



# Biomarkers and Drug Development

*Can we improve safety and efficacy at the same time?*

By **Gil Y. Roth**  
Editor

THE MORE VENTURE CAPITAL MONEY an industry has, the more buzzwords accumulate around it; this is one of several laws I've learned in my years around the world of business. The Pharma and Biopharma field, with their accompanying technology toolsets, is just packed with these buzzwords. In recent years, we've been told about genomics, bioinformatics, proteomics, metabolomics, transcriptomics and metabonomics. These have begun to make contributions to the Pharma/Biopharma industry, but they've also been misapplied and overused in their brief star turns as The Next Big Thing.

So I found myself wondering whether the more prosaic term "biomarkers" is a hot VC buzzword, or if it represents something deeper, a sign of an ongoing process that may have lasting effects on drug development. As I asked around the industry, I found there were plenty of definitions being offered. They overlapped, but each covered areas exclusive of the others. There was a common, conventional wisdom about the long-term effects of biomarkers on drug development, as well as some dissension on what's driving the field.

But you can't have a discussion without defining your terms. So I started out my interviews with the question, "What is a biomarker?" and here's a sampling of what I heard:

"There's definitely a lot of debate as to the definition of what a biomarker is. We see it as any experimental model or endogenous chemical that gives us a view between drug concentration and likely therapeutic effect. Some people restrict their definition solely to the world of endogenous substances, but we feel experimental models and imaging techniques qualify."

—Dr. Steven Toon

senior vice president of clinical pharmacology,  
and head of Medeval unit of ICON

"Biomarkers are predictors of a clinical response to a particular drug in the context of a disease."

—Dr. Manuel Worcel

chief medical officer, NitroMed

"A biomarker can really be anything: a gene, a protein, an endpoint, a visualization of something through an imaging technique, and so on. It really does cover a very broad spectrum."

—Bryce McMurray,

product development director,  
Wolters Kluwer Health Pharma Solutions

"Good question. There are cynics who say 'biomarker' is just a new name for clinical chemistry, just as others say 'nanotechnology' is a new name for chemistry and materials science. In that same vein, 'tall' is a new name for small and 'vente' is a new name for large."

— Dr. Pete Kissinger

chief executive officer of Bioanalytical Systems, Inc.

## More Breakdowns

Of course, in our business it's what the Agency says that matters, more often than not. And according to the FDA, a biomarker is a "quantitative measure of biological effect that provides informative links between mechanism of action and clinical effectiveness." Which is to say, it's something you can measure—be it through blood, tissue, imaging or some other mode—that says something about the state of a disease. That wasn't so tough.

Eric Kaldjian, senior scientific director at Gene Logic, offered a little more fine-tuning of the definition, "People needed to have a way of systematizing how they think about this stuff, so I break down biomarkers into two categories: phenotypic and dynamic."

Phenotypic biomarkers provide a baseline snapshot of a condition, while dynamic ones measure changes after some kind of therapeutic intervention. "Both may be involved with efficacy and/or toxicity," Mr. Kaldjian said. "They may have slightly different purposes. Dynamic biomarkers can reflect pharmacokinetics (did the drug get in?) and pharmacodynamics (did it have an effect on the target?), and give us a better handle on who will respond to a particular substance. A phenotypic biomarker will help us determine whether a patient should receive a particular drug at all."

## Critical Path

Biomarkers received a serious push when the FDA placed them prominently in its March 2004 report, "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products" (hereafter known as the Critical Path initiative). A year later, the Agency followed up with discussion of biomarkers in its pharmacogenomics guidance.

The Critical Path initiative arose because of a disconnect between R&D and drug submissions. "The disparity was between what the industry was spending on R&D and the end product, which the FDA quantified in terms of submissions (and the quality of the submissions they were receiving)," said ICON/Medeval's Dr. Toon. "If you look at the spiraling R&D costs and the flat or diminishing number of submissions the FDA was receiving, it was clear that something was going wrong. There was a genuine belief that we needed a radical rethink of how drugs are developed. It's tough to justify how all

**Gil Y. Roth** is the editor of Contract Pharma. He can be reached at [gil@rodpub.com](mailto:gil@rodpub.com)

that money and technology has led to fewer submissions.”

Ira S. DuBey of Tandem Labs contends that biomarkers are pivotal for the future of drug development. “The whole purpose of the Critical Path initiative as I understand it is to speed approval for innovative products, to make medicines more effective and safe, and to maximize drug benefits and minimize toxicity,” he remarked. “It’s about integrating new science into the regulatory process. Biomarkers have a place in every aspect of this. A big part of the Critical Path is the use of biomarkers for better decision making.”

Dr. Kissinger of BASi contended that the field is moving further and further into mainstream development. “The big challenge in the industry is finding new biomarkers that are relevant and validating that relevance. In addition, we have to assure that methods—including immunoassays, for the most part—are robust,” he remarked.

### Fail Fast

Developing new biomarkers may not simply lead to a proliferation of new drug candidates. If anything, it’s believed that they’ll *limit* the number of drugs that go into the clinic. Mr. McMurray of Wolters Kluwer remarked, “If your biomarker measures no effect for a drug, then you can fail fast, which is critical for a small company.”

Dr. Toon added, “Smaller companies must spend their available funds efficiently. One of the pivotal studies in preclinical is the dose-escalation study, where you’re trying to map out the dose-concentration/effect surface. Now, Big Pharma would approach this by testing 10 or 11 dose levels, but the smaller company might not have the resources to do so. They want to get the same level of information from four or five studies. So you need to build in a design that’s driven by some sort of biomarker to steer you to a desired endpoint. Smaller companies face commercial pressures; they want to use the available drug substance in the most effective way they can.”

This “fail fast” concept will separate wheat from an awful lot of chaff in the early stages of development. That could lead to fewer compounds actually entering the clinic, but a higher rate of success for those that get out of the lab.

### Restoration Software

In addition to failing fast, the use of biomarkers can also help save drugs that were thought to be failures. Gene Logic has a Drug Repurposing & Selection division that’s devoted to this process, but the biggest story this year in “drug resurrections” has to be NitroMed’s heart failure drug BiDil.

In June 2005, BiDil was approved by the FDA, rescued after receiving a “not approvable” letter from the Agency. In its original Phase III trial, BiDil, an orally delivered, fixed-dose, combination drug, didn’t show efficacy for its endpoints of reducing risk of mortality and reducing hospitalization in patients at risk of heart failure.

But a funny thing happened on the way to the scrap heap: NitroMed researchers looked back at the data and noticed that the results were overwhelmingly positive in the trial’s African-American participants.

As a result, NitroMed organized a new clinical trial, involv-

ing only African-American patients. The results were so overwhelming—43% reduction in risk of mortality, and 39% reduction in rate of first hospitalization for heart failure—that the trial was halted early in July 2004. The drug was approved by the FDA less than a year later and reached the market in July 2005.

Dr. Worcel, NitroMed’s chief medical officer, explained, “In heart failure, there’s absolutely no surrogate endpoint or biomarker that could safely indicate, patient by patient, a favorable response to the drug. So that brings you to clinical trials, which are the only way to derive this information.”

He believes that BiDil will show results in more patients who are *not* of African descent. To that end, the company has run the Genetic Research Assessment for Heart Failure (GRAHF) study in parallel with its clinical trials. GRAHF has helped NitroMed identify 10 genomic markers related to identifying nitric oxide issues, angiotensin-converting enzymes and other genetic receptors. Since BiDil enhances nitric oxide, NitroMed is exploring biochemical markers related to metabolism of nitric oxide in the body, having analyzed the DNA of 360 patients out of the 1,050 who were in the trial. “We’re looking at correlations between the presence or absence of particular alleles in these cardiovascular genomic markers with outcome results in the clinical trial: risks of mortality, hospitalization, etc.,” Dr. Worcel commented.

### Shrinking

In the case of BiDil, NitroMed can include smaller numbers of patients in its new trials. As more biomarkers get developed, it’s likely that clinical trial populations will shrink drastically. If you can recruit 2,000 patients who test for a particular biomarker that will respond to a drug, then recruiting another 8,000 who won’t respond is silly.

If biomarkers are developed that help stratify patient populations, what effect will that have on clinical trials and the CROs who help conduct them? Everyone I spoke to agreed that the immediate result will be to shrink the size and timeframes of late-stage trials. Theoretically, if you can identify the best responders to a treatment, then sheer statistical power dictates that you won’t need as many patients to demonstrate an effect.

### Four Corners or Multiplex?

Pharma and Biopharma companies are scrambling to utilize biomarkers in drug development, both for early stage discovery work and late-stage efficacy and safety issues. CROs are working alongside them to build up their capabilities, especially as they face the prospect of diminished trial-sizes and fewer clinical candidates.

MDS Pharma Services is helping push the field by joining with Caprion Pharmaceuticals, Gentriss Corp. and Massachusetts General Hospital’s radiology department to form The Biomarker Alliance. The Alliance is meant to offer a broad selection of biomarker technologies through a single point of access. Said Fred J. Pritchard, MDS’ vice president of drug development programs, “About a year ago, we made a concerted effort to bring this emerging, broad platform of technologies together for clients in a convenient way. The Alliance covers four corners of the technological map: imaging (MA General), proteomics (Caprion),

pharmacogenomics (Gentris) and analytics (MDS)."

He added, "We define the field in terms of technologies because that's where the challenge is: how do we measure things that are out there now? In a sense, it's more important to focus on the metric, not on the substance you study to get it."

Mr. Pritchard explained that the Biomarker Alliance isn't a tight business partnership; rather, it's an "agreed-upon way of operating, so that we can bring clients into a space and give them access to experts and technologies to figure out quickly the best way to go," he said.

MDS isn't the only company that's enhancing its biomarker strengths. Utah-based Tandem Labs recently moved in that direction when the company formed a Biomarker and Immunoanalytical Division, and brought in Ira DuBey to serve as its vice president and general manager. Mr. DuBey had previously directed the immunochemistry business at Covance. "Tandem Labs had recognized the growing importance of biomarkers," said Mr. DuBey. "Previously, they were limited to LC-MS-MS techniques, performing the quantification of a drug in biological fluid. This new division gives Tandem a whole different area to be involved in."

He added, "We're positioning ourselves technologically, developing methodologies and expertise in biomarker assays and validation, as well as regulatory issues."

## **Personalization**

Where will all this lead? Well, the holy grail for biomarkers is the development of personalized medicines, with patients receiving the drugs that would be most efficacious (or maybe a little less efficacious but a whole lot safer) for their particular condition and disposition.

The prototype for this type of drug is Herceptin, the breast cancer MAb that is indicated for tumors that overexpress the HER2 protein. HER2 overexpression occurs in about one-quarter of breast cancer cases, and the drug is highly effective in those cases. "With Herceptin," said Syd Gilman, of Gene Logic, "Genentech took a known, valid biomarker and tried to use it to distinguish between patients who will get a response and those who won't."

MDS's Fred Pritchard commented, "Herceptin's a great example, because it combines the pharmacogenomic marker to identify the patient in whom effect is going to occur, but it also used that marker as the early target for the disease." In other words, it wasn't a coincidence that patients with HER2 overexpression were going to benefit from Herceptin, but it also made for an excellent diagnostic.

Mr. Pritchard added, "The concept of biomarkers used to be nearly synonymous with diagnostics, so a lot of companies developing drugs would shrug and say, 'We're not a diagnostic

company.' The Herceptin example shows that, for truly innovative drug development, you must develop a marker in parallel with the drug."

Said Mr. DuBey, "The potential exists to develop Herceptin-like information on many more drugs."

Herceptin's case is pretty easy to make, but most drugs (and diseases) have much more complicated biomarkers associated with them. Mr. Kaldjian, at Gene Logic offered AstraZeneca's Iressa as an example. "As it happens, it took a lot of time and a lot of patients for AZ's

researchers to tease out a clinical benefit in a relatively small subset of patients. It's quite a pronounced benefit, but it's a small group, and difficult to ascertain the benefit over other therapies.

"Once the information came out regarding the mutations that existed in higher frequency in certain populations—like Asian women non-smokers in adenocarcinomas—one realizes that, if one had at one's disposal that information earlier on in the clinical development process, boy, you could've run that trial in a lot fewer patients, shown its activity, and probably gotten the drug approved for that indication really simply.

"That science hadn't been developed at that point, but if you had that alteration in the receptor as a biomarker for patient stratification, I think that drug would've been off and running in no time."

Issues like this one raise the chicken-and-egg question of just how some important biomarkers are going to be developed. Will it be possible to discover how those mutations will interact with new drug mechanisms *without* having to go through broader trials?

Dr. Worcel at NitroMed commented, "We've been asked many times, why did we study the effect of BiDil in black patients following that signal of response, instead of looking at biomarkers and pharmacogenomics and *then* doing the clinical trials? All I can say is, we have a drug approved by the FDA; we've found a product with a remarkable effect on survival and that can keep patients out of the hospital. I wouldn't want to be a member of this patient population and be told I have to wait five to 10 years for a pharmacogenomic marker to be developed and validated before I can have access to this drug."

He concluded, "Pharmacogenomics provides plenty of possibilities—tremendous analytical possibilities—but we still have to do clinical trials that will allow us to translate pharmacogenomic signals into clinical outcomes."

Mr. Kaldjian agreed, "We'll always go back after large-scale trials and retrospectively puzzle out the data." But, he countered, "Now we also have the technology and the tools that allow us to start looking earlier, which can increase our chances of finding something worthwhile."

We also have to be cautious about getting over-optimistic with some biomarkers. As Dr. Kissinger put it, "The PSA test for prostate cancer went from, 'Wow, this is cool,' a decade ago to 'Wow, this doesn't tell us as much as we'd hoped,' today. The issue is that

'one test' rarely helps all that much; we need to develop the combination of tests that will be more accurate. Ideally, we'd understand 'systems biology' and monitor, say, three to 10 markers that, in combination, provides us some direction."

### **Class Warfare**

So which therapeutic classes stand to benefit the most from advances in biomarkers? Most people I spoke to felt that central nervous system (CNS) diseases would see advantages from increased use of biomarkers. Said Mr. Pritchard of MDSPS, "With Alzheimer's disease and neuromuscular degenerative conditions, clinical signs occur almost too late for treatment. New technologies offer the ability to identify markers that are present well before clinical signs." He added that this may be more of a curse than a blessing if you have yet to develop a treatment for the disease.

Dr. Toon agreed, "Psychiatric drugs could really benefit. If you look at the late stages of clinical development for those drugs, they're very difficult, very complicated. The differences you're trying to pick up are very subtle."

The key with discovering new CNS biomarkers is to develop non- (or minimally) invasive techniques. In all likelihood, blood-based or imaging-based biomarkers will be necessary in that field, whereas cancer will remain predominantly tissue-based, since tumors will be surgically accessible.

In fact, Dr. Gordon Kapkey, vice president of global technical affairs at Covance Central Laboratory Services, contends that oncology may benefit most from these new approaches. "Historically, oncology's been about pathological interpretation," he said. "The ability to do rapid expression profiling and genotyping is potentially going to give us a much better understanding of what we're treating. That's the biggest area where biomarkers are going to have an impact, I believe."

Dr. Kapkey added, "Our pure knowledge of biology gives us a great number of new targets. We get interesting requests every day for unique analytes for us to measure. There are opportunities to do things with traditional safety biomarkers, and esoteric efficacy ones are an exciting field to be in right now." ■

**Next issue:**

**Could biomarkers  
have helped Vioxx?**