

The Biopharmaceutical Industry Wakes Up to Pharmacogenetics

It's no new insight to say that the biopharmaceutical industry is facing an almost unprecedented series of challenges to its future growth and development. What is a new insight though is the realisation that pharmacogenetics is one of the key approaches that biotechnology and pharmaceutical companies can embrace in order to make the future look more rosy.

Pharmacogenetics is the study of how genetic make-up affects the way individuals respond to drugs, and has a role to play in nearly all aspects of drug discovery, development and delivery. The extent to which the industry is announcing partnerships, collaborations and initiatives in this area shows that it really is putting its money where its mouth is. The casual observer at recent industry conferences will have observed big pharma's increased embrace of the concept of personalised medicine – focusing on the delivery of healthcare services in a way that is tailored to the individual. In this global industry, this was emphasised still further in comments made as companies reported their 2009 earnings and discussed the outlook.

In this article we will concentrate on how the biopharmaceutical industry is adopting pharmacogenetics approaches into its drug development processes. While some of the

Hurdles	Challenges
Safety	Patent cliffs and genericisation
Efficacy	The need for increased productivity
Quality	The need for innovation
Cost-effectiveness	Declining growth in developed markets
	Constrained global healthcare budgets

potential of pharmacogenetics has been recognised, with the emergence of high-profile companion diagnostics in areas such as cancer, its importance in all stages of drug development, not just at the prescribing step, has been somewhat underappreciated. It is in these drug development areas, such as an increased understanding of drug response profile and identifying the patient sub-populations in clinical trials, that London Genetics is an expert.

Hurdles and challenges

As well as facing their traditional four hurdles, biopharmaceutical companies are also grappling with a series of challenges we believe, as outlined in the table below.

The good news is that approaches like pharmacogenetics can help companies find their way through the tricky route ahead.

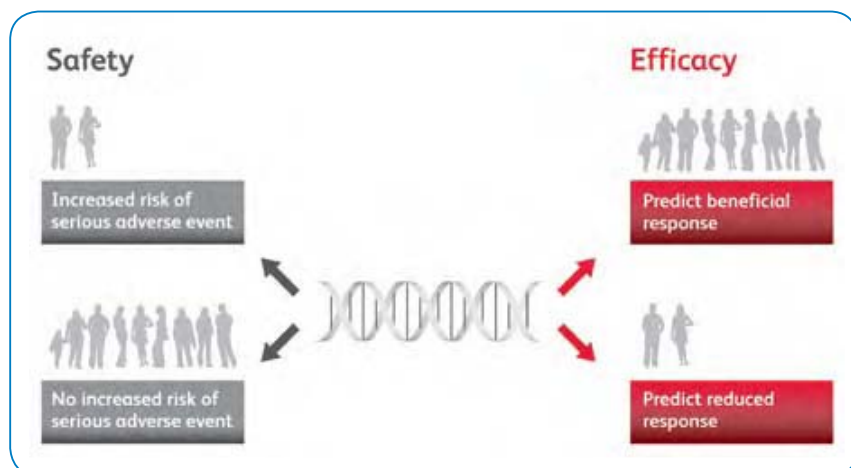
Increased focus on safety

The safety of drugs has always been of paramount importance, and where pharmacogenetics is seeing most of its current success. Recent high-profile safety

scares, such as that surrounding Merck & Co's COX-2 inhibitor Vioxx, and GSK's antidiabetic Avandia, have sharpened regulators' vigilance in this area (as well the antennae of shareholders, since according to an analysis by the Deloitte Center for Health Solutions, the British company lost \$17bn worth of shareholder value between the two weeks before the safety scare arose and the two weeks afterwards). What with the continued threat of lawsuits the impact is still very much in evidence.

The widely used generic anticoagulant warfarin illustrates many of the ways in which pharmacogenetics can add value in the biopharmaceutical industry, not least by increasing patient safety. For this drug, metabolism is affected by genetic variation among other factors. Getting dosing right is difficult and risks are high, since underdose can lead to strokes and overdose to bleeding, for example in the gut or brain. Deloitte estimates that genetic testing could prevent 85,000 serious bleeds and 17,000 strokes a year, leading to healthcare savings of \$1bn per annum.

As a response to this, tests for warfarin-metabolising genes are being developed. The drug label, which was first modified in 2007, was updated for a third time in January 2010 to provide information on how specific genetic variants may influence a patient's response. In Europe, the EU-PACT study is looking at the effect of gene-based dosing on 2000 patients. This study is taking place across eight centres, including some of the academic founding partners of London Genetics. Following work by the International Warfarin Pharmacogenetics Consortium, which developed an algorithm with the potential to help doctors prescribe the



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optimal warfarin dose, the NIH has started a large clinical trial to test whether gene-based dosing leads to optimal outcomes. It will involve 1200 patients and report in 2012. Backing up these trials, in March it was announced that a Medco Research Institute/Mayo Clinic real-world study had shown that when genetic data was available to warfarin-prescribing doctors, hospitalisations due to bleeding fell by nearly a third.

For this well-established generic, pharmacogenetics is enabling it to be prescribed in a more cost-effective and safe way, with significant impact on the product's lifecycle expectations. The point to note here is that not only do these studies show how pharmacogenetics can inform increasingly safe treatment of patients, but also effective patient treatment. The other upside for the pharma companies involved may well be increased revenues from a boost in confidence about warfarin prescription.

Moving on from how warfarin prescribing may be resurrected, there have recently been suggestions that pharmacogenetics might be able to lead to the relaunch of a high-profile painkiller pulled from many markets following a safety scare. Novartis' COX-2 inhibitor Prexige was approved in Europe in 2006 but was withdrawn from many markets in 2007 as a result of concerns over liver toxicity. It was not approved in the US.

Now, however, following the discovery of a genetic biomarker shown to predict those most at risk of side-effects, lumiracoxib was resubmitted to the EMA for approval for treatment of the signs and symptoms of osteoarthritis at the end of 2009. Under a risk mitigation system, a test based on the marker could be used to exclude from treatment those patients most likely to suffer from hepatic side-effects, and Novartis is believed to be discussing with the FDA the possibility of a similar application in the US. The genetic marker was discovered via retrospective genetic analysis of patient samples from a lumiracoxib clinical trial.

If approved, it is believed that this would be the first example of a drug being resurrected based on a molecular diagnostic. Given the size of the European and US osteoarthritis markets, this would be a notable boost for Novartis, with significant implications for the rest of the sector as well. Indeed, in 2002 the FDA launched an initiative to assess whether pharmacogenetics could improve prescribing decisions for marketed drugs – and it seems that it can.

The efficacy hurdle

Clearly one of the hurdles that a pharmaceutical product must get over before it is approved is that of efficacy. According to 2007 PhRMA data, around 75% of the industry's R&D spend is accounted for by clinical trials, so there is a huge annual investment in this activity. What is interesting to learn though is that the result of all this spend is drugs that generate response rates of around 50% with wide variation around the mean, as the picture below shows. What this rate masks is the proportion of patients in whom the product is not effective or minimally so, and those for whom it is extremely effective. In development this can mask a potential efficacy signal, and in the marketplace can hide a potential efficacy differentiator in the most responsive patient group – a factor which is crucial to a drug's success.

The genome of an individual predicts how effective a drug is likely to be in that person, as well as what side-effects, if any, could result. Imagine then the efficacy figures that could result if it was possible to exclude from your trial cohorts patients most likely to gain little benefit or suffer from side-effects, instead including only those most likely to respond well with minimal risk of serious adverse events.

The potential efficacy impact of this stratified medicine approach, pharmacogenetics and personalised medicine is being recognised at AstraZeneca. In a recent interview (1), executives noted that at the company, 'we demand that every product in our pipeline has a biomarker... (to) increase magnitude of treatment effects'. It's not just biopharmaceutical companies that are seeing the value of biomarker technologies such as pharmacogenetics. Contract research organisations, increasingly important in today's outsourcing world, work closely with the companies in the sector in order to develop their drugs effectively.

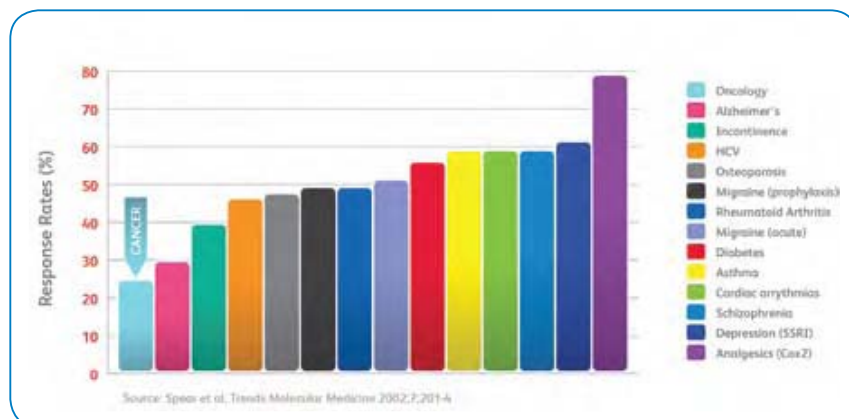
The importance of these technologies to CROs was emphasised in the recent link-up between Parexel and Proteome Sciences to enhance the former's biomarker capabilities at an early stage.

Healthcare penny-pinching – the need to show cost-effectiveness

How to demonstrate cost-effectiveness is a big question in the biopharmaceutical industry, and one with which it is just starting to grapple. According to a Journal of the American Medical Research Association (JAMA) analysis reported in PharmaTimes (2), in the past just 2% of comparative effectiveness trials have looked at cost-effectiveness. However, with billions of dollars being thrown at comparative effectiveness studies in the USA, there is a real potential for pharmacogenetics to show its potential in comparative and cost-effectiveness studies.

US President Obama's recent political success in the form of healthcare reform also increases the focus on cost-effectiveness data. Industry commentators are of the view that the pressure on costs and for cost savings will increase the influence of the bodies that ultimately foot the bill – insurance companies, Medicare, Medicaid and other payers. All this is expected to bring about further changes in how the industry operates, with doctor-focused sales reps losing their jobs and the focus turning to the payers, moves which Merck & Co and Novartis are already believed to be adopting. The data these new clients will be wanting to see will have a big emphasis on comparative effectiveness. Of course, constrained national healthcare budgets and the emergence of regulatory bodies such as the UK's NICE have been a fact of life for some time in many European territories and in Japan.

As an example of cost-containment focus, at the end of last year the pharma-

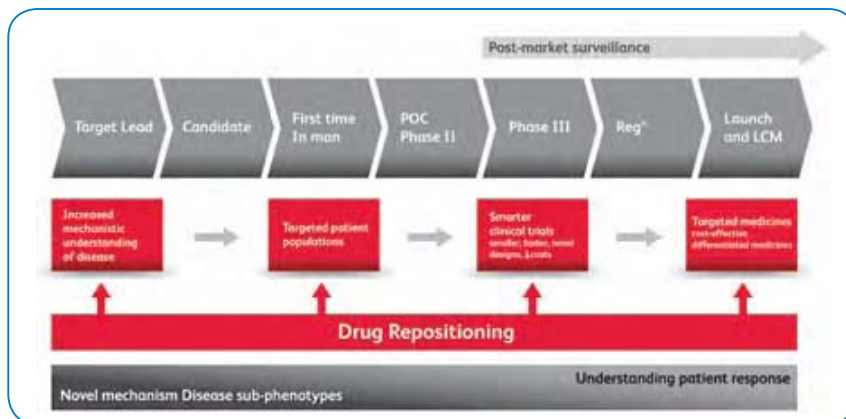


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ceutical benefits manager MedCo initiated a comparative effectiveness study of sanofi-aventis' Plavix (clopidogrel) versus Lilly's Effient looking at the role of genetics in outcomes. Only 75% of the population are believed to be effective metabolisers of Plavix, gaining full benefit from the drug, and studies have shown that poor response to the drug is associated with an increased likelihood of further cardiovascular events. Since generic competition to Plavix is anticipated from 2011, the results could lead to considerable cost savings.

With the increased focus on cost-effectiveness, companion diagnostics are increasingly important. Use of genetic and pharmacogenetic data throughout drug development, and concomitant development of a diagnostic, is the efficient way ahead, meaning that the drug and diagnostic can be launched simultaneously. In this way, approval applications can be based on prospective rather than retrospective analyses, and therefore be more likely to be met with approval by the regulators.

Pfizer has recently shown that it appreciates the value of developing companion diagnostics concomitantly with clinical trials. In February it announced an agreement with the DxS subsidiary of Qiagen to develop a companion diagnostic for PF-04948568, an immunotherapy in Phase II



trials for the treatment of glioblastoma. The drug candidate targets a mutated form of the EGF receptor present in up to 40% of glioblastomas.

How pharmacogenetics can help to ease the productivity crisis

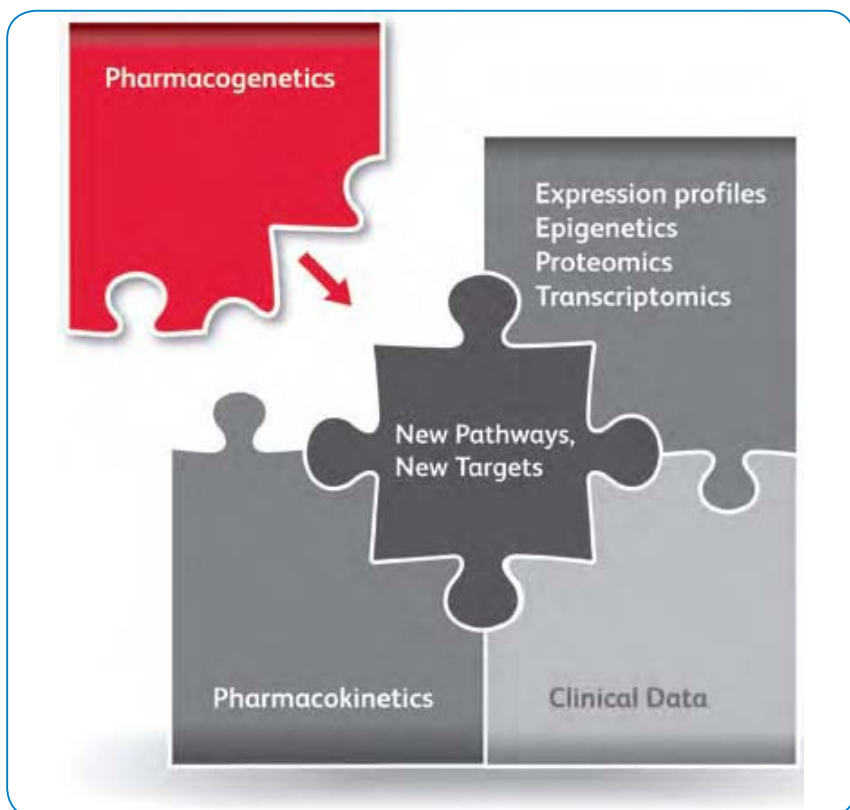
Productivity is traditionally measured in the biopharmaceutical sector by looking at the number of new drugs launched each year. When pitched against the increasing amounts being spent by companies annually on R&D, it is clear that the sector is struggling to reap the benefits from the increased levels of spend seen. While much debate is raging about how to increase the return on this resource, it is likely that several new approaches will be pivotal to this effort.

With the potential to refine drug response profiles and select the correct patient populations at an early stage, such as at the proof-of-concept step, pharmacogenetics can bring increased confidence that a drug will be effective in larger scale clinical trials. In addition, the ability to exclude poor responders or those who could suffer from side-effects should increase the response rate of the drug in clinical trials and therefore its chances of approval. Finally, the faster trials and smaller patient cohorts needed to get a strong efficacy signal should also have a beneficial effect on productivity. This is the basis of the recently launched I-SPY 2 trial, as discussed below.

The traditional approach to drug development is fairly rigid in terms of the sequence of clinical trials, the sanctity of the agreed protocol and the impact on the validity of the trial data if unapproved changes are made. With the timelines and costs associated with drug development, amending an ongoing clinical trial is a risk very few companies are prepared to take.

It does seem, however, that some of the calls for change to this process (such as the use of adaptive trial designs) are starting to be heard, with bodies as august as the FDA in the vanguard and pharmacogenetics playing a role. The recent announcement of the I-SPY 2 trial for the development of breast cancer drugs is a case in point – it will use biomarkers and adaptive trial design to assess a number of potential products in a rapid way. Under this protocol, data and outcomes used in the earlier stages of the trial will be used to adjust the treatment given to later patients, and ineffective or unsafe drugs will be dropped from the process.

The trial has been launched by the Biomarkers Consortium, a public-private partnership that involves the FDA, the National Institutes of Health and major



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pharma companies. It will use genetic or biological markers from the tumours of individual patients to screen new treatments, in order to elucidate which work best in which setting. One of the unique features of the trial is the number of drug candidates it will involve – as many as 12. Approval of this trial meant that the FDA had to approve a master IND, so that failed drug candidates could be withdrawn and new ones added without the need to rewrite the trial protocol. Five drug candidates have already been selected, from companies including Abbott, Amgen, and Pfizer, and all differ from each other in how they work, adding to the value of the clinical trial.

In contrast to the usual 12-15 year timeframe and in excess of \$1bn financial resource, I-SPY 2 aims to reduce both the time and cost of drug development. Through the use of fewer patients and earlier assessment of drug safety, a new strategy that pleases both the regulators and the industry could result. According to BioCentury (3), Phase III trials of drugs that succeed in I-SPY 2 are expected to involve only 300 patients or so, with the probability of success increased from 60-70% to 85%.

Biopharma is turning to the developing markets

Big pharma is increasingly turning to the emerging markets for growth, as initiatives such as healthcare cost containment stymie that in the developed world. According to a recent presentation from AstraZeneca based on IMS data (4), emerging markets are expected to contribute around 70% of pharmaceutical sales growth in the next five years. It expects global pharma sales to grow from \$765bn in 2009 to \$955bn in 2014, with \$55bn of the growth from established markets versus \$130bn from emerging markets.

Emerging markets therefore represent key territories for biopharmaceutical companies, with around 85% of the world's population believed to live within them, and tackling them is a key challenge. It's not just a case, however, of launching existing drugs into these markets, as there are significant genetic differences between different populations across the world, variation that contributes to differential response between these groups. For example, in the case of the anti-epileptic carbamazepine, there are in Han-Chinese genetic variants associated

with serious adverse events which are not seen in Caucasians. Understanding these differences and the pharmacogenetics will therefore play a key role in tapping into these important territories.

This has recently been recognised by Lilly, Merck and Pfizer with the formation of the Asian Cancer Research Group to 'accelerate research and ultimately improve treatment' for cancer patients in Asia. Under this pre-competitive collaboration which will share data with the scientific community, the companies plan to create a comprehensive pharmacogenomic cancer database and are currently focused on collecting tissue samples and data in lung and gastric cancers.

As we have discussed here, pharmacogenetics is one of the new enabling translational medicine technologies with the potential to help the biopharmaceutical industry overcome the hurdles and challenges ahead. With its potential to help increase efficacy, safety, cost-effectiveness and productivity, pharmacogenetics is being increasingly adopted by companies in the sector, a trend which is expected to increase.

References:

- 1 BioCentury, February 1 2010, p A7
- 2 Pharmatimes, 16 March 2010 <http://www.pharmatimes.com/worldnews/article.aspx?id=17554>
- 3 BioCentury, March 22 2010, p A7
- 4 AstraZeneca Emerging Markets Investor Day, March 16 2010 http://www.astrazeneca.com/_mshost3690701/content/resources/media/investors/2010-presentations/request-azn-full-presentation.pdf

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