

Executive Summary

Biomarkers for use in drug discovery and development have grown markedly in importance during the past decade, due in large measure to the following factors:

- Pharma's perceived need to reduce costs and increase NCE (New Chemical Entity) introductions by achieving early attrition of unsuitable compounds
- The availability of Genome Era technologies that accelerate discovery of new biomarkers and facilitate the use of multicomponent pattern biomarkers
- Improvements in imaging technologies that facilitate in vivo studies of disease processes and drug targeting
- The rise of the translational medicine paradigm, which uses biomarkers to help ensure continuity in moving from animal models to human subjects
- The increased proportion of programs dealing with new and relatively unprecedented drug targets

As biomarkers have grown in importance, pharma R&D people have moved from relatively informal, intuitive ways of dealing with biomarker discovery and implementation to more formal means, often employing strategic planning, tactical planning, and business analysis fairly early in the discovery stage. The extent to which planning and business analysis are formalized differs among companies, and the organizational structures used in these processes vary as well. In all pharmaceutical companies, systems for planning, implementation, and employment of biomarkers remain a work in progress, continually evolving as still-scarce information on outcomes of biomarker-driven programs collects.

This report deals with 4 primary issues:

1. Strategic planning for biomarkers in drug discovery and development
2. Tactical planning for the implementation of biomarkers in programs
3. Organizational structures for biomarker implementation
4. Approaches to risk/cost-benefit analysis for biomarker programs

In gathering information to address these points, we have relied heavily on semiformal interviews with pharma managers and other knowledgeable individuals and on a survey conducted among a more general population of pharmaceutical and biotechnology R&D personnel.

The current paradigm in pharma specifies that biomarkers are not being used merely to assuage scientific curiosity but to answer specific questions that provide decision-support data as a compound or series moves down the pipeline to increasingly expensive stages of development. Such questions generally correspond to a series of biomarker categories. Companies differ in their biomarker taxonomies, but the following is a common breakdown into 4 categories (Hurko O. *Drug Disc World*. 2006;7:63–74).

1. Clinical response biomarkers that identify subjects who will be optimally responsive to a drug in initial human testing. This is especially important when a drug addresses a high-risk target that has never been proved in humans.
2. Mechanism-of-action biomarkers that directly quantify drug-target interactions. These are especially useful in early development to guide initial dosing regimens before the drug-response relationship with respect to clinical outcomes has been established.
3. Efficacy biomarkers that demonstrate the relevance of a drug candidate to the pathophysiology of the disease in question. In this sense, the biomarker serves as a surrogate for the clinical endpoint, even though it may not have achieved official status as a surrogate endpoint. Such biomarkers can provide support for advancing or dropping a drug, especially one that addresses a high-risk target.

4. Safety biomarkers that can exclude subjects who might react adversely to a drug or at least identify an adverse reaction at an early stage in a subject receiving a drug. Another type of safety biomarker characterizes toxicity and can be used in preclinical studies to predict whether a compound will be toxic in humans.

Biomarkers can also be divided into those that relate to the compound or drug mechanism in question and those that relate strictly to the disease process. The latter often act as surrogates for a clinical measurement and allow monitoring the response to therapy without waiting for, for example, death to intervene. Biomarkers in this category become candidates for precommercial development, and several consortia have formed to discover and develop methods for such biomarkers. The latest and most significant of these is the FDA/NIH/PhRMA (Food and Drug Administration/National Institutes of Health/Pharmaceutical Research and Manufacturers of America) Biomarkers Consortium, which was officially launched October 5, 2006. As with the SNP (Single Nucleotide Polymorphism) Consortium, participating pharmaceutical companies will contribute funds so that they, possibly together with academicians and diagnostics companies, can identify and develop assays for biomarkers to be used by any or all participants. These biomarkers will be mainly or entirely disease related.

A second major external factor is affecting both the way biomarkers are used and the nature of the drug discovery and development paradigm. Although it has always been possible in the United States to apply for INDs (Investigational New Drug Applications) that permit microdosing of humans with drug candidates based on minimal supportive data, the FDA's CDER (Center for Drug Evaluation and Research) unit published a guidance in January 2006 clarifying what have come to be called *exploratory INDs*, and encourages their use. The guidance clarifies microdosing limited numbers of subjects to help identify pharmacokinetic and mechanistic properties of compounds before starting formal Phase I trials. The guidance was given high priority since it is viewed as supporting the FDA's Critical Path Initiative. Pfizer and several other pharma companies are already conducting such "Phase 0" trials, and many more are in the planning stage. The exploratory IND concept may also permit biomarker-enabled studies of efficacy for unprecedented targets with limited numbers of patients enrolled in Phase I studies.

The increasing use of novel, unprecedented targets, about which relatively little is known, challenges the classical drug discovery and development pipeline sequence of activities. More than half of all programs now address such targets, which carry the burden of increased risk of failure in late-stage clinical trials. According to Orest Hurko, Wyeth's Assistant Vice President, Translational Research, and a member of the Advances Reports Advisory Board, major reasons for such failure include the following:

- A drug is administered to the wrong subjects, that is, a mixture of responders and nonresponders.
- The drug is given at the wrong dose: Either too little is administered for adequate receptor occupancy or too much is given so that receptors are saturated and excess drug is more likely to cause off-target effects.
- Indirect efficacy indications provided by clinical measurements are either too noisy or come too late for adequate initial testing of new and unproven targets.
- Some patients become ill from drug exposure.

Strategic planning for biomarkers attempts to answer these questions for a given program. Planners must decide such issues as whether a clinical measurement will suffice, whether an existing validated biomarker can do the job, or whether a new biomarker must be discovered and a method for its measurement developed and validated. If a biomarker is indicated, it will usually be intended to provide the following information:

- Biomarkers for identification of optimally responsive subjects for initial clinical testing. These are particularly beneficial for high-risk targets that have never been proved in humans.
- Biomarkers that permit direct quantification of drug-target interactions for selection of initial dosing regimens, especially in early-stage development before the drug-response relationship for clinical effects has been established.
- Efficacy biomarkers that can cost-effectively demonstrate the relevance of an unproven drug target to the pathophysiology of the disease under consideration, before committing major financial resources to large registration studies with clinical endpoints.

- Safety biomarkers that ideally can be used to exclude subjects who are likely to become ill after exposure to the drug in question, or at least that can identify adverse reactions early on after dosing so that subjects can be withdrawn from the study before becoming ill.

Although big pharma companies differ somewhat in the methods and timing for biomarker strategic planning, they generally either start such planning very early in the discovery process or intend to do so in the near future. In some instances, planning and implementation for efficacy-related biomarkers actually begin before a final disease target is determined. Since getting a new biomarker on-line can take a year or more of effort, planning for biomarkers to be used in early development clearly needs to begin as soon as strategic issues can be clarified. Planners must also decide early on whether to develop biomarkers in-house or to outsource the effort.

The types of biomarkers and levels of validation differ depending on the stage of a program. Essentially all scientific experiments done in pharmaceutical R&D require a molecular or functional readout that could formally be considered a biomarker. Many such experiments are conducted at the prediscovery stage in the process of characterizing potential targets. The readouts from such experiments are not usually considered biomarkers. However, as mentioned earlier, disease-related biomarker development may actually precede target identification. During the discovery phase, mechanism-of-action biomarkers are particularly useful to verify that a compound is hitting its intended target, whether using cells in culture, tissues, or intact animals. The degree of validation of a biomarker typically increases in stringency as a compound or series advances down the pipeline.

Biomarkers become especially valuable at the preclinical development stage of a program, when spending rates start to accelerate markedly. Preclinical studies with animal models often use biomarkers as a means to strengthen predictability of successful translation to humans. In fact, translational medicine departments in pharma are increasingly becoming centers of biomarker planning and development. Biomarkers for preclinical development are typically related to pharmacodynamics, efficacy, and safety. Naturally, biomarkers that are suitable for use in animal models often cannot be translated to human clinical studies, since specimens may be collected from animal sites that are not accessible in humans (e.g., brain tissue). Therefore, although it may be permissible to do gene expression profiling on tissue collected from animal models, this must often be replaced with protein or metabolite

signatures accessible in biological samples from humans. Biomarkers based on in vivo imaging studies can be particularly useful in translation if they are equally applicable to animals and humans.

Much of the biomarker work in human studies occurs in Phase 0 or Phase I development. Biomarkers to aid in dose-ranging and to confirm the mechanism of action have their greatest usefulness in these early stages, whereas biomarkers to select patients who are most likely to respond to a drug and to predict adverse reactions become useful in Phases II and III. Usually, the proof of concept for a drug candidate must await Phase II studies, but increased use of high-quality biomarkers to predict efficacy suggests that, in some cases, patients can be included in Phase I trials. Clinical endpoints for efficacy monitoring are preferred when possible, especially since validating biomarkers for status as surrogate endpoints can be a long and arduous process.

Pharmaceutical companies employ one of several organizational structures to deal with biomarkers. Wyeth's Dr. Orest Hurko describes 3 major models:

1. The *Explicit Model*, where the biomarker or translational medicine group stands independently alongside the discovery and clinical development organizations
2. The *Implicit Model*, where biomarker activities are absorbed into pre-existing research and development organizational entities
3. The *Hybrid Model*, where biomarker activities are segmented independently, but report in a matrix arrangement to discovery and clinical development organizations

Bristol-Myers Squibb employs something approximating the Explicit Model, in which biomarker work centering on the translation from preclinical development through proof of concept in early development is centralized. However, early discovery and safety biomarker work are decentralized into functional organizations. AstraZeneca employs an Implicit Model, in which most biomarker planning and implementation work are done within existing functions, although a separate group is charged with bringing new biomarker-related technologies into the company. Lilly employs a Hybrid Model in which a governing Biomarker Working Group assures that project teams properly formulate a biomarker strategy and plan for its timely implementation. Pfizer also employs a Hybrid Model, in which a translational medicine group deploys representatives into therapeutic

area teams to influence the course of biomarker needs. The translational medicine department retains budgetary control for biomarker outsourcing.

Once the biomarker strategic plan is in place, researchers need to assemble a tactical plan for implementation of biomarkers in their project. The tactical plan must include the means for biomarker acquisition (if possible), biomarker discovery (if necessary), method development, and biomarker validation. Whereas strategic plans vary considerably according to the needs of the project, tactical plans become increasingly formatted and subject to company guidances and standard operating procedures.

Since validation of biomarker assays is critically important, it has become the subject of intense consideration, and this focus has led to the emergence of the fit-for-purpose validation concept. An intercompany group recently published a position paper setting forth guidelines for 4 levels of validation, in order of increasing rigor: (1) pre-analytical and method development, (2) exploratory method validation, (3) advanced method validation, and (4) in-study validation (Lee JW et al. *Pharm Res.* 2006;23:312–328). Assay parameters considered at each validation level include dynamic range, sensitivity, selectivity and specificity, analytical precision and accuracy, and biological recovery/accuracy. Details for each level are presented in Chapter 3.

Companies differ in the degree to which they have centralized and formalized method development and validation. For example, Bristol-Myers Squibb has a Biomarker Best Practices guidance that allows a great deal of latitude depending on the needs of the project. Eli Lilly provides its researchers with a brief guideline setting forth mainly objectives and expectations for biomarkers in a program. Pfizer provides an extensive guideline to its project teams that includes details on all manner of issues and perspectives that may need to be considered in deploying biomarkers for a project. A description and extracts from this document can be found in Chapter 6.

Companies also differ in their decision processes for developing biomarkers in-house versus outsourcing. For example, although Bristol-Myers Squibb generates biomarkers for early development primarily in-house, it does do some outsourcing. Decisions are based primarily on cost-effectiveness. Lilly develops essentially all biomarkers for use up through the preclinical phase in-house; biomarkers for later stages may

be developed either way. However, Lilly has chosen not to establish the capability to develop imaging biomarkers in-house. Pfizer does a limited amount of imaging biomarker development in-house, choosing to outsource it for the most part. For molecular biomarkers, the decision is made for each case, considering in-house resources and capabilities, cost, quality if outsourced, track record of potential vendors, need to maintain control, and speed. Pfizer and others now add the option of giving development of some biomarkers over to the emerging precommercial Biomarkers Consortium.

In viewing organizational structures for biomarker work, we consider the 3 models delineated by Wyeth's Orest Hurko (see above). As was mentioned, Bristol-Myers Squibb exemplifies the Explicit Model, AstraZeneca the Implicit Model, and Lilly and Pfizer the Hybrid Model. Details for each organization are presented in Chapter 4.

When researchers decide they need to discover new biomarkers or develop new assays, they may require funding that can run into the millions of dollars spent over a year or more. Clearly, when time and cost start to mount, some level of business analysis can be beneficial. This can take the form of ROI (return on investment) analysis, cost/risk-versus-benefit analysis, or both. Pfizer is one of the few pharma companies to provide its project teams with a formal software tool for ROI analysis and to encourage its use. Although gaining momentum, it has not yet been universally adopted by project teams. As demonstrated in the Pfizer case study in Chapter 6, business analysis in biomarker programs can aid in choosing whether to take on a biomarker program, whether to do the work in-house or outsource it, or even whether to wait for an industry consortium to provide a solution. Unfortunately, many programs employing new-wave biomarkers are still in development, so that ultimate benefits (or lack thereof) of biomarkers are not yet visible for use in business analysis.