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Guest Editors - Brian P. Booth and Jogarao V. Gobburu

Biomarker Qualification Pilot Process at the US Food and Drug Administration

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Federico Goodsaid[1] and Felix Frueh[1]

[1]Genomics Group, Office of Clinical Pharmacology, Office of Translational Science, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Avenue, Building 21, Room 3663, Silver Spring, MD 20903-0002

ABSTRACT

New biomarkers of safety and efficacy are becoming powerful tools in drug development. Their application can be accelerated if a consensus can be reached about their qualification for regulatory applications. This consensus requires a review structure within the US Food and Drug Administration (FDA) that can evaluate qualification data for these biomarkers and determine whether these biomarkers can be qualified. A pilot process and corresponding Biomarker Qualification Review Team have been developed to test how the FDA can work on biomarker qualification.

KEYWORDS: Biomarker, validation, FDA

INTRODUCTION

The validity of preclinical and clinical biomarkers has been traditionally settled by debate, consensus, and the passage of time. Although intellectually painless, this process is slow: many years must pass before a consensus on qualification can be reached. The urgent need for accelerated application of biomarkers in drug development means that a process for accurate, comprehensive, and aggressive qualification of biomarkers from the perspective of the US Food and Drug Administration (FDA) is needed. This cannot be simply an extension of the process for reviewing drug submissions. An agencywide collaborative effort is required to address the structural issues associated with developing a new biomarker qualification process.

The acceptance of biomarker validity is limited by uncertainty about several factors associated with the emergence of new metrics in drug development and regulatory review.

Corresponding Author: Federico Goodsaid, Genomics Group, Office of Clinical Pharmacology, Office of Translational Science, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Avenue, Building 21, Room 3663, Silver Spring, MD 20903-0002. Tel: (301) 796-1535; Fax: (301) 796-9736; E-mail: Federico.goodsaid@fda.hhs.gov

Additional biomarkers for which data are required in drug submissions represent an additional test burden, for which a corresponding benefit in safety, efficacy, and/or cost must be clearly established. This benefit must be transparent to the industry and the agency before new biomarkers are accepted.

A related source of uncertainty is the limitations in sensitivity and specificity of any biomarker. Exceptions in the sensitivity and specificity of biomarkers, while expected for any 1 metric of safety or efficacy, are unsettling in a discussion of new biomarker candidates. These exceptions are often related to an inaccurate definition of the context for which a biomarker should be qualified, and they should be minimized if the context is accurately defined.

An additional source of uncertainty is the difficulty in establishing biomarker context. Why, when, and how should well-established biomarkers be replaced with new ones? The net benefit we have discussed here should justify the need for a new biomarker, as well as the timing for its integration into drug development and regulatory review, but how can we judge how much better a new biomarker will be? Context and qualification for new biomarkers are assessed relative to current biomarkers. If the sensitivity and specificity of current biomarkers are not perfect relative to a specific end point, the context and qualification of new biomarkers may not be accurately established. This is a particularly difficult problem if current biomarkers have pseudo-quantitative, qualitative, or subjective metrics associated with them.

An example of this difficulty is the use of histopathological data as a reference to establish context and qualification. Histopathological assessments depend on the nomenclature, institutional norms, and personal preferences of individual pathologists. Peer review in pathology mitigates but does not eliminate this problem, since it does not quantify the damage but facilitates consensus about qualitative assessment.

New biomarkers are needed in drug development and regulatory review. These biomarkers will have a positive impact on how quickly new drugs are submitted to and reviewed by the FDA, how many there are, and how safe they are. With safer drugs in greater numbers approved more quickly, public

health will be improved by these new biomarkers. But first, biomarker context will need to be accurately defined and the corresponding qualification protocol developed.

How Do We Know That a Biomarker Is Valid?

The pharmacogenomics guidance[1] defines a valid biomarker as "a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results." The validity of a biomarker is closely linked to what we think we can do with it. This biomarker context drives not only how we define a biomarker but also the complexity of its qualification.

One example of biomarker validity is implicit in the definition of biomarker use in drug labels. A significant increase in the number of labels containing such information has occurred over the past decade. The Genomics Group in the Office of Clinical Pharmacology has assembled a Web-based Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels.[2] This Web-based table sets precedents in the definition of clinical biomarkers in specific contexts and in the "valid" classification justified within the label context. A table like this is useful both because it contains examples of text that accurately defines biomarker context and because it provides an updated list of valid biomarkers.

How Does an Exploratory Biomarker Become Probable or Known Valid? Biomarker Qualification Process Map

The pharmacogenomics guidance[1] classifies biomarkers as exploratory, probable valid, or known valid; however, it does not describe a process by which an exploratory biomarker can be qualified as a valid biomarker. A known valid biomarker is defined as "a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, pharmacologic, or clinical significance of the results." A probable valid biomarker is defined as "a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is a scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, pharmacologic, or clinical significance of the test results." The difference between these 2 classes of biomarkers is in the broad consensus indicated by classification as known valid.

The qualification gap between exploratory and valid biomarkers is a gap not only between scientific proposals and consensus but also between the inefficient process through which biomarkers have been customarily introduced and accepted in drug development and a process through which these biomarkers could be seamlessly applied in drug development and regulatory review. The process needed to bridge this gap is closely aligned with the review of drug submissions at the FDA. The application for these biomarkers is drug development and regulatory review, and any process developed to support this application should reflect this. Therefore, it is incumbent on the FDA and drug sponsors to collaborate in the design of an efficient qualification process and review structure to reflect this context.

During the past 2 years, through a Collaborative Research and Development Agreement (CRADA), the FDA has worked on the design of a qualification process map[3] with Novartis[4] reflecting qualification needs for preclinical biomarkers. This process map reflects the expectation of a true partnership between sponsors and the FDA in the critical steps in this process of initial evaluation, qualification protocol draft, and data review. The work of the Predictive Safety Testing Consortium (PSTC)[5] coordinated by the C-Path Institute is expected to lead within the next year to multiple preclinical qualification packages with which to confirm the assumptions of this process map.

Biomarker Qualification Pilot Process

The FDA has set up a pilot structure to start a qualification process for biomarkers in drug development. This pilot structure has been designed around the Interdisciplinary Pharmacogenomic Review Group (IPRG), to allow contributions of expertise from different FDA Centers, such as the Center for Drug Evaluation and Research (CDER), the Center for Biologicals Evaluation and Research, the Center for Devices and Radiological Health, and the National Center for Toxicological Research, as well as across clinical divisions and from nonclinical toxicology reviewers in CDER. The new responsibilities of IPRG in this pilot structure include creation of a specific review function for the assessment of biomarker qualification data sets: the IPRG Biomarker Qualification Review Team (Figure 1).

The IPRG Biomarker Qualification Review Team will evaluate study protocols and review study results for the qualification of novel biomarkers of drug safety, using appropriate preclinical, clinical, and statistical considerations. The team will then develop recommendations and guidance for the submission of biomarker data, assess the original biomarker context proposal through voluntary data submission (VXDS, where the X underlines a wide range of data sources), and then evaluate the qualification study protocol together with the sponsor to reach a consensus protocol. Finally, this team

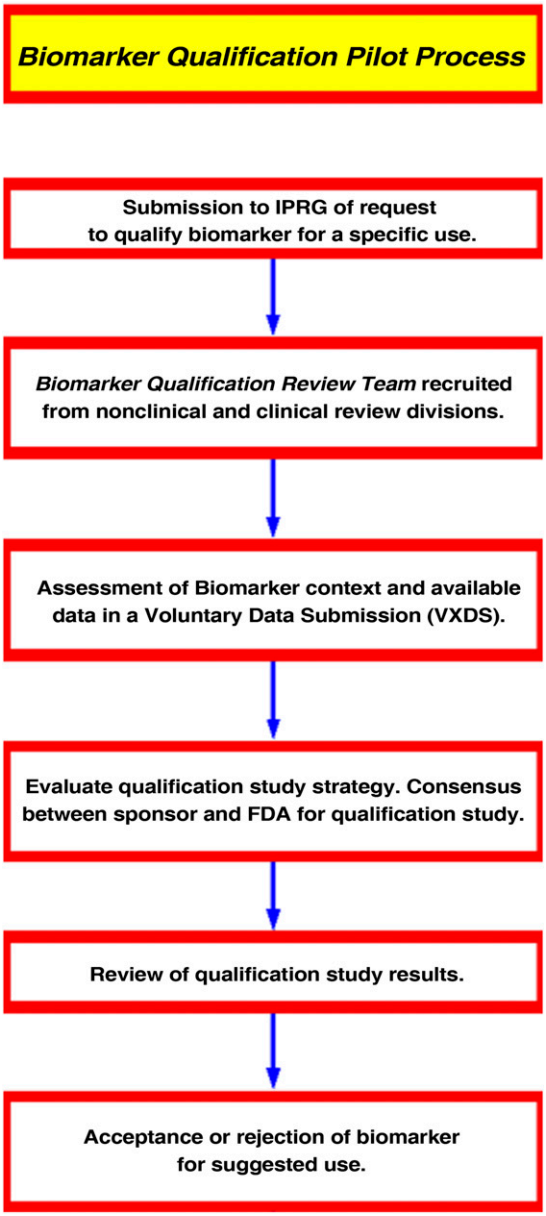

Figure 1. Biomarker qualification pilot process at the US Food and Drug Administration.

will review qualification study results and draft a recommendation for the clinical divisions.

Case Study: Nephrotoxicity Biomarkers

Consider the example of how a preclinical biomarker of nephrotoxicity will proceed through the qualification process. Data from the CRADA and the PSTC for the biomarker will be presented through a VXDS in which the specific context for the biomarker will be established. This meeting will cover the scientific basis and experimental data supporting the context for qualification of the biomarker and proposed applications for the biomarker. Preclinical biomarkers of nephrotoxicity may have several possible applications in mechanistic, diagnostic, or predictive contexts. Nephrotoxicity biomarkers under qualification at this time are likely to be mostly diagnostic, correlating with histopathology. The key question here will be whether the proposed biomarker is likely to have a long-term impact on the safety and/or cost of new drugs. The outcome of this meeting will be a decision regarding a recommendation on whether to proceed with qualification of the exploratory biomarker in question.

If needed in order to bridge data gaps from the VXDS, a first draft for a qualification protocol proposal will be reviewed by the Biomarker Qualification Review Team so that a consensus may be reached with the sponsor concerning data needed in a qualification package. A qualification study proposal from the sponsor will initiate this step. The qualification study proposal will be reviewed in the context of the number and type of nephrotoxicants and control compounds included in it, as well as the extensive use of current metrics to measure the effect of these compounds in the model animal. This reflects an iterative process to reach a consensus between the sponsor and the IPRG Biomarker Qualification Review Team regarding the qualification study.

The Qualification Data Report will be reviewed by the IPRG Biomarker Qualification Review Team, and the results of this review regarding the qualification of the biomarker submitted for approval will be communicated to the appropriate division. The review will include an assessment of data or analysis gaps. The sponsor is required to fill those gaps for a successful biomarker qualification. A decision to accept, reject, or amend the Qualification Data Report will be made by the review team.

Summary

A pilot process is being tested at the FDA for the qualification of preclinical and drug-independent clinical biomarkers. The process will be driven by the IPRG Biomarker Qualification Review Team. This team will draft a recommendation for the appropriate clinical division regarding the approval or rejection of the qualification submission.

Acknowledgments

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