

The Strategic Importance of Biomarkers to the Pharmaceutical Industry

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Introduction

In the last few years, pharmaceutical companies have become increasingly interested in biomarkers and their incorporation into company drug development programmes and use as companion tests for targeted therapeutics. Identifying patients that will benefit from a drug and eliminating those that will not is increasingly important. A simple analysis of the number of biomarker deals recorded in PharmaVentures' PharmaDeals[®] database shows a rise from just seven in 2001 to 130 in 2007. There are a number of drivers for this, and these include: the increasing cost of drug development and associated decline in new molecular entities (NMEs) achieving registration; patient and regulatory authorities requesting upfront evidence of therapeutic benefit; and reimbursing bodies requiring proof of likely beneficial outcomes before payment. One would imagine that the combination of these factors would result in a highly positive outlook for biomarker researchers and developers. However, the situation is not as simple as it appears because, despite the factors listed above, it is hard to capture the value created by the addition of a biomarker into the drug development or patient identification process, and thus to apportion returns from subsequent commercialisation of the drug and/or biomarker.

Biomarker vs. Diagnostic

Diagnosis can be defined as 'the translation of data gathered by clinical and radiographic examination into an organized, classified definition of the conditions present,'¹ whereas a biomarker can be defined as 'A characteristic

¹ Mosby's Dental Dictionary, 2nd edition. © 2008 Elsevier, Inc.

that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacological responses to a therapeutic intervention.'

The former may tell us nothing about how a therapeutic might impact on an individual, and the latter may be of no utility in identifying the presence of a disease. There is a degree of crossover between the two, but the terms are often used interchangeably, which is not always appropriate. A good diagnostic does not necessarily make a good biomarker, and vice versa. For example, the PSA (prostate specific antigen) test was first commercialised by Hybritech over 20 years ago to assist in the diagnosis of prostate cancer. However, it has a positive predictive value of only 13 to 69%, indicating that it is not a particularly good stand-alone diagnostic tool. Determining rising or falling PSA levels before, during and following treatment though is an excellent way of monitoring efficacy and predicting outcomes, i.e. PSA is a good biomarker. The same is true for other diagnostic biomarkers, particularly in oncology, e.g. CA125 and CEA.

Blockbusters vs. Nichebusters

In the past, the pharmaceutical industry has sought to develop drugs that can be administered as widely as possible on the grounds that sufficient patients with a given diagnosis who took the drug would benefit, while those who did not benefit would not be unduly harmed. Patent protections allowed pharmaceutical companies to achieve revenues from such 'blockbusters' that gave good returns on the original R&D investments, permitted new investment into the next generation of therapeutics, and offset the massive associated development costs. In oncology in particular, this model has started to break down as a result of the very high cost of treatment plus the reluctance of reimbursing bodies to foot the bill for treatments that do not work in a significant minority (and in some instances, a majority) of cases. Additional resistance has also been met from patients who do not wish to be subjected to prolonged unpleasant treatments for no clinical benefit. This has led to the dawn of the 'nichebuster' or personalised medicine age, whereby drugs will be prescribed and funded only for those patients for whom there is a demonstrable probability that they will gain some benefit. This means that pharmaceutical companies will see their potential market size (in terms of number of patients) significantly reduced. A way must be found to translate the benefit derived from identifying positive responders in a patient population using biomarkers, into sufficient revenues to give adequate returns on investments that must now also encompass the additional development and clinical validation costs of the biomarkers.

Where Can Biomarkers Have a Big Impact?

It is widely acknowledged that the use of biomarkers will not just be restricted to identifying responder or non-responder populations for therapeutics. They will also have a significant role to play in the drug development process. It is estimated that if biomarker data could improve just 10% of the Go/No Go decisions in the drug development process, then savings of up to \$100 million per drug could be achieved.² Some 50% of Phase III clinical trials fail to support marketable therapies as a result of flawed trial design, lack of understanding of dose response relationships and lack of drug efficacy. All areas of drug development could benefit from the inclusion of a companion biomarker. However, executing the development of such a companion biomarker so that it can be validated in time to participate in a Phase III trial requires significant commitment on behalf of the biomarker and drug development partners. Commencing a collaboration later than Phase I may not leave sufficient time to include the biomarker in trials that would allow co-labelling on the therapeutic.³ In addition, the pharmaceutical partner will not want to commit additional expensive resource to include a biomarker in a costly Phase III trial if the biomarker is likely to indicate that the drug is not sufficiently efficacious to deliver the desired commercial outcomes. Equally, the biomarker developer will not want to commit to costly development and validation if this process does not facilitate a commercial success for the drug, and hence deliver additional value. The third interested party in this is, of course, the end user and payer, who does not want to use or pay for a therapy that might not work. The challenge for the biomarker and drug developers is to form appropriate alliances early in the development process and acknowledge the value that both sides bring to the table.

We have already seen a number of examples of the area where biomarkers have had their biggest impact. This is in the determination of patient populations that are more or less likely to respond to a given therapeutic, often termed 'enrichment'. The most well known of these is Herceptin® (trastuzumab) and the Her2 test. Whilst all would acknowledge that this drug, with its companion biomarker, is a major success (Herceptin generated revenues in excess of \$4 billion in 2007) the therapeutic and biomarker were not 'co-developed' in the traditional sense. The biomarker was originally declined by Roche, and was commercialised in the first instance by Dako, although without it Herceptin would have been very unlikely to have gained approval. The response rates in actual patients who were tested for the biomarker was 50% (n=470, follow-up

² Barton CL (2006) Commercial Opportunities from Biomarkers Transforming drug discovery, clinical development and molecular diagnostic. London, UK: Business Insights Ltd.

³ Blair E (2004) Surrogates & diagnostics in today's pharmaceutical development. Caxton, UK: Integrated Medicines Ltd.

duration 1.6 years, $p=0.05$). The calculated response rate in untested patients was 10% ($n=2200$, follow-up duration 10 years, $p=0.05$). The combined figures give a response rate of 17%.⁴

A second example of biomarker benefit is vilazodone. This drug, an SSRI (selective serotonin reuptake inhibitor) for the treatment of depression, had failed to show efficacy in a number of Phase II clinical trials with Merck KGaA and GlaxoSmithKline and, as such, was destined not to reach the market. The rights were acquired by Clinical Data, which has developed a companion genetic test to identify the responder population. The company has completed successful Phase III trials and an NDA filing is imminent. The biomarker not only revived a beneficial therapeutic, but will also deliver savings in the cost of care through this targeting strategy.

The Deals and Alliances Landscape

Figure 1 shows the increasing number of deals in the biomarker/diagnostics space. Both categories are included to cover the overlap in utility mentioned previously.

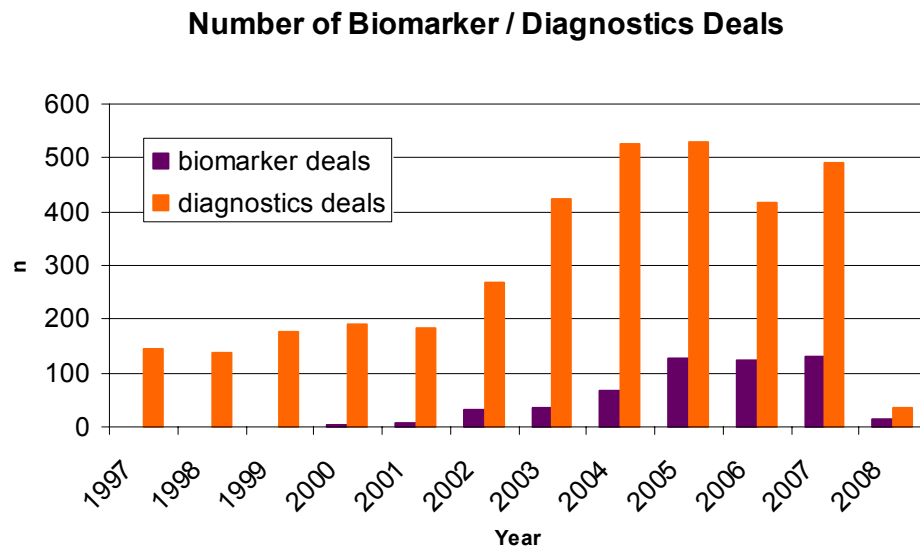


Figure 1

It is noteworthy that before 2001 the term 'biomarker' hardly ever appeared in deal terms, and that the last 7 years have seen large increases in the number of both diagnostics and biomarker deals.

⁴ From the Aclara Biosciences website, accessed via The Wayback Machine, <http://www.archive.org/web/web.php>

Therapeutic Focus

Analysing the deal landscape for 2007 (Figure 2) we can see clearly that the hot therapeutic areas are oncology, anti-infectives, immunological, neurological.

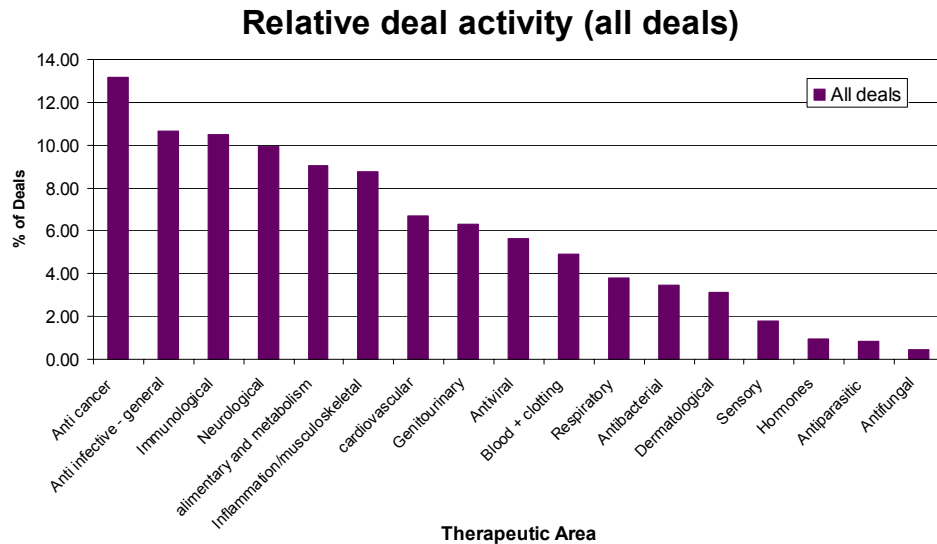


Figure 2

Reanalysing the data to look at the relative proportion of diagnostics deals versus therapeutics deals in each disease area throws up some interesting observations (Figure 3).

Relative Deal Landscape 2007

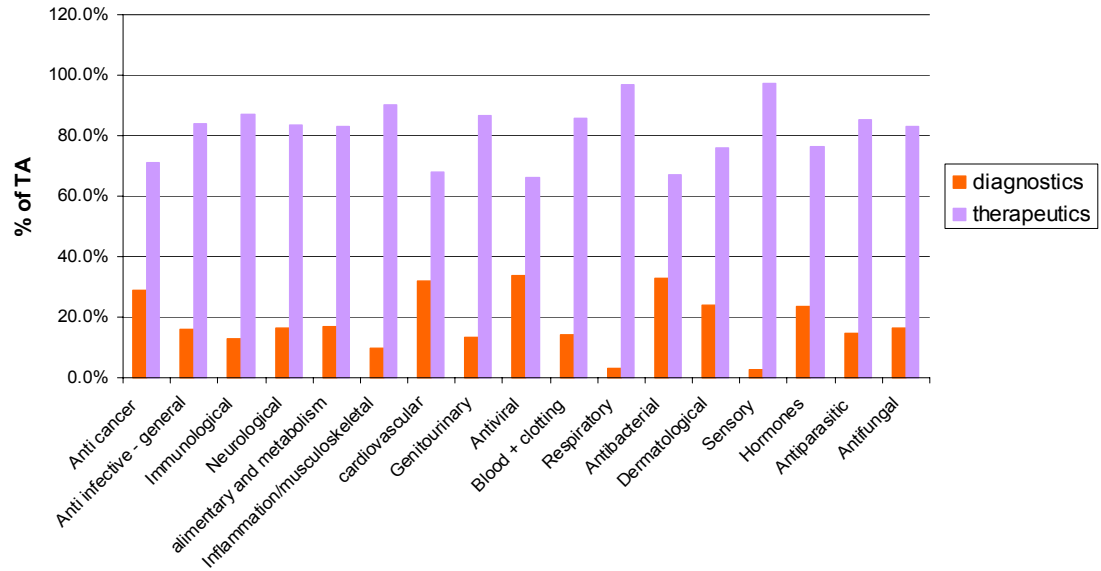


Figure 3

There are six therapeutic areas where over 20% of the deals done involved diagnostics. Those areas were oncology, cardiovascular, antiviral, antibacterial, dermatological and hormones. Notable absences from this top six are the neurological and immunological areas. The presence of antiviral and antibacterial diagnostics is understandable as there is a direct link between identifying the nature of the infection and the therapeutic to be used to cure it. Hormone diagnostics have been in existence almost since the birth of the diagnostics industry, and the ability to measure hormonal imbalances as a diagnostic tool is equally useful as a biomarker in determining therapeutic benefit and disease progression monitoring. There is a clear value add in these cases. The case for oncology has been established by Herceptin, although it is interesting that the quest for cancer-specific diagnostics has been largely unsuccessful, whilst the use of cancer biomarkers for responder identification and outcomes determination is probably the most vibrant area. PSA, mentioned earlier, is a case in point. The lack of diagnostic/biomarker activity in the neurological sector may be attributable to a number of factors. Patient presentation is not routinely at the asymptomatic phase (unlike cardiovascular or oncology), and there are no formalised screening programmes in place unlike the cardiovascular and genitourinary/cancer (for women's health) areas.

Intellectual Property

Strong intellectual property (IP) and patent portfolios underpin and enhance the value of any technology offering, and this is no different in the case of diagnostics and biomarkers. The diagnostics world has traditionally been something of a patent minefield, with a history of cross-licensing between the major players to carve out commercial opportunities. It is useful, therefore, to review the nature of IP being generated in terms of the therapeutic areas, in the light of the dominant deal areas identified earlier. Figures 4 and 5 below provide data on IP filings in 2005.

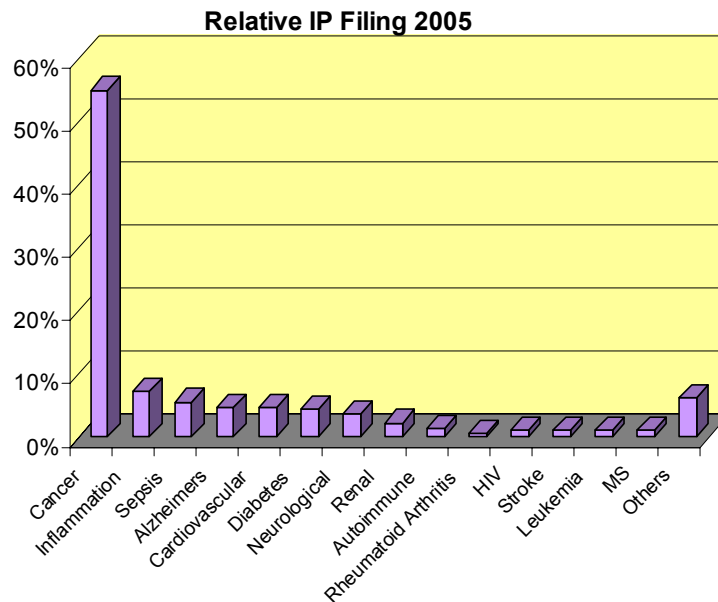


Figure 4

It is unsurprising that more than 50% of biomarker IP filed in 2005 was in the field of cancer (Figure 4). This therapeutic area can be further broken down to identify the most active areas within the cancer field.

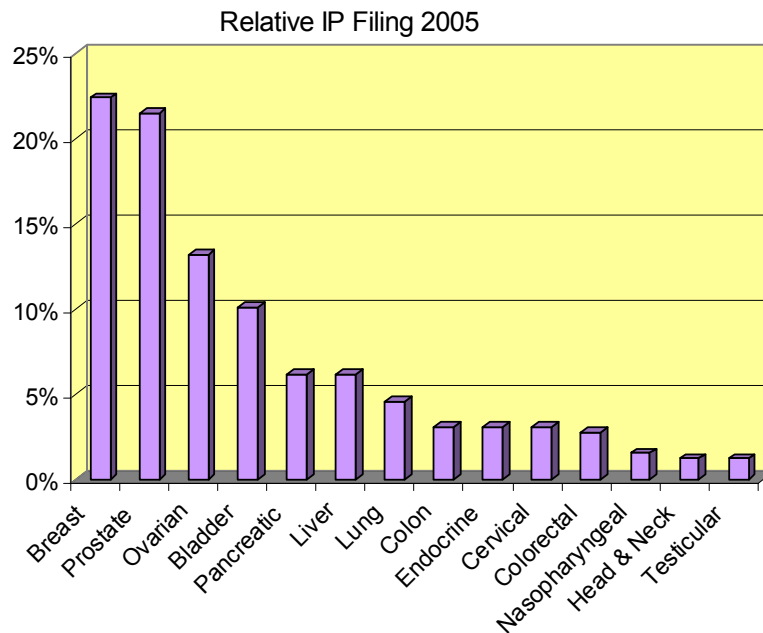


Figure 5

Unexpected features of this analysis are the relatively fewer filings for colon, colorectal and lung cancers, given that mortality rates in the UK in 2005 were 22% for lung, 10% for bowel, 8% for breast and 7% for prostate cancers (rates for other types of cancer were 5% or less).⁵ This, again, may be related to the timing of patient presentation and the likely prognosis with current therapies, given that the number of cases/deaths for these high mortality areas in the UK in 2005 were 38,313/33,465 for lung cancer, 36,109/16,092 for colorectal cancer, 44,659/12,509 for breast cancer and 34,985/10,000 for prostate cancer.

Academic and other 'not for profit' institutes have historically been prominent in discovering and filing IP in the biomarker area, and more so since governments have encouraged such institutions to adopt a more commercial focus to their research endeavours. One would anticipate that large pharmaceutical companies would find this a rich seam to tap into to secure companion biomarkers for their therapeutics in development, with the potential for deal terms that should be acceptable to all.

Figure 6 below shows that this is not the case.

⁵ Cancer Research UK, <http://info.cancerresearchuk.org/cancerstats/mortality/cancerdeaths/>

Biomarker deals between Academic Institutions and either Globals or Other Pharma

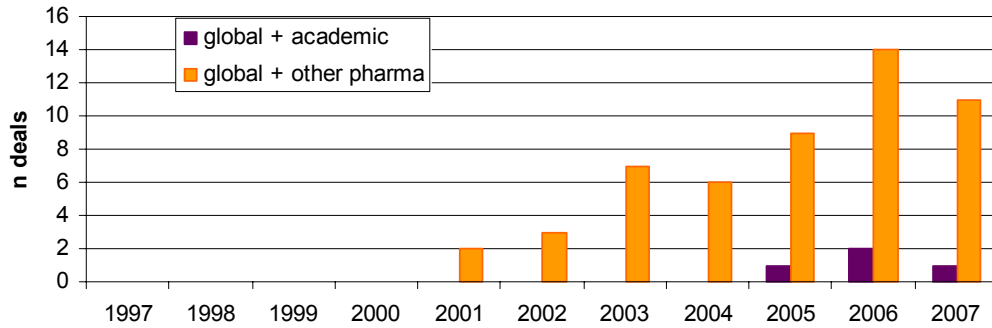


Figure 6

Large pharmaceutical companies have only just started to strike deals with academia in the last 3 years, and deals are done predominantly with other pharmaceutical companies. When these data are broken down a little further (Figure 7), it can be seen that academic institutions strike deals mostly with start-up or emerging companies. What is not clear from the data is what proportion of the start-up companies in these deals were spun out from the originating institution with the IP in question.

Biomarker deals between different types of organization

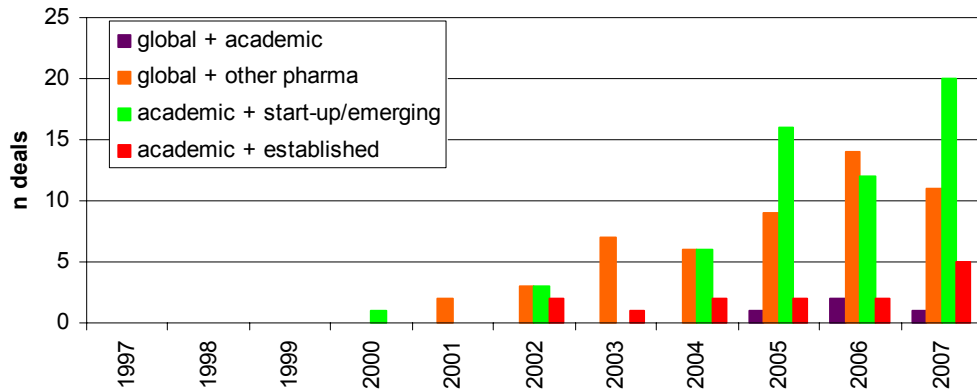


Figure 7

Deal Value

The diagnostics industry has historically been the poorer cousin of the pharmaceutical industry. Depending on the therapeutic area, it typically takes 7 to 12 years for a therapeutic entity to reach peak sales,⁶ although some have achieved this in as little as 2 years. Diagnostics products typically take longer. This is largely because diagnostics companies are unable to put equivalent sales and marketing muscle behind their products.

Figure 8 below shows the value of deals involving cancer, and compares those involving therapeutics with those involving biomarkers. Deals identifying 'diagnostics' were not included in order to give a clearer picture of the value of biomarkers.

⁶ Drug Researcher, <http://www.drugresearcher.com/news/ng.asp?id=51870-therapeutic-class-determines>.

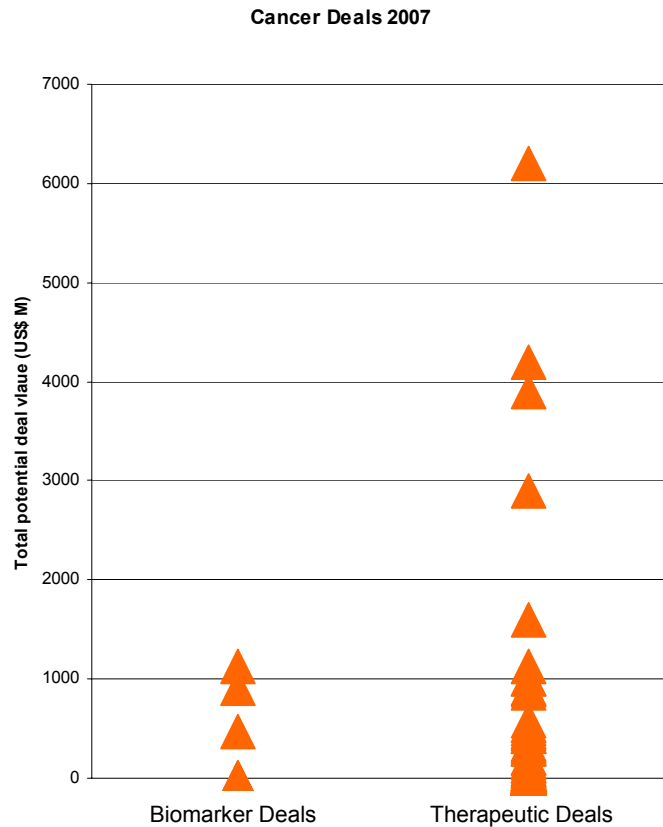


Figure 8

It is clear that the pure biomarker deals are of less total value than the therapeutic deals, and that there are significantly fewer. Only one biomarker deal has a total potential deal value exceeding \$1 billion. Only two biomarker deals involved an upfront payment. By comparison, all therapeutic deals in the same period involved an upfront payment to the licensor.

Industry experts are advocating collaboration between big pharma and biomarker developers, but valid models must be established to determine the added value from inclusion of a biomarker with a therapeutic. With this information, the biomarker developers can then strike appropriate deals with large pharmaceutical companies. However, establishing such models is not straightforward. Pharmaceutical companies have, in the past, been averse to disclosing the nature of their pipelines, making it difficult for biomarker developers to dovetail with their processes. This is particularly important, as lead times for biomarker development and validation mean that collaborations should begin no later than Phase I clinical trials for the therapeutic. Additionally, pharmaceutical companies want a biomarker that will inform the end users that their therapeutic will work. What they absolutely do not want is a biomarker that

tells them in a Phase III clinical trial that their original understanding of the biology on which their therapeutic is based was not correct, and that consequently it has less value. Given that biomarker and diagnostic companies are usually playing catch-up, there is an opportunity for pharmaceutical companies to exploit the wealth of clinical samples generated in their trials to conduct retrospective validation trials of biomarkers. This approach has many merits in that it forges strong ties between the biomarker developers and the pharmaceutical companies and establishes their interdependency. It also allows the pharmaceutical company to use clinical samples as a currency, which is of great value for the biomarker developer. What it does not do is determine how much value is added by the biomarker in terms of sales volumes, time to peak sales and pricing strategies. A second issue with this approach is the requirement from the US FDA that prospective trials should be run with biomarkers to establish their utility and fitness for the purpose for inclusion on the therapeutic label. This requirement does not exist in Europe in order to obtain CE marking.

Attempts have been made to determine the value added to the commercial opportunity of a therapeutic by the inclusion of a biomarker, but this has not been simple because of the lack of precedents. Trusheim et al. have presented some interesting comparative data.⁷ Peak annual sales of Gleevec® (imatinib) in 2006 were \$2.5 billion, covering the treatment of approximately 55,000 patients. Peak annual sales of tamoxifen in 2001 (used for comparison as this was the last year that it was under patent protection) generated sales of \$630 million and covered the treatment of over 500,000 patients. This is a somewhat extreme example, and does not really compare like with like, but it does illustrate that 'blockbuster' level revenues can be generated with targeted 'nichebuster' drugs (Gleevec is a biomarker-directed therapeutic for the treatment of chronic myeloid leukaemia (CML) and gastrointestinal stromal tumours (GIST)). Trusheim et al. further speculate that a biomarker that is used as a gatekeeper, i.e. to determine which patients are appropriate for treatment with a given drug, would be used to evaluate all patients. With a price point of \$500, such a test could potentially be more profitable than a periodically prescribed therapeutic.

Summary

The pharmaceutical and biomarker/diagnostics industries are in complete agreement that there need to be close collaborative arrangements between them in order to deliver efficiencies in the drug development process, maximise safety and efficacy for the patient, and maintain revenues and margins for the

⁷ Trusheim MR, Berndt ER, Douglas FL (2007) **Stratified Medicine: Strategic and Economic Implications of Combining Drugs and Clinical Biomarkers**. Nature Reviews Drug Discovery 6: 287-293, April 2007.

companies. What remains to be determined is how this will happen. There is no established collaborative pathway that they can walk together to reach this desirable destination, but more and more are embarking on the journey. The relative contributions to the value chain, and thus the rewards, still need to be determined if the partners in the process are to remain discrete bodies, or there will be a growing programme of strategic acquisitions by large pharmaceutical companies, as evidenced by the acquisitions of Roche in 2007.

About PharmaVentures

A leading results driven organisation, PharmaVentures (www.pharmaventures.com) assists pharmaceutical and biotechnology companies across the world in all aspects of deal making. The Company's core business is the provision of tailored consulting and transaction advisory services to the Life Science industry, with additional deal making support provided through the PharmaDeals range of intelligence products which include analysis tools, reports and workshops. An innovative business, PharmaVentures additionally provides industry insight, business reviews and deal making trends through the world's first online pharmaceutical television show www.pharmatelevision.com. Now in its 10th year PharmaVentures is based in Oxford, UK, employs over 30 people mostly educated to PhD or above, and has increased its turnover five fold with 80% of revenues from outside the UK. With offices in the USA and Australia, the Company works for a variety of clients from start-ups to global corporate pharmaceutical companies.

If you would like to speak to one of our consultants to see how we could help your company achieve its strategic goals, please contact: Dr Adrian Dawkes, Managing Consultant, PharmaVentures Ltd., Tel: +44 (0)1865 784193, Email: adrian.dawkes@pharmaventures.com