The new
BLOCKBUSTERS
healthcare packages for particular disease pathologies

With the cost of bringing a new drug to market now exceeding $800 million there is no doubt that the pharmaceutical industry has to fundamentally address the way in which it operates. This article offers a vision of change that could alter the entire economic foundation on which Pharma functions.

Most of the billion-dollar blockbusters the pharmaceutical industry (Pharma) has produced have a similar therapeutic profile. They are typically first-line treatments for chronic conditions, come in a single, 'one-size-fits-all' form and relieve the symptoms of a particular disease rather than changing the way it progresses. In the past few years, Pharma has also produced a number of blockbusters with a different therapeutic profile – second-line treatments designed for clinically defined populations and administered by specialists, some of which modify the course of a disease.

But there are signs of far greater change in the pipeline. A report recently published by IBM Business Consulting Services predicts the birth of a new sort of blockbuster within the next eight years. *Pharma 2010: The Threshold of Innovation* argues that a better understanding of the molecular sciences, massive advances in computing power and widespread recognition that the commercial potential of one-size-fits-all drugs is increasingly limited will collectively spur companies into defining diseases much more precisely – and creating healthcare packages for people with specific disease subtypes.

A disease-centric approach

It is widely known that most drugs only work for between 40% and 60% of the patients for whom they are prescribed, and that drugs which work well for some patients cause intolerable side-effects in others. This is sometimes because drugs act in unpredictable ways, but it is often because scientists have such a limited understanding of many common diseases that they can only define them in very simplistic terms – and patients who do not respond, or do not respond well, to a particular drug actually suffer from a different disease.

Now, thanks to the genomic sciences, researchers are gradually acquiring a much better grasp of the factors involved in a particular disease state, including its severity, how it progresses and why particular individuals are susceptible in the first place[1]. This will inevitably fragment the market and end the monolithic approach that has characterised past blockbusters. But it will also enable Pharma to define diseases much more accurately and make highly profitable drugs for smaller patient populations.

Take asthma and cancer, both general terms for a cluster of diseases with a variety of molecular mechanisms, environmental triggers and underlying genetic susceptibilities. Early treatments for asthma, such as steroids, worked through non-specific suppression of the immune system. But with more sophisticated molecular techniques, Pharma has begun to redefine asthma as a series of distinct disease states and biomolecular pathways like epithelial mediators and IgE pathways, and to develop different drugs for different states. Similar efforts are now

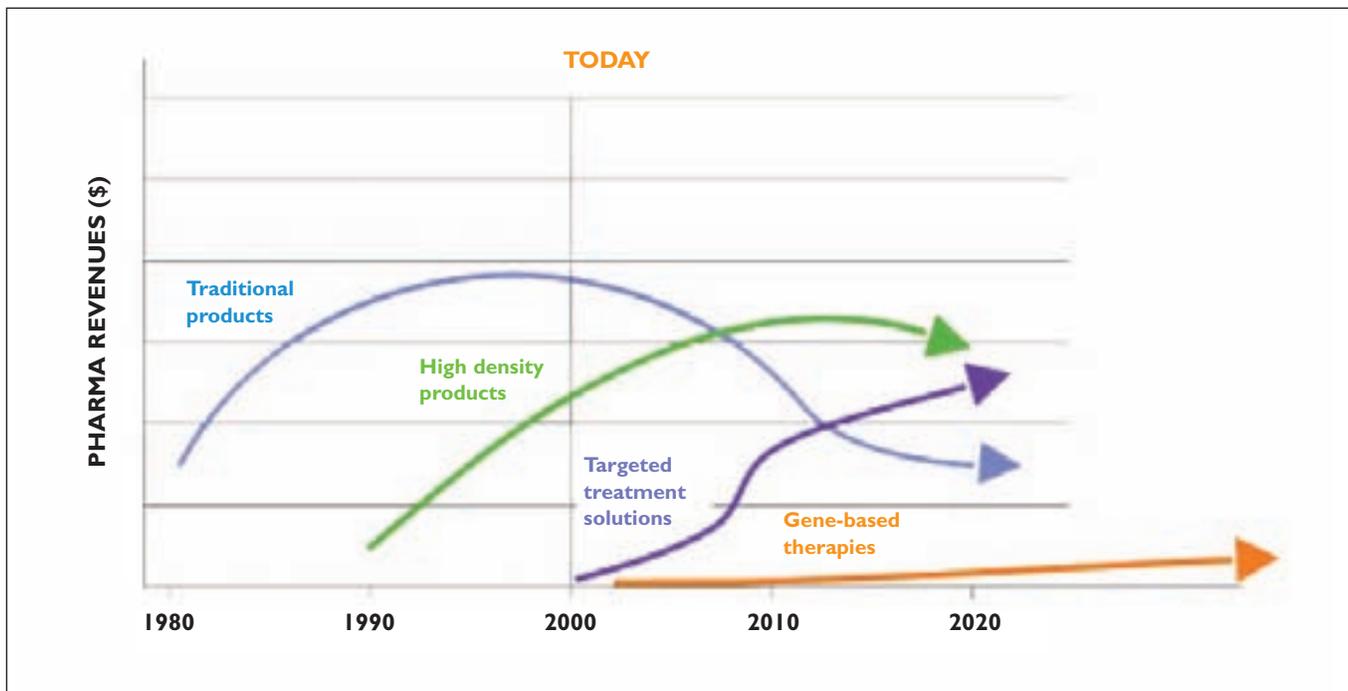**By Dr Nick Davies and Dr Steve Arlington**

being made to segment breast, prostate, lung and other kinds of cancer into different subtypes – and experts predict that the 200-odd forms of the disease which are recognised today could eventually be subdivided into as many as 2,000 forms.

Targeted treatment solutions

This redefinition of disease will culminate in the development of healthcare packages for treating specific disease pathologies – or 'targeted treatment solutions', as IBM Business Consulting Services calls them. They will typically consist of biologics rather than chemical entities, be based on clinically validated targets derived from a better understanding of a particular disease pathology, and be aimed at specific disease populations. They will modify the course of the diseases they treat, with outcomes data and disease progression markers providing proof of efficacy. And they will come with a network of services for diagnosing, treating, monitoring and supporting patients.

The emergence of targeted treatment solutions for specific disease states will benefit patients, healthcare professionals and payers, and the industry alike. It will give patients a comprehensive package of therapies that work for them – including diagnostics, prophylactics, molecular markers for defining and tracking the disease states from which they suffer, and monitoring mechanisms to help them comply with their medical regimens. It will give doctors the means with

which to provide better care and healthcare payers better value for money by enabling them to get the right drugs to the right patients and eliminating the cost of treating people with adverse drug reactions.

Similarly, it will provide Pharma with the opportunity to charge premium prices for treatments that demonstrably work for particular disease states, even though the target market may be smaller; to add value by providing diagnostics, biomarkers and monitoring devices; to increase drug utilisation with better compliance and persistence; and to build on its expertise in one disease state by moving on to other disease states in the same disease family, and developing entire treatment packages as distinct from single drugs. In short, targeted treatment solutions will be the main blockbusters of the future (**Figure 1**).

Drug discovery in 2010

But if Pharma is to alter its focus, it will have to transform the way in which it discovers drugs. The existing process consumes an enormous amount of time and resources – a situation that has been compounded by the current constraints on the industry's understanding. The Human Genome Project has ensured that an unprecedented number of potential molecular targets are now in the public domain, but scientists do not yet know very much about them. Nor do they yet have technologies that are capable of coping with this target-rich

environment, a fact that is likely to result in a massive increase in the number of 'undruggable' targets.

Fortunately, the experience of companies such as Amgen, Human Genome Sciences and Cambridge Antibody Technology suggests a way forward. These companies have already begun to use a disease-centric, biological approach to discovery, with impressive results: they have reduced target validation cycles to about two years. By 2010, most pharmaceutical companies will follow the same principles (**Figure 2**). They will decide which disease families they want to work on and begin defining the different disease pathologies and molecular mechanisms in those families. They will then harness the power of the molecular sciences to identify targets and develop rapid clinical proof-of-concept studies using various biological molecules that have been designed to interact with the targets – and simultaneously, start developing diagnostics based on molecular markers.

Defining diseases much more narrowly makes it very much easier both to validate a target and to find molecules that will interact with the target. Moreover, since biologics are usually less toxic than chemical entities, using biological molecules reduces the risk of producing a drug that fails because it has undesirable side-effects. The latest figures from CMR International show just how big an improvement that could produce. Only 8% of the new chemical entities that entered clinical development between 1996 and 1998 reached the market, compared with 34% of biotech and gene treatments[2].

Figure 2
In 2010 drug discovery will begin with an understanding of disease at the molecular level
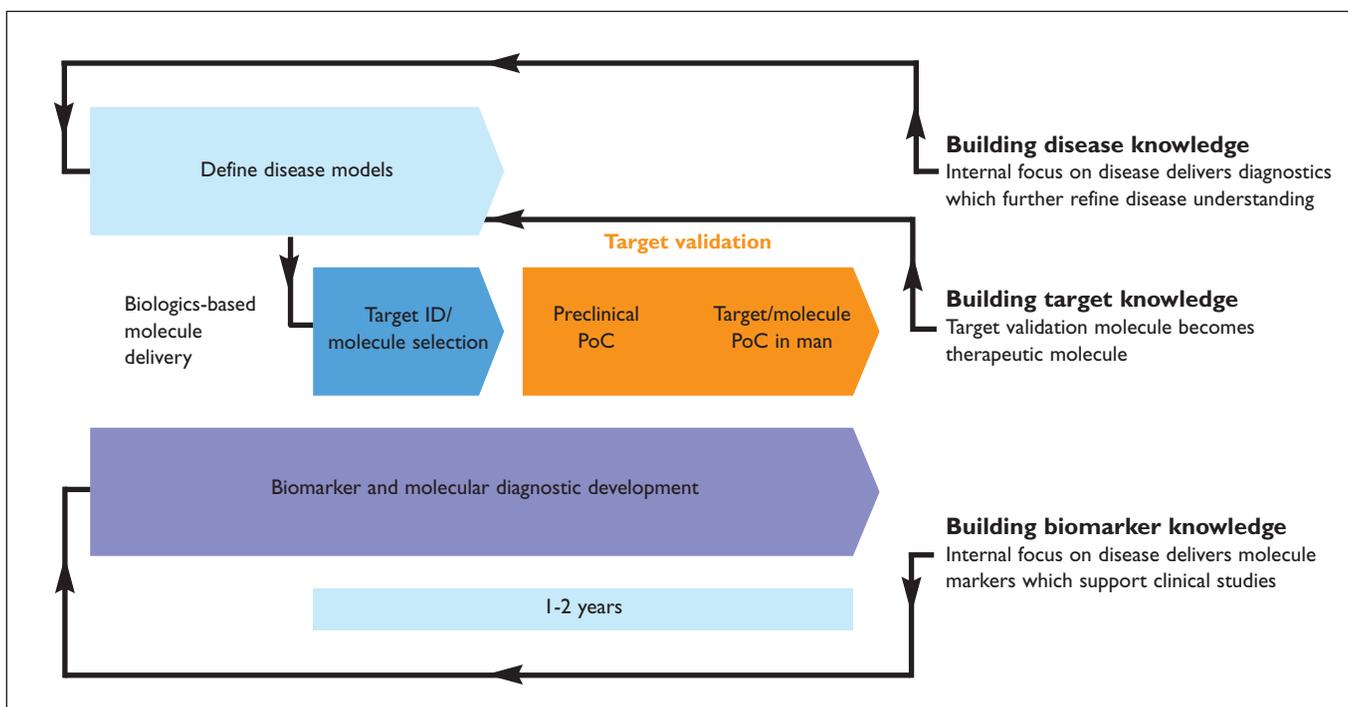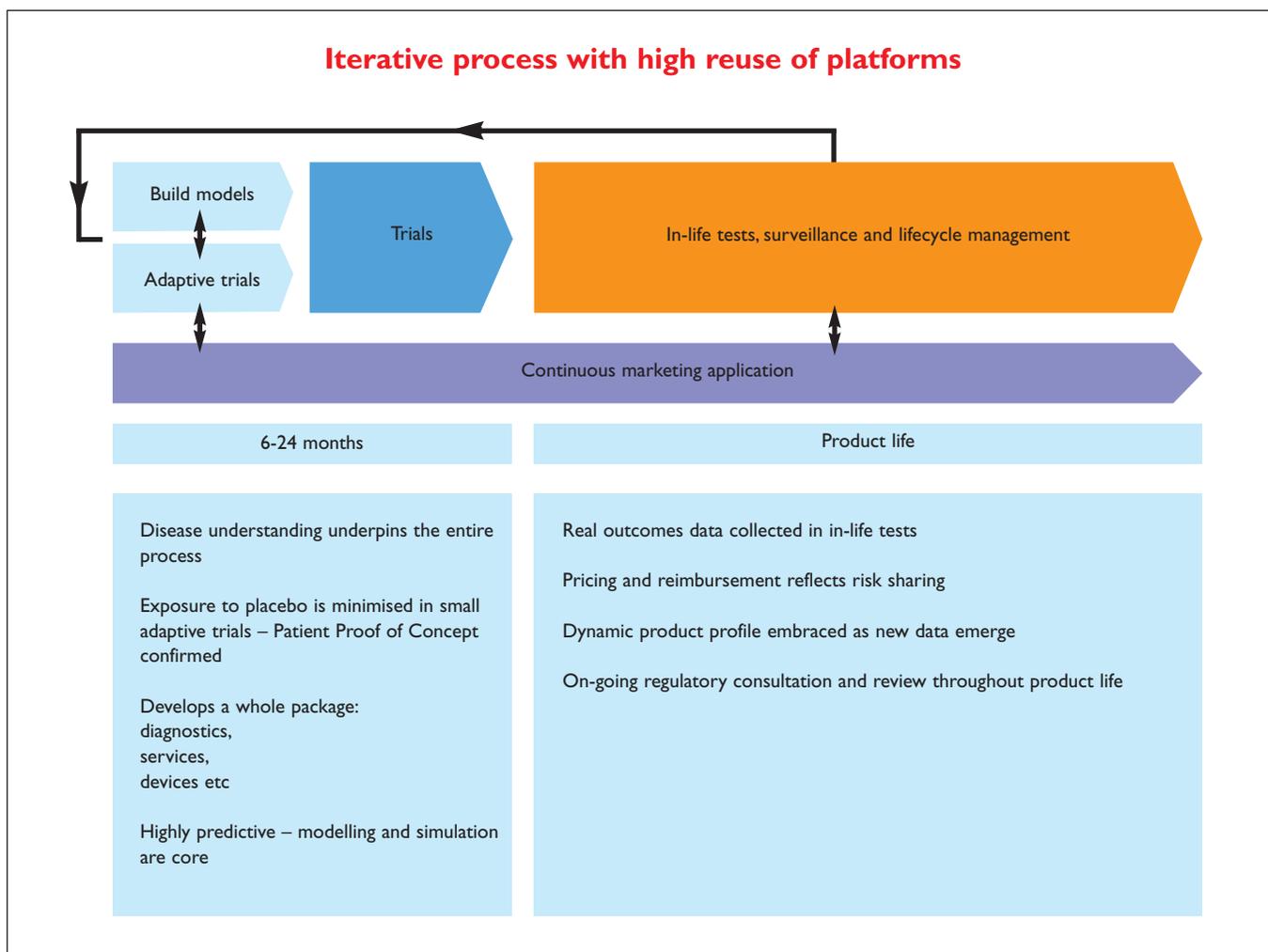
Drug development in 2010

So much for discovery, but what about development? The current approach is very expensive and inefficient – and the molecular 'burn rate' is by no means the only problem. Clinical trials cannot detect rare side-effects or drug interactions (and often even quite common reactions) because they take place in a controlled environment that bears little resemblance to the complexities of real life. One recent study shows that 45 of the 548 drugs approved by the US Food and Drug Administration between 1975 and 1999 acquired one or more new black box warnings and 16 drugs were pulled from the market. In total, it estimates that 20% of all new drugs are eventually found to have serious side-effects which are unknown or undisclosed at the time of their approval[3].

Moreover, even though most of the industry leaders have experimented with electronic data capture, about 95% of clinical trials are still run using multiple, paper-based systems which, inevitably, increases error rates. The redefinition of disease states will exacerbate these problems since it will then be necessary to test new drugs on patients who have the 'right' disease subtype and genotype, and that will compound both the bottlenecks in the process and the amounts of data the industry must store, share and manage.

So how will the development process evolve? Modelling and simulation will enable the industry to model how drugs act in whole body systems,

Building disease knowledge
Internal focus on disease delivers diagnostics which further refine disease understanding

Target validation

Building target knowledge
Target validation molecule becomes therapeutic molecule

Building biomarker knowledge
Internal focus on disease delivers molecule markers which support clinical studies

Define disease models

Biologics-based molecule delivery

Target ID/ molecule selection

Preclinical PoC

Target/molecule PoC in man

Biomarker and molecular diagnostic development

1-2 years

Iterative process with high reuse of platforms

Build models		
Adaptive trials	Trials	In-life tests, surveillance and lifecycle management

Continuous marketing application

6-24 months	Product life
Disease understanding underpins the entire process Exposure to placebo is minimised in small adaptive trials – Patient Proof of Concept confirmed Develops a whole package: diagnostics, services, devices etc Highly predictive – modelling and simulation are core	Real outcomes data collected in in-life tests Pricing and reimbursement reflects risk sharing Dynamic product profile embraced as new data emerge On-going regulatory consultation and review throughout product life

organs and at a sub-cellular level; and to design much more accurate trials (**Figure 3**). Electronic data capture and other such technologies will likewise accelerate drug testing by providing access to data in near real time.

Meanwhile, the scope of the development process will expand. Most companies currently make a collection of disparate medicines but, with the trend towards targeted treatment solutions, they will increasingly make a collection of disease-specific packages. The process will also become much more iterative, as work on a product for one disease in a particular disease family gets fed into work on successive products for other diseases in the same disease family.

Lastly, the way in which clinical trials are conducted will change. The traditional distinction between the various phases will collapse, with greater use of 'adaptive' trials – where information acquired during a trial is used to alter the course of that without compromising its statistical validity. Several companies have already conducted adap-

tive trials. Lilly, for example, has used adaptive design principles in Phase I cancer trials for some years. Similarly, Pfizer used adaptive dose-ranging trials to test neutrophil inhibitory factor on stroke patients and 'kill' the drug rapidly when the results proved disappointing. By 2010, most pharmaceutical companies will follow suit.

Regulation in 2010

These changes in drug discovery and development hinge on a much closer relationship between the industry and its regulators. At present, the first formal contact with the regulator occurs when a company files an investigational new drug application before starting Phase I trials. But when testing in man starts in late-stage discovery – with proof-of-concept studies for target and molecule validation – it will clearly be necessary to consult the regulators long before this point.

Companies will also have to work much more closely with the regulators to ensure they are using

Figure 3
In 2010 drug development will be an iterative process that relies heavily on modelling and simulation

Business

References

1 A general term for genomics, proteomics, metabonomics, phosphonomics, glycomics, pharmacogenetics, etc.

2 CMR International. Industry Success Rates 2002: Including Trends in Success Rates (April 2002): 13.

3 Lasser, KE et al. Timing of New Black Box Warnings and Withdrawals for Prescription Medications, JAMA, Vol. 287 No. 17 (May 1, 2002): 2215-2220.

4 CMR International. Industry Success Rates 2002: Including Trends in Success Rates (April 2002): 12.

5 Liikanen, E. Commission's proposal to review EU pharmaceutical legislation. Transcript of speech /01/354, Brussels (July 18, 2001): 4.

6 Tufts CSDD. Tufts Center for the Study of Drug Development Quantifies Savings from Boosting New Drug R&D Efficiency. Press release (September 9, 2002). Accessible at http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=20

robust simulations and monitoring outcomes data properly; and they will have to submit data on an ongoing basis, via rolling dossiers. Forging such links is difficult, but the advantages far outweigh the drawbacks. According to CMR International, a fifth of all new drug applications fail to reach the market after they are first submitted[4]. So, rather than investing many years and a lot of money in a drug that ultimately fails, it makes sense to submit data on an ongoing basis and spike the weakest products at earlier stages of development.

But the very premise on which permission to market a drug is granted is also likely to change. The European Community already plans to introduce marketing authorisations that would be valid for a year, 'in particular cases when there is a specific and identified patient need' and 'sufficient, but perhaps not definitive scientific data'[5]. This concept may well be extended, so that the traditional one-off endorsement gives way to a continuous process in which the right to market a drug is granted and reconfirmed subject to regular reviews of its safety and efficacy – reviews that are even more stringent than the checks that occur with adverse-event reporting.

Relations with the marketplace in 2010

If Pharma is to ensure that its products really add value, it will also need to get much more feedback from the marketplace, and do so at a much earlier stage in the process. The need for such information will ultimately help to fuel a much bigger change – the use of 'in-life' testing instead of Phase III trials. In-life testing will dispense with the need to expose numerous patients to placebos or dosing levels that are pharmacologically ineffective. It will also be better able to pick up rare side-effects and drug interactions, thereby making the move from the rarefied atmosphere of the lab to real clinical practice much safer.

Pervasive computing will play a vital role in this respect. In-life testing is currently too risky and too costly to be practicable on a large scale, but greater bandwidth and the new network technologies will make it much easier and cheaper to transmit and collect biological data on a real-time basis by 2010. Mobile telecoms, radio frequency technologies and individual tracking devices will also make it much easier to collect the data outside a clinical setting. These same technologies can be used to improve compliance and persistence rates in patients taking drugs for chronic treatments; to detect danger signs such as an irregular heartbeat in patients with a history of cardiac problems, or a surge in blood sugar levels in patients with diabetes; and to individualise medical care.

Electronic medical records and online prescribing will also play a part in the transition, by ensuring that everyone in the healthcare provider network has a composite clinical and administrative record. But electronic medical records will soon be vital in yet another regard; they will make it very much easier to find trial patients with a particular biomarker profile as well as a particular disease. The Mayo Clinic in the US is currently participating in a pilot project to convert all its records, including genotypic data, from paper to electronic files. However, very few healthcare payers or providers have taken this step – and here Pharma could play an invaluable role in helping to create the necessary infrastructure.

Of course the use of medical records (and genotypic data, in particular) is a very sensitive subject because patients fear their privacy may be abused. But robust encryption technology that authenticates individuals through biometric characteristics such as a finger print or retinal scan already exist. The barriers are social and cultural rather than technological, and the advantages of creating an electronic health record system are so great that they will ultimately be overcome.

A new economic foundation

The scale of the change is enormous, then, but the potential benefits are commensurate. The Tufts Center for the Study of Drug Development estimates that costs per drug now average $802 million. It recently concluded that using the most modern preclinical screens to boost success rates would save about $242 million. Cutting development and regulatory review times by 25% would save another $129 million, reducing costs per drug to just $431 million – 54% of the current sum[6].

The new model of discovery and development outlined above could do more, as experience in the most pioneering companies shows. It could reduce the time from target identification to launch from 10-12 years to between three and five years; increase success rates from first human dose to market by a factor of four; and slash pre-launch development costs to about $200 million. In other words, it could alter the entire economic foundation on which Pharma operates.   **DDW**

Dr Nick Davies is a senior consultant in IBM Business Consulting Services' Life Sciences practice. He has a PhD in molecular biology from Cambridge University and spent seven years working in pharmaceutical discovery before joining IBM.

Dr Steve Arlington is Global Industry Leader for IBM Business Consulting Services' Life Sciences/Pharma practice.