editorial

Nafees N. Malik*

Yasmeen Khan

Personalized medicine: potential impact on the biopharmaceutical industry

The pharmaceutical industry currently faces unprecedented drug discovery challenges. On the one hand, research and development (R&D) is becoming ever more expensive; on the other hand, the number of new drugs entering the market continues to remain low. Member companies of the Pharmaceutical Research and Manufacturers of America – the pharmaceutical industry's main trade group, to which all of the leading drugmakers belong – spent US$ 26.0 billion on R&D in 2000 versus US$ 45.8 billion in 2009 [1]. The average cost of developing a new medicine, including the cost of product failures, has risen from an estimated US$ 802 million in 2001 to US$ 1.3 billion for a conventional drug and US$ 1.2 billion for a biological drug in 2005 [2,3]. In addition to the high financial cost, a substantial time investment of 10–15 years is required to bring a new medicine to the market [1]. Yet, despite R&D investment increasing, the number of new drugs to be launched in the USA has fallen, from an average of 29 per year during 2000–2004 to an average of 22 per year during 2005–2009 [4].

How can R&D costs be controlled? Substantial savings could be made by reducing pipeline product attrition rates. Approximately 75% of the quoted cost of bringing a new drug to the market is due to product failures [5]. Today, for every five compounds that begin clinical studies, only one will ultimately be approved [6]. Even more alarming is the fact that approximately 50% of experimental drugs in phase III development fail [6]. This is very detrimental to pharmaceutical companies, as a phase III programme characteristically consists of many thousands of patients with a cost per patient that is estimated to exceed US$ 26,000; by comparison, a phase II programme may have a few hundred patients with an estimated cost of around US$ 19,300 per patient and a phase I programme generally has fewer than a hundred patients with an estimated cost of nearly US$ 15,700 per patient [7]. One of the key reasons for such high experimental drug failure rates is that most of the 'low hanging fruit' has already been picked, and hence drug discovery is becoming intrinsically harder.

Two other key factors, in addition to high pipeline drug attrition rates, that are contributing to rising R&D costs are that clinical trials are, in general, becoming both longer in duration and bigger in size. The average length of a clinical study increased 70% between 1999 and 2005 from 460 days to 780 days [1]. In addition, between the 1980s and the early 2000s, the average number of patients per trial grew 7.5% annually [8].

In order to control rising R&D costs, biopharmaceutical companies must endeavour to reduce experimental drug failure rates, as well as decrease the duration and size of clinical studies. The

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field of personalized medicine can help achieve these goals. It aims to identify the 'right' drug – one that has maximum efficacy or minimum side-effects – for a patient based upon the genetic profile of their disease (e.g. as in cancer) or upon the physiological state that their genome dictates (e.g. ability to metabolize a specific drug). Key to the realization of personalized medicine is biomarkers, which are substances, such as DNA, RNA or proteins, that denote a particular pathological or physiological state. It has been estimated that genomic technologies could reduce the investment needed to bring a new drug to the market by up to US$ 300 million and two years [5].

The number of pipeline failures could be reduced by excluding subjects from clinical studies who, due to their genetic makeup, would not be expected to respond to an experimental drug or who are predicted to be at risk of adverse effects. Poor drug response and side-effects remain major problems even for medicines that are already on the market, so the situation with respect to this is far worse for pipeline products. At present, most commonly prescribed drugs are effective in only around 50–60% of patients [9]. In addition, more than two million hospitalized patients have serious adverse drug reactions each year in the USA and around 100,000 hospitalized patients die from them [10]. As a result of their genetics, individuals exhibit variability in their drug metabolizing enzymes, drug transporters and drug targets. Genetic differences are believed to account for 20–95% of discrepancies in drug effects between individuals [11].

Excluding subjects from phase I and II studies will probably be difficult as limited information is likely to be available as to what gene variants (i.e. variations in a given gene that exist stably in a population), and hence biomarkers, correlate with what drug response. DNA analysis of phase I and II subjects could, however, be performed to establish non-responding and side-effect-prone gene variants. Sequencing the genome of participants in clinical studies will become increasingly viable as the cost falls (a fierce race is presently on to hit the US$ 1000 mark). Patients with non-responding and side-effect-prone gene variants could then be excluded from costly phase III studies. This strategy has the potential to allow substantial cost savings to be made because 50% of phase III experimental drugs presently fail [6] and, of the failures, 50% are due to lack of efficacy and 30% due to safety concerns [12]. In addition, focusing on the right patients would not only reduce pipeline product failure rates but also decrease the length and size of clinical studies needed to show a statistically significant benefit.

This approach would, however, limit the patient population for which a new drug could receive marketing authorization. But a particular personalized medicine should have a superior efficacy or safety profile in a given disease subpopulation compared to conventional drugs, and so would stand a high chance of becoming the first-line treatment. Therefore, a smaller target population could be compensated for by a higher uptake of the drug within that population. In addition, healthcare payers – who are increasingly analyzing the cost effectiveness of drugs to help guide their reimbursement decisions – are much more likely to be willing to pay for costly medicines, such as cancer biologics, if robust clinical data exist to demonstrate that the drug has a high chance of actually working in a given patient subpopulation with a particular disease.

Furthermore, by applying the principles of personalized medicine, drugs that have been abandoned in the general population in the past, due to efficacy or safety issues, could possibly be 'rescued' for given subgroups.

Patient adherence rates for medications are generally in the region of 50% [13] and key reasons as to why people are non-compliant are side-effects and poor therapeutic response. One could hence postulate that personalized medicines, due to their superior safety or efficacy profiles, would be taken for longer periods of time by patients, translating to higher product sales for biopharmaceutical companies.

To reap the benefits of personalized medicine, biopharmaceutical companies should allocate resources to identify biomarkers that indicate whether a drug will work or be safe in a patient. Given that personalized medicines will be prescribed on the basis of companion biomarker tests, drug companies should strengthen their own diagnostic arms (through increased investment or acquisitions) or form alliances and partnerships with existing diagnostic companies. Drugmakers that have both strong pharmaceutical and diagnostic divisions will be in an outstanding position strategically. The field of personalized medicine will almost certainly result in strong growth in the diagnostics industry in the coming decade.

The Food and Drug Administration (FDA) in the USA is also encouraging the development of personalized medicines, and drugmakers should take advantage of this supportive regulatory environment. The FDA's Critical Path Initiative aims to help new scientific discoveries, such as in genomics, reach the bedside, so that they actually benefit patients.

In conclusion, biopharmaceutical companies need to think of personalized medicine as a key opportunity and not as a threat. Drugmakers have come to rely upon the blockbuster model, which, in essence, seeks to produce drugs for chronic conditions affecting large proportions of the population (in monetary terms, a blockbuster product generates at least US$ 1 billion annually). In contrast to blockbuster drugs, personalized medicines will be for smaller subpopulations with a given disease, and so are, in general, expected to generate lower sales, which concerns pharmaceutical companies. The blockbuster model is now failing to deliver, as reflected by rising R&D costs, low new product approvals, reduced pharmaceutical innovation, large numbers of patent expiries and negative sentiment against 'me-too' drugs. In light of these issues, personalised medicine should be seen as a key opportunity in difficult times to make the R&D process more efficient and to bring innovative drugs to the market that help fulfil unmet medical needs. This will in turn help generate solid profits for biopharmaceutical companies and create shareholder value.

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Nafees N. Malik*
Institute of Biotechnology, University of Cambridge, Tennis Court Road, Cambridge CB2 1QT, UK

Yasmeen Khan
The Hillingdon Hospital, Piel Heath Road, Uxbridge, Middlesex UB8 3NN, UK

**Corresponding author:*
email: nafees_malik@hotmail.com