Biomarkers Qualification – FDA Experience

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Abstract

Biomarker Qualification is a drug development tool (DDT) that guides uniformity of usage for biomarker across all drug development portfolios. Typically, biomarker qualification is undertaken by a consortium rather than individual sponsors so that common knowledge can be shared by all in a particular context of clinical usage.

In this paper, we will discuss definition of the word "qualification" in this paradigm, context of use, scope and process for biomarker qualification at the FDA, considerations for best practices related to this drug development tool. This is followed by a regulatory case example illustrating the concepts.

Definition and Background

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes (abnormal biologic processes) or responses to a therapeutic intervention. It is not a clinical assessment of the patient, those evaluating or closely relating to how a patient feels or functions, or survival.

Biomarkers are categorized by how they are used in drug development and may have utility in more than one category.

- **Prognostic biomarker** indicates future clinical course of the patient with respect to a specified clinical outcome in the absence of an intervention. So, there is no connection to any particular new treatment. Post-Therapy marker-clinical relationship may differ among treatments.
- **Predictive biomarker** is measured prior to an intervention and identifies patients susceptible to a particular drug effect versus less susceptible patients of a certain benefit or harm. These biomarkers are developed treatment by treatment and are not necessarily prognostic of the Post-Treatment clinical course.
- **Pharmaco-dynamic biomarker** (PD) or Response-indicator biomarker reveals whether, or how large, a biological response has occurred in that particular patient and may or may not be therapy specific. Development occurs in a treatment by treatment manner.
- **Surrogate endpoint** or Efficacy-response biomarkers are a small subset of biomarkers that predicts the clinical outcome of the patient at a distal time. Usually they have some prognostic utility; else placebo group measurements cannot be interpreted. Surrogate markers have been used extensively for accelerated approval of drugs that meet an unmet medical need.

[1] This article reflects the views of the author and should not be construed to represent FDA's views or policies.

Use of biomarkers in drug development programs can be for multiple purposes. They can be used as a patient selection tool for enrollment in enrichment study designs, as prognostic biomarkers or predictive biomarkers, or as a patient stratification tool to ensure balance within strata across randomized groups in other characteristics.

In Phase I study outcome assessment biomarkers demonstrate drug is bio-active and may indicate actions on early cellular effects rather than clinical outcome. Then it may aid in selecting dose / regimen for later studies and help justify putting resources into further development. In Phase II study outcome assessment, PD biomarkers evaluate dose-response relationships, identify patient characteristics that may be predictive markers, help design adequate and well-controlled studies, selection of doses, selection of patient population, aid estimation of sample size and can be critical to efficient and successful development program.

In Phase III adequate and well-controlled studies, biomarkers may assist the primary analysis by serving as a surrogate endpoint if there is a well established relationship to the clinical outcome. Under accelerated approval provisions of regulations, surrogate markers "reasonably likely to predict" clinical relationships can drastically cut down the time needed for conventional marketing approval.

How have biomarkers been accepted? Most often, they are considered case by case. They are often considered within a specific IND/NDA/BLA/labeling update and for a specific drug, driven by a specific drug developer's needs. General use is accepted over extended period as scientific experience accumulates through varied uses. One of the limitations of this approach is that usually an extended time-frame is required and the evidence collection not always cohesively directed.

How can a biomarker become accepted? Co-development of a drug and diagnostic test assay in companion diagnostics is an established path and a guidance is in development detailing this regulatory path. In addition, an International Council of Harmonization (ICH) document "E16-Biomarkers related to Drug or Biotechnology product development: context, structure and format of qualification submissions" provide a regulatory paradigm.

The Biomarker Qualification Process (BQP), a developing program within CDER, is an outgrowth of the Critical Path Initiative. The Center for Drug Evaluation and Research (CDER) at FDA has published draft guidance on this drug development tool (DDT) process. This guidance discusses the qualification process for both biomarkers as well as clinical outcome assessments (PROs and other rating scales). The full guidance is available at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceREgulatoryInformation/Guidances/UCM230597.pdf

Biomarker Qualification is a conclusion that within a carefully and specifically stated "context of use", the biomarker can reliably support a specified manner of interpretation and application in drug development. Its utility in regulatory decisions is central to the qualification process. Biomarkers are expected to have application in multiple different drug development programs. A qualified biomarker can be applied as a DDT without the need for submission of extensive biomarker-supportive information to each IND or re-evaluation to confirm that application is justified. It may make the biomarker more attractive to use and accelerate the drug development program.

What becomes "qualified"? A biomarker is a patho-physiological measurement or an analyte. Assay methods are needed to measure the biomarker, but assay method is not the biomarker. A biomarker can have multiple assays that are capable of measuring the biomarker. Assay method performance characteristics are important and Center for Devices and Radiological Health (CDRH) within FDA has regulatory authority to clear or approve commercial testing devices for clinical measurements. Note that CDRH clearance does not equal CDER qualification, as they are for two very different purposes.

How do Biomarkers Become Developed? Disease biochemistry, pathophysiology, and natural history may serve as a guide to selecting assessments to develop. Collection of scientific data related to a particular context of use justifies relying on the biomarker. Substantial amount of effort may be required and collaborative model for this work including pharmaceutical industry in the "pre-competitive" space is being evaluated. This model reduces resources per participant; however, development resources are needed well in advance of applying biomarker in drug development.

Context of Use (CoU) and its elements

Biomarkers are qualified for a specific context of use (CoU). A CoU is a comprehensive statement of the manner and purpose of use, including how to apply results to decision making and the impact on drug development. The CoU identifies the boundaries of known reliability as shown by evidence and not all boundaries of non-reliability are known. A biomarker may also have utility outside the currently qualified CoU, when they are accepted on case by case (IND specific) basis and expand qualified CoU as further data justifies.

Context of Use (CoU) depends on when and how the biomarker is sampled, how the samples are analyzed, how the data are analyzed and interpreted and what decision is made based on the data. It is also important to consider how drug development is altered by the biomarker results. Adequately specifying the CoU is often a difficult first step towards qualification since it determines what kind of data is needed. Comparative claim to another biomarker is not a CoU.

There are several elements of a CoU that play an important role in design and analysis of the trial. Identification of the biomarker or a composite of several biomarkers that fully describe biomarker and its characteristic as needed is critical. For example if an imaging biomarkers is considered, the lesion length or volume, number of lesions, or change from baseline should be considered. If serum protein biomarkers are considered then steady state level, peak, and area under the curve (AUC) play an important role. If thresholds are used, pre-specification on the categorization such as greater than a specific threshold value or doubling from baseline should be done. The species of measurement is also important – is it being measured in human or in specific non-clinical species? The patient population plays an important role – is it being done in a clinical setting with healthy volunteers or in a specific disease or disease subset or, it is done in a non-clinical setting being measured in healthy animals or in a disease model?

The elements of a CoU can be considered in two categories – general purpose and specific drug development decisions made based on the biomarker. The general purpose elements identifies the intended interpretation, subject selection or categories for stratification, pharmaco-dynamic measurement for proof of concept study as well as

surrogate efficacy endpoint to demonstrate effectiveness. Specific drug development decisions made based on the biomarker are sometimes stated as part of general purpose such as eligibility criterion in clinical trial, selection of doses to be tested in phase 3 study, assurance of absence of toxicity to permit dose escalation by identifying study subjects who are experiencing toxicity for special management.

Biomarker Qualification in Drug Development Program

Qualification is not required in all situations; case by case approach for accepting use in a single IND/NDA/BLA program remains valuable. Qualification is a voluntary activity as the holder of biomarker data can choose to pursue or not pursue qualification. Qualification is intended for biomarkers that will be used in multiple drug development programs and public knowledge and availability is essential. Consortia or collaborative groups are most likely to be sources for biomarkers for qualification.

The qualification process has three major parts -

1. Initial evaluation for agreement to collaborate
2. Interactive Consultation and Advice Stage
3. In depth Review Stage

In the first phase, which is the initial high level evaluation, the submitter proposes the project to FDA with a Letter of Intent. In this document, they identify the biomarker and proposed context of use as well as information on current state of development. The FDA decides to collaborate based on whether potential is sufficient to justify Agency resources. An interdisciplinary working team is then assembled to guide submitter, and ultimately review the complete evidence.

In the second phase, which is the Advice & Consultation stage begins when summaries of available information are reviewed and advice on how to advance development for intended use are provided. Additional studies may need to be conducted as needed and summary results discussed with submitter as developed. Advice on next steps for development usually involve cycles of briefing documents, meetings and doing needed next steps until ultimately development is thought to be complete.

In the third phase, which is the biomarker review stage begins with submission of full data package. Full review and CDER decision on qualification is discussed and communicated to the submitter. Formal qualification is granted if appropriate. The qualification statements are made public on the FDA website.

Examples of Biomarker Qualification

An example of a BQ initiative is the Predictive Safety Testing Consortium (PSTC). A separate session solely outlining this initiative was presented at the ASA Joint Statistical Meetings 2012, so discussion here will be restricted to outlining the background and activity milestones. Details of the project can be found at http://c-path.org/pstc.cfm

The PSTC brings together pharmaceutical companies to share and validate each other's safety testing methods under the advisement of the FDA, the EMA (European Medicines Agency), the PMDA (Japanese Pharmaceutical and Medical Devices Agency). Ten EMA and twenty-eight FDA scientists serve as advisors along with more than 250 participating scientists.

The tests used to determine drug safety have not changed in decades. Although companies have developed newer safety testing methods, these are not generally accepted by the FDA or EMA as proof of safety. This is due, in part, because the methods used for testing are often different from company to company. That discrepancy leaves regulatory scientists uncertain about which methods should be preferred. Another key factor is that the tests have not, in the past, been independently validated. PSTC serves as a neutral third party to assess drug safety tests with eighteen corporate members. The members share their internally developed methods and test these methods developed by one another across the Consortium. C-Path leads the collaborative process and collects and summarizes the data. The testing is done with pre-clinical and clinical safety biomarkers in six working groups: cardiac hypertrophy, kidney, liver, skeletal muscle, testicular toxicity, and vascular injury. All biomarker research programs have a strong translational focus to select new safety tools that are applicable across the drug development spectrum.

Conclusion

Biomarker Qualification is an evolving science so quick reassessments through early and frequent contacts with the regulatory agencies will be needed to ensure a successful outcome. Active collaboration with the Consortium in a pre-competitive space cuts down on redundancies and streamlines the drug development process.

References:

1. Guidance to Industry: Qualification Process for Drug Development Tools http://www.fda.gov/downloads/Drugs/GuidanceComplianceREgulatoryInformation/Guidances/UCM230597.pdf
2. International Council of Harmonization (ICH) document “E16-Biomarkers related to Drug or Biotechnology product development: context, structure and format of qualification” available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM267449.pdf
3. Predictive Safety Testing Consortium http://c-path.org/pstc.cfm