

Biomarkers – boon or bane for researchers?

Today, as regulators increasingly exhort the use of biomarkers in drug development, trials that lack biomarker evidence run the risk of being considered inadequate, even with swathes of safety and efficacy data. **Gordon Kapke** and **Jeffrey J Stoddard** report on initiatives to accurately define and qualify these substitute endpoints

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By providing detailed insights into drug efficacy and safety, biomarkers have become one of the most promising areas of investigation in pharmaceutical development. The US FDA's 2006 Critical Path Initiative listed biomarkers as one of two areas with the greatest impact on modernising drug development and approval.

The Biomarkers Definitions Working Group defines a biomarker as 'A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.'¹ Any anatomic or physiologic finding can serve as a biomarker, as can levels of proteins, genes, small molecules, metabolites or minerals, provided there is a validated link between the biomarker and a relevant physiologic, toxicologic, pharmacologic, or clinical outcome.

Biomarkers differ from surrogate endpoints, an elite subset of biomarkers which are capable of predicting clinical outcomes, as described in the Box on page 28.² Biomarkers also differ from diagnostics, which define or predict the outcome of a disease. From a clinical perspective, one can think of biomarkers as measures or endpoints obtained independent of diagnosis. Perhaps the most prominent examples of biomarkers are blood pressure and low-density lipoprotein (LDL) cholesterol. Blood pressure readings drive the nearly US\$10 billion market for antihypertensive agents; LDL cholesterol tests guide clinical trials of cholesterol-lowering drugs, and help to monitor patients' responses to statins and general cardiovascular health.

Similarly, the use of polymerase chain reaction (PCR), an amplification method for gene biomarkers, has revolutionised the clinical development of antiviral medications and the monitoring of patients undergoing therapy, particularly for HIV³ and hepatitis.⁴ Although some controversy exists over whether older immunoassay technology is more cost-effective, PCR continues to push down the lower detection

level for persistent infectious viruses, to the benefit of patients and developers of antiretroviral therapies alike.

The potential benefits of a biomarker stretch across a drug's lifecycle, from helping to accelerate preclinical and clinical drug development to assisting in post-approval safety surveillance. For these reasons clinicians, regulators and insurers increasingly embrace biomarkers as enablers of safer, more effective, less costly therapies.

Regulatory biomarkers

The FDA has established four classifications of biomarkers based on their ability to objectively measure and evaluate normal biological processes, pathogenic processes or pharmacologic response to therapeutic intervention. These classifications include exploratory, probable valid, known valid and regulatory; indicating the degree to which a particular biomarker can be used for decision-making in any clinical trial or in an animal trial used to support safety. Only regulatory biomarkers can be used to support scientific arguments made by the sponsor about drug dosing, safety, patient selection or effectiveness.

New biomarkers can be quite useful in drug development and regulatory review to positively impact how quickly new drugs are submitted to and reviewed by the FDA. With safer drugs in greater numbers approved more quickly, public health should be improved by these new biomarkers, but first, biomarker context must be accurately defined and the corresponding qualification protocol developed.⁵

Designed around the Interdisciplinary Pharmacogenomic Review Group (IPRG), the FDA has set up a pilot structure to start a qualification process for biomarkers in drug development (see Figure 1). The process begins when a request to qualify a biomarker is submitted to the IPRG where experts from various FDA centres, comprising the IPRG Biomarker Qualification Review Team, assess biomarker context and available data. The review team will then develop recommendations and guidance for the submission of biomarker data,

Biomarkers versus surrogate endpoints

The Biomarkers Definitions Working Group defines a surrogate endpoint as 'a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.'

Surrogate endpoints represent an elite subset of biomarkers, meaning that few biomarkers achieve surrogate status. Surrogates are recognised by regulators as a viable measure of efficacy, even to the point of granting approval. 21 C.F.R. § 314.510 states, in part, the '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.'²

assess the original biomarker context proposals through voluntary data submission, and then evaluate the qualification study protocol together with the sponsor to reach a consensus protocol. As a final step, this team will review qualification study results and draft a recommendation for the clinical divisions.

Once approved, regulatory biomarkers can be described in the drug label as proposed by the sponsor, and are essential to achieve the dosing, safety or effectiveness described in the drug label. This information assures prescribers access to useful data suggesting ways to optimise efficacy and manage risk. The FDA has published the list of biomarkers that may be used for rendering regulatory decisions at www.fda.gov/cder/genomics/genomic_biomarkers_table.htm.

Towards a biomarker strategy

Every drug development stage could potentially benefit from a biomarker strategy that articulates and defines how the biomarker will drive value throughout the drug's lifecycle. Whether the objective is clinical trial support, a regulatory submission, identifying enriched study populations, post-marketing safety or an eventual companion diagnostic, drug developers must justify their biomarker investment and be prepared to articulate where biomarkers fit within their development strategy.

While a validated linkage between a biomarker and a clinical outcome is not absolutely necessary early in the development cycle, the connection between biomarker and outcome takes on greater importance as the drug progresses through development. By the time a drug approaches launch, having a solid foundation of efficacy data built around validated biomarkers can be critical. Biomarker data that corroborate clinical outcomes help build the scientific case for approval, particularly when that data support a drug's known mechanisms of action. Clinical programmes employing multiple, well-validated biomarkers may encounter an approval path that is smoother, shorter and less costly.

Throughout preclinical development, biomarkers provide information related to candidate molecule selection, target validation,

toxicology, and dosing, and may serve as early indicators of biological activity and/or toxicity. The use of multiple biomarkers permits a rapid and cost-effective generation of drug action data from single test animals, thereby reducing development time and potentially lowering costs.

During clinical phases, biomarkers evolve from knowledge gathering to true decision-enabling tools. Biomarkers assist in clinical trial design and in identifying patients likely to benefit from therapies or suffer adverse events, thereby creating 'enriched' study populations. Post-treatment, biomarkers can assist in monitoring therapy, determining appropriate dosages and predicting adverse events. Biomarkers have helped bring numerous therapies to market, including Herceptin, Gleevec, Iressa and Enbrel.

An example of a biomarker that serves as a validated surrogate efficacy endpoint is the HAI (hemagglutination inhibition) antibody assay for testing the efficacy of influenza vaccines. The FDA has approved several flu vaccines under accelerated review based on small immunogenicity studies that relied exclusively on HAI antibody data as their endpoints. While the FDA has imposed post-marketing commitments (for field efficacy trials) on recently approved flu vaccines, these products were approved rapidly, principally on the basis of biomarker data.

Biomarkers can assist in patient selection and the monitoring of large populations for adverse events (for example, serum aminotransferase levels, serum creatinine, etc), an increasingly critical activity for safety-conscious regulators. Biomarkers have also been used to develop economic value arguments for or against the use of expensive or widely-used therapies, and generally to optimise therapy decisions.

For example, a standard regimen of PEG-interferon and ribavirin for hepatitis C costs approximately US\$3,800 per month. In patients with no viral load response after three months (as measured by PCR-based viral load assays), discontinuation of combination therapy can save approximately US\$34,200 per patient (not to mention treatment-associated toxicities) by avoiding a full nine months of therapy. In patients with excellent early response and viral eradication, therapy can be shortened by three months.⁶

Clinical researchers' views on biomarkers are constantly evolving as new scientific evidence becomes available. For example, lowered serum cholesterol, particularly LDL, has for years been used as a surrogate marker for clinical endpoints, such as heart attack and stroke, to support statin drug approvals. Recently, researchers learned that clinical endpoints like narrowing of the lumen inside carotid arteries might provide more relevant insights into the clinical effectiveness of statins. The recent, highly publicised ENHANCE study compared the combination ezetimibe/simvastatin to conventional statin therapy with simvastatin on three measures: cholesterol lowering, narrowing of the carotid arteries and cardiac events/death. While the ezetimibe/simvastatin combination was superior in reducing cholesterol, it was no better than the single statin in reducing plaque

buildup and did not reduce carotid intima-media thickness.⁷

Insurers have become discriminating over which drugs they list in their formularies, and which products they reimburse at premium price points. Payors increasingly demand head-to-head comparison studies that rely strongly on multiple biomarkers. A developer of an antidiabetes medication cannot expect top-tier formulary status, and concomitant reimbursement levels, without presenting superior haemoglobin A1c data, for example.

The added emphasis on safety outlined in the recently-enacted Food and Drug Administration Amendments Act (FDAAA) of 2007 assures that biomarkers will continue to play a central role in post-marketing surveillance. Traditionally, the CRO conducting Phase IV studies had at best a minor role in biomarker selection, validation, and clinical utilisation. With the continued use of outsourcing for lab testing, CROs are expected to provide scientific direction on biomarker selection and testing.

Biomarkers in the real world

The value of biomarkers lies beyond their quantification of obscure biological events. In practice, they are only useful if they measure a quantity linked to an identifiable and meaningful clinical outcome. And, during clinical development, biomarkers should ideally serve as regulatory endpoints as well. Most biomarkers fail to meet this rigid criterion, and are only useful in narrow contexts such as validating a drug's mechanism of action, proof-of-concept testing or patient selection.

A poorly validated biomarker may obscure or exaggerate a therapy's clinical effectiveness, which may be worse than having no biomarker at all. The efficacy of gamma interferon in reducing recurrent infections in patients with chronic granulomatous disease is poor, as measured by phagocyte activation, a biomarker.⁸ However, it is now well established from clinical observation that interferon significantly reduces infections in this patient population.⁹ Similarly, some of the clinical benefits of statin drugs may be explained by their anti-inflammatory properties as measured by reduced levels of C-reactive protein, rather than reductions in the more conventional LDL cholesterol biomarker.^{10,11}

Biomarkers may help identify critical issues with respect to safety. Examples of this are the erythropoiesis stimulating agents (ESAs), which have been associated with thrombo-embolic events when haemoglobin levels rise above 12 grams per g/dL. As a result, the leading biologics in this class are now subject to safety warnings,¹² Medicare will not pay for their utilisation in patients with haemoglobin levels of 12 grams per g/dL or greater,¹³ and the FDA is considering requiring manufacturers to implement risk evaluation and mitigation strategies for these products.

Identifying patients who will benefit or be harmed by a drug is essential for maximising patient benefits and minimising patient risks. Failure at Phase III, however painful, is always preferable to a recall. Smart utilisation of safety and efficacy biomarkers during development through Phase II,

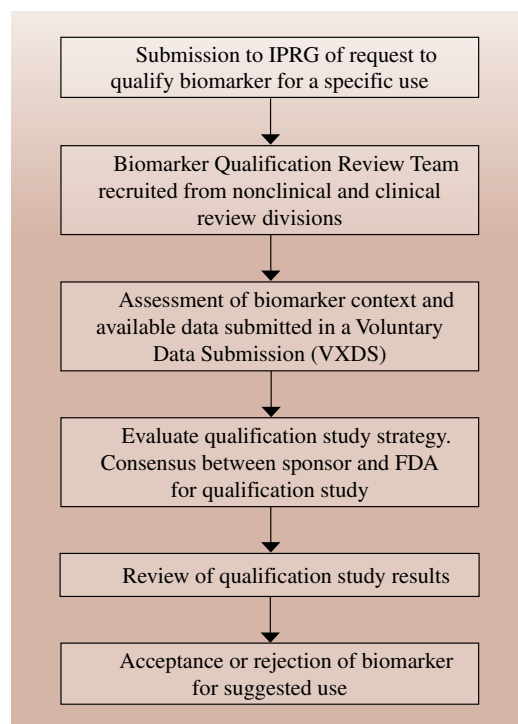


Figure 1: The US FDA's biomarker regulatory qualification pilot process. Source: AAPS Journal 2007

holds the potential to decrease development failures in Phase III and post-approval.

Acquiring biomarker expertise

Pharmaceutical scientists have traditionally been the source of both the analytic science underlying drug-response assays, and the expertise needed to promote these analytics to full biomarker status. Translating the sometimes raw science of a biochemical assay or instrumental analysis into a robust, scalable, clinically available, regulatory-worthy biomarker is difficult. Assays for biological analytes developed during *in vitro* proof-of-concept may not transfer to a clinical setting.

Consequently, the burden of biomarker implementation often falls to either third-party service providers or CROs. CROs offer advantages because they are familiar with study protocols and the limitations of data-gathering in a preclinical or clinical environment. In addition, using a CRO for biomarker implementation can help to limit the number of parties involved in a project and therefore enhance efficiency.

It is important to note that assays are only biomarkers if they work in the real world, such as a clinical setting. The ability to scale a biomarker without loss of analytic rigour is paramount. A dedicated analytical lab measures biological molecules with exquisite sensitivity and specificity, but laboratory assays are not viable biomarkers if they cannot be run expeditiously and reliably by laboratory technicians on dozens or hundreds of samples in a short time period using routine analytics and reagents that are easily sourced.

Moreover, if the biomarker used in development is too removed from clinical practice, obtaining the desired drug label based on the biomarker will be difficult if the drug is approved at all. When patients

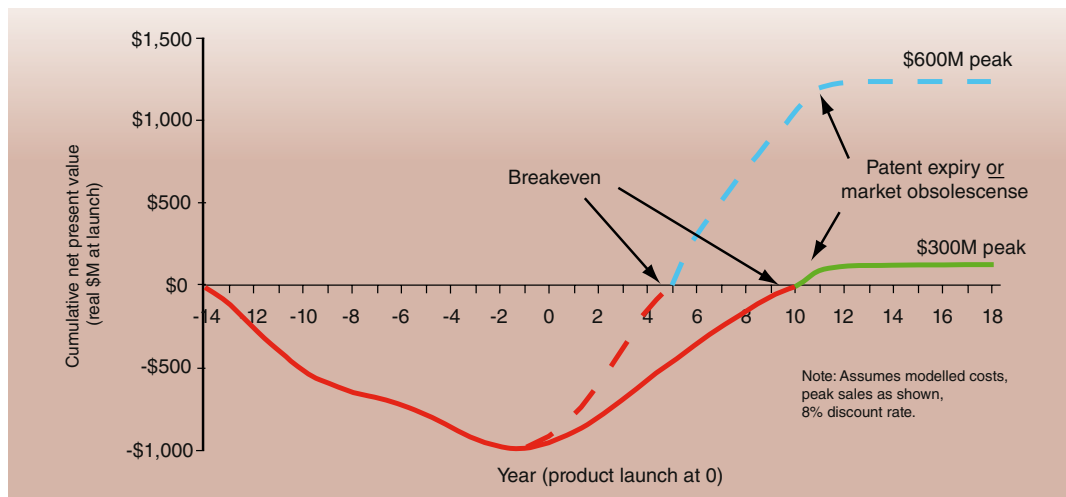


Figure 2: Break-even requires US\$300 million in peak annual sales. Sources: PERI, Lehman and Tufts

and clinicians do not understand the endpoint, and insurers do not trust it, the drug will face many difficulties in the marketplace even if it is approved.

Biomarker selection will be either hypothesis-based or discovery-based. If one has good knowledge of the drug's mechanism of action, hypothesis-based biomarker selection may be effective. If the fundamental knowledge of the drug is limited, a screening discovery approach to biomarker identification may be required. In some cases both approaches may be necessary. While discovery screening has a high risk of minimal benefit, it has the high reward option if a new marker is identified. Given the analytical progress in biomarker screening, a small investment in biomarker screening on all drugs may be beneficial.

Once a biomarker has been selected, the delivery of the biomarker data will require a clinically robust assay. Such an assay may be validated and commercially available. Alternatively GMP reagents may be available for the assay but the assay may require validation. Finally, if reagents do not exist for the analyte, an assay may need to be developed.

The most-attractive option is to employ a test in the public domain, and validate it for purposes of preclinical or clinical development. Fundamental chemical analysis is next in order of difficulty. Laboratory analysis techniques, such as LC/MS, are suitable provided a general method exists for the analyte class, and if the desired sensitivity is within instrument capabilities. Such off-the-shelf analytic methods are a particularly attractive platform for biomarker work, but they can only serve an ongoing clinical programme if their detection limits keep pace with the need for analytical precision and sensitivity through the development process.

The most difficult option for biomarker development involves working from first principles, that is, to discover the analyte or develop a completely novel way to detect it. This option can take a year or more, so sponsors should allow enough time during the preclinical stage for biomarker 'discovery.' Development of a biomarker from first principles often involves immunoassay work, which is a specialised competency that sponsors may not possess. Immunoassay development may be efficiently outsourced to diagnostics companies

and CROs, particularly when the goal is to develop clinical biomarkers.

Personalised medicine

Drug discovery has become fantastically expensive and time-consuming. Estimates for the costs of introducing one new molecular entity, from discovery through Phase III, have been estimated at US\$860 million¹⁴ to US\$1.7 billion.¹⁵ Genentech claimed in a *New York Times* interview that it spent US\$2.25 billion to launch its cancer drug, bevacizumab.¹⁶

These trends have profound lifecycle management implications and can hit large innovative companies the hardest. According to information from Lehman Brothers and Tufts University, to reach break-even at the point of patent expiry, a product needs US\$300 million in annual sales (see Figure 2). Enabling personalised medicine through companion diagnostics and biomarkers presents an exciting opportunity for helping the pharmaceutical industry and perhaps changing the current drug development paradigm.

Herceptin,¹⁷ and more recently Gleevec,¹⁸ are prominent examples of drugs that are only prescribed after patients undergo a test to confirm that the drugs will benefit them. The point is not to limit utilisation, but to provide optimum value to insurers, and limited exposure to patients who will not benefit from and may be harmed by inappropriate therapies. The biomarker helps to rationalise therapy, rather than to ration it.

A recent example of how a biomarker can support regulatory approval involved the monoclonal antibody panitumumab. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) had, in early 2007, rejected the drug as a monotherapy for patients with metastatic colorectal cancer when a clinical study involving 463 patients failed to demonstrate meaningful benefit in time to progression.¹⁹


Colorectal cancer patients show varying expression levels of a gene, K-ras, which is associated with tumour growth. Close examination of the study population revealed that 40% of patients possessed a mutated form of K-ras, and 60% had the

normal, non-mutated form of the gene. When the efficacy data were re-examined in light of the K-ras defect, investigators found the progression-free survival among subjects with the wild-type gene was 12.3 weeks, compared to 7.4 weeks for individuals with the mutated gene and 7.3 weeks for the control group.²⁰ Thus, in a representative sample of 100 patients, 60 could be expected to benefit from the drug if the K-ras companion diagnostic was used. Based on these data, CHMP recommended approval of panitumumab in late 2007.

Insurers have generally embraced companion diagnostics, but these are only as reliable as the underlying statistical characteristics of laboratory assays. One must understand that every test has false positives and false negatives, but a successful biomarker that offers sound fundamental characteristics can discriminate between targeted populations. Biomarkers may be used to discriminate toxicity versus no toxicity; efficacy versus no efficacy; or population selection, for example.

Conclusion

Biomarkers can help provide drug developers with new opportunities to provide safe, effective pharmaceuticals at reduced cost, while extracting maximum value over a product's lifecycle. The question for drug developers should not be whether to implement a biomarker strategy, but how – and how soon after discovery.

Many options exist for acquiring and validating biomarkers, but the path is not always as direct or straightforward as desired. Optimising the benefits of biomarkers requires a confluence of analytic, validation, clinical and data skills that few pharmaceutical companies possess within a single group. Moreover, the relationship between biomarkers and clinical development suggests that an appropriate source of biomarker expertise lies with a sponsor's CRO – provided, of course, that the CRO has appropriate biomarker expertise. 

References

1. AJ Atkinson Jr, WA Colburn, VG DeGruttola, *et al.* 'Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework,' *Clinical Pharmacology and Therapeutics*, 69(3), pp89–95, 2001.
2. The Food and Drug Modernization Act of 1997, Title 21 Code of Federal Regulations Part 314 Subpart H Section 314.510.
3. SS Kumar, S Ananthan, AG Joyee. 'Detection of *Enterocytozoon bieneusi* (Microsporidia) by polymerase chain reaction (PCR) using species-specific primer in stool samples of HIV patients,' *Indian Journal of Medical Research*, 121, pp215–219, April, 2005.
4. V Levy, RM Grant. 'Antiretroviral therapy for Hepatitis B virus–HIV–coinfected patients: Promises and pitfalls,' *Clinical Infectious Diseases*, 43:904–910, 2006.
5. F Goodsaid, F Frueh. 'Biomarker qualification pilot process at the US Food and Drug Administration', *The AAPS Journal*, 9(1), pp105–108, 2007.
6. J Powis, KM Peltekian, SS Lee, *et al.* 'Exploring differences in response to treatment with peginterferon alpha 2a (40kD) and ribavirin in chronic hepatitis C between genotypes 2 and 3', *Journal of Viral Hepatitis*, 15(1), pp52–57, 2008.
7. Merck/Schering-Plough Pharmaceuticals provides results of the ENHANCE trial (http://www.sch-plough.com/schering_plough/news/release.jsp?releaseID=1095943).
8. TJ Mühlebach, J Gabay, CF Nathan, *et al.* 'Treatment of patients with chronic granulomatous disease with recombinant human interferon-gamma does not improve neutrophil oxidative metabolism, cytochrome b558 content or levels of four anti-microbial proteins', *Clinical and Experimental Immunology*, 88(2), pp203–206, May 1992.
9. LS Bemiller, DH Roberts, KM Starko, JT Curnutte. 'Safety and effectiveness of long-term interferon gamma therapy in patients with chronic granulomatous disease', *Blood Cells, Molecules, and Disease*, 21(3), pp239–247, 1995.
10. SE Nissen, EM Tuzcu, P Schoenhagen, *et al.* Statin therapy, LDL cholesterol, C-reactive protein and coronary heart disease, *New England Journal of Medicine*, 352(1), pp29–38, Jan 6 2005.
11. MA Albert, E Danielson, N Rifai, *et al.* 'Effect of statin therapy on C-reactive protein levels: The Pravastatin Inflammation/CRP Evaluation (PRINCE): A randomized trial and cohort study', *Journal of the American Medical Association*, 286, pp64–70, 2001.
12. FDA press release (<http://www.fda.gov/bbs/topics/NEWS/2007/NEW01740.html>).
13. Morningstar, CMS limits Amgen ESA reimbursement (<http://quicktake.morningstar.com/Stocknet/san.aspx?id=194182>).
14. AJ Wood. 'A proposal for radical changes in the drug-approval process', *New England Journal of Medicine*, 355, pp618–623, 10 August 2006.
15. P Landers. 'Cost of developing a new drug increases to about \$1.7 billion', *The Wall Street Journal*, 8 December 2003.
16. 'Costly cancer drug offers hope, but also a dilemma', *New York Times*, 8 July 2008.
17. EL Wiley, LK Diaz. 'High-quality HER-2 testing: Setting a standard for oncologic biomarker assessment', *Journal of the American Medical Association*, 291, pp2019–2020, 28 April 2004.
18. C Ensinger, W Sterlacci. 'Implications of EGFR PharmDx™ kit for cetuximab eligibility', *Expert Review of Molecular Diagnostics*, 8:2, pp141–148.
19. EMEA Press Release 20 September 2007 Document reference: EMEA/405113/2007 (<http://www.emea.europa.eu/pdfs/human/opinion/40511307en.pdf>).
20. Amgen press release 'New Biomarker Data Links KRAS Gene to Vectibix(TM) Clinical Response' 25 September 2007.

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