Biomarkers in Clinical Development:
Implications for Personalized Medicine and Streamlining R&D

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Expert Interviews

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Executive Summary

The “one drug fits all” paradigm of drug discovery has been the standard for many years, but the pharmaceutical industry is experiencing a shift toward “the right drug at the right dose in the right patient” approach, also known as personalized medicine. Biomarkers have the potential to play a critical role in personalized medicine. This report will look at the current state of biomarker development and application, with a close look at the technologies and how they are being deployed from research to the clinic. A biomarker discovery discussion will include the areas of theranostics, proteomics, pharmacogenomics, and molecular imaging. The FDA’s view on validated and unvalidated biomarkers will be examined, as well as the influence of pharmacogenomics on new drug therapies and biomarker detection devices. Examples of successful biomarker programs will be discussed. Interviews with industry leaders are presented to specify current and future biomarker programs. Deals involving biomarkers between pharmaceutical companies and biotech and non-profit companies are detailed and discussed. Finally, technologies that are required to discover and screen biomarkers are discussed, particularly with regard to their impact on both biomarker identification and application in wide-scale clinical use.

One goal of biomarker usage in clinical research is to expedite the drug development process to produce drug therapies as efficiently as possible, while maintaining the safety profile. Biomarkers have been used for decades, from monitoring blood pressure to lipid levels.

Biomarkers can be influential in every phase of drug development, from drug discovery and preclinical evaluations, through each phase of clinical trials and into post-marketing studies (Figures 1.1 and 1.3).
Figure 1.1. Phases of the Drug Development Process That Are Impacted by Biomarkers

Source: Reprinted from Disease Markers, Volume 18, AB Kantor, “Comprehensive phenotyping and biological marker discovery,” pages 91–97, Copyright 2002, with permission from IOS Press.

Figure 1.3. Value Proposition of Biomarkers Throughout the Therapeutic Development and Application Phases

Source: Beachhead Consulting
Protein biomarkers and corresponding tests can be used to predict and monitor drug response. This enables the stratification of patients into groups that are most likely to respond to a certain drug treatment regimen with minimal side effects. A diagnostic test that can increase the clinical utility of a drug and reduce the risks and costs associated with developing and marketing that drug creates synergy, which leads to improved disease management.

Technologies used to identify and measure biomarkers are as diverse and numerous as the biomarkers themselves. From the traditional \textit{in vitro} analyses of gene patterns, gene expression, protein expression, and metabolite quantification, to the \textit{in vivo} measurement of biological processes in both animal and human subjects using functional imaging technologies, the goal of these technologies is to correlate the biomarker to clinical data. One way to describe these technologies is by measuring the throughput (or measure of data transmission) as low, medium, or high. The list below gives examples of some of the more commonly used technologies available today:

- **Pharmacogenomics**
  - Microarrays

- **Proteomics**
  - 2D-PAGE
  - Isotope-coded affinity tags
  - MALDI
  - LC-MS/MS
  - Imaging MS
  - Free flow electrophoresis
  - Protein arrays
  - Affinity-based MS techniques
  - Tissue arrays

- **Metabolomics**
  - 2D-PAGE
  - Mass spectrometry
  - Protein arrays – Suspension and solid-support based
  - Tissue arrays
Executive Summary

- **Systems Biology**
  - Protein pathway mapping
  - Modeling and predicting biological response

- **Molecular Imaging**
  - Computed Tomography (CT)
  - Magnetic Resonance Imaging (MRI)
  - Positron Emission Tomography (PET)
  - Single-Photon Emission Computed Tomography (SPECT)
  - Biophotonic imaging

All of these technologies have greatly impacted the drug discovery process. Figure 2.2 demonstrates the flow of information from the clinic into discovery to enable biomarker discovery and application.

The approach to biomarker discovery and development varies within the pharmaceutical industry. These approaches are discussed for several pharmaceutical companies, including Pfizer, Bristol-Myers Squibb, Roche, and Novartis. Biotechnology companies, such as SurroMed, are also profiled, and a table listing deals made between the two industries is included. Interviews were conducted with individuals from Personalized Medicine Partners, Pfizer, Merck, SurroMed, BG Medicine, Indiana Center for Applied Protein Sciences, Ingenuity Systems, and the FDA; their insights are presented.

Many of today’s therapies that have been brought to market by biomarker technologies are discussed, including Iressa, Herceptin, Gleevec, Amevive, and Enbrel. Diagnostic tools associated with these medications, including DakoCytomation’s HercepTest (Herceptin) and Ventana Medical System’s VentanaDx c-Kit Test (Gleevec), which are essential to the drug’s success, are examined.

The FDA’s view on biomarker research and development is highlighted in this report. The FDA has issued guidelines to help guide the industry with regard to biomarkers and the approval process. The agency is encouraging pharmaceutical companies to share their pharmacogenomic data so that both the agency and the pharmaceutical industry can benefit from this learning process.
The cost to discover and develop a drug is increasing dramatically; however, the number of approved new drug products is on the decline. Drug manufacturers are desperately searching for ways to expedite the drug discovery process while decreasing the expense. They are turning to the area of biomarkers as one possible solution to this problem. Patient-enrichment strategies use biomarkers to identify certain patient populations that are more likely to respond to the drug therapy or to avoid specific adverse events.
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CHAPTER 1

INTRODUCTION

1.1. Scope of Report

The “one drug fits all” paradigm of drug discovery has been the standard for many years. However, the pharmaceutical industry is experiencing a shift toward “the right drug at the right dose in the right patient” approach, also known as personalized medicine. Biomarkers have the potential to play a critical role in personalized medicine. This report will examine the current state of biomarker development and application, with a close look at the technologies and how they are being deployed from research to the clinic. A biomarker discovery discussion will include the areas of theranostics, proteomics, pharmacogenomics, and molecular imaging. The FDA’s view on validated and unvalidated biomarkers will be examined, as well as the influence of pharmacogenomics on new drug therapies and biomarker detection devices. Examples of successful biomarker programs will be discussed. Interviews with industry leaders are presented to specify current and future biomarker programs. Deals involving biomarkers between pharmaceutical companies and biotech and non-profit companies are detailed and discussed. Finally, technologies that are required to discover and screen biomarkers are discussed, particularly with regard to their impact on both biomarker identification and application in wide-scale clinical use.

1.2. Overview of Biomarkers

With so many new molecular entities entering the drug development pipeline, more powerful discovery and screening technologies are much needed to streamline the process to make therapeutic agents available to patients as efficiently and safely as possible. One approach to achieve this goal is to avail oneself of the multitude of analytical tools that can assess biological parameters known as biomarkers.
Biomarkers represent the real entrée into the world of personalized medicine. While a lot of hype and speculation has occurred in the press about the availability of the $1,000 genome, modern medicine is a long way from every individual having their own personal genome, or even their own personal genotype, on a CD or implantable “biochip” that can be used to predict disease and diagnose the appropriate therapeutic.

Biomarkers have been used for decades, primarily to diagnose and prescribe the appropriate treatment. Blood pressure, for example, is a biomarker that drove the development and use of antihypertensive compounds, a market that reached $9.2 billion in the United States in 2004. Similarly, LDL cholesterol levels have driven the entire statin market to $10.5 billion in U.S. sales in 2004, led by Pfizer’s Lipitor.

Applications in Clinical Research

Pharmaceutical companies are currently panning for new types of biomarkers, in a targeted pharmacological gold rush. Driven by examples coming from a small number of compounds, the industry is looking to biomarker programs to predict clinical failure and success, often through limiting the targeted patient population for the designed therapeutic. So-called “patient-enrichment strategies” are under development in an effort to create a set of biological measurements to refine the clinical population—all geared toward a better success rate for the drug.

In clinical trials, the measurement of biomarkers can help explain empirical results by noting the effects of interventions on molecular and cellular pathways and relating these to clinical responses. In this way, biomarkers provide researchers an understanding of the differences in clinical response that may be influenced by uncontrolled factors (The Biomarkers Definitions Working Group, 2001).

Predicting clinical outcomes based on biological measurements is the goal of all biomarker discovery. Successfully establishing biomarkers as surrogate endpoints is believed to add substantial value to the modern pharmaceutical development process, thereby accurately predicting the success or failure of compounds before they enter the costly phases of drug development.

Although a biomarker may be discovered in early phase research, the ability to adequately screen for this biomarker in the context of preclinical and clinical studies may not always be possible. The
technical feasibility of method validation and biomarker qualification needs to be thoroughly investigated before the development plan is finalized. Molecular imaging technologies are seen as potential methods to successfully translate between research, preclinical, and human trials. Other measurement technologies are applicable; however, they suffer from a variety of issues, including specificity, ability to measure in vivo, sensitivity, and screening costs.

Biomarkers can be beneficial to many aspects of drug development. Biomarkers can help identify patient populations, alter pathophysiologic mechanisms, and achieve clinical outcomes. The ability of a biomarker to predict a patient’s response to a drug is the challenge. Biomarkers may also help regulators approve new drug products faster and more effectively. The goal of all of these factors, in effect, is to provide new drug products to the patients as expeditiously and safely as possible.

Biomarkers can be influential in every phase of drug development, from drug discovery and preclinical evaluations through each phase of clinical trials and into post-marketing studies (Figure 1.1).

**Figure 1.1. Phases of the Drug Development Process That Are Impacted by Biomarkers**

Source: Reprinted from Disease Markers, Volume 18, AB Kantor, “Comprehensive phenotyping and biological marker discovery,” pages 91–97, Copyright 2002, with permission from IOS Press.
Beneficial Impacts of Biomarkers

Attrition rates in drug development are alarming. Among the ten largest pharmaceutical companies, during the period 1991–2000, attrition rates were as follows:

- 38% of the drugs dropped out in Phase I due to safety/blood levels
- 60% of those remaining failed in Phase II due to basic efficacy failures
- 40% of the remaining candidates failed in Phase III, again due to efficacy failures
- 23% of those that made it through the clinic failed to be approved by the FDA

That translates to about an 11% success rate from starting in the clinic (Kola and Landis, 2004). The question is, can biomarkers have an impact on attrition rates?

Patients rely on innovations such as biomarkers to maintain their health and well-being and to aid in fighting ever-more-complex diseases. The pharmaceutical market is highly competitive, providing incentives for pharmaceutical companies to be the first to bring a new innovation to the market. As shown in Figure 1.2, not all released drugs result in profits for the drug makers. In fact, 70% of released compounds are less than break-even propositions. This does not take into consideration the number of compounds that fail to be released.

Overall, innovations like biomarkers do not merely have to save time and money in the development cycle; they must also drive the released pharmaceutical into a more profitable proposition for the manufacturer. This can be accomplished in a number of ways: the compound can be significantly more effective than its competitors; the compound can demand a higher price based on its value and effectiveness; or the compound must be effective for its intended target market.
Biomarkers in Clinical Development: Implications for Personalized Medicine and Streamlining R&D

Figure 1.2. Effective Profitability of Approved and Released Pharmaceuticals


Biomarker-based drug development can offer both faster development time as well as higher efficacy based on a selected patient population. It can, however, also be used competitively to allow companies to pursue a leading edge over existing compounds.

Some therapeutic areas are more amenable to biomarker usage than others. Neurology, cardiology, and oncology appear to be three therapeutic areas generating the most biomarker research. Dr. David Lester, New York Site Head for Worldwide Clinical Technology at Pfizer, Inc., states, “There are therapeutic areas where biomarkers are used more, and there are more traditional biomarkers. The cardiovascular area is dominated by biomarkers, whereas an area like oncology has recently exploded with biomarker research as we are really beginning to understand the importance of the population and the disease itself. So it is different for each therapeutic area.”
An executive at Merck expands on this: “Merck’s interest in biomarkers is across the therapeutic areas of our current investigation, although we recognize that there are areas of greater tractability of biomarkers in some therapeutic areas that are better than in others, which factors into the kind of effort we apply. For example, in neuroscience, many of the traditional, circulating blood biomarkers are fewer and farther in between, but an experimental model may be feasible and could be used instead of a biomarker in that case. Also, we endeavor to make sure that we have our biomarkers represented in the earliest drug development studies as possible.”

By focusing as early in the process as possible, pharmaceutical companies realize that increased profitability comes from “killing off” bad compounds as early as possible. A lot is discussed in the press and at conferences about clinical biomarkers that predict a patient’s response to a drug. This is not hype, but it does represent only a small percentage of the biomarker potential.

Novartis’ Gleevec (imatinib) targets an enzyme called Bcr-Abl, which leukemia cells use to proliferate. Gleevec attaches to the cancerous cells and stops them from growing and spreading. In the case of Gleevec, the molecular translocation called the Philadelphia chromosome defines chronic myelogenous leukemia (CML). The Philadelphia chromosome produces a specific tyrosine kinase enzyme, Bcr-Abl, which is the target of Gleevec. Clinicians use this mutation as a biomarker that determines the level of receptor expression to better identify those patients who will respond to therapy.

Gleevec is Novartis’ second-biggest product, with sales of $1.1 billion in the first nine months of 2004. But in some patients, perhaps 12%, the cancer cells mutate just enough to be resistant to Gleevec.

Bristol-Myers Squibb is targeting patients whose response to Gleevec declines over time. Its drug is known by the experimental name BMS-354825. According to a Bristol-Myers Squibb press release in December 2004, “BMS-354825 is a rationally designed oral investigational agent that inhibits five tyrosine kinase proteins, including Bcr-Abl, the protein that accounts for abnormal cell growth in CML, and SRC, proteins that may play a role in imatinib resistance.”

During a trial, 31 of 36 patients with advanced CML who had not been helped by Gleevec had a complete hematologic response to BMS-
BMS-354825 affects a different enzyme called SRC, pronounced “sark.” (Novartis is reported to be working on its own “Super-Gleevec.”) In this case, Novartis has a clear advantage with its released compound, which is specific to a set of patients with a particular biomarker. Through further study of additional biomarkers, thereby widening the net, Bristol-Myers Squibb may be able to address part of Novartis’ billion-dollar market.

Figure 1.3. Value Proposition of Biomarkers Throughout the Therapeutic Development and Application Phases

Source: Beachhead Consulting

As shown in Figure 1.3, the implementation and success of biomarkers is not limited only to the pharmaceutical industry. From the drug companies and their partner biotechnology companies, through to the patients and the insurance industry, better and more successful pharmaceuticals imply better healthcare and increased profitability for the various stakeholders involved.
1.3. Biomarkers: Definitions and Taxonomy

A biological biomarker, as defined by the Biomarkers Definitions Working Group, is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention. A molecular biomarker is an early sign of change in an organism’s physiological state, such as adaptation, stress, or injury, due to environmental factors or disease (The Biomarkers Definitions Working Group, 2001). For example, it is possible to tell that animals have been exposed to the toxic metal cadmium by measuring their levels of a specific molecule that binds to cadmium, the protein called metallothionein. Increased levels of metallothionein, as well as increased expression of the gene that leads to elevated protein levels, are called molecular biomarkers of exposure. Changes in molecules such as these are sensitive and specific, making them useful sentinels of an organism’s exposure to a specific environmental agent.

Other molecular changes indicate progression of a disease process. For example, hemoglobin is the protein that carries oxygen in red blood cells. A form of hemoglobin called hemoglobin 1AC is a biomarker of diabetes. As blood glucose levels increase in people with adult-onset diabetes, the levels of this form of hemoglobin in their blood increase accordingly, providing a diagnostic marker of the progression of disease. Measurements of hemoglobin 1AC are considered a molecular biomarker of effect (Center for Environmental Health Sciences at Dartmouth). A surrogate endpoint is a biomarker that is intended to substitute for a clinical endpoint (a characteristic or variable that reflects how a patient feels, functions, or survives). A surrogate endpoint is expected to predict clinical benefit based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. Biomarkers can be validated (those for which evidence has established that a drug-induced effect on the surrogate predicts or results in the desired effect on the clinical outcome of interest) or unvalidated (a surrogate that is “reasonably likely” to predict the clinical benefit of interest, but for which there is not sufficient evidence to establish this).
The Biomarkers and Surrogate Endpoint Working Group agreed on a classification system for biomarkers based on their differences.

**Type 0:** Markers of the natural history of a disease which correlate longitudinally with known clinical indices, such as symptoms over the full range of disease states

**Type I:** Markers which capture the effects of an intervention in accordance with the mechanism of action of the drug, even though the mechanism might not be known to be associated with clinical outcome

**Type II:** Markers that are considered surrogate endpoints because change in that marker predicts clinical benefit (The Biomarkers Definitions Working Group, 2001)

As a Type II biomarker (or surrogate endpoint) must be relevant to both the mechanism of action of the drug and the pathophysiology of the disease, this type of biomarker would most likely have the greatest impact on reducing both the overall time and cost of drug development. However, Type II biomarkers are much more difficult to develop than Type 0 or Type I.

### 1.4. The Role of Biomarkers in Drug Development

There are many examples of established biomarkers used today in the drug development process. Blood pressure is an accepted surrogate endpoint (Type II) for antihypertensive agents, as it predicts cardiovascular disease, heart failure, stroke, and kidney failure. Cholesterol has long been recognized as a surrogate endpoint for reduced mortality. Discovered more recently, a protein known as C-reactive protein (CRP) has been shown to be a predictor of heart disease progression. Statin drugs lower CRP, and these are the same drugs that are used to lower cholesterol. The studies have shown that lower levels of CRP were linked to a slower progression of atherosclerosis and fewer heart attacks and death (Ridker et al., 2005). Several classes of agents for bone mineral density have shown to have good correlation with fracture rates; however, conflicting data in the literature preclude the use of these markers as surrogates for any efficacy endpoints in clinical practice. Table 1.1 lists biomarkers already used in drug development.
Validated molecular biomarkers have been instrumental in diagnosing disease and have begun to assume a greater role in drug discovery and development. Biomarkers can greatly enhance the objective of providing more efficacious and safer drugs in an expedient manner. However, the part the biomarker will play needs to be taken into consideration very early in the drug development process, while the therapeutic agent is still being identified and conceptualized.

From 1991 to 2000, the pharmaceutical industry realized the importance of studying the metabolism of an investigational compound in the earlier stages of drug design, thereby producing a dramatic decrease in attrition rates due to pharmacokinetic failures (Figure 1.4; Frank and Hargreaves, 2003).

### Table 1.1. Biomarker/Surrogate Endpoints That Have Aided Drug Development

<table>
<thead>
<tr>
<th>Biomarker/surrogate endpoint</th>
<th>Type of drug</th>
<th>Clinical endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>Antihypertensives</td>
<td>Stroke, atherosclerosis, heart failure</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>LDL-lowering statins</td>
<td>Coronary artery disease, heart attacks</td>
</tr>
<tr>
<td>Viral RNA</td>
<td>Antiretroviral agents</td>
<td>Survival, decrease in infections</td>
</tr>
<tr>
<td>HbA1C, glucose</td>
<td>Antidiabetic agents</td>
<td>Diabetic neuropathy</td>
</tr>
<tr>
<td>CD4+ T cells</td>
<td>Antiretroviral agents, cytokines</td>
<td>Sustained reduction in viral RNA</td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td>Antiglaucoma agents</td>
<td>Preservation of peripheral vision</td>
</tr>
<tr>
<td>Bone mineral density (BMD)</td>
<td>Antosteoporotic agents</td>
<td>Fracture rate</td>
</tr>
<tr>
<td>MRI scans</td>
<td>Agents for treatment of MS</td>
<td>Decrease in rate of progression disease</td>
</tr>
<tr>
<td>CT scans for tumor size</td>
<td>Anticancer agents</td>
<td>Survival</td>
</tr>
</tbody>
</table>

Source: Reprinted from Disease Markers, Volume 18, CD Lathia, “Biomarkers and surrogate endpoints: how and when might they impact drug development?” Pages 83–90, Copyright 2002, with permission from IOS Press.
In order to meet the requirements set forth for pharmacokinetic parameters, in vitro screens for absorption and metabolism have been validated by subsequent correlation with clinical measurements. By using this type of innovation and foresight, biomarkers can have a major impact on attrition rates in the pharmaceutical arena.

The use of mechanism-based biomarkers (biomarkers whose activity is mediated through the theoretical disease mechanism of action) in drug discovery and development can assist in making cost-effective and efficacious decisions. Their use in later phases of drug development can be instrumental with regard to dose selection and disease prognosis. After careful investigation of the disease under study, the identified biomarker needs to represent a critical mechanistic process of the disease progression and be impacted by the appropriate therapeutic intervention. False positive results occur when it is assumed that the biomarker is an integral part of the disease process, when in fact it is associated in a minor way (Colburn, 2003). Biomarkers can be categorized into three distinct compartments, based on their contribution to the logic of the clinical plan. Although they seem to
parallel the three phases of drug development, the objective is to deploy them as early as possible, first to confirm hitting the target and then to test two concepts—namely, that hitting this target alters the pathophysiological mechanism, and altering this mechanism affects clinical status (Frank and Hargreaves, 2003) (Figure 1.5).

**Figure 1.5. The Biomarker Research and Development Process**

Another important consideration in choosing a biomarker is the technical feasibility of method validation and biomarker qualification. Method validation is a process of assessing the assay or measurement performance characteristics of the biomarker. Qualification is the evidentiary process of linking a biomarker with biological processes and clinical endpoints. (The Development of Biomarkers for Decision-Making in the Development and Regulatory Evaluation of New Drugs. A Discussion Paper by the Biomarker and Genomics Working Groups, PhRMA.)
1.5. Risks Associated with Biomarker Usage

There are several inherent risks associated with biomarker usage that need to be investigated carefully before the decision is made to implement the drug development plan. These include:

1. The drug affects the biomarker but does not affect the clinical outcome. In this case, the biomarker is non-specific. If such a biomarker is chosen in early phase clinical development, the pharmaceutical company could end up wasting a lot of money on clinical development that relies on an inappropriate biomarker.

2. The drug affects the biomarker and clinical outcome to a different extent. In this case, there will be some correlation between the biomarker and clinical outcome, but the biomarker will not be able to fully account for the effect on clinical outcome. If the chosen biomarker accounts for a small portion of the clinical benefit, the pharmaceutical company could make a wrong decision to discontinue the development of a good drug.

3. The biomarker may be associated with only an aspect of the effects on clinical outcome. For example, quinidine was found to suppress cardiac arrhythmias, leading to normalization of sinus rhythm. Quinidine treats the arrhythmia, but has not been found to decrease the incidence of sudden death associated with arrhythmias; in fact, no antiarrhythmic drugs have shown this. However, it also caused premature deaths (Lathia, 2002). Like many other antiarrhythmic drugs, quinidine can provoke new lower-chamber or ventricular arrhythmias of a particular type known as torsades de pointes. Torsades is a life-threatening arrhythmia and can result in fainting spells, cardiac arrest, or sudden death.

1.6. FDA’s Perspective on Biomarkers in Clinical Development

Although current law and regulations permit the Food and Drug Administration to base the approval of a therapeutic agent on an unvalidated biomarker, interpreting the data of the surrogate marker as a primary measure makes the approval process much more difficult. On the other hand, the use of biomarkers to obtain information in early phases of drug development is considered appropriate and noncontroversial.
Accelerated Approval Provisions

Typically, approval has been based on well-controlled clinical trials, which show the drug has a beneficial effect that is directly and obviously related to the patient’s clinical status. With the advent of HIV-related diseases in the early 1990s, it was felt that delaying approval of products due to inability to complete trials of reasonable duration or size was inappropriate. The Agency adopted new regulations designed to hasten approval of important new therapies, known as the Accelerated Approval provisions. This provision included verbiage that drug approvals could be based on a surrogate marker in lieu of clinical outcome. The relevant portion of the regulation is as follows:

“The United States Food and Drug Administration (FDA) may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.”

The FDA furthermore required that drugs given accelerated approval based on surrogate markers undergo post-launch confirmatory studies. It is important to recognize that the above regulation applies to the use of unvalidated biomarkers in clinical trials—not validated biomarkers (Katz, 2004).

FDA’s Guidelines on Pharmacogenomic Markers

The FDA has set forth specific guidelines to categorize pharmacogenomic markers based on their degree of validation; namely, the greater the degree of validation, the greater the FDA’s submission requirements (Table 1.2).
Table 1.2. Classification of Biomarkers as Described by the FDA

<table>
<thead>
<tr>
<th>Exploratory Biomarker</th>
<th>Probable Valid Biomarker</th>
<th>Known Valid Biomarker</th>
<th>“Regulatory Biomarker”</th>
</tr>
</thead>
<tbody>
<tr>
<td>A biomarker based on general exploratory or research information, such as broad gene expression screening, or collection of sera or tissue samples, and that has not reached the status of a probable valid biomarker.</td>
<td>A biomarker that has not reached the status of a known valid biomarker because, for example, the supporting data has not been independently replicated or is not conclusive.</td>
<td>A biomarker that is not being used as a regulatory biomarker, but for which there is widespread agreement in the scientific community about its biological significance and which is measured in an analytical system with well-established performance characteristics.</td>
<td>A biomarker being used to support scientific arguments made by the sponsor about drug dosing, safety, patient selection, or effectiveness; or that the sponsor proposes to describe in the drug label; or that are essential to achieve the dosing, safety, or effectiveness described in the drug label, or that will be used for decision making in any clinical trial or in an animal trial used to support safety.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IND</th>
<th>Voluntary data submission (not used for FDA decision making)</th>
<th>Voluntary data submission (not used for FDA decision making)</th>
<th>Abbreviated report and voluntary data submission</th>
<th>Full report and data submission mandatory</th>
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<tbody>
<tr>
<td>Existing NDA</td>
<td>Voluntary data submission (not used for FDA decision making)</td>
<td>Abbreviated report OR synopsis, and voluntary data submission</td>
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<td>Full report and data submission mandatory</td>
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<tr>
<td>New NDA</td>
<td>Synopsis, and voluntary data submission</td>
<td>Abbreviated report and voluntary data submission</td>
<td>Abbreviated report and voluntary data submission</td>
<td>Full report and data submission mandatory</td>
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By working closely with the pharmaceutical industry, the FDA has developed this set of guidelines to provide the pharmaceutical industry with a decisive framework on which to structure clinical studies utilizing pharmacogenomic biomarkers.

Furthermore, new genetic biomarker discoveries, along with their pharmacogenomic-based drug therapies, bring a different set of challenges to the FDA and the pharmaceutical industry. Genomic information allows the pharmaceutical industry to target a specific patient population that is more likely to respond to the drug therapy, or to avoid individuals who are likely to develop specific adverse events, in their clinical studies. This patient-enrichment strategy will reduce clinical study costs and accelerate the drug development process.

The FDA is encouraging pharmaceutical companies to utilize pharmacogenomic data in their clinical investigations and to share this data, as described in the guidelines set forth in November 2003:

“It is important for the FDA to have a role in the evaluation of pharmacogenomic tests, both to ensure that evolving FDA policies are based on the best science and to provide public confidence in the field. It is also important that FDA policy facilitate, not impede, the use of pharmacogenomic tests during drug development and, to the extent possible, encourage open and public sharing of data and information on pharmacogenomic test results.” (FDA Guidance for Industry, Pharmacogenomic Data Submissions. November 2003)

Industry’s Response to FDA’s Request for Pharmacogenomic Data

Drug manufacturers are using pharmacogenomic information to better understand their clinical compounds throughout the phases of clinical studies, but are reluctant to share this information with the FDA for fear that questions arising during the review may delay the approval of the product.

Another reason the industry may be hesitant to provide the FDA with this information relates to the technologies used in obtaining the genomic information. Pharmaceutical companies are worried the FDA may require the company to co-develop a diagnostic test to accompany the new biomarker in order to bring the product to market. The FDA is currently working on guidelines surrounding devices. With the emergence of more genomic biomarkers that can identify high- and low-responding patients, the development of the diagnostic tool that
can identify which patients should be treated with these therapies is what the regulators are seeking.

In July 2004, drug manufacturers and FDA officials from CDER and the Center for Devices and Radiological Health participated in a workshop entitled “Co-development of Drug, Biological, and Device Products.” Manufacturers voiced their concerns regarding drug-device development. One participant noted that a “partner product” approach, where different companies may manufacture the therapy and the device, might be a good approach. They stated that the FDA needed to be flexible in its guidelines, and consider different scenarios where either the diagnostic test or the therapy could develop first, or both develop simultaneously. “What I’ve seen lately from the FDA is very encouraging in terms of their recognition that companion products are going to be a part of the future and are already appearing now. They are going to be more and more the norm in the future and we need to ask how we proactively develop that data during the clinical development activities that surround the pharmaceutical and leverage that data later, as the drug approaches the marketplace. The FDA has this initiative,” states Michael Stocum, Managing Director of Personalized Medicine Partners LLC, and former Director Business Development and Alliance Management at GlaxoSmithKline’s Human Biomarkers Center.

As the guidelines are still under construction, the FDA has begun to consider whether new drug applications and therapies already approved should require labeling based on new pharmacogenomic information and testing associated with it (Wechsler, 2004). For example, Strattera (atomoxetine HCl, Eli Lilly) is a therapy for Attention-Deficit/Hyperactivity Disorder (ADHD). During clinical studies, it was found that poor metabolizers (PMs) of CYP2D6 had a 10-fold higher area under the curve (AUC) and a 5-fold higher peak concentration to a given dose of Strattera compared to extensive metabolizers (EMs). As approximately 7% of the Caucasian population is PMs, the agency recommended that wording be inserted into the labeling regarding this issue (Package insert for Strattera, Eli Lilly and Company).