

## Establishing the standards in biomarker research



Biomarkers have the potential to encourage innovation, improve efficiency, and gain research organizations an advantage over their competitors. In this white paper, Thomson Scientific shows how the pharmaceutical industry is already beginning to rely on this information, and explains how important it is to establish the standards that will support increasing biomarker implementation in the future.

## Introduction

There seems little doubt that biomarkers will be one of the major drivers of pharmaceutical research and drug development in the 21st Century. Biomarkers have the potential to encourage innovation, improve efficiency, save costs, and gain research organizations a valuable advantage over their competitors. Increasingly, decision-makers throughout the development pipeline will turn to biomarker evidence to support their stage gate judgments, and patients will benefit from drugs that are more efficacious and have fewer side effects.

However, at the present time research organizations face a number of hurdles in realizing and passing on these benefits. Regulatory agencies are reluctant to accept biomarker-based evidence to support a drug approval without reliable standards of biomarker documentation. The information provided by a biomarker must be absolutely trustworthy if it is to be used to support a key decision. And biomarkers must become established enough that they shift the research paradigm away from the 'blockbuster' model to smaller-market but more carefully targeted products.

In this white paper, we'll remind you why biomarkers are so important to pharmaceutical innovation, and show how research organizations are already beginning to rely on this information. We'll then explain how Thomson Scientific is uniquely placed to establish and develop the necessary standards, and to provide the trusted, authoritative biomarker database that can properly support biomarker acceptance and implementation into the future.

To find out more information on the Thomson Scientific Biomarkers offering please complete the web form at [scientific.thomson.com/forms/biomarkers](http://scientific.thomson.com/forms/biomarkers)

## An intermediary between treatment and disease

'Biomarker' is a good example of a term whose dictionary definition is not keeping pace with the word's changing significance in the real world. Originally, it referred to such physiological indicators as body temperature, blood pressure or heart rate that signaled an imbalance in the body—direct, evidential symptoms of disease. Later, the term took on the additional meaning of detectable foreign substances such as radioactive isotopes whose passage through the system could indicate problems with specific organs or body functions.

Today, we can more precisely define a biomarker as a blood-based test, gene sequence or mutation, mRNA expression profile or tissue protein that can be used to provide evidence of the state of an organism. The US National Institutes of Health Workshop in December 1998, published in *Biomarkers And Surrogate Endpoints: Preferred Definitions and Conceptual Framework (Clinical Pharmacology & Therapeutics, Volume 69, No 3, 2001)*, calls a biomarker "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention." The presence of a specific antibody in the blood, for example, might indicate a specific infection. The important point is that the biomarker is both objective and measurable.

Once the association between the biomarker and the disease is clearly established, the one can be used to signal the other, and to a high degree of certainty. Changes in the prevalence of a biomarker in the organism can immediately and reliably signpost the patient's response to treatment, whether beneficial or toxic. In preventative medicine, by monitoring their blood-glucose levels, diabetics can manage their disease and avoid exacerbating its symptoms: the biomarker is an intermediary between the disease and the patient's behavioral regime.

### Biomarkers in research: Roche

Roche's Herceptin—which benefits only those 20 per cent of patients with Her2-positive breast cancers—in fact still serves as the best example of how biomarkers can benefit the whole drug life cycle, right from the earliest stages of development.

It was estimated that from the eight-year acceleration of Herceptin's approval, Roche saved \$35 million in clinical trial costs and generated \$2.5 billion of income, with 120,000 patients gaining access to the drug before they might otherwise have done.

## Discovery, documentation and quantifying

It is believed that every disease process may have a number of biomarkers associated with it, though the presence of a biomarker by itself may not be useful in clinical practice. To be worthwhile, the biomarker must be a signaling characteristic (in other words, a characteristic with a known correlation between the evidential quantity and the disease state) that can be measured accurately, easily and cheaply, preferably using non-invasive techniques such as medical imaging, blood or urine analysis, or gene chips.

Most scientists, indeed, already use a core set of these biomarkers, but this is insignificant compared to the thousands of biomarkers that may exist and have yet to be discovered, documented or quantified. Even excluding those that are less reliable, or less easy to measure, this suggests a huge wealth of indicative information that can be employed in every phase of drug discovery, development and clinical practice. As biomarker research gathers pace, our understanding of the role of these signalers is increasing in almost every therapy area, but most rapidly in cancer, cardiology, neurology, metabolic, autoimmune and inflammatory diseases.

Since biomarkers can provide their discoverers with tangible benefits, in terms of speeding up and focusing the development of associated treatments for the disease they indicate, most biomarker research is proprietary, and biomarkers are themselves commodities just like the drugs they help to bring to market. Biomarker research, too, follows a similar pipeline to drug research: from discovery, through initial documentation, exploratory use in pre-clinical and clinical development, to publication and regulatory approval, and ideally onward into widespread adoption in the clinics. There's undoubtedly as high an attrition rate in biomarker development as in drug development. The end point for a biomarker researcher may not simply be to support drug development, but to establish and manufacture diagnosis kits and software, with all the licensing opportunities that suggests.

Of this research pipeline, the key stage is, naturally, regulatory approval. Without the approval of diagnosis equipment by regulatory authorities, a biomarker remains what we will term 'non-validated', meaning that it is unusable for clinical practice or to support the claims made during drug development. Even if this is the case, the non-validated biomarker may still be useful in the early proof-of-concept stages of drug discovery and research. Similarly, even those biomarkers that regulatory authorities do not feel confident enough to validate may still be used widely in laboratory, biochemical, molecular or physiological tests both by drug researchers and scientific societies and by the medical community at large.

A single biomarker may have different uses, only some of which are validated. The Her2 biomarker is an established indicator of breast cancer, and is validated for cardiovascular toxicity in patients taking certain drugs, but it is not yet validated for ovarian and prostate cancer.

Until now, the association between an intermediary and a disease state seems to be largely retrospective. The role of the intermediary as a reliable indicator is known first, and then the intermediary becomes established as a biomarker. For example, cholesterol levels are a method of measuring risk for heart disease, blood pressure for stroke or renal failure. The role of an authoritative biomarker database is to establish standards that can reverse this process: to help to wrap around new biomarkers that wealth of objective evidence, supported by the published literature, that can help them to reach validation.

### Biomarkers in research: GlaxoSmithKline

GlaxoSmithKline has obtained informed consent from all patients in phase I, II and III trials for collection of DNA samples for biomarker analysis since 2003 (and phase IV trials from 2006). The importance of doing this is huge as the evolving science and regulation of the field are increasingly likely to necessitate retrospective screening, which can save huge amounts of time and even rescue a drug from the scrap heap.

The company has practical experience to demonstrate the impact of biomarkers. In the case of Tykerb (lapatinib), to predict the occurrence of side effects in patients. Around 15 per cent of 107 patients treated in phase I/IIa trials of lapatinib experienced diarrhea and mild rash, leading to three withdrawals.

In preclinical studies, however, a strong correlation had been established between variations in the metabolizing enzyme CYP2C19 and instances of rash or diarrhea. Notably, of the three individuals who had withdrawn from trials, all were homozygous for CYP2C19\*2.

Side effects of the drug are, therefore, predictable, and the dose can be adjusted, as required, in susceptible patients.

## A path out of the catch-22

Given their potential benefits throughout the drug development process, it's surprising that biomarkers are still not adopted universally. The side bars in this report demonstrate a few of the ways in which pharmaceutical innovators are using biomarker evidence now, but it's clear that the entire field is as yet undervalued.

Some innovators do a great deal of biomarker research, while others do none. Even among the ones that do, most companies lack a separate group charged with the effort. The catch-22 is that while biomarkers remain undervalued by innovators, they will also be undervalued by regulatory authorities, and while regulatory authorities lack confidence in biomarker evidence, innovators will be reluctant to rely on them to support their stage gate decisions.

Naturally, there are some diseases where biomarker research is seen as less important than others, but even among these, future developments may lead to unexpected and beneficial innovations. For example, if a researcher is working on defining the genetic basis of hypertension, then the genomic aspects of that disease will be critical, especially if they can find a biomarker that indicates which patients are likely to respond to which types of therapy.

The paradox mentioned above doesn't necessarily halt biomarker research—biologists, pharmacologists, clinicians, business development professionals and academic institutions alike all need and push for better biomarkers—but without trusted, validated biomarker information it is likely to remain a paradox. However, once this information is in place, there's a path out of the catch-22, and the possibilities are immense:

- Biomarkers can be used to detect the predisposition for disease in a population, screen for its presence, confirm its diagnosis, assess its severity, predict its response to available therapies, and measure its clinical course.
- Biomarkers can be used as targets to discover new drugs, providing improved systems for screening a library of compounds for promising candidates and decreasing the number of false positive and false negative results. Effectively, new biomarkers mean new drugs.
- The existence of viable biomarkers can be a decisive factor in determining whether or not to continue research on an entity, particularly at the proof-of-principle and proof-of-mechanism stage gates.
- Biomarkers can show early in the development phase whether an entity could lead to side effects that should terminate further research, thus reducing attrition rate further down the pipeline and minimizing risk. It is estimated that as many as 1.5 million patients are hospitalized each year due to the adverse effects of prescription drugs.

- When it comes to clinical trials, biomarkers can help to make efficacious decisions that save huge amounts of time and money, for example by identifying suitable subjects for initial human testing. They can also provide data sooner, with objective reliability—an anticancer drug could be tested against tumor growth or progression-free period, rather than mortality.
- Biomarkers can reduce treatment overheads by optimizing dosage and measuring a patient's response more quickly and accurately. This in turn may introduce the need to measure additional biomarkers, more closely targeting the therapy to the individual patient.

For both innovator and patient, these are tangible rewards. But there's a third beneficiary: the payer. If, as analysis suggests, the vast majority of prescription drugs only work in less than half of the patients who receive them, clinicians are wasting an enormous amount of health authority or employer insurance scheme money on ineffectual treatments, an amount that is easily in the hundreds of billions of dollars every year. Meanwhile, cost pressure on those same payers means regulatory bodies will only approve drugs that are shown to be more effective than the established treatments. And it's the regulatory bodies who ultimately need to be convinced by biomarkers.

### Biomarkers in research: Bristol-Myers Squibb

Bristol-Myers Squibb's use of biomarkers provides a good example of three key ways in which biomarkers can benefit pharmaceutical R&D.

#### 1) To differentiate a phase III compound from its generic competition

In a selected patient population from a phase II trial involving 161 patients, the response rate to ixabepilone rises from 18 per cent to 45 per cent, compared with a generic taxane, based on markers of sensitivity identified in studies of 18 different breast cancer cell lines.

#### 2) Line extension of a late-stage drug

Dasatinib has been launched in the US and EU for chronic myelogenous leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), and is in early-stage development for solid tumors. A strong correlation has been observed between solid tumor Src activation profile and patient response to dasatinib.

#### 3) To improve the risk-to-benefit ratio of an existing therapy

Markers to predict incidence of lipodystrophy induced by highly active antiretroviral therapy (HAART) include an alteration in the resistin gene (coding for an adipocyte-derived hormone linked to obesity and diabetes), which has been associated with high risk of lipodystrophy.

## The position of the FDA

As we've seen, during the early stages of drug discovery and development, a pharmaceutical organization can use whatever biomarkers it feels are most reliable, regardless of whether or not they have been validated by regulatory agencies. This is also true, to a lesser extent, during phase I and II clinical trials, so long as the biomarkers are ethically acceptable. Later, when the candidate approaches phase III trials, the organization has no choice but to switch to those biomarkers that will be accepted by regulatory agencies as evidence for approval.

In other words, if a regulatory agency accepts one biomarker as valid for establishing efficacy, but does not accept another, it is in reality supporting research in some biomarkers but not in others. The suspicion is that, whatever their intentions, the regulatory agencies are exacerbating the paradox of biomarker research. Since very few of the biomarkers that have the potential to be used as indicators of efficacy or toxicology in trials have yet been validated to the standards of the FDA and other agencies, the confusion threatens to stifle research altogether.

Nevertheless, the stated position of the FDA is to encourage and support biomarker research, suggesting that the appropriate inclusion of biomarker evidence is likely to speed up approval. In its Critical Path Opportunities Report, March 2006, the FDA endorsed the importance of biomarkers, and declared it was taking the lead in trying to establish a regulatory framework that could expedite incorporation of biomarkers into the development process. However, it also noted that "much development work and standardization of the biological, statistical, and bioinformatics methods must occur before these techniques can be easily and widely used."

By claiming that biomarker research had "stalled", the FDA was actually highlighting its own barrier to regulatory acceptance of biomarker evidence. The Authority rarely has an issue accepting biomarker data as evidence of a secondary clinical endpoint, but accepting them as evidence of a primary endpoint is a quite different matter. If the state of the art is to assess efficacy by looking at a biochemical or physiological or molecular endpoint, the FDA generally rejects it as a satisfactory clinical endpoint for approving the drug to market, telling the innovator that the primary endpoint must be clinically relevant to the disease and the patient's well-being. Though the FDA has attempted to provide specific indications on the data that can be submitted, it has so far covered only genomic biomarkers.

## Seizing the initiative

Despite all this, the FDA does at least recognize that biomarkers are an area of supreme importance to pharmaceutical innovation and personalized medicine, and its efforts at building a framework for regulatory acceptance can only be welcomed by the industry. Other agencies, including the EMEA, are engaged with the same issue. In Japan, the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labor and Welfare have proposed biomarker development as a national project, and are actively promoting biomarker research. For example, they have announced a program to investigate Beta-42 Amyloid approaches to Alzheimer's disease, and are seeking a compound related to salivary amylase and peroxidation in fat as a biomarker for stress.

Recent history shows that biomarker research can be accelerated to swift approval where the need arises. With minds sharpened by the explosion in AIDS, it took only a few years of intensive search for a biomarker to combat HIV to accept CD4 cell counts as a validated primary endpoint.

Once a biomarker approaches or achieves validation, there's no lack of interest from pharmaceutical researchers to further develop and employ it, particularly if the biomarker may be able to gain more rapid acceptance of the marketing applications of their own candidate drugs. Physicians will also want to use biomarker diagnosis as soon as practicable, particularly if that diagnosis is simple (a lab test of blood or urine samples, say) for a relatively common disease. The biomarker PSA, used to assess prostate function, is an example of one such diagnosis that moved rapidly from introduction to widespread adoption in the clinics.

But the fast-track biomarkers are exceptions. If gaining biomarker acceptance is perceived to be an enormous uphill battle, taking many years and countless millions of dollars, and faced with the Sisyphian stone of an intransigent regulatory agency, researchers are likely to tire of the effort. The trend will then be to shift focus elsewhere.

Meanwhile, no single innovator is likely to step forward to take the entire weight on their shoulder, as this is a fiercely competitive commercial industry where each organization works independently of its rivals. Many companies state that they have no intention of coordinating their efforts with others. The academic field is in no position to take the lead either.

It therefore falls to an objective outside body to seize the initiative—and Thomson Scientific is ideally placed to do just that.

### Biomarkers in research: Pfizer

Pfizer has been using biomarkers to optimize the dose of irinotecan given to cancer patients. Like GlaxoSmithKline, the firm now routinely obtains informed consent from all patients and volunteers participating in clinical trials to take DNA samples for retrospective analysis.

## Evolving information into knowledge

There's no lack of biomarker information already in the public domain, and more is released on a daily basis. But little of this has the level of trust and authority necessary if it is to provide the evidential framework needed for biomarker validation by the regulatory agencies, let alone to support stage gate decisions by innovators that may cost, save or generate millions of dollars for their organizations.

Public initiatives by the Biomarkers Consortium, a biomedical research partnership managed by the Foundations for the National Institutes of Health, and the Korean NIH database claim to provide free access to biomarker information to a worldwide audience. However, it is unclear how quality and timeliness can be assured in public offerings when research in the field is under constant acceleration, and these initiatives are limited by the degree to which pharmaceutical companies decide to share internal information in the public domain. Worse still, the information cannot truly evolve into knowledge when it lacks a concerted effort to standardize the vocabulary.

To date, the existing commercial sources have also not taken a lead in the area, either due to a lack of resources, industry expertise, content depth and breadth, or editorial rigor. Simply identifying and documenting new biomarkers is not the issue—that can be done relatively easily. What is far more important, and far more difficult, is compiling the data from all its disparate sources into usable formats, and then expertly comparing the relative values of each biomarker that can be used to determine the same effect or physiological activity.

Most important of all, researchers must learn from the database to what degree they can trust the biomarkers that could support their work. There is no doubt that a single, authoritative and trusted repository of biomarkers data is urgently required.

### Biomarkers in research: Johnson & Johnson

At Johnson & Johnson, work is underway to identify markers of CNS disease. The firm has collaborated with Genset and Signalgene to identify markers in the D-amino acid oxidase (DAAO) gene, which Johnson & Johnson is now pursuing as a target for schizophrenia.

In addition, a large-scale genetic study in Alzheimer's disease is being carried out in collaboration with Genaissance, with results now being published. Some 89 candidate genes have been identified, although the company is frank in stating that it is likely to be many years before drugs based on this information come to market.

## The Thomson Scientific initiative

Thomson Scientific is uniquely positioned to provide this repository, thanks to its size, industry knowledge and the objective, cross-discipline pharmaceutical expertise it is able to draw upon. Over more than fifty years, Thomson Scientific has built up the respect that makes it the information partner of choice not just for the world's largest and most successful pharmaceutical corporations and research institutions, but for those companies on the leading edge of research and innovation.

By drawing on the real-world knowledge of scientists in Prous Science, a Thomson business, as well as extensive participation by thought leaders and stakeholders in industry, academia and regulatory bodies, it is able to build a biomarker solution that is trustworthy in content, rich in analysis, and backed up by rigorous editorial standards.

Its biomarkers initiative is based on in-depth interviews with a huge number of pharmaceutical, biotechnology and diagnostic companies, talking to both senior management and business development specialists, and the front line of discovery at the bench. In addition to key opinion leaders identified based on a series of criteria (including seniority, number of published articles and hosted conferences, carrier mentors and participation in scientific or medical societies), it has also engaged with the industry's most eminent strategists. Their participation endorses and guarantees the quality of the Thomson Scientific solution.

### Biomarkers in research: Abbott

Toxicity is another area where biomarkers will impact on drug development. Abbott has been keen to reach a situation where initial safety testing of lead compounds can be carried out with less than 10g of drug over 1 to 3 days in rats.

This would be impossible with traditional methods, but in collaboration with Rosetta Inpharmatics, a US-based wholly-owned subsidiary of Merck & Co, Abbott has compiled a liver toxicity gene expression database using 52 known hepatotoxicants and 10 non-hepatotoxicants, which has been refined to 40 markers. Prediction accuracy for the liver toxicity of select kinase inhibitors has proved to be 88.5 per cent.

Abbott has also explored cardiotoxicity in collaboration with California-based Iconix, using its DrugMatrix database. For its part, Rosetta has stated that "molecular profiling technology is ready" and that predicting compound toxicity using transcriptional profiling at early time points is now routinely feasible.

## The definitive biomarkers database

Thomson Scientific is now at work defining, standardizing and populating the entire breadth of biomarker information in a definitive global biomarkers database. This database will form a repository of knowledge covering the different uses of biomarkers that are actively being researched or employed, and those uses that have been discontinued.

Each record will include the biomarker's name, classification, biological entities/processes involved, associated drugs, roles or utilities, measurement techniques, development status of diagnostic kits and validation status. It will place this knowledge in context, enabling users to assess at a glance the relative importance of different biomarkers, and indicate for the first time exactly how much an organization can put its trust in the biomarker results it is getting.

Around the core biomarker data, Thomson Scientific will wrap vital contextual information including related literature, patents, genomics/targets, drugs and biologics, companies or research institutions, toxicology and clinical studies. It will enrich each record by retrospectively searching the literature and providing links to all source documents.

Continually updated and enlarged, the Thomson Scientific biomarkers database will enable researchers to connect experimental research, drug development and clinical studies for pivotal insights and decision-making. Thanks to its standardized terminology and classification, researchers will be able to navigate seamlessly from the core data to the whole wealth of related information owned by Thomson Scientific, and to search it quickly and easily by discipline and target.

Thomson Scientific believes that by establishing and curating this knowledge, it can reduce the confusion in the regulatory agencies, and aid widespread acceptance of biomarkers, encouraging innovation for decades to come.

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