A new formula for finding drugs



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The pharmaceutical industry concentrates on making drugs that conform to a particular therapeutic profile, but the model that has served the sector so well for so long is now breaking down. Lack of productivity in the laboratory, the imminent expiry of the patents on numerous blockbusters, intense competition and a more demanding marketplace are all evidence of the need for a new approach.

Fortunately, there are grounds for hope. Two developments will help the industry reinvigorate its pipeline. First, the widespread recognition of the fact that the commercial potential of drugs that fit the conventional therapeutic product profile is declining and second, the increase in the understanding and application of the molecular sciences. Together with massive advances in computing power, these developments will enable the industry to make profitable treatments for people with specific disease subtypes [1].

An old prescription

The majority of the blockbuster drugs on the market have a similar therapeutic profile, which has effectively become institutionalized. In other words, the industry giants have set up their pipelines to deliver drugs that possess the 'right' features and judge any potential products accordingly.

Thus, the 'ideal' drug is a chemical entity because the traditional expertise of the pharmaceutical industry lies in small molecules. It is a first-line treatment (i.e. generally prescribed by primary care physicians) because that provides access to a large pool of potential patients. It works on the premise that 'one-size-fits-all' because developing such products is easier and cheaper than developing different products for different patient sub-populations. It comes in an oral formulation because patients prefer pills to injections, and it usually treats a chronic condition. Scientific restrictions explain one last characteristic – many of today's most successful drugs ameliorate the symptoms of the disease they were developed to treat, rather than changing the way it progresses, because scientists still know relatively little about the underlying disease mechanisms.

This 'ideal' therapeutic product profile dictates what happens at the start of the pipeline. Any drug that does not conform is jettisoned during discovery, and because biological molecules are more unfamiliar than chemical entities and more difficult to formulate orally, most pharmaceutical companies are reluctant to pursue them. Yet chemical entities typically carry higher toxic loads than biologics, so it is more difficult to produce a small molecule that is potent enough to be efficacious and specific enough to reach the right parts of the body without harming the patients who take it. In other words, the therapeutic window is extremely narrow for most chemical entities.

These difficulties partly explain why chemical entities are over four-times less likely than biologics to reach the market from the point at which they are first tested in humans. CMR International (http://www.cmr.org) tracked the progress of 477 chemical entities and 66 biotechnology or gene therapy products through clinical development. The data show that only 8% of chemical entities proceed from first human dose to launch, compared with 34% of biological molecules or gene therapies [2].

Ironically, therefore, the search for drugs that match an ideal therapeutic profile has proved counter-productive in several respects. It has restricted the scope of the industry's research and has curbed innovation. It has also increased the competition for market share and driven up costs.

New blockbusters for old

However, signs of change are afoot. The pharmaceutical industry has recently produced a number of drugs with a different profile. Similar to conventional blockbusters, they come in a one-size-fits-all format and often treat a chronic condition. However, they are typically second-line treatments (generally prescribed by consultant physicians) with a wider range of delivery mechanisms than traditional drugs, they serve a clinically defined population and sometimes modify the progression of the diseases for which they were developed.

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Several well-known products fit this new profile, including Herceptin (Genentech; http://www.gene.com), Gleevec (Novartis; http://www.novartis.com) and Enbrel (Amgen and Wyeth; http://www.amgen.com and http://www.wyeth.com). However, approximately a third of the 200 most successful drugs possess similar therapeutic features, as do half of the potential blockbusters expected to emerge from the pipeline over the next five years. In short, a significant percentage of the biggest money-spinners on the market during the next decade will have a profile that is quite different from the conventional 'ideal'.

Furthermore, a growing number of new products are biologics, many of which were developed by biotechnology or biopharmaceutical companies. However, pharmaceutical companies will soon have little choice but to adopt a different therapeutic profile and, given the massive increase in the diversity and number of targets that the molecular sciences have uncovered, they will have to include biologics within their scope. There are now estimated to be as many as 500 000 different proteins in the human body – or 500 000 potential points of pharmacological intervention, many of which will prove difficult to treat with small molecules.

Familiar diseases redefined

The molecular sciences, therefore, will not immediately produce a stream of new drugs. However, they will enable the pharmaceutical industry to define and classify diseases much more accurately, separating diseases that are currently clustered together as if they were the same disease, and treat them as clinically defined subtypes within a disease family (or collection of related diseases).

This is already happening with many diseases, including asthma and cancer. Research is now focusing on the pathways implicated in the pathogenesis and underlying molecular mechanisms of particular disease subtypes. For example, in the case of asthma, the role of IgE signalling and IL-5 pathways in atopy and neurokinins and epithelial mediators in bronchial hyper-responsiveness (BHR), among others, and in the case of cancer, the fact that overexpression of the HER-2 neu gene occurs in various cancers, including 20% of breast cancers. This discovery resulted in the simultaneous definition of a disease subtype and target – and ultimately in the development of Herceptin. It also shows that when a company works on a specific disease mechanism and develops the diagnostic tools to identify the clinical subset of patients who suffer from that disease subtype, it can no longer produce one-size-fits-all drugs. Thus, science will soon enable the industry to make medicines that do not fit within the existing commercial paradigm.

Some companies have already experienced this conflict between scientific progress and commercial practice. One such case is that of Novartis, which is developing a new treatment called Xolair, in conjunction with Genentech and Tanox (http://www.tanox.com). Xolair is a humanized monoclonal antibody and the first in a new class of asthma therapies that target the IgE signalling pathway, a key underlying molecular mechanism. The product therefore has huge potential for the treatment of a particular subset of patients – those with moderate or severe forms of allergy-induced asthma – but not for the entire one-size-fits-all patient population. Previously, such a product would have had a tough time fighting to prove its economic potential.

In fact, Novartis has already created a successful model for developing and selling highly specialized drugs with Gleevec. However, few pharmaceutical companies have been so bold. The discovery portfolios of the industry leaders are weighted towards targets that have been well documented in the scientific literature. And the reason for this is simple – discovery scientists might be thinking outside the traditional therapeutic profile, but most senior executives have yet to make the transition.

Tests and treatments for all

Nevertheless, defining diseases more accurately does have commercial potential. It is widely known that most drugs work, at best, for 60% of the patients for whom they are prescribed, and that drugs that work well for some patients make others ill. Several factors account for this, including individual variations in metabolism. In addition, our scientific understanding of many common diseases is also so limited that we can only define them in loose clinical terms, and sometimes patients who do not respond, or respond badly, to a particular drug actually have a different disease.

The knowledge gleaned from the molecular sciences will eventually solve this problem. It will facilitate the development of tests to identify people with specific metabolic variations and disease subtypes, and thus fragment the market. It will also create new opportunities, enabling researchers to link diseases and targets much more clearly, thus improving target validation and will provide the means to develop biomarkers for diagnosing specific disease states (including their severity and probable progression), and hence to capture patients who are currently misdiagnosed. Companies will also be able to develop biomarkers for identifying those who are susceptible to a particular disease and prophylactic treatments to prevent them from falling ill.

Evidence of some of these trends is already apparent. When Genentech developed Herceptin, for example, DAKO

(http://www.dakocytomation.com) simultaneously devised a test to identify patients who over-express the HER-2 neu protein. Roche (http://www.roche.com), which has a substantial stake in Genentech, now aims to include a parallel biomarker feasibility study in all of its discovery programmes. Similarly, the treatment of coronary heart disease points to how the use of prophylactics will evolve. Patients with a history of cardiac problems are generally prescribed statins. However, tests already exist for measuring some of the less visible risk factors associated with heart disease, and a growing number of patients are given statins when they show signs of being at risk.

Faster and more effective technologies for monitoring outcomes will enhance this trend. They will show when preventative treatments are really working and will also increase persistence and compliance because a patient who knows that a drug is efficacious is more likely to keep taking it than one who has to rely on infrequent visits to the doctor.

Targeted treatment solutions

So how do all these elements add up? Clearly, they herald major changes. Instead of making one-size-fits-all drugs for large groups of people with broadly defined diseases, we believe that the pharmaceutical industry will ultimately make healthcare packages for clinically defined groups of people with specific disease subtypes.

We believe that these packages – or 'targeted treatment solutions' – will typically include biological molecules, although this concept does not preclude the inclusion of a chemical entity as the therapeutic molecule. In fact, in the short term, this is certainly more likely to be the case as the industry's experience in discovering, developing and manufacturing large molecules steadily builds. These packages will be based on clinically validated targets derived from a better understanding of particular disease pathways and mechanisms, and will be focused on specific populations, using diagnostics and biomarkers developed in parallel with the therapeutic molecule. They will measurably modify the diseases they treat, with outcome data and disease progression markers providing proof of efficacy. A network of services for diagnosing, monitoring and supporting patients will also be included.

The emergence of targeted treatment solutions for specific disease subtypes will give patients a comprehensive package of therapies that work for them, will give doctors the means with which to provide better care and healthcare payers better value for money. It will also enable the industry to charge premium prices for treatments that demonstrably work for particular disease subtypes, even though the market might be smaller. Additional value will come from providing diagnostics, biomarkers and monitoring devices, and increasing drug utilization with better compliance and persistence. In short, targeted treatment solutions will be the main blockbusters of the future.

References

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