

# FDA CASE STUDY

Biomarker Qualification

March 2017

## BIOMARKER QUALIFICATION—COLLABORATIVE EFFORT TO QUALIFY A DRUG DEVELOPMENT TOOL

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 potential benefits of biomarker qualification in drug development
- To understand the collaborative efforts involved in the qualification of a biomarker and the role that patient advocates can play in the process

### Topics:

- Biomarkers, biomarker qualification, regulatory pathways for integration of biomarkers into drug development, the role of patient advocacy groups in biomarker development

### Osteoporosis: A Bone Disease

Jane has just returned from visiting her husband Arthur in the hospital. Arthur broke his hip and he has been diagnosed with osteoporosis. Jane is concerned about Arthur and wants to find out more about osteoporosis.

Jane finds some valuable information on the website of the National Osteoporosis Foundation (NOF) that helps her understand the disease (NOF 2016). Jane learns that osteoporosis is a bone disease. Osteoporosis results in weakened bone, making fractures like Arthur’s more likely.

People develop osteoporosis due to bone loss and/or the failure to make enough bone. While everyone loses old bone and makes new bone all of the time, osteoporosis can occur when you lose more bone than you make. This results in weakened bones. And weakened bones can result in broken bones. For some with osteoporosis, even minor mishaps can result in a broken bone.

Fifty four million Americans suffer from the disease. Approximately one in every two women and one in every four men over the age of 50 will break a bone due to osteoporosis. Broken bones from osteoporosis can be very painful and serious and can affect physical, mental and emotional health. Complications can result from the break itself or from surgery, which may be needed to repair the break.

Jane tells Arthur, “I didn’t realize how serious osteoporosis is. Based on your experience and what I’ve learned about the disease, I’m going to see if there is some way for me to get involved to help you and others with osteoporosis.”

### Osteoporosis: Challenges in Diagnosis and Treatment

Although there has been progress in the diagnosis and treatment of osteoporosis, there are still many challenges.

Jane is having a difficult time evaluating the potential risks and benefits of osteoporosis treatments for her husband. Osteoporosis therapies may have side effects and the effectiveness of osteoporosis treatment in men has not been well studied (USHHS 2012).

There is also a lack of biomarkers that can predict which patients have a high risk of developing osteoporosis. This can make it difficult to find the right patients to test new preventative medications.

Jane can see that there is a clear need for new medications to prevent and treat osteoporosis and that new biomarkers are also needed.

## Challenges in Developing New Drugs

Jane learns about the challenges associated with developing new drugs, including those for osteoporosis, in the [2004 Critical Path Report](#) published by the Food and Drug Administration (FDA) ([FDA 2004](#)).

The report noted that many new medicines studied in clinical trials are not approved by the FDA. The path for the development of drugs to treat patients needs to be streamlined. New tools that aid medical product development could help.

The report concluded that there was an urgent need for a new product development toolkit with powerful new scientific and technical methods, including biomarkers that measure safety and effectiveness, to improve the

predictability and efficiency of drug development along the critical path from laboratory to patients.

This idea is interesting to Jane in light of her husband's diagnosis of osteoporosis and she begins to think that there might be a way that she can help to hopefully get new osteoporosis drugs to market faster.

## Biomarkers

In the FDA's 2004 Critical Path Report, Jane learned that biomarkers are one of the tools being used to improve the drug development process and she wants to learn more about biomarkers.

Online, Jane finds a helpful glossary of terms put together by the FDA-NIH Biomarker Working Group called the [BEST](#) (Biomarkers, EndpointS, and other Tools) Resource ([FDA-NIH 2016](#)).

Here she learns that 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. A biomarker is not an assessment of how an individual feels, functions, or survives.

Jane realizes that she already knows something about biomarkers. For example, at her yearly physical, Jane has her cholesterol measured and Jane realizes cholesterol is a biomarker. To learn about more biomarkers, Jane calls her friend Mary and asks about biomarkers for diabetes.

### 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 Working Group ([Robb et al. 2016](#)).

Mary says, “As you know, I have diabetes. Hemoglobin A1c (HbA1c) is a biomarker that can be measured in blood to diagnose and monitor diabetes. HbA1c can inform me or my physician regarding how I am doing on my medicines, or how my diabetes is progressing.

“But I’ve also learned that besides being a clinical lab test, HbA1c can also be a very useful biomarker for the development of diabetes drugs. In fact, I am in a clinical trial right now for a new diabetes drug and they are measuring my HbA1c to determine if the drug is working.”

In this case, HbA1c is being used as a pharmacodynamic/response biomarker to evaluate patients with diabetes to determine if they are responding to the new diabetes drug.

Within drug development, biomarkers can be used in many different ways. And Jane learns

that there are several different [categories of biomarkers](#). The different biomarker categories are explained in the [BEST Resource](#).

### **Biomarker Integration through Scientific Community Consensus**

Historically, biomarkers have been integrated into drug development over time. The integration process began with scientific community consensus and was followed by regulatory acceptance of the biomarker. ([Amur et al. 2015a](#)). Unfortunately this can take a long time. Jane reads about three specific examples; hemoglobin A1c (HbA1c), HIV virus level, and alanine aminotransferase (ALT), that highlight how long this route of biomarker acceptance can take.

#### **Hemoglobin A1c (HbA1c)**

Monitoring HbA1c to determine how well patients were controlling their diabetes was first proposed

in 1976. Twenty three scientific publications in 1999 supported the association between HbA1c and patient death in diabetics. However, it wasn’t until 2008 that the FDA published a [guidance document](#) that said that HbA1c could be used in drug development as a well-validated surrogate for the short-term clinical consequences of elevated glucose levels and long-term vascular complications of diabetes mellitus ([FDA 2008](#)).

#### **HIV Virus Levels in Blood**

The measurement of HIV virus levels offers several advantages over traditional clinical trial endpoints for HIV treatments, including ease of measurement, earlier evaluation of drug activity, and rapid identification of loss of response. These advantages make it possible to speed approval of new AIDS drugs to patients. In this case it took about 7 years, from first publication to FDA

## **Categories of Biomarkers**

**Diagnostic Biomarker**—A biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.

**Monitoring Biomarker**—A biomarker measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.

**Pharmacodynamic/Response Biomarker**—A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent.

**Predictive Biomarker**—A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.

**Prognostic Biomarker**—A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.

**Safety Biomarker**—A biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect.

**Susceptibility/Risk Biomarker**—A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition (From: [BEST resource](#)).

acceptance, to establish HIV virus levels as a surrogate endpoint.

### **Alanine Aminotransferase (ALT)**

In 1955, scientists at the University of Naples discovered that increased levels of alanine aminotransferase (ALT) in the blood can be an indicator of liver damage.

However, it took many years for the scientific community to accept the utility of ALT, and it wasn't until 2009 that the FDA published a final guidance document addressing how laboratory measurements such as ALT can be used to identify the potential for drug induced liver injury (FDA 2009).

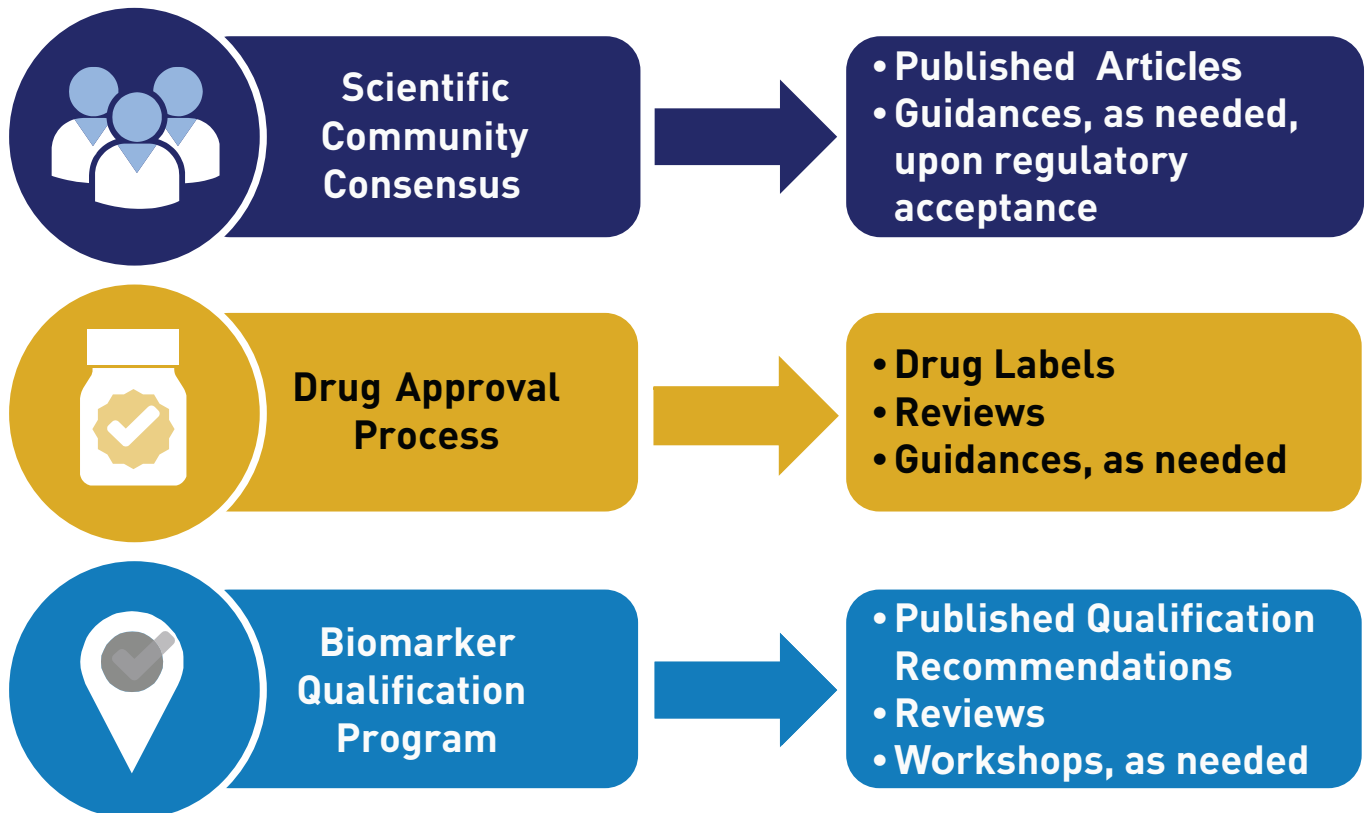
“Wow”, thought Jane, “this really is a slow process. I wonder if there are other, faster ways for the scientific community to adopt new biomarkers.”

### **Two Pathways for Biomarker Integration in Drug Development through CDER, FDA**

Jane discovered that the FDA's Center for Drug Evaluation and Research (CDER) now has two pathways to get new biomarkers integrated into drug development. These processes, with clearly defined steps, are likely to be more streamlined than the scientific community consensus process used for HbA1c, HIV virus levels or ALT (Exhibit 1).

During the drug development process, a pharmaceutical company may engage directly with the FDA to reach agreement on the value of a particular biomarker in a given drug's development program and the biomarker can be accepted through the drug approval process (in an IND/NDA/BLA submission). While this pathway may be efficient for drug developers, it has limitations. The confidential discussions between the FDA and the drug developer do not allow for input from the larger scientific community, because the information about the biomarker may not be publicly available. This process also puts the entire burden of developing a biomarker on a single pharmaceutical company.

Exhibit 1. Pathways to Integrate Biomarkers in Drug Development



Alternatively, biomarkers can be qualified through the [Biomarker Qualification Program](#) at CDER ([Woodcock et al. 2011](#), [Amur et al. 2015b](#)). Under this program, pharmaceutical companies, patient- or disease-specific foundations, health research organizations, or consortia made up of any or all of these groups, may collectively generate the data necessary for making drug-product independent decisions with respect to biomarkers used in drug development.

Qualification of a biomarker with FDA is particularly useful for biomarkers that will have a broad application. Qualified biomarkers are publicly communicated to the drug development and research communities through regulatory guidance documents by the FDA's CDER.

Qualification is intended to facilitate widespread use of the biomarker and continued evaluation to develop further evidence supporting use of the biomarker, including potential new uses.

## Patient Advocacy

Jane talks to an osteoporosis patient advocacy group, the American Osteoporosis Association (AOA), to learn more about how she might be able to help catalyze biomarker development for the diagnosis and treatment of this disease.

Jane meets with Sylvia, an osteoporosis patient and a patient advocate at AOA.

Jane and Sylvia discuss the disease and what biomarkers

are under development for osteoporosis. Jane gets a much better understanding of the disease and also begins to understand how patient advocates can play a role in advancing new medicines.

Sylvia says, "We, as osteoporosis patients, have a role to play in making sure that our perspective is clear to those treating the disease, making policy, and working to discover new medicines. The AOA works to educate patients, policy makers, healthcare professionals and regulators and looks for ways to promote collaboration and data sharing to make progress on new treatments."

Sylvia continues, "One of the ways that we can help progress new treatments is through the use of new biomarkers in clinical trials. I want you to meet, Dr. Carlsen. He and his team at the University are working on a very promising biomarker of bone turnover. Maybe there is a way for us to help him."

## A Promising Osteoporosis Biomarker

Jane and Sylvia make an appointment to talk to Dr. Carlsen to learn more about a promising osteoporosis biomarker under development that has come to the attention of AOA.

Dr. Carlsen starts by explaining a little more about osteoporosis. He says, "Your body is constantly making new bone and breaking down or reabsorbing old bone. You make more bone than you lose when you are young, so you build bone mass. After your mid-30s, your body continues to make new

bone, but more slowly. The amount of bone you have in your 30s helps determine your risk of developing osteoporosis later in life."

He continues, "The new biomarker of bone turnover (BBT) that we have identified is a protein that regulates bone cell reabsorption, is easily measured in blood, and has the potential to be a [prognostic biomarker](#) to help identify early stage osteoporosis patients who are at greater risk for a substantial decrease in bone mass and density because they have higher rates of bone cell reabsorption. The hope is that BBT will help companies that are developing new osteoporosis drugs conduct more efficient clinical trials."

Jane says, "And that would mean that patients would potentially have access to new medicines for osteoporosis."

## Biomarkers for Enrichment of Clinical Trials

Jane and Sylvia learn that BBT, the osteoporosis biomarker, could help identify patients that are at greatest risk for rapid progression of the disease, so that these people could be enrolled in clinical trials.

Dr. Carlsen says, "This approach is called "[enrichment](#)" and would encourage and support the development of better osteoporosis treatments ([FDA 2012](#)).

Enrichment is defined as the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population."

Dr. Carlson tells them, “If a completely random sample of patients is selected for a clinical trial for a new osteoporosis drug, the drug may be incorrectly deemed ineffective because the majority of patients may not have had the targeted disease and, therefore, would not respond to the drug. Instead, researchers need tools to be able to select the patients that would be most likely to respond to the new treatment to best identify which treatments are effective.

“This enrichment process, when used by researchers to design a clinical trial and select patients that are most likely to respond to a treatment, can make the difference between the success and failure of a clinical trial.

“We have data that suggest that BBT would be a good prognostic biomarker to select patients with osteoporosis who are at greatest risk of rapid disease progression enabling efficient, streamlined, and more informative clinical trials for new osteoporosis drugs.”

## The Need for Robust Biomarker Data

Preliminary data from Dr. Carlsen’s laboratory suggest that BBT is a promising prognostic biomarker for use in the enrichment of osteoporosis clinical trials. However, resources are needed to continue developing the biomarker.

The way the biomarker is measured must be reliable, reproducible, sensitive and specific to provide data that can be relied on by the scientific community, the FDA, and patients.

Robust testing is essential for validating promising biomarkers because if a biomarker is not properly established, it can do more harm than good in clinical trials. Decisions based on such non-robust biomarkers may end up being incorrect.

The AOA begins discussions about the next steps for BBT. They decide that they would like to use the biomarker in drug development and need information on the potential regulatory processes. They learn that CDER provides opportunities for engagement during biomarker development ([Exhibit 2](#)) in addition to the individual drug approval process.

### Critical Path innovation Meeting

They learn of an FDA program that will allow them to have a conversation with the FDA, to discuss BBT and next steps, called the [Critical Path Innovation Meeting](#) (CPIM).

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

In this case, the AOA can request a CPIM to talk about the potential of their osteoporosis biomarker BBT, which is still in the early phase of biomarker development.

Through this process, CDER will identify some of the larger gaps in existing knowledge that the team might consider addressing in the course of their work.

In return, CDER expects to become more familiar with prospective innovations in drug development, broadening its regulatory perspective.

With this knowledge, AOA successfully requests a CPIM with CDER.

### Letter of Support Program

During the CPIM, Jane, the AOA, and Dr. Carlsen learn about the [Letter of Support \(LOS\) Program](#) at the FDA. Through this Program, a letter is issued to a requester that briefly describes CDER’s thoughts on the potential value of a biomarker and encourages further evaluation. The intent of the LOS is to enhance the visibility of a promising biomarker, demonstrate the FDA’s support for the development of the biomarker, and encourage collaborative efforts. To obtain an LOS, a requester needs to show promising biomarker research findings and also demonstrate a potential application for the biomarker in drug development.

There is a clear need to collect more data on BBT, and to obtain more resources and collaborators to help with the process.

Therefore, Jane, the AOA, and Dr. Carlsen request and successfully obtain an LOS that demonstrates FDA’s support for the continued development of BBT. With their newly obtained LOS, they decide to look for a partner with the expertise and resources to continue development of BBT.

Dr. Carlsen says, “A consortium, made up of members from academia, the pharmaceutical

## Exhibit 2. Opportunities for Engagement with CDER During Biomarker Development



### Critical Path Innovation Meeting

Discussion on potential biomarkers that might enhance drug development



### Letter of Support Program

Letter issued for promising biomarkers based on research findings



### Biomarker Qualification Program

Guidance issued for qualified biomarkers

industry, patient advocacy groups and government regulatory agencies would be the perfect partner. These groups share data, expertise and the cost of developing new tools like BBT.”

### Consortia-pedia

In order to find interested collaborators, they consult [Consortia-pedia](#), a web-based resource where one 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.

Consortia-pedia defines consortium as a “temporary

association of researchers that share resources and effort for a common objective” which in this case is developing a prognostic biomarker for use in the enrichment of osteoporosis clinical trials. This partnership model integrates multiple types of knowledge, data from multiple sources, and aligns multiple interests to enable everyone to share the cost and work of developing a new biomarker. Patients and patient advocacy groups are important partners in this process and act to provide the patient’s perspective to the other consortia members.

Jane, Dr. Carlsen, and the AOA find a potential partner in the American Bone Consortium (ABC) through [Consortia-pedia](#). They request a meeting with the consortium and after speaking with the consortium members,

they discover that they have a similar interest in developing new prognostic biomarkers for osteoporosis and decide to join forces.

### Biomarker Qualification

The ABC begins discussions about the next steps for BBT. They decide that they would like to qualify the biomarker with FDA and review the [Biomarker Qualification Program website](#) to obtain information on the process.

### Biomarker Qualification (BQ) and BQ Process

The ABC reads about the biomarker qualification process and learns that the context of use (COU) requested in the submission is central to biomarker qualification. The COU is a

## Exhibit 3. The Context of Use Determines the Level of Evidence Needed to Support Biomarker Qualification



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 COU determines the level of evidence necessary to obtain biomarker qualification ([Exhibit 3](#)). When requesting biomarker qualification, there are several key steps in the review process.

The process begins when a biomarker developer (referred to as a requester) submits a Letter of Intent (LOI) to the FDA that seeks qualification of a biomarker for a specific COU. This letter is a comprehensive document that includes the background information about the biomarker and an overview of the supportive data. Once the LOI is received, FDA will post information about the submission on the external program website. FDA reviews the LOI, decides whether to accept the biomarker submission into the qualification review process, and provides feedback on next steps.

If the FDA accepts the LOI, the requester is invited to submit a plan for qualification, which includes a discussion of how all the necessary data will be generated to support qualification. The FDA will review the information in the qualification plan and provide feedback about additional data needed for submission of the Full Qualification Package (FQP).

The requester generates the additional data needed and submits an FQP to the FDA. The FDA reviews the package and renders a decision on the qualification of the biomarker. If the FDA qualifies the biomarker, the qualification decision is published on the program's website along with the supportive evidence, review documents, and instructions for how to use the biomarker in drug development.

### **Qualification of Osteoporosis Biomarker**

To begin the biomarker qualification process, ABC submits

an LOI to the FDA that states their intent to seek the qualification of BBT as a prognostic biomarker for use in the enrichment of osteoporosis clinical trials and provides an overview of the supportive data. FDA publishes on the program website that ABC is seeking the qualification of BBT as a prognostic biomarker for use in the enrichment of osteoporosis clinical trials. FDA reviews the LOI, determines that the proposed COU is valuable to drug development, accepts BBT into the biomarker qualification program, and provides feedback on additional items ABC should provide for submission of a qualification plan.

Next, ABC writes a comprehensive description of the existing BBT data, creates a plan for continued BBT development including a detailed approach for generating all the necessary data to support qualification of BBT, and submits these documents to the FDA. FDA reviews the submission, provides comments, and suggests additional data from a new study be included



in the FQP.

Using this advice, ABC performs an additional study to address FDA's response, writes, and submits the FQP. The FDA reviews the documents and makes the decision to qualify BBT as a prognostic biomarker for use in the enrichment of osteoporosis clinical trials. FDA writes the qualification recommendation for BBT and posts it on the program's website along with the supportive evidence, review documents, and instructions for how to use BBT in drug development.

ABC is excited to hear the news that BBT biomarker is qualified!

## Getting the Word Out about Biomarkers

Jane is very excited about the BBT qualification but realizes that this is not the final step in the process. She knows that the information will be posted on the FDA website, but she also wonders if there are other ways to get the word out about BBT and help to make sure that BBT is commonly used in the osteoporosis drug development process in order to enable development of new medicines for patients like her husband that need them.

### Outreach to Drug Companies

Jane partners with Sylvia and the AOA to spread the word about BBT. They begin by contacting pharmaceutical companies that are interested in bone health. The AOA contacts people within each company to alert them to the qualification of BBT. Through this

outreach to drug companies, they promote the use of BBT in drug development to help identify the appropriate patients to enroll for clinical trials of new osteoporosis medicines.

These efforts help companies to begin to work on new osteoporosis medicines, with the knowledge that they now have a path, using this prognostic biomarker, to be able to find the appropriate patients to enroll in their clinical trials.

### Patient Focused Drug Development Meeting

Jane, Sylvia, and the AOA also request an externally-led Patient-Focused Drug Development (PFDD) Meeting with the FDA. The request is made 1 year in advance of the meeting so that the team has time to develop an agenda and invite participants that will be important to the discussion.

The FDA states that the PFDD meetings are important because, "The patient perspective is critical in helping FDA understand the context in which regulatory decisions are made for new drugs. PFDD meetings give FDA an important opportunity to hear directly from patients, patient advocates, and caretakers about the symptoms that matter most to them, the impact the disease has on patients' daily lives, and patients' experiences with currently available treatments. This input can inform FDA's decisions and oversight both during drug development and during our review of a marketing application."

Jane, Sylvia and the AOA bring in other patients and patient

advocacy groups to provide their experience to FDA. In addition, they reserve some time to highlight the use of biomarkers in the development of drugs for osteoporosis and to talk about Jane's experience being involved in the qualification of BBT.

Their efforts are a success. Many of the meeting participants also become advocates for the use of BBT to select patients for osteoporosis drug clinical trials. New drug companies are alerted to the qualification of BBT through this process and also begin using the biomarker to successfully obtain appropriate enrollment for their clinical trials.

### Outreach to Patient Groups

Jane also performs outreach with osteoporosis patient groups in her community and around the country to increase patient enrollment in clinical trials. Patients and advocacy groups can make an important contribution to keeping the patient community interested and engaged, as well as providing valuable perspectives on the acceptability of proposed clinical trial designs to minimize burdens to patients and their families.

### Success and Continued Outreach

Jane continues to spread the word about the exciting potential of biomarkers for improving the drug development process. Jane knows her efforts will make a real difference in the treatment of osteoporosis. She and others from the AOA speak to patients, advocacy groups, and drug developers. They also write articles

in patient focused journals that are read by many in the scientific community.

Through these efforts, Jane receives a call from an Alzheimer's patient advocacy group that read about her success with the osteoporosis biomarker BBT, and wants to know how to achieve the same success for Alzheimer's treatments.

Jane is excited to reach out to advocates in other disease areas and educate them on biomarkers, the FDA [Biomarker Qualification Program](#), and the efforts involved after a biomarker is qualified to continue to advocate for its use, including informing drug companies of newly qualified biomarkers, and performing outreach with patient groups

to increase patient enrollment in clinical trials. Jane knows biomarkers have the potential to improve the drug development process and is excited to empower other people to get involved and make a real difference in advancing medical treatments!



## APPENDIX A: 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 Program Website:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/default.htm>

### Consortia-pedia

<http://consortiapedia.fastercures.org/>

### CPIM (Critical Path Innovation Meeting) Guidance Document:

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

### CPIM (Critical Path Innovation Meeting) Website:

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

### Critical Path Initiative

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

### Drug Development Tool (DDT) Guidance Document:

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

### Drug Development Tools Process Manual of Policies and Procedures:

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

### Letter of Support (LOS) Program

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

### List of Qualified Biomarkers (Bottom of Website):

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535383.htm>



## APPENDIX B: 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* 98:34–46. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25868461>
- 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26526897>
- FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. 2016. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK338448/>. Accessed on July 8, 2016.
- National Osteoporosis Foundation. What is Osteoporosis and What Causes It? Available at: <https://www.nof.org/patients/what-is-osteoporosis/>. Accessed on July 8, 2016.
- Robb MA, McInnes PM, Califf RM. Biomarkers and surrogate endpoints: Developing common terminology and definitions. *JAMA*. 2016. 315(11):1107-1108. Available at: <http://jama.jamanetwork.com/article.aspx?articleID=2503184>. Accessed on September 23, 2016.
- U.S. Department of Health & Human Services. Treatment To Prevent Osteoporotic Fractures: An Update. 2012. Available at: [https://www.effectivehealthcare.ahrq.gov/ehc/products/160/1048/lbd\\_clin\\_fin\\_to\\_post.pdf](https://www.effectivehealthcare.ahrq.gov/ehc/products/160/1048/lbd_clin_fin_to_post.pdf). Accessed on September 26, 2016.
- U.S. Food and Drug Administration. 2004. Innovation/Stagnation Challenge and Opportunity on the Critical Path to New Medical Products. Available at: <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM113411.pdf>. Accessed on September 26, 2016.
- U.S. Food and Drug Administration. 2008. Guidance for Industry – Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. Available at: <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071624.pdf>. Accessed on September 1, 2016.
- U.S. Food and Drug Administration. 2009. Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation. Available at: <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf>. Accessed on September 19, 2016
- U.S. Food and Drug Administration. 2012. Guidance for Industry - Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products. Available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf>. Accessed on June 6, 2016.
- Woodcock J, Buckman S, Goodsaid F, Walton MK, Zineh I. Qualifying biomarkers for use in drug development: A U.S. Food and Drug Administration overview. *Expert Opin Med Diagn*. 2011;5(5):369-374. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23484625>



## GLOSSARY

**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 the 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. Once qualified, the biomarker information is made publicly available (through an FDA Guidance Document) and the biomarker can be used in multiple drug development programs under its qualified COU.

**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 detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.

**Drug development tools (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.

**Letter of Intent (LOI):** A concise document requesting an initial consultation with CDER concerning the potential value of a biomarker that is submitted in Stage 1 (Initiation) of the biomarker qualification process. Submitters should send the LOI when they have a well-identified biomarker concept. The LOI should include a short description of the biomarker, 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 for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.

**Patient-Focused Drug Development Meeting:** A means to gather patients' perspectives on their condition and available therapies to treat their condition to help inform drug development and evaluation.

**Predictive Biomarker:** A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.

**Prognostic Biomarker:** A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.

**Pharmacodynamic/Response Biomarker:** A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent.

**Safety Biomarker:** A biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect.

**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 medical condition in an individual who does not currently have clinically apparent disease or the medical condition.