U.S. FOOD & DRUG ADMINISTRATION

FDA CASE STUDY

A collaborative effort to qualify a novel biomarker | Nov 2016

BIOMARKER QUALIFICATION—DEVELOPING AND OBTAINING REGULATORY ACCEPTANCE OF A NEW BIOMARKER

This fictionalized case study is part of an educational series published by the Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration.

Learning Objectives:

- To understand the role of biomarker qualification in drug development
- To understand the validation studies necessary to support the qualification of a biomarker for use in drug development
- To understand the collaborative efforts involved in qualification of a biomarker for a specific context of use

Topics:

- Biomarkers, biomarker qualification, drug development tools, drug approval process, regulatory pathways for integration of biomarkers into drug development

Discovery of a New Biomarker

Dr. Stephen Smith, a medical researcher interested in kidney disease, is busy working on a publication describing a new renal biomarker that his laboratory discovered in a rat model of drug-induced acute kidney injury.

The biomarker, which he has termed Renal Injury Biomarker or RIB, is a protein that can be measured in blood in rats using a mass spectrometry assay. Dr. Smith has also shown that RIB can be measured in human blood.

Dr. Smith found that in rats, RIB is measurable at low levels in blood prior to drug-induced acute kidney injury, increases markedly in blood within 2–3 hours after injury to the kidney, and then returns to baseline levels when the injury resolves, suggesting that RIB may be a useful biomarker for monitoring kidney injury during drug development. Dr. Smith has asked his colleague, Dr. John Maxon, a clinical

What is a Biomarker?

A biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathologic processes, or responses to an exposure or intervention, including therapeutic interventions.

A biomarker can be a physiologic, molecular, histologic or radiographic characteristic or measurement that is thought to relate to some aspect of normal or abnormal biological function or process. Biomarkers can be considered individually or collectively as a composite biomarker.

Biomarkers can help reduce uncertainty in drug development by providing supportive quantifiable predictions. Biomarkers measured in patients before treatment can be used to select patients for inclusion in a clinical trial and can also be used for dose selection. Changes in biomarkers following treatment may predict or identify safety problems related to a candidate drug, reveal a pharmacological activity, or indicate clinical benefit from treatment.

Definition from the BEST (Biomarkers, EndpointS, and other Tools) Resource, published by the FDA-NIH Biomarker Working Group (Robb et al. 2016).

Categories of Biomarkers

Diagnostic biomarkers are used to identify individuals with the disease or condition of interest or to define a subset of the disease.

Monitoring biomarkers are 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.

Pharmacodynamic/response biomarkers are used to show that a biological response has occurred in an individual who has received an intervention or exposure.

Predictive biomarkers are used to identify individuals who are likely to experience a favorable or unfavorable effect from a specific intervention or exposure.

Prognostic biomarkers are used to identify likelihood of a clinical event, disease recurrence or progression.

Safety biomarkers are used to indicate the presence or extent of toxicity related to an intervention or exposure.

Susceptibility/risk biomarkers indicate the potential for developing a disease or sensitivity to an exposure in an individual without clinically apparent disease. (From: BEST Resource)

nephrologist at the university and a consultant to a pharmaceutical company, to read his manuscript on RIB.

Dr. Maxon walks in to Dr. Smith's office and says, "I read your paper, and your data suggest that RIB may be useful as a nonclinical biomarker of drug-induced acute kidney injury in rats. I wonder if it may also be a useful biomarker in humans."

Dr. Smith understands that there is a need for new kidney injury biomarkers—especially biomarkers that would be capable of predicting drug-induced acute kidney injury. He is excited about the possibility of his discovery contributing to the detection of drug-induced acute kidney injury for monitoring safety in clinical trials.

Drug development would be enhanced by a greater understanding of early markers of renal injury. Although serum creatinine, blood urea nitrogen, and albumineria have traditionally been used to monitor for drug-induced renal toxicity, these biomarkers may be poor predictors of drug-induced renal damage, because they lack sensitivity and specificity for renal injury and provide little information on the region of the kidney affected by the drug and/or the mechanism(s) by which this injury occurs. As a result, much research has focused on the development of novel biomarkers to detect early signs of renal toxicity (Gobe et al. 2015).

Dr. Smith asks Dr. Maxon for his advice on how to determine whether RIB might be useful in drug development. Dr. Maxon says, "Well, there are several things to consider. Right now we have some initial data in rats, which is a good starting point. We must confirm the reproducibility of the rat data, ensure that the mass spectrometry assay is analytically validated, and then collect the appropriate clinical data to support any use of RIB in drug development."

Specifically, they discuss the need to confirm that a measurable change in RIB correlates with drug-induced acute kidney injury in rats, confirm that RIB data are reproducible in rats, determine whether RIB can be measured across multiple species (including humans), and determine whether RIB can be detected and measured in humans by robust analytical methods to indicate drug-induced acute kidney injury.

Dr. Smith comments, "This will take us some time. However, I do understand how important this work will be to the future of this project, so we will get started right away."

Dr. Smith finds that substantial effort is required to confirm the RIB data and validate the assay. He suggests, "We should think about establishing collaborations with other researchers to assist with this process."

Dr. Maxon agrees, saying, "We should form an RIB Working Group (WG) that will bring

Analytical Validation: Establishing that the performance characteristics of a test, tool, or instrument are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol (which may include specimen collection, handling, and storage procedures). This is validation of the test's, tool's, or instrument's technical performance, but is not validation of the item's usefulness. (From: BEST Resource)

together others with the interest and the necessary expertise to confirm your findings."

A Collaborative Effort to Advance the Biomarker

Drs. Maxon and Smith approach colleagues with similar interests to talk about joining the RIB WG to collaborate on next steps.

They identify one partner who will test the reproducibility of the RIB assay and confirm that the assay can be used to measure RIB in human blood samples. A second partner joins the RIB WG to reproduce the data that Dr. Smith's lab originally generated in rats. Dr. Smith's lab will be responsible for testing the translatability of the RIB assay across multiple species. To ensure that standardized data will be produced, all partners agree to perform their studies following the Center for Drug Evaluation and Research (CDER) Study Data Standards.

After all of the data are collected and analyzed, the RIB WG meets to discuss the results and the next steps. Dr. Smith summarizes, "These initial results suggest that the RIB assay is sensitive, specific, and reproducible in humans as well as in rats."

The team discusses publishing these results but also wants to understand whether there are any additional ways to make these data broadly available and bring RIB to the attention of researchers and clinicians who might be able to use it in clinical trials to monitor drug-induced acute kidney injury.

Dr. Maxon suggests, "Maybe we can do a pilot study and investigate whether RIB levels are increased in patients with drug-induced acute kidney injury. However, we will have to find another partner with access to the samples we need."

Dr. Smith suggests contacting a colleague, Dr. Andrea Hope, a nephrologist at the Kidney Health Center (KHC), who has samples from patients with drug-induced acute kidney injury and samples from healthy volunteers who were both enrolled in a study approved by an Institutional Review Board. These samples can be used to investigate RIB.

The goal of the pilot study using Dr. Hope's samples will be to collect preliminary data on the level of RIB in healthy volunteers and confirm that RIB levels increase in patients with drug-induced acute kidney injury. The study will also measure the traditional kidney safety biomarkers in these samples to begin to understand how RIB might provide additional useful information.

The samples are sent to Dr. Smith's lab for analysis, and he determines that, in this limited dataset, there is a measurable increase in RIB in patients with drug-induced acute kidney injury compared to healthy volunteers. The increase in RIB in these patients can be detected in earlier stages of kidney injury when compared to traditional kidney safety biomarkers.

Dr. Maxon then says, "Based on our preliminary data and the discussion today, it sounds like RIB might be useful as a safety biomarker to monitor patients in clinical trials for drug-induced acute kidney injury." The team agrees.

However, the RIB WG soon realizes that alone they cannot do the types of translational studies that will likely be needed to establish the clinical utility of RIB, including multi-center, duplicative trials. They decide to seek additional information to understand what data might be needed to gain acceptance of RIB as a safety biomarker for use in clinical trials to monitor drug-induced acute kidney injury.

On the FDA website, they discover the Critical Path Innovation Meeting (CPIM), which is a mechanism to have a scientific discussion with FDA regarding innovative strategies to address challenges in drug development that are not associated with a particular product approval pathway. The RIB WG would like to obtain general advice about their strategy for developing RIB for use in drug development, so they contact CDER to request a CPIM.

Critical Path Innovation Meeting

Introduction to Critical Path Innovation Meetings

Dr. Smith gives a presentation to the RIB WG that introduces the CPIM and explains that the purpose of requesting a CPIM with FDA is to discuss and seek advice on potential advances that could improve the efficiency and success of drug development (Appendix C).

After the presentation, the RIB WG agrees that the CPIM is the logical next step in order to understand how to proceed with the RIB project. Their purpose for the meeting fits with one of the specific FDA goals for CPIMs of discussing "biomarkers in the early phase of development for use in drug development and not yet ready for the Biomarker Qualification Program (BQP)."

At this point, the team is not clear what "biomarker qualification" means. Dr. Smith suggests, "Gaining an understanding of the biomarker qualification process and determining whether it is something that we want to pursue will be one goal of the CPIM."

Critical Path Innovation Meeting and Outcome

During the CPIM, FDA advises the need for confirmation of:

- Clinical validation of RIB
- Analytical validation of the measurement method
- RIB sensitivity and specificity
- RIB utility to make safety decisions in drug development

The RIB WG then asks about the regulatory pathways to obtain biomarker acceptance in drug development.

CDER's Regulatory Pathways for Biomarker Acceptance in Drug Development

Historically, biomarkers have gained acceptance in drug development over time as they were used by the scientific and medical community. To improve the efficiency of the acceptance process for biomarkers used in drug development, FDA CDER currently has two review pathways (Amur et al. 2015a and Duke-Margolis Center for Health Policy 2016).

Clinical Validation: Establishing that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest (e.g., the aspect of an individual's clinical, biological, physical, or functional state or experience). (From: BEST Resource)

FDA states, "One pathway is through submission of biomarker data to FDA in a candidate Investigational New Drug (IND) Application or New Drug/Biologics License Application (NDA/BLA), during the course of the development of a particular drug for marketing. Broad acceptance of the biomarker in drug development can be challenging with this approach because the supporting biomarker data are retained with the specific candidate drug/biologic submission the biomarker was reviewed in and are not necessarily available for others to use. Therefore, in the context of IND/NDA/BLA submissions, drug developers who would like to use an unqualified biomarker may need to submit data to support its use and additional review by the FDA may be required.

"Another pathway is through the BQP. FDA's CDER established the BQP as part of the FDA's Critical Path Initiative in order to make drug development tools publicly available to expedite drug development and regulatory review (Woodcock et al. 2011). Qualification through the BQP is intended for biomarkers that will be used in multiple drug development programs. Once qualified, a biomarker can be used under its qualified context of use (COU) during the development of any candidate drug without re-review."

Introduction to the Biomarker Qualification Program

FDA states, "The BQP was established to support CDER's work to develop biomarkers in collaboration with external scientists and clinicians like Dr. Smith and Dr. Maxon and the RIB WG" (Appendix D).

After the CPIM, the RIB WG decides to pursue biomarker qualification in order to make information supporting the use of RIB publicly available to bring efficiency into the drug development and regulatory review process. Once qualified, RIB can be used under its qualified COU during the development of any candidate drug without re-review.

Context of Use

Qualification of a biomarker means that within a COU, the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in drug development (Amur et al. 2015b). FDA defines a COU as "a comprehensive and clear statement that describes the manner of use, interpretation, and purpose of use of a biomarker in drug development." There are seven biomarker categories which can be used in drug development for multiple COUs (Exhibit 1).

A COU is composed of a concise biomarker Use Statement and a comprehensive description of conditions for the biomarker to be used in the qualified setting, termed the Conditions for Qualified Use. An example COU for a hypothetical biomarker is available online.

Qualification starts by defining the intended COU of the biomarker in drug development and then determining the data sources and level of evidence required for that COU. The precise COU is often refined as new data are accumulated and analyzed during biomarker development toward biomarker qualification (Exhibit 2).

Exhibit 1. Biomarker categories and potential contexts of use in drug development

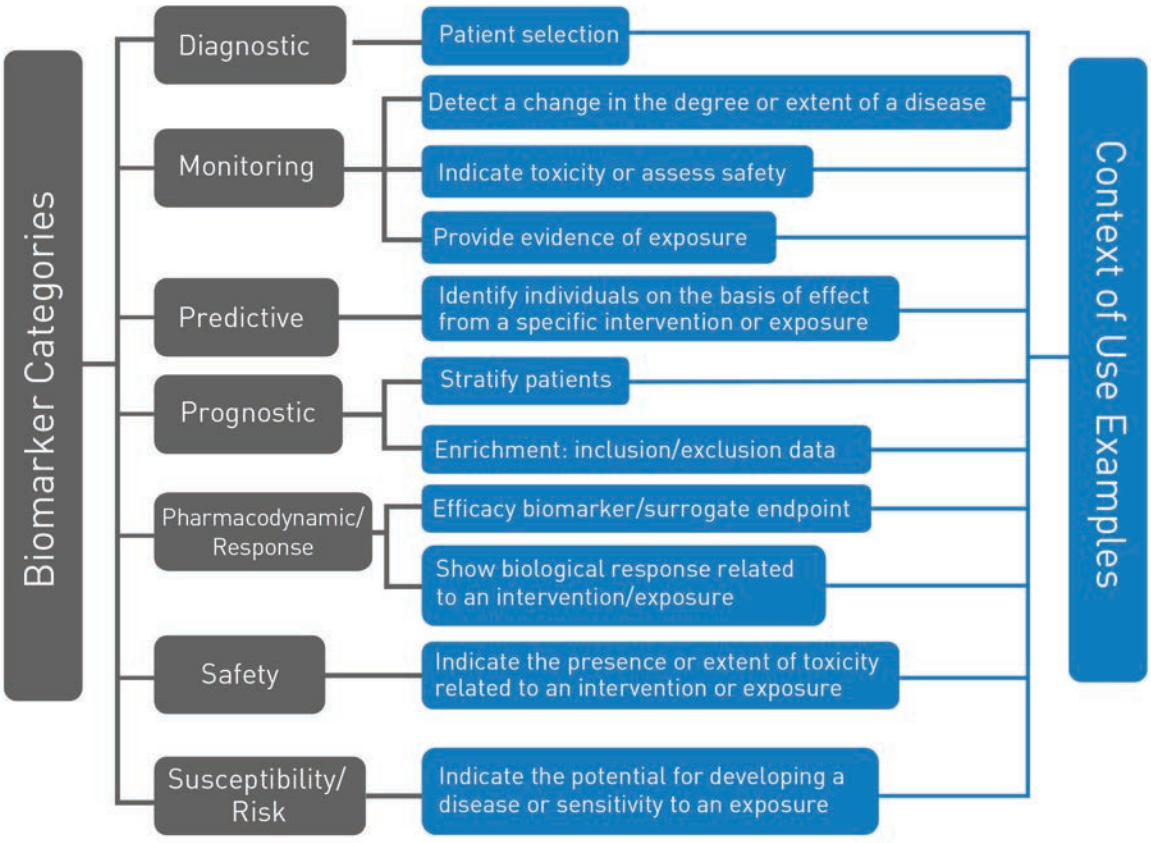


Exhibit 2. The proposed context of use determines the level of evidence needed to support qualification

Level of Evidence for Biomarker Qualification

FDA states, "Clearly, different evidence is needed for the different types of biomarkers and their varying COUs, based on the impact of the decision made using the biomarker results (Exhibit 3).

"Data used for qualification can be retrospective or prospective, registry data, and/or randomized controlled trial (RCT) data and should include an exploratory dataset and a confirmatory dataset.

"Assay considerations include analytical validation and understanding of potential sources of variability in the measurement."

RIB WG Discussion

Dr. Smith, speaking for the RIB WG, says, "We would like to pursue biomarker qualification for the use of RIB as a safety biomarker to monitor drug-induced acute kidney injury in clinical trials. But we are also keenly aware that we do not have sufficient resources to replicate our studies and to collect the data that FDA would need to see to qualify RIB."

FDA then suggests, "Recently, FasterCures launched a tool called 'Consortia-pedia,' an online directory that can be searched to find out whether other groups in the world are doing the same type of work as you are doing under the framework of a consortium. A consortium is an association of researchers that share resources and effort for a common objective, utilizing a partnership model that integrates multiple types of knowledge, data from multiple sources, and aligns different interests."

FDA continues, "You might see if there are other groups with similar efforts underway that the RIB WG might join forces with to achieve your stated goals."

The RIB WG thanks FDA for their time and leaves the CPIM with a plan to consult Consortia-pedia for potential partners.

Consortia-pedia

Introduction to Consortia-pedia

After the CPIM with FDA, Dr. Hope is tasked with looking into Consortia-pedia. She opens the Consortia-pedia Catalogue online and searches the keywords "biomarker" and "kidney injury."

Several potential partners are identified, and the team is able to learn more about their mission, accomplishments, funding, financing, sponsors, and partners through Consortia-pedia.

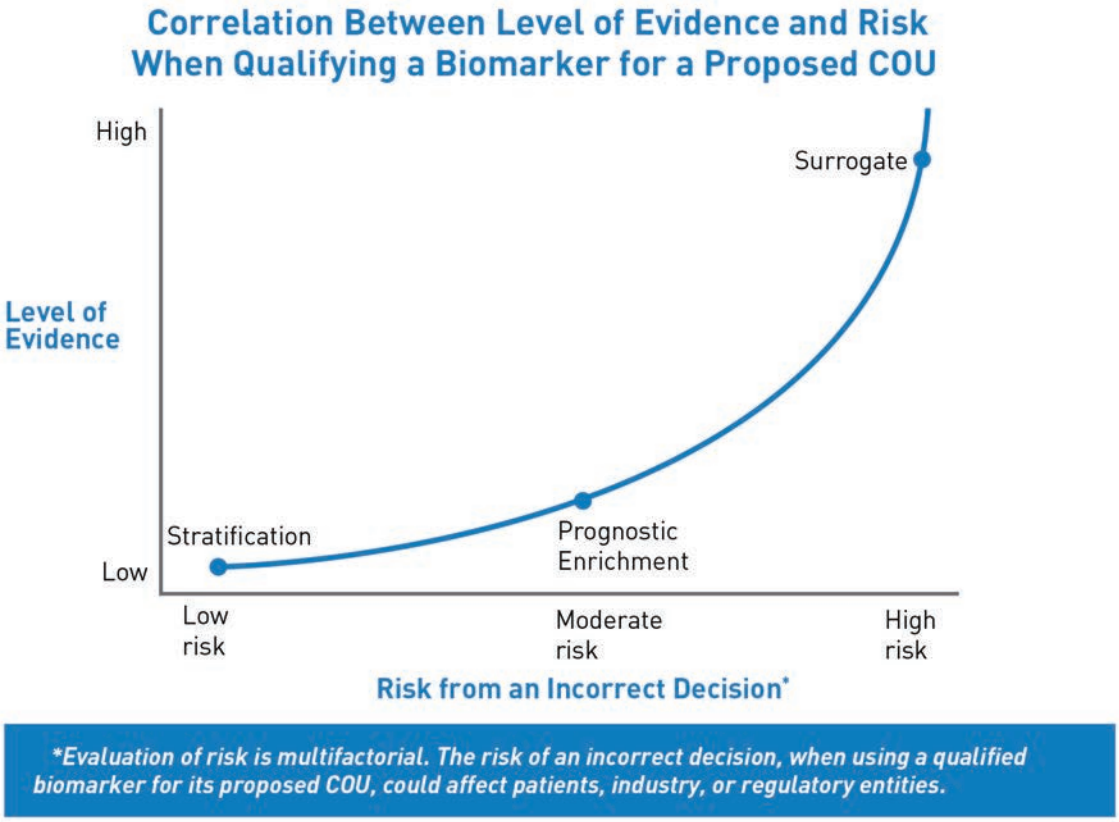
One in particular, the Kidney Injury Consortium (KIC), has a mission to spur development of new drugs to treat kidney injury.

Letter of Support Initiative

Another option to consider in lieu of biomarker qualification or as a step toward biomarker qualification is requesting a Letter of Support (LOS). An LOS briefly describes CDER's thoughts on the potential value of a biomarker and encourages further evaluation by the research community of promising biomarkers that are not ready for qualification.

An LOS does not connote qualification of a biomarker. The LOS is meant to enhance the visibility of the biomarker, promote data sharing, and encourage additional studies that could be used for qualification of the biomarker if the submitters decide to pursue this path at a later time.

Exhibit 3. Evidentiary Considerations Based on Risk–Benefit Profile



KIC, composed of members from the pharmaceutical industry, academia, and other stakeholders with funding for and expertise in regulatory qualification of biomarkers, seems like a good fit to the members of the RIB WG.

Dr. Maxon suggests, "Let's contact KIC to see if they are interested in partnering with us, as they appear to have what we need to move RIB forward." The RIB WG agrees.

A New Partner

Dr. Smith contacts KIC, and they plan a teleconference to discuss the RIB data and the path forward.

Based on the preliminary data collected by the RIB WG, the consortium decides to perform additional studies to support the utility of RIB as a safety biomarker for monitoring drug-induced acute kidney injury in clinical trials.

Dr. Michael Phillips, from KIC, leads the discussion, and the team establishes a plan to gather the data needed to begin the qualification process for RIB.

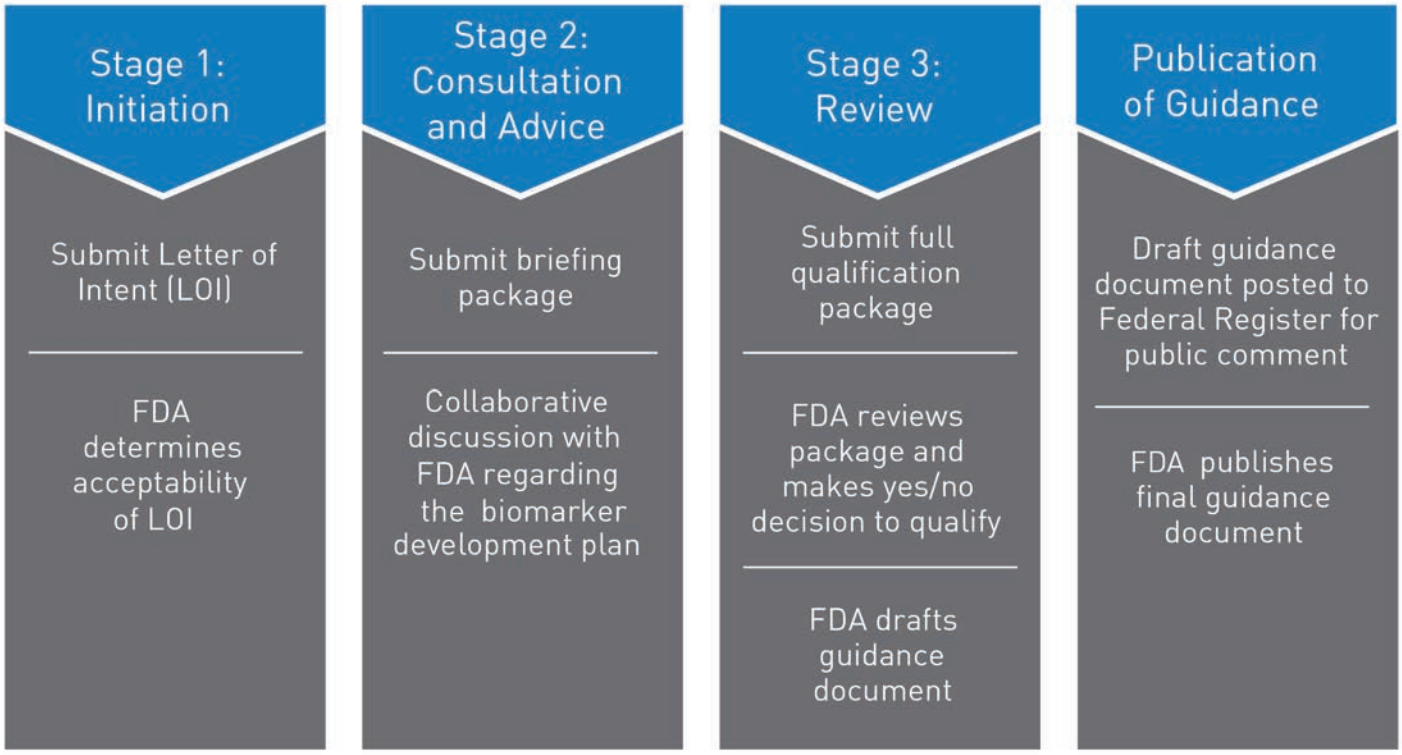
1. Perform further validation of the RIB assay in a consortium member laboratory.
2. Collect additional exploratory data to measure RIB levels to establish a reference value for RIB in healthy volunteers and to establish the levels of RIB in patients with drug-induced acute kidney injury to determine measurement decision points.
3. Use these exploratory data to design the next set of studies, based on sample collection times, sample stability and storage, and the specific patient population that will be tested.
4. Design a statistical analysis plan (SAP) for the study.

The Three Stages of Biomarker Qualification

Dr. Phillips reviews the BQP, Drug Development Tool Guidance, and the Drug Development Tool Qualification Programs Manual of Policies and Procedures (MAPP) on the FDA website with Dr. Smith. Dr. Smith learns that the BQP process consists of three stages: Initiation, Consultation and Advice, and Review (Exhibit 4).

Dr. Smith says, "In the Initiation Stage, a Biomarker Qualification Review Team (BQRT) is formed of reviewers with the appropriate expertise from

Exhibit 4. The Three Stages of the Biomarker Qualification Program



various FDA offices. During the Consultation and Advice Stage, the BQRT provides advice to the submitter through an iterative process. Finally, in the Review Stage, the BQRT reviews the full qualification package and develops qualification recommendations, which are published as draft guidance in the Federal Register."

The Consortia-pedia Catalogue is a web-based resource where users can view profiles on more than 400 research consortia to learn about their work, including their mission, structure, data sharing, partners, and more. This tool allows public and private partners to find one another, survey the landscape of activity in research areas, and identify practices of established and completed consortia.

The Biomarker Qualification Process for Renal Injury Biomarker

Stage 1: Initiation

Initiation of Request

KIC begins by contacting CDER to request a biomarker tracking number for their submission to include with their letter of intent (LOI).

KIC also schedules a pre-LOI teleconference with FDA, in order to ask specific questions about the BQP submission process.

Letter of Intent

Dr. Phillips says, "The LOI should be a brief document (approximately 3–4 pages). There is also option for a joint submission to FDA and the European Medicines Agency (EMA)."

The LOI will communicate the following information to FDA:

- Introduction
- Proposed COU
- High-level data description (1–2 pages in length). This description should provide a data overview that not only supports the use of the biomarker for the proposed COU, but also encourages FDA engagement because of drug development applicability
- Additional resources that support the COU, as well as data the submitter plans to obtain from ongoing or future studies
- Indication of any plans to submit the biomarker for qualification by other international regulatory agencies

Elements of a COU

A COU is composed of:

1. Concise biomarker Use Statement
2. Comprehensive description of conditions for the biomarker to be used in the qualified setting, termed the Conditions for Qualified Use

Proposed RIB COU (Use Statement Only)

Serum Renal Injury Biomarker (RIB) is a safety biomarker used to monitor drug-induced kidney injury in clinical trials in normal, healthy volunteers.

FDA Response to the Letter of Intent

The BQP accepts the LOI from KIC and provides advice about what is needed to achieve a qualification.

The response from FDA states in part that "the information on RIB and its utility is promising for use in drug development and regulatory decision-making, even though the data overview indicates the submission does not contain enough data to support qualification at this time."

The BQP reminds KIC about the Letter of Support (LOS) Initiative (as sufficient data for an LOS was generated in the LOI package).

Letter of Support

KIC discusses its options and decides to request an LOS. The LOS provides visibility to the RIB development. They feel that the LOS will help them recruit partners and generate the data needed to support RIB qualification. KIC requests an LOS and includes a draft LOS for FDA consideration.

After convening a review team, FDA issues an LOS citing RIB as a promising biomarker. FDA posts the LOS on its public website.

New Collaborators Generated by the Letter of Support

The LOS does indeed generate interest from several sponsors that are not part of KIC but have the same interest in promising kidney injury biomarkers.

The sponsors suggest measuring RIB in ongoing clinical trials and analyzing existing biological samples from past trials to measure RIB levels.

All of the new collaborators understand the importance of using validated analytical methods and CDER Study Data Standards to generate data for eventual biomarker qualification for a specific COU.

KIC works with their new partners and summarizes and pools the supporting information in order to proceed with the qualification of RIB.

Revised Letter of Intent Based on New Data Generated

With the new data in hand, Dr. Phillips says, "We are ready to submit a revised LOI to FDA."

At FDA, the BQP staff review the revised LOI, decide to accept the submission into the BQP, and obtain the resources and personnel needed for the qualification. The BQP then convenes a BQRT composed of reviewers with relevant expertise. Generally, the review team includes clinical pharmacologists, statisticians, and clinical reviewers from CDER, as well as other Centers within FDA, as appropriate.

The BQRT assesses the LOI and provides feedback as well as recommendations to KIC about the initial Briefing Package.

Stage 2: Consultation and Advice

Preparation of the Initial Briefing Package

At the team's first meeting after acceptance of the LOI and receipt of FDA advice on the Briefing Package, Dr. Phillips presents the Biomarker Qualification Submission Checklist, which provides a detailed list of information that will go into the initial Briefing Package.

After answering all of the team's questions, Dr. Phillips says, "If you have other questions, there is also an FDA website that contains more in-depth information on the Briefing Package document."

The team then spends some time assigning responsibility for writing each section of the initial Briefing Package and establishing a timeline to generation of a first draft that the entire team will read and comment on.

Meetings are held with consortium members regarding questions that arise during preparation of the initial Briefing Package in order to reach consensus and finalize the document. KIC also contacts the BQRT with specific questions when necessary.

Submission of the Initial Briefing Package

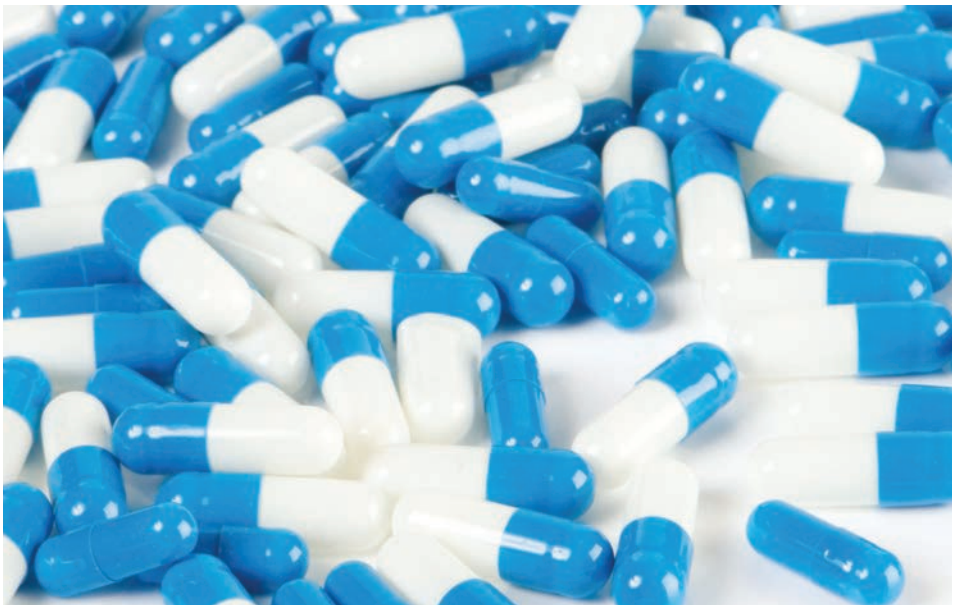
After several iterations, KIC determines that they will soon be ready to submit the document to FDA.

They email the BQP to alert them to expect the submission in 30 days so that internal FDA meetings can be planned and scheduled to review the document.

KIC prepares the cover letter to accompany the submission and submits it to FDA.

Meeting with the Biomarker Qualification Review Team

After receiving the Briefing Package, the BQRT begins reviewing the submission and provides continuing advice to KIC about the evidence needed for qualification.



A face-to-face meeting is held between the BQRT and KIC after submission of the initial Briefing Package to discuss questions that the BQRT raises about the submission.

At the meeting, KIC obtains alignment with the BQRT around the evidence needed to support RIB qualification.

However, the BQRT has advice for the consortium on how to refine the COU for RIB and some revisions for the study plan.

Further Development and Consultation

As they discuss the requests, Dr. Phillips says, "We can communicate with the BQRT through correspondence or additional meetings as needed to seek advice relevant to the RIB proposal."

During these meetings, discussions and advice will focus on:

- The rationale for the proposed biomarker and its COU
- Newly acquired data
- Questions about the COU that require further data
- Potential studies and methods to obtain that data
- Statistical analysis plan (SAP)
- Identification of other gaps in the existing information that should be addressed before proceeding to the review stage of the qualification process

Per the BQRT's advice, KIC modifies the COU to be more limited in scope, submits this to FDA as a supplementary Briefing Document along with

the statistical analysis plan, and requests a meeting to discuss the submission.

At this meeting with the BQRT, the revised COU is discussed and considered acceptable by FDA. The team leaves this meeting with the go-ahead to submit a full qualification package (FQP) to CDER.

Proposed Revised RIB COU (Use Statement Only)

Serum Renal Injury Biomarker (RIB) is a safety biomarker to be used in addition to standard renal injury biomarkers to assist in monitoring drug-induced kidney injury in normal healthy volunteers enrolled in phase 1 clinical trials.

Stage 3: Review

After submitting the FQP for RIB to FDA, KIC is officially notified by CDER that Stage 3, the review stage, has started.

The FQP contains a complete and detailed description of the studies and analyses providing the evidence to justify qualification, the revised COU, and primary data from the studies performed.

Along with the FQP, KIC also provides a statement acknowledging that a summary of the information in the qualification package will be made public on FDA's BQP Web page.

Review of Full Qualification Package

The BQRT reviews the FQP for qualification of RIB and discusses the project at internal meetings in order to arrive at a qualification recommendation.

The BQRT contacts KIC during the review process for clarification of some aspects of the qualification package but does not request additional data.

Members of the BQRT prepare individual discipline reviews and a combined executive summary for the qualification recommendation for RIB.

Qualification

The review and decision-making process results in a CDER recommendation to qualify RIB as a safety biomarker to monitor drug-induced acute kidney injury in clinical trials.

A draft guidance summarizing the qualification recommendation, the redacted reviews, and an executive summary are posted on FDA's BQP Web page.

FDA notifies the team of the publication of the draft guidance.

Dr. Phillips calls a meeting of KIC. He announces, "RIB has officially been qualified by FDA! All of our hard work has paid off. There is now a new safety biomarker that can be used in addition to standard renal injury biomarkers to assist in monitoring drug-induced acute kidney injury in clinical trials for the development of new medicines."

FDA issues a notice in the Federal Register to seek public comments on the draft Qualification Guidance. After 90 days, FDA addresses the public comments received and issues a final Qualification Guidance.

The Importance of Biomarker Qualification

Executives at pharmaceutical company ABC are meeting to decide whether their company should continue to develop new rheumatoid arthritis drugs that have a risk of causing acute kidney injury. The clinical safety team recommended that the company end their efforts, as the ability to monitor kidney safety is not clear.

However, at the meeting, Dr. Greene, a nephrologist, argues against the decision to terminate efforts.

"Recently, FDA qualified a new safety biomarker for monitoring drug-induced acute kidney injury, called RIB. I read the information about RIB on the FDA website, and I believe that this will give us more certainty in our clinical trials."

The team reviews the information on RIB, and determines that RIB will help them with their efforts to monitor kidney for drugs under development to treat rheumatoid arthritis that have potential kidney safety risks.

The team decides to include RIB as a safety biomarker for monitoring drug-induced acute kidney injury, in line with its qualified COU, in an IND submission.

While drug development has been hampered by a lack of accessible markers of renal injury, the increased sensitivity and specificity of RIB for detecting renal injury—when used in addition to the standard renal injury biomarkers—provides more sensitive monitoring for drug-induced acute kidney injury in their clinical studies.

The company submits the IND application to CDER for review. Because RIB was a qualified biomarker, the CDER reviewer does not need to re-review the RIB biomarker data to accept the use of RIB under its qualified COU. RIB is allowed for use in healthy volunteers in the phase 1 clinical trial for the promising rheumatoid arthritis drug.

RIB is a new addition to the drug development toolkit and leverages data to reduce uncertainty in regulatory decision-making.

APPENDIX A: REFERENCE LIST OF PUBLICATIONS

Amur S, LaVange L, Zineh I, Buckman-Garner S, Woodcock J. 2015a. Biomarker qualification: toward a multiple stakeholder framework for biomarker development, regulatory acceptance, and utilization. *Clin Pharmacol Ther 98(1)*:34–46.

Amur SG, Sanyal S, Chakravarty AG, Noone MH, Kaiser J, McCune S, Buckman-Garner SY. 2015b. Building a roadmap to biomarker qualification: challenges and opportunities. *Biomark Med* 9(11):1095–1105.

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Gobe GC, Coombes JS, Fassett RG, Endre ZH. 2015. Biomarkers of drug-induced acute kidney injury in the adult. *Expert Opin Drug Metab Toxicol* 11(11):1683–1694.

Robb MA, McInnes PM, Califf RM. 2016. Biomarkers and surrogate endpoints: Developing common terminology and definitions. *JAMA* 315(11):1107–1108.

Woodcock J, Buckman S, Goodsaid F, Walton MK, Zineh I. 2011. Qualifying biomarkers for use in drug development: A U.S. Food and Drug Administration overview. *Expert Opin Med Diagn* 5(5):369–374.

APPENDIX B: REFERENCE LIST OF FDA DOCUMENTS AND WEBSITES MENTIONED IN CASE STUDY

BEST (Biomarkers, EndpointS, and other Tools) Resource:

http://www.ncbi.nlm.nih.gov/books/NBK338448/

Biomarker Qualification Website:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm

Consortia-pedia:

http://consortiapedia.fastercures.org/

Context of Use (COU):

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284620.htm

Critical Path Initiative:

http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/

Critical Path Innovation Meeting (CPIM) Website:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm

CPIM Guidance Document:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM417627.pdf

Drug Development Tool (DDT) Guidance Document:

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm230597.pdf

Drug Development Tools Manual of Policies and Procedures:

http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407254.pdf

Example of a Context of Use:

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Drug Development ToolsQualificationProgram/UCM375892.pdf

Letter of Support (LOS) Initiative:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm434382.htm

List of Qualified Biomarkers (bottom of website):

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm

APPENDIX C: CRITICAL PATH INNOVATION MEETING (CPIM)

The CPIM is a means by which CDER and investigators from industry, academia, patient advocacy groups, and government can communicate to improve efficiency and success in drug development.

The goals of the CPIM are to discuss a methodology or technology proposed by the meeting requester and for CDER to provide general advice on how this methodology or technology might enhance drug development.

Through this process, CDER will identify some of the larger gaps in existing knowledge that requesters might consider addressing in the course of their work, and CDER also expects to become more familiar with prospective innovations in drug development through CPIMs, broadening its regulatory perspective.

The discussions and background information submitted through the CPIM are nonbinding on both FDA and CPIM requesters. The meeting does not substitute for formal pre-IND, IND, NDA, or BLA meetings. Appropriate FDA experts attend as resources allow.

The types of CPIM discussions include (but are not limited to):

- ✓ Biomarkers in the early phase of development for use in drug development and not yet ready for the Biomarker Qualification Program (BQP)
- ✓ Clinical Outcome Assessments in the early phase of development and not yet ready for the Clinical Outcome Assessment Qualification Program
- ✓ Natural history study designs and implementation
- ✓ Emerging technologies or new uses of existing technologies
- ✓ Innovative conceptual approaches to clinical trial design and analysis

CPIM preparation packages may be sent electronically to CPIMInquiries@fda.hhs.gov

APPENDIX D: BIOMARKER QUALIFICATION PROGRAM (BQP)

The BQP offers a formal process to guide submitters as they develop biomarkers and to rigorously evaluate them for a specific COU in the regulatory process for drug development.

The FDA defines qualification as a conclusion that within the stated context of use (COU), the biomarker can be relied on to have a specific interpretation and application in drug development and regulatory review.

The COU describes the way the biomarker is to be used and the purpose of the use. A complete COU statement should describe fully the circumstances under which the biomarker is qualified and the boundaries within which the available data adequately support use of the biomarker.

Once a biomarker has been qualified, CDER review staff are confident of the application of the biomarker within the qualified COU and do not have to re-confirm the biomarker's utility if it is to be used again within the stated COU.

The goals of the CDER BQP are to:

- Provide a process for qualifying biomarkers for use in drug development
- Facilitate integration of qualified biomarkers in the regulatory review process
- Perform outreach to encourage the identification of new and emerging biomarkers for utilization in regulatory decision-making

Drug developers can use a biomarker that has been qualified for a specific COU in drug development as long as:

- The study is conducted properly (e.g., all procedures and protocols specified in the COU are followed).
- The biomarker is used for the qualified COU.
- At the time of qualification, there is no new information that conflicts with the basis for qualification.

The biomarker can be used by drug developers for the qualified context in IND, NDA, and BLA submissions without the relevant CDER review group reconsidering and reconfirming the suitability of the biomarker. Drug developers can use qualified biomarkers, but are not required to do so.

Biomarkers being considered for qualification are conceptually independent of the specific test performing the measurement. However, a biomarker cannot become qualified without a reliable means to measure it. Therefore, the performance characteristics of the test(s) used to provide the biomarker data will be considered by FDA.

However, FDA clearance of a testing device for marketing does not imply that the biomarker it measures has been demonstrated to have a qualified use in drug development and evaluation.

Additionally, qualification of a biomarker does not automatically imply that a specific test device used in the qualification process for a biomarker has been reviewed and approved by FDA for use in patient care.

The biomarker may also have potential value outside the boundaries of the qualified COU. As data from additional studies are obtained over time, submitters of biomarkers will be able to continue working with the BQP to submit additional data and expand the qualified COU.

GLOSSARY

Biologic License Application (BLA): Biological products are approved for marketing under the provisions of the Public Health Service (PHS) Act. The Act requires a firm who manufactures a biologic for sale in interstate commerce to hold a license for the product. A biologics license application is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology, and medical effects of the biologic product. If the information provided meets FDA requirements, the application is approved and a license is issued allowing the firm to market the product.

Biomarker: 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. A biomarker is not an assessment of how an individual feels, functions, or survives.

Biomarker Qualification: A conclusion by FDA that within the stated context of use (COU), the biomarker can be relied on to have a specific interpretation and application in drug development and regulatory review. The COU describes the way the biomarker is to be used and the purpose of the use.

Biomarker Qualification Review Team (BQRT): A team composed of a multidisciplinary group of FDA staff empaneled to review biomarker qualification submissions. Each team is recruited based upon the specific drug development tool(s) and the context of use proposed by the submitter.

Context of use (COU): A complete and precise statement that describes the appropriate use of the biomarker, and how the qualified biomarker is applied in drug development and regulatory review. The context of use statement would describe all important criteria regarding the circumstances under which the biomarker is qualified.

Critical Path Innovation Meeting (CPIM): A means by which CDER and investigators from industry, academia, patient advocacy groups, and government can communicate to improve efficiency and success in drug development.

Diagnostic biomarker: A biomarker used to identify individuals with the disease or condition of interest or to define a subset of the disease.

Drug development tool (DDT): A measurement or method (and associated materials) that aids drug development. DDTs include, but are not limited to, biomarkers, clinical outcome assessments, and animal models. DDTs should be intended for potential use, over time, in multiple drug development programs.

Full Qualification Package (FQP): A complete and detailed description of the studies and analyses providing the evidence to justify qualification of the biomarker for the intended COU submitted in Stage 3 (Review) of the biomarker qualification process.

Initial Briefing Package (IBP): A document submitted in Stage 2 (Consultation and Advice) of the biomarker qualification process with additional data to support the qualification of the biomarker for the proposed COU that incorporates the IBP specifications provided by the BQRT.

Investigational New Drug (IND) application: Investigational new drug means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used *in vitro* for diagnostic purposes. The IND application must contain information in three broad areas: Animal Pharmacology and Toxicology Studies; Manufacturing Information; and Clinical Protocols and Investigator Information. Once the IND application is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND application for safety to ensure that research subjects will not be subjected to unreasonable risk.

Letter of Intent (LOI): A concise document requesting an initial consultation with CDER concerning the potential value of a drug development tool (DDT). Submitters should send the LOI (see section VII for details) when they have a well-identified DDT concept. The LOI should include a short description of the DDT, its proposed COU, and a rationale to support qualification.

Letter of Support (LOS): A letter issued to a requester that briefly describes CDER's thoughts on the potential value of a biomarker and encourages further evaluation. This letter does not connote qualification of a biomarker. It is meant to enhance the visibility of the biomarker, encourage data sharing, and stimulate additional studies.

Monitoring biomarker: 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.

New Drug Application (NDA): An application for FDA approval to market a new drug in the United States. The NDA must contain data from specific technical viewpoints for review, including chemistry, pharmacology, clinical, toxicology, biopharmaceutics, and statistics.

Predictive biomarker: A biomarker used to identify individuals who are likely to experience a favorable or unfavorable effect from a specific intervention or exposure.

Prognostic biomarker: A biomarker used to identify likelihood of a clinical event or disease recurrence or progression.

Pharmacodynamic/response biomarker: A biomarker used to show that a biological response has occurred in an individual who has received an intervention or exposure.

Safety biomarker: A biomarker used to indicate the presence or extent of toxicity related to an intervention or exposure.

Submitter: A person, group, organization or consortium that takes responsibility for and initiates a DDT qualification proposal.

Surrogate endpoint: 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.

Susceptibility/risk biomarker: A biomarker that indicates the potential for developing a disease or sensitivity to an exposure in an individual without clinically apparent disease.