificity, e) spike-recovery, f) interference, etc.
Note 2: The scientific and biological underpinnings of the biomarkers can be summarized
Note 3: In relevant animal and human studies conducted with test agents the performance attributes and weaknesses discovered can be summarized
Note 4: May include adjustments for covariates or patient factors.

Summary of Evidentiary Criteria Level Assessment

Summarize the assessed level of validation achieved regarding the analyte assays for each of the biomarkers proposed.

Summarize the assessed strength of the underlying biological rationale for the proposed use and strength of linkage of the injury response pathways to histopathologic outcome and interruption of organ function.

Summarize data analyses generated for each of the proposed safety biomarkers using published studies of toxicants and non-toxicants in animals, and any limited clinical data using fewer known toxicants or similar disease states demonstrating preservation of biomarker biological responsiveness across species and in humans. Comment on evidence for dose-exposure-response characteristics, and sensitivity and specificity relative to known conventional biomarkers where possible. Describe known performance limitations.

Final Step: Integrated Evaluation of Available Evidentiary Criteria Levels against the Proposed COU and the Benefit/Risk Assessment

The assay validation data for each of the analytes are evaluated to determine whether minimal requirements will be met or exceeded. The level of biological understanding of the biomarkers, and the current understanding of performance of the safety biomarkers across animal species and humans shall be summarized and evaluated to highlight remaining gaps and how these gaps should be filled.

Potential weaknesses include (x, y, and z: e.g., specificity is less completely understood, etc.) and so then what steps are being taken to limit these risks within the specified COU.

The clear benefit to patients of the use of the biomarkers once qualified are succinctly summarized.

Finally, if the outcome of the proposed prospective study meets the primary objective defined in the statistical analysis plan, the proposal to qualify the new translational safety biomarkers for clinical drug development research is reasonable and would be considered to significantly benefit drug development programs while guarding patient safety.

References and other related publications

A Brookings Institute meeting in October 2015 titled "Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration". http://www.brookings.edu/events/2015/10/27-biomarkers-development-and-qualification

A National Biomarker Development Alliance (NBDA) workshop titled "Collaboratively Building a Foundation for FDA Biomarker Qualification" (December 2015). http://www.nbdabiomarkers.org/nbda-events/nbda-workshop-vii-"collaboratively-building-foundation-fda-biomarker-qualification"

Altar CA, Amakye D, Bounos D, Bloom J, Clack G, Dean R, Devanarayan V, Fu D, Furlong S, Hinman L, Girman C, Lathia C, Lesko L, Madani S, Mayne J, Meyer J, Raunig D, Sager P, Williams SA, Wong P, Zerba K. A prototypical process for creating evidentiary standards for biomarkers and diagnostics. Clin Pharmacol Ther. 2008 Feb;83(2):368-71. Epub 2007 Dec 19.

Amur S, LaVange L, Zineh I, Buckman-Garner S, Woodcock J. Biomarker Qualification: Toward a Multiple Stakeholder Framework for Biomarker Development, Regulatory Acceptance, and Utilization. Clin Pharmacol Ther. 2015a Jul;98(1):34-46. doi: 10.1002/cpt.136. Epub 2015 Jun 6.

Amur SG, Sanyal S, Chakravarty AG, Noone MH, Kaiser J, McCune S, Buckman-Garner SY. Building a roadmap to biomarker qualification: challenges and opportunities. Biomark Med. 2015b;9(11):1095-105. doi: 10.2217/bmm.15.90. Epub 2015 Nov 3

Boissel JP, Collet JP, Moleur P, Haugh M. Surrogate endpoints: a basis for a rational approach. Eur J Clin Pharmacol. 1992;43(3):235-44.

Downing (Editor), Biomarkers and Surrogate Endpoints: Clinical Research and Applications: Proceedings of the NIH-FDA Conference, Bethesda, MD, 15-16 April 1999, ICS 1205, 1e (International Congress)

Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease IOM study in 2010 https://iom.nationalacademies.org/Reports/2010/Evaluation-of-Biomarkers-and-Surrogate-Endpoints-in-Chronic-Disease.aspx

FDA Critical Path publication in 2004. (http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM113411.pdf)

FDA's Drug Development Tools Guidance (January, 2014) http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm230597.pdf A symposium co-sponsored by the University of Maryland CERSI/FDA/Critical Path Institute (August 2015)

Hayes, D.F., Bast, R.C., Desch, H.F.Jr., Kemeny, N.E., Jessup, J.M., Locker, G.Y., Macdonald, J.S., Mennel, R.G., Norton, L., Ravdin, P., Taube, S., Winn, R.J. Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J Natl Cancer Inst. 1996 Oct; 55(20): 1456-1466.

Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products U.S. Department of Health and Human Services Food and Drug Administration March 2004

Kakkis ED, O'Donovan M, Cox G, Hayes M, Goodsaid F, Tandon PK, Furlong P, Boynton S, Bozic M, Orfali M, Thornton M. Recommendations for the development of rare disease drugs using the accelerated approval pathway and for qualifying biomarkers as primary endpoints. Orphanet J Rare Dis. 2015 Feb 10;10:16. doi: 10.1186/s13023-014-0195-4.

Katz R. FDA: evidentiary standards for drug development and approval. NeuroRx. 2004 Jul;1(3):307-16.

Lee JW, Devanarayan V, Barrett YC, Weiner R, Allinson J, Fountain S, Keller S, Weinryb I, Green M, Duan L, Rogers JA, Millham R, O'Brien PJ, Sailstad J, Khan M, Ray C, Wagner JA Fit-for-purpose method development and validation for successful biomarker measurement. Pharm Res. 2006 Feb;23(2):312-28. Epub 2006 Jan 12.

Lesko LJ, Atkinson AJ Jr. Use of biomarkers and surrogate endpoints in drug development and regulatory decision making: criteria, validation, strategies. Annu Rev Pharmacol Toxicol. 2001;41:347-66.

Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med. 1989 Apr;8(4):431-40.

Simon RM, Paik S, Hayes DF. Use of Archived Specimens in Evaluation of Prognostic and Predictive Biomarkers J Natl Cancer Inst 2009;101(21):1446-1452.

The ICH E9 Guidance, (1998) Published in the Federal Register, 16 September 1998, Vol. 63, No. 179, p. 49583

Wagner JA. Early clinical development of pharmaceuticals for type 2 diabetes mellitus: from preclinical models to human investigation. J Clin Endocrinol Metab. 2002 Dec;87(12):5362-6.

Williams SA, Slavin DE, Wagner JA, Webster CJ. A cost-effectiveness approach to the qualification and acceptance of biomarkers. Nat Rev Drug Discov. 2006 Nov;5(11):897-902.

Appendix 1 - Context of Use: Previous Definitions

The current version of the FDA website on **Biomarker Qualification Context of Use** (accessed 11/17/15) states:

"Context of use," or COU, is a comprehensive and clear statement that describes the manner of use, interpretation, and purpose of use of a biomarker in drug development. This document provides guiding principles in formulating a **Context of Use (COU)** statement for biomarkers being proposed for qualification through FDA's Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP)[1].

The following table with examples and notes is provided:

Table 1. Elements of the Context of Use Statement for Biomarker Qualification*

	Elements of *Context of Use*	Examples	Notes
1	Identity of the biomarker	- Specific type of radiologic exam with specific imaging modalities (e.g., MRI, PET, Doppler) - Specific substance/analyte in physiologic fluid - Specific genomic biomarker	The term "biomarker" may refer to a single biomarker with a single, specific context of use, or to a "composite biomarker" that is made up of several individual biomarkers combined in a stated algorithm to reach a single interpretive readout. A context of use applies to the composite biomarker as a unified entity. Individual components of the composite biomarker do not have separate COUs unless they are intended for use as stand-alone biomarkers.
2	Aspect of the biomarker that is measured and the form in which it is used for biological interpretation	- Specific aspect of radiologic findings such as lesion number, volume, diameter, area, perimeter or other characteristics (e.g., tumor volume). - A specific measure of organ size - Serum level of an analyte; possibly also specified in relation to time (e.g., at a specific time, steady-state, AUC, post-treatment minus pre-treatment) - Used in graded measurement form or after threshold categorization (e.g., change relative to a reference such as baseline, historical control, or normal range, or X-fold change)	Certain biomarkers may require explicit temporal statements such as the window of measurement time if applicable. Specify the mode(s) of measurement when applicable (e.g., MRI, PET, and Ultrasound). Specific physiologic fluid/tissue or site of sampling may need to be noted (e.g., plasma, serum, urine, saliva, sweat, CSF).
3	Species and characteristics of animal or subjects studied	- Animal species or range of species - For each species, important characteristics (e.g., strain, age, sex, disease model, healthy) - Human and important characteristics (e.g., age, race/ethnicity, sex, disease, healthy, genotype, disease phenotype)	Provide the relevant details needed to understand the target species, group of species, or patients for which biomarker qualification is sought. Certain qualified biomarkers may apply specifically to a sub-set of individuals or strain of the species studied. If so, this sub-set or strain should be specified in the COU document.

4	Purpose of use in drug development	- Demonstration of absence of toxicity (Nonclinical or Clinical). - Demonstration of organ toxicity without performing extensive histopathology (Nonclinical biomarkers) - Evaluation of exposure-response - Utilization in clinical study subject enrollment or randomization (e.g., diagnostic, enrichment, stratification)	A general description of this element will usually be a part (explicit or implicit) of the Use Statement component of the COU. In addition, a more precise description may need to be part of the Conditions for Qualified Use section. For many biomarkers this will be the biological interpretation of the biomarker measurement, and that interpretation is then applied to make the decision described for element #6.
5	Drug development circumstances for applying the biomarker	- Non-clinical: · determination of "no observable adverse effect level" (NOAEL) for a specific toxicity when prior toxicology studies did not identify NOAEL with adequate precision; · selection of the best drug candidate among several drug candidates based upon a specific toxicity; · demonstration of activity of the drug on the disease pathophysiology (via an animal disease model) - Clinical : · selection of doses to take into phase 3 study (i.e., apply biomarker in dose finding studies intended to predict efficacy); · ensuring patient safety in dose escalation safety studies; · demonstration of activity of the drug on the disease pathophysiology (i.e., clinical proof-of-concept studies)	Describe the situation in drug development where application of the biomarker improves the drug development process. This might be a description of a type of problem that arises in drug development and for which the biomarker enables making a decision.

| 6 | Interpretation, and decision/action based on biomarker | - Biomarker levels above N indicate cellular injury in [organ X]. The NOAEL level is below the exposure in which the signal was observed, and should be used in determining starting doses in clinical studies

- Biomarker levels above N indicate a physiologic response has occurred, and the drug compound can be advanced for development

- The absence of biomarker levels above N indicated no significant organ injury has occurred and the drug candidate(s) with this profile can be advanced for further development

- The absence of biomarker levels above N indicate no significant organ injury has occurred and dosing may continue in such patients

- Patients with biomarker levels greater than N are expected to have an endpoint event rate of approximately Y or greater and should be enrolled in the clinical study

- Patients with the biomarker positive for the presence of Z have at least a N-fold greater risk of an adverse response to drugs acting via mechanism of action Y, and should not be enrolled in clinical studies (or, if the biomarker is a response biomarker, such patients should have dosing discontinued). | This element of the COU statement defines the interpretation that is drawn from measurement of the qualified biomarker and the effect of that interpretation on the drug development program.

For composite biomarkers, the algorithm used to combine components leads to a single interpretation; and that single interpretation is applied to decision-making and has an effect on the drug development program.

For some biomarkers, the decision (drug development action) cannot easily be separated from the description of the purpose and circumstances of use or the interpretation of the biomarker, and two or more of these elements would be combined in phrasing the appropriate condition of use (i.e., there may not be separate statements for each of these elements in all cases). |

[Note: text from the FDA website]

* The table is a guide to the elements of COU statement but should not be the format for submission of the COU. A COU can be formatted in paragraph form, or as a Use Statement plus Conditions for Qualified Use as a list.

Note: Not all elements in **Table 1** are relevant for every biomarker. In addition, the COU statement does not need to have all the elements in the same order as the table. The elements listed in **Table 1** should be incorporated on an as-needed basis for the respective COU statement. This list of elements is also not intended to be exhaustive. Some biomarkers have other elements such as drug classes/categories (e.g., drugs that activate a specific receptor or that cause toxicity by a given mechanism), that may need to be stated as part of the COU statement to ensure clarity. Submitters should include these as needed.

Appendix 2 – List of Acronyms

Acronym Name	Acronym Definition
BC	Biomarker Consortium
BEST	Biomarkers, EndpointS, and other Tools resource
BM	Biomarker
BQP	Biomarker Qualification Program
CDER	Center for Drug Evaluation and Research
CERSI	Center for Excellence in Regulatory Science and Innovation
COU	Context of Use
C-Path	Critical Path Institute
CSF	cerebrospinal fluid
DDT	Drug Development Tool
ES	Evidentiary Standards
FDA	Federal Drug Administration
FNIH	Foundation for the National Institutes of Health
GLDH	Glutamate Dehydrogenase
IND	Investigational New Drug
IOM	Institute of Medicine
NIH	National Institutes of Health
PhRMA	Pharmaceutical Research and Manufacturers of America
PSTC	Predictive Safety Testing Consortium

RCT	Randomized Controlled Trial