

Advancing the Use of Biomarkers and Pharmacogenomics in Drug Development

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Discussion Guide

Introduction

Modern advances in the basic biomedical sciences have greatly improved our understanding of the underlying genetic and molecular causes of disease. With the emerging fields of genomics and proteomics, tailoring medical treatments to the individual characteristics of patients is increasingly becoming a reality in all stages of care. Despite these scientific advances, the development of targeted therapeutics remains a long and costly process. Biomarkers hold the potential to reduce the time and cost of drug development by improving the efficiency of the clinical trials required to demonstrate the safety and efficacy of new therapeutics. The development and application of clinically valid biomarkers, as well as companion diagnostics capable of accurately identifying and measuring biomarkers, has garnered the interest of many stakeholders. In response to Congress' most recent reauthorization of the Prescription Drug User Fee Act (PDUFA V), FDA has committed to working with patients, drug manufacturers, and other stakeholders to support the use of biomarkers and pharmacogenomics in drug development to ensure that patients have timely access to needed therapeutics. However, there are several challenges to the widespread adoption of biomarkers and companion diagnostics, spanning from discovery and validation to clinical utilization.

Background

A biomarker is typically defined as any characteristic that can serve as an objective indicator of biological or pathologic processes, or may be used to measure pharmacologic responses to a therapeutic intervention.¹ This definition broadly captures both pharmacokinetic/pharmacodynamic (PK/PD) and clinical biomarkers. PK/PD biomarkers are generally used in early drug development to determine dosage levels and establish that the therapeutic agent is acting on its intended target.² Clinical biomarkers can be classified into three categories: prognostic biomarkers, predictive biomarkers, and surrogate biomarkers, with some biomarkers fitting into more than one category.^{3,4} Clinical biomarkers serve several functions, allowing for the approximation of disease progression in untreated patients (prognostic), the identification of subpopulations of patients that are more likely to respond to treatment (predictive), or assessment of the safety and efficacy of therapeutics (surrogate biomarker or surrogate endpoints).⁵

Biomarkers may be applied in a number of ways to enhance clinical trials to support both more efficient drug development and use of new therapeutics once they enter the market. For example, predictive biomarkers may allow developers to specifically target patients who are likely to respond positively to treatment. This strategy—referred to as “enrichment”—has the potential to reduce the cost of drug development by reducing the size of the study population required to demonstrate an experimental drug's safety and efficacy. Further, by demonstrating that a drug will only have clinical utility for a particular subpopulation of patients, biomarker-based enrichment strategies can reduce the adverse effects and unnecessary spending associated with the administration of drugs to patients in the biomarker-negative population, who are less likely to benefit from such treatment. For example, patients with *KRAS* wild-type colon cancer are most likely to respond to treatment with cetuximab. Limiting the use of cetuximab to this subpopulation would save about \$600 million annually.⁶ Prognostic biomarkers differ from predictive biomarkers in that they provide information about the likely course of a disease in the absence of treatment or with the use of a standard therapy, rather than whether or not a patient is more likely to respond positively to a new therapeutic. For

example, tumor size is a prognostic biomarker in breast cancer because of the association between larger tumors and worse outcomes.⁴

Biomarkers, such as blood pressure, may also be used as surrogate endpoints.⁷ Because biomarker-based surrogate endpoints may be measured sooner or more conveniently than the clinical endpoints they substitute for, they have the potential to reduce the length and thereby the cost of clinical trials. However, few biomarkers have met the evidentiary standards needed to justify their use in drug development or guiding treatment decisions.⁸ Further, payers also have concerns about the link between improvement on biomarkers and subsequent improvement in major clinical outcomes of interest.

The current lack of progress in biomarker development and adoption reflects the many challenges that must be overcome – from candidate discovery, verification, and biomarker test optimization to biomarker evaluation and commercialization.⁹ The Food and Drug Administration (FDA) has recognized the potential for biomarkers and the emerging field of pharmacogenomics to transform drug development. As part of its mandate under PDUFA V, the agency is committed to advancing the development and use of biomarkers by enhancing its regulatory review and communication processes.¹⁰ Public input from this meeting will be used to identify opportunities for biomarker-related regulatory guidance, improving understanding and consistency in regulatory review of individual drug applications that incorporate biomarkers in the design of clinical trials, and potential strategies to facilitate scientific exchanges in regulatory and non-regulatory contexts.

Critical Issues in Biomarker Development for Clinical Trial Enrichment

Once a biomarker candidate has been selected on the basis of biological plausibility and technical feasibility, statistical validation is required to justify its use in a clinical trial. Validation of a biomarker begins with an initial demonstration that a correlation exists between the marker and the clinical endpoint of interest, followed by independent statistical validation of this relationship.¹¹ For prognostic biomarkers, which offer information about the likely course of a disease if there is no change in treatment of an individual, statistical validation is relatively straightforward and can be accomplished through retrospective studies using data from well-conducted clinical trials.¹² In the case of predictive biomarkers, however, more rigorous standards must be met to justify their use in a clinical setting. Since predictive biomarkers seek to prospectively identify patients likely to have a favorable clinical outcome in response to targeted therapies, validation often may require comparing outcomes between biomarker-positive and biomarker-negative patients.¹³ Thus, prospective, randomized controlled trials (RCTs) remain the best approach for establishing the clinical utility of predictive biomarkers.¹⁴ Yet traditional RCTs only allow for the estimation of the average treatment effect in the overall study population rather than in marker-defined subpopulations. Therefore, alternative trial designs need to be considered for the evaluation and application of biomarker-based therapies.¹⁵⁻¹⁷

It has been recognized that adaptive clinical trials can drastically improve the efficiency of the drug development process by allowing for more streamlined trial designs that collect data from both biomarker-positive and biomarker-negative patients.^{18, 19} Yet, clinical trial design methodologies to test the clinical utility of candidate biomarkers are still in development. The choice of an appropriate design for a trial will largely depend on the strength of existing evidence for a biomarker, the nature of conclusions to be drawn, the strength of evidence desired at the trial's conclusion, and available resources.^{20, 21} If evidence suggests that the benefits of a treatment are limited to the biomarker-positive subpopulation, an enrichment design strategy, in which only biomarker-positive patients are enrolled, may be the appropriate choice. Because they require relatively small sample sizes to demonstrate safety and efficacy, enrichment strategies may improve trial efficiency.²² However, such designs only allow for partial evaluation of the clinical validity of biomarkers since they do not provide information on the effects of treatment in biomarker-negative patients. For example, enriched clinical trials that enrolled women with human epidermal growth factor receptor 2 (*HER2*) positive breast cancer demonstrated that a targeted cancer therapeutic combined with adjuvant chemotherapy

significantly improved disease-free survival.²³ However, subsequent studies suggested that the benefit may not be limited to patients with that biomarker.²⁴

If there is sufficient reason to suggest that a biomarker can predict that a therapy will be more effective in biomarker-positive patients, but the evidence is not compelling enough to rule out clinical efficacy in biomarker-negative patients, a biomarker-stratified trial design or an adaptive enrichment trial design may be more appropriate.^{15, 18, 19} In the biomarker-stratified trial design, biomarkers are used to guide analysis but not treatment assignment. In the adaptive enrichment trial design, biomarkers are used to guide the enrollment and not treatment assignment. By assigning biomarker-positive and -negative patients to both experimental and control groups, the biomarker-stratified trial design provides more information on the effects of treatment in both subpopulations, as well as more definitive evidence for the clinical utility of the biomarker.¹⁴ Alternative, yet problematic, biomarker-based strategies exist in cases where the evidence for a biomarker's predictive ability is weak.¹⁸⁻²⁰ FDA has previously released two comprehensive draft guidance documents for industry on (1) various enrichment strategies, including a detailed discussion of each strategy with examples; and (2) adaptive design clinical trials.^{17, 25} Ultimately, the selected trial design has implications for both the length and cost of a study, in addition to the generalizability of its results.

Approaches to Collaborative Co-Development of Therapies and Diagnostics

The timely co-development of companion diagnostics that can accurately measure biomarkers of interest is becoming increasingly important and necessary for both the biomarker evaluation process and the application of biomarkers to the development of new therapeutics. However, several operational and logistical challenges exist in the co-development of companion diagnostics.²⁶

Ideally, companion diagnostics should be developed contemporaneously with their corresponding therapeutic so that analytical* and clinical validation† of the diagnostic can be established using data from the clinical development program of the corresponding therapeutic product. However, co-development can be difficult due to fundamental differences in development models for diagnostics and therapeutics.²⁷ Other significant challenges to co-development of companion diagnostics include uncertainty about the regulatory pathway to market, weak financial incentives for investment, and clinical, logistical, and resource-related constraints during the development process.²⁸ Greater regulatory clarity may help resolve these issues and assist stakeholders, especially payers, in determining the value of companion diagnostics. To that end, FDA has published guidance documents and a concept paper for industry that seek to address various regulatory concerns.²⁹ Other stakeholders have proposed biomarker evaluation frameworks that recognize analytical validation – the assessment of a test's measurement performance characteristics and the range of conditions under which the test will give reproducible and accurate data – as a prerequisite component in the biomarker evaluation process.⁸

Co-development of therapeutics and companion diagnostics is increasing, yet FDA has traditionally regulated these medical products separately.³⁰ Because of growth in this area, FDA's Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH) have taken a range of steps to coordinate and clarify the review process for co-developed therapies and diagnostics.

Accelerating the Use of Biomarkers as Replacement or Surrogate Endpoints

Clinical trials designed to evaluate a therapeutic intervention require clinical endpoints – events or outcomes that can be measured objectively to determine whether the intervention being studied is beneficial. In some disease areas, including oncology, a common clinical endpoint is survival. Since cancer may progress slowly,

* Analytical validity refers to how well a test measures the biomarker of interest.

† Clinical validity refers to a test's ability to diagnose a disease or predict response to a treatment (e.g., whether test result correlates with target condition of interest in a clinically significant way).

however, clinical trials seeking to evaluate the benefits of a therapeutic on survival may require years of observation before conclusions can be drawn.³¹ Surrogate endpoints—that is, biomarkers that are intended to substitute for primary clinical endpoints but can be measured sooner or more conveniently—also hold promise to reduce both the length and cost of clinical trials. The possibility of demonstrating clinical benefit sooner using surrogate endpoints has generated much interest among stakeholders. FDA has developed guidance on review programs, including the Accelerated Approval Program, which is intended to expedite the approval of therapeutics (based on surrogate endpoints) that treat serious conditions where there is unmet need. A drug that demonstrates an effect on a surrogate endpoint reasonably likely to predict clinical benefit may qualify for accelerated approval or breakthrough therapy designation.³²

However, evaluation of biomarkers as surrogate endpoints is a challenging task. It has been proposed that for a biomarker to be considered a surrogate, it must be (1) a correlate of the true clinical outcome and that (2) the treatment effect on the surrogate should capture the full effect of treatment on the clinical endpoint.³³ While the first criterion is relatively simple to demonstrate, the second is not. For example, although the risk that human immunodeficiency virus (HIV)-infected pregnant women will transmit the infection to their infants is strongly correlated with maternal CD4 counts, the provision of therapy to increase maternal CD4 counts has not been found to impact transmission risk because the CD4 count is not in the causal pathway of the disease processes that are responsible for transmission. Rather, CD4 count and risk of transmission are both influenced by viral load, which appears to be the causal factor for risk of transmission.³⁴ The use of pathological complete response (pCR) to support accelerated approval in neo-adjuvant treatment of high-risk breast cancer is a recent example of the difficulty of evaluating potential surrogate endpoints. Although it has been found that patients who achieve a pCR live longer than those who do not, a recent meta-analysis led by FDA could not establish the magnitude of pCR effect necessary to predict a meaningful improvement in event-free survival.³⁵

Other reasons why surrogates may fail to capture the effect of an intervention on clinical outcomes include cases where a disease has multiple pathways and the intervention affects only one pathway mediated through the surrogate, when a surrogate is not affected by the intervention's effects, or when the intervention has mechanisms of action independent of the disease process.³⁶ Given these ongoing difficulties, alternative approaches have been developed that seek to demonstrate surrogacy based on correlation. Meta-analysis approaches, for example, seek to demonstrate that the surrogate is correlated with the disease outcome and that the effect of the intervention on the surrogate is sufficiently correlated with the effect on the true endpoint. Nevertheless, the appropriate use of surrogate endpoints remains difficult, as a particular biomarker's status as a surrogate is context-specific and cannot be assumed to be a general surrogate endpoint separate from its designated use.⁸

Evidentiary Needs and Implications of Biomarkers as Surrogate Endpoints

Payers have recognized the potential for personalized medicine to improve quality of care and, in some cases, to reduce costs. However, in an increasingly cost-sensitive environment, payers are becoming more cautious in making coverage decisions, seeking to find a balance between cost and benefit for their beneficiaries.³⁷ Therapeutics approved through expedited programs are required to meet postmarket commitments, including postapproval studies that demonstrate the clinical benefits of therapeutics on relevant outcomes. Yet data suggests that a significant proportion of pharmaceutical sponsors are failing to meet their postmarket commitments.³⁸

For patients, providers, and payers, the clinical and economic benefits of a new treatment compared to existing treatments must be demonstrated to justify coverage and use. Therefore, future efforts should seek to align the values and expectations of relevant stakeholders through early engagement during the drug development process and in the postmarket setting.

Meeting Objectives

The Engelberg Center for Health Care Reform at the Brookings Institution, in cooperation with FDA, is holding a public meeting to discuss current scientific and regulatory approaches to biomarker development, acceptance, and utility in therapeutic development programs. This meeting will bring together diverse representatives from industry, academia, patient advocacy groups, payers, and government agencies. Through this meeting, stakeholders will have the opportunity to identify and prioritize the most promising strategies for advancing the use of biomarkers and pharmacogenomics in drug development. Input from the meeting will be used to: 1) identify opportunities for biomarker-related regulatory guidances; 2) improve understanding and consistency in regulatory review of therapeutic product applications that incorporate biomarkers in the design of clinical trials; and 3) identify potential strategies to facilitate scientific exchanges in regulatory and non-regulatory contexts. This meeting will not specifically focus on discussion involving rare diseases and biomarkers as drug development tools under the Biomarker Qualification program.

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