PERSONALISED MEDICINE

what's in it for big pharma?

"There is nothing more difficult to take in hand, more perilous to conduct, or more uncertain in its success, than to take the lead in the introduction of a new order of things. Because the innovator has far enemies all those who have done well under the old conditions, and lukewarm defenders in those who may do well under the new..."

Machiavelli – The Prince

By Dr Stephen Little

When Machiavelli was writing *The Prince* he probably wasn't thinking of the development of personalised medicine but his comments accurately reflect one of the issues slowing down its uptake. The pharmaceutical industry has done well under the old conditions and industry executives are only lukewarm defenders of personalised medicine – a system where pharmacodiagnostic tests are used to identify individuals likely to respond well to a particular medicine.

The potential commercial downsides of the requirement for a diagnostic test prior to receiving a medicine are obvious to the pharmaceutical industry – the benefits are a little more difficult to discern. Until Pharma understands what's in it for them they are unlikely to be enthusiastic supporters of a new order of things. The key to the problem is to understand that the primary motivation of the pharmaceutical industry is the sale of medicines. Changes that increase sales will be embraced; changes that decrease sales are resisted. Once the pharmaceutical industry understands how personalised medicine can be used for its own benefit then it will begin to be applied more widely.

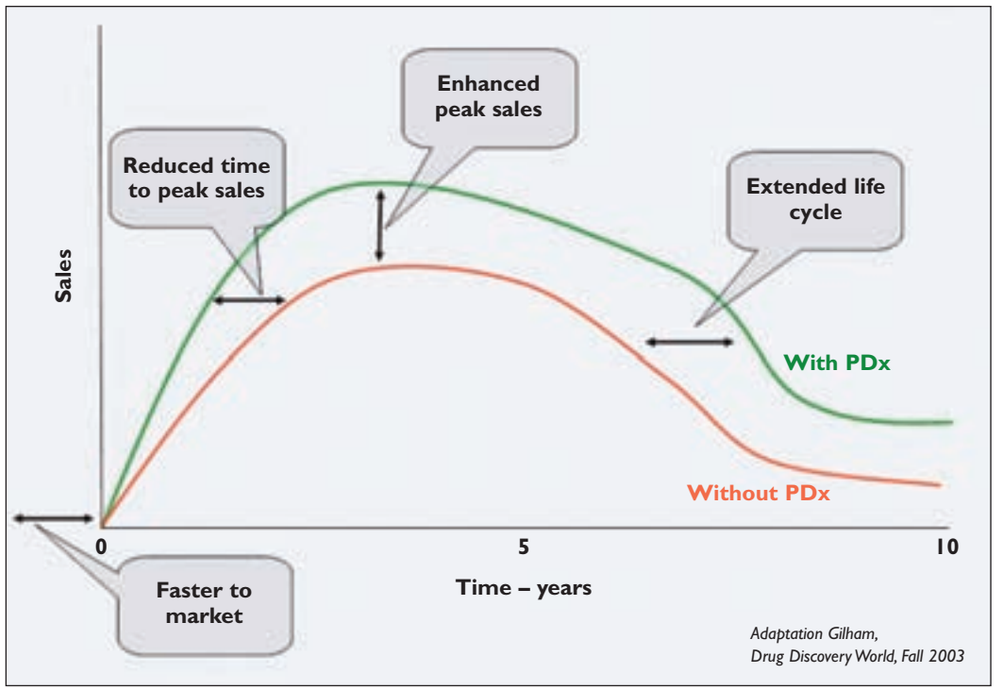
Pharma does not exist in a vacuum – there are many other stakeholders with an interest in the development of personalised medicine. Some of these stakeholders are going to cause changes independently of the pharmaceutical industry so when answering the 'what's in it for me?' question the industry needs to consider not only 'how can we use personalised medicine to sell more drugs?' but also 'how can the use of personalised medicine protect our existing sales against changes in the marketplace?'

The following sections illustrate some of the ways that Pharma can use personalised medicine both to increase and also to protect sales.

1. Use personalised medicine to differentiate a 'me-too' product in a crowded marketplace

For some diseases there are already many excellent treatments available. A new drug coming to

Figure 1



market needs to be able to compete with these established products to be successful. From Pharma's perspective the situation is deteriorating as patent protection of existing therapies expires and they become available as low-cost generics. In an ideal world the new products would be better than the old – an alternative is to make better use of the new products by targeting them to individuals likely to respond well. In this way a marginal performance benefit in the general population can be transformed into a significant benefit in the target population. For common conditions such as diabetes or heart disease a sub-group of the total market is still large target population. Clearly there is the complication of providing a pharmacodiagnostic test but it surely shows a lack of imagination on the part of the pharmaceutical marketing divisions if this requirement could not be promoted as a real strength of the therapy and be used as a positive sales tool.

Figure 1 shows the four ways in which a pharmacodiagnostic can improve sales:

- Faster time to market
- Reduced time to peak sales
- Enhanced peak sales
- Extended life cycle

2. Obtain extended patent protection on the drug/diagnostic combination

The reason that personalised medicine is a good idea is because drugs aren't perfect and any given medicine will not work well for all sufferers of a particular disease. To discover whether or not a drug works in most, some, or just a few patients requires a clinical trial. Until the drug has actually been tested in humans it is impossible to be certain just how well or how badly it will perform. This observation has important implications for the timing of pharmacodiagnostic discovery.

Drug patents cover the compound itself and are filed early in the drug discovery process. In contrast differential drug response and hence the potential for a pharmacodiagnostic is not discovered until several years later when the drug has entered the development pathway. By obtaining intellectual property on the combination of drug and pharmacodiagnostic it may be possible for Pharma to extend the period of marketing exclusivity.

3. Reduce time to market by the use of orphan drug status

The Orphan Drug Act offers incentives for drugs which treat diseases affecting small numbers of

patients. For example in the US orphan drug status is available for conditions affecting fewer than 200,000 people. Normally the 200,000 refers to the incidence of the disease but by using a pharmacodiagnostic to target the therapy the number is reduced from the number of patients with the disease to the number of patients eligible to receive the therapy on the basis of a positive pharmacodiagnostic test.

By using this approach a manufacturer can achieve rapid approval for its therapy – later the applications for the drug can be expanded into other fields if appropriate

4. Resist the threat of the diagnostics industry

The diagnostics and pharmaceutical industries have markedly different dynamics. The $550 billion pharmaceutical industry has a high risk/high reward profile, its customer is the clinician and its key strengths are *in vivo*. In contrast the $25 billion diagnostics industry has a much lower risk/lower reward profile and uses its engineering and technology skills to provide products to laboratories. It is hardly surprising that the diagnostic industry is very interested in capturing some of the value of a therapeutic by controlling a pharmacodiagnostic test required for the optimum use of the drug.

Over the past three years the regulatory authorities have shown they are very willing to relabel a drug to reflect new diagnostic information. Examples of drugs which have undergone this process are GSK's purinethol which now carries a recommendation for TPMT testing and Pfizer's Campto which shows increased risk of neutropenia in the 50% of individuals who carry the *28 variant of the UGT gene.

The pharmaceutical industry can protect itself against these changes by taking control of the discovery of biomarkers which can lead to the development of pharmacodiagnostics. **Figure 2** illustrates the drug lifecycle overlaid with the three phases of pharmacodiagnostic discovery.

In the left-hand pane of the diagram the drug has been developed for a pre-defined population specified by a diagnostic. The middle section represents the situation when differential drug response has been identified early in clinical development and a suitable diagnostic identified to allow appropriate targeting and on the right the drug has been launched, differential response observed and a potential pharmacodiagnostic discovered. As we move from left to right in the diagram the balance of power moves from Pharma to the diagnostic industry. The reasons for this change are urgency and IP.

If a requirement for a pharmacodiagnostic is

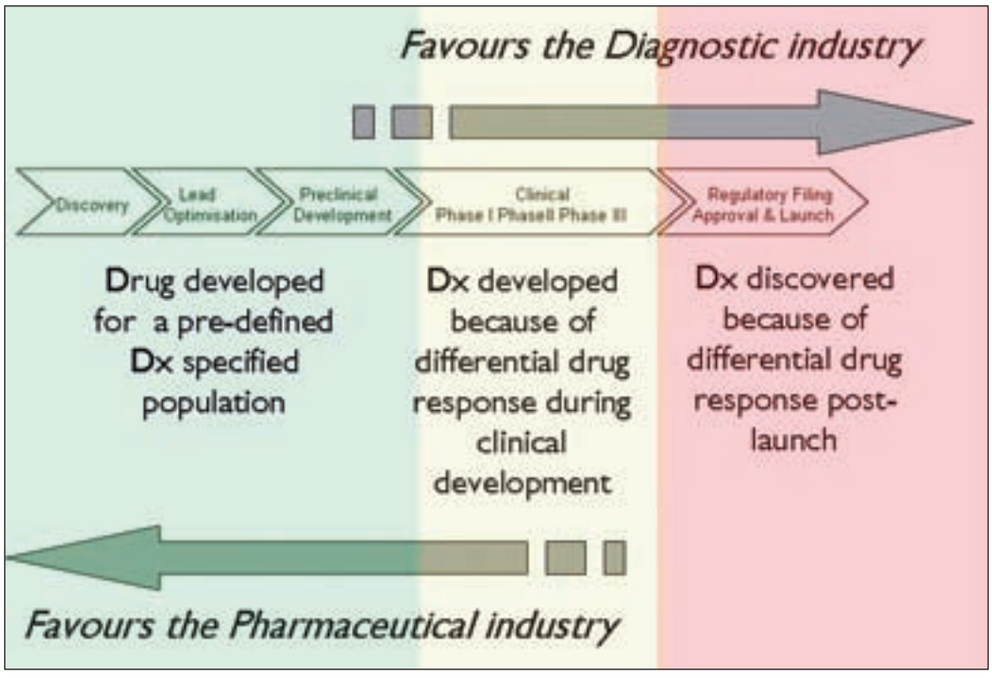


Figure 2

identified late in the development process there will be increased urgency to make it available. This pressure means that the diagnostic industry is in a stronger position to negotiate a share of the drug revenues for making the assay available. The situation is even worse if the pharmacodiagnostic is discovered post-launch – here the diagnostics industry may control both delivery of the pharmacodiagnostic and any IP associated with it. For example after the launch of both Iressa (AstraZeneca) and Tarceva (Hoffman-La-Roche) it was discovered that mutations and copy number alterations in the gene encoding the drug target (EGFR) could predict drug response.

The pharmaceutical industry is in a very strong position to discover these associations for itself by careful analysis of samples from phase II and III clinical trials. By controlling this process the threat from the diagnostics industry can be minimised.

5. Meet the needs of the regulators

The regulatory authorities, particularly the FDA, are showing considerable enthusiasm for the use of pharmacodiagnostics to improve drug efficacy or safety. In addition to their previously mentioned willingness to relabel approved drugs they are also taking significant steps to encourage the uptake of the use of pharmacogenetics and other markers during drug development. For example, in April 2005 Janet Woodcock, Director of CDER at the FDA, said: "Biomarkers are the foundation of evidence based medicine. Without new markers treatment remains empirical and it is imperative that biomarker development is accelerated along with drug development …drug development is done as it is because previously there wasn't any other option – now that there are new tools available there is a need to change thinking both from the perspective of industry and the regulators."

The need to meet regulatory requirements is essential for the sale of all pharmaceuticals. If a personalised medicine approach is a pre-requisite for certain therapies then it is very clear what is in it for Pharma.

Summary

This brief article began with a quotation from Machiavelli on the difficulties of innovation. The same author also had wise words on the dangers of vacillation. The words below have been modified but the sentiment remains the same and represents good advice to the pharmaceutical industry:

"There is no avoiding personalised medicine; it can only be postponed to the advantage of others." DDW

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