editorial

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Drug discovery: past, present and future

The past: the golden age

Historically, big pharma delivered! The secret of its success was simple: Pharmaceutical companies brought a plethora of innovative products to the market that genuinely helped sick people, and so were readily prescribed. Ultimately, patients got better and drug manufacturers generated solid sales. Even during times of economic hardship, drugs continued to be an essential purchase. The marvel of modern medicine is indisputable: life expectancy in the USA has risen from 47 years in 1900 to 77 years in 2003 [1].

During this flourishing period from the mid-1980s to the beginning of this decade, major drug companies routinely generated double-digit growth in sales year after year [2], a key indicator of their past prosperity. The sector's main association Pharmaceutical Research and Manufacturers of America (PhRMA), which represents all of the top drugmakers, reported that global sales of member companies grew from US$ 36 billion in 1986 to US$ 178 billion in 2001 [3].

The present: a difficult period

The story this decade has been different. According to IMS Health, a leading healthcare information and consulting company, annual growth of global drug sales has slowed down considerably to just 6.4% [4]. This is predominately because pharmaceutical firms can no longer generate double-digit growth in sales each year—only two of the top 10 drugmakers managed to do so in 2007 [4]. The global pharmaceutical market is worth US$ 712 billion and the US market, which is the world's largest accounting for 40% of the global figure, has been particularly badly affected [4]. Last year, it suffered its lowest growth rate since 1961 [5]. The general slowdown is expected to persist [6] and by 2011 global drug sales are anticipated to decline for the first time in four decades [7].

Big pharma's plight has several root causes. Top drugmakers have relied overwhelmingly on the blockbuster model. This means that a few blockbuster products – each generating a minimum of US$ 1 billion annually – make up the majority of a company's sales. To illustrate: in 2007, Pfizer, the world's No. 1 drugmaker, reported global pharmaceutical sales of US$ 44 billion, and eight blockbuster products accounted for 58% of this figure [8]. The problem is that a huge proportion of the industry's current blockbuster drugs will lose patent protection in the coming years. Sales from these highly priced branded products will then drop by up to 80% within 6–12 months owing to intense competition from cheaper generic copies [9]. In the USA alone, drugs worth around US$ 62 billion – accounting for almost 25% of the American market – will suffer patent loss between 2008 and 2012 [7,10].To make matters worse, competition from generics is intensifying. At the turn of the decade generics accounted for 51% of all dispensed prescriptions in the USA. This figure now stands at 67% [3]. Governments are strongly advocating generic usage to control healthcare costs. Generic manufacturers are also

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no longer idly waiting for patents on blockbuster medicines to run out naturally, but are increasingly challenging them in court because the financial rewards are huge.

To sustain their profits, pharmaceutical companies must replace blockbuster medicines losing patent protection with equally successful new ones. But the number of new drugs to be launched globally since the mid-1990s has dropped from an average of 44 per year during 1995–2000 to 33 per year during 2001–2006 [4]. Last year, only 27 new drugs received approval, the lowest number for at least a quarter of a century [4].

The dearth of would-be blockbuster medicines is down to weak product pipelines, despite astronomical investment in R&D. Last year, member companies of PhRMA spent US$ 44 billion on R&D, an increase of 70% since 2000 [3]. This makes the pharmaceutical industry one of the most research-focused sectors in the world. From the mid-1990s to the mid-2000s drugmakers underwent a series of mega-mergers, predominately to replenish their waning pipelines, but this strategy has clearly failed to deliver more medicines.

A simple explanation for the drought of new products is that after many decades of modern drug research all of the easy-to-discover drugs have already been found, while the difficult ones remain elusive.

The problem of plummeting product approvals appears certain to worsen. The FDA has arguably started to exhibit stricter drug approval standards owing to serious accusations it has faced of not assessing drug safety adequately. Recent high-profile cases include Merck's painkiller Vioxx and GlaxoSmithKline's diabetes drug Avandia. In 2007, FDA product approvals hit a 24 year low [11]. Particularly alarmingly is the fact that the FDA has recently rejected several potential blockbuster products that have gained approval in Europe [12].

The fear is that the FDA may start to request extremely detailed safety data. Drugs will consequently spend longer in clinical trials and cost more to develop but ultimately stand a lower chance of being approved. This is bad news for drugmakers: It already takes 10–15 years and US$ 1.3 billion to bring a new product to the market, up from US$ 800 million in 2001 [3].

Tougher approval standards would not be good for the public either, if it means that patients with life-threatening illnesses have to wait longer than absolutely necessary to receive new treatments. Sadly, first-in-class drugs, which can potentially revolutionize disease management, will probably be most affected because the FDA will have no prior experience of the therapeutic category and so will be especially cautious. A balance must be struck between ensuring drug safety without holding back pioneering drug development.

The USA is a free market where companies set drug prices without any government regulation. Consequently, Americans pay the highest prices for patented medicines in the world. In other industrialized countries governments regulate prices, so drugs are 35–55% cheaper [13]. Big pharma claims that without the higher US drug prices it could not meet today's sky-high R&D costs; hence, implying that drug discovery is funded mainly by Americans, with the rest of the world not paying its fair share and getting a 'free-ride'.

But considerable numbers of Americans can no longer afford their medications, causing public outcry. To combat this problem politicians have proposed two strategies. Firstly, to legalize the importation of cheaper drugs into the USA, but critics of this idea argue that it will equate to introducing foreign drug price controls. Secondly, to allow federal government to negotiate drug prices with pharmaceutical companies for Medicare's prescription drug program. Medicare is the federal government's health insurance program for approximately 37 million senior and 7 million disabled Americans, 25 million of whom have opted to receive government-subsidized drugs [14].

These measures, if implemented, will cause US pharmaceutical sales to fall. Drugmakers claim that they will consequently be forced to cut R&D expenditure, resulting in fewer new medicines, and people the world over will ultimately lose out.

The future: the era of biologics and personalized drugs

To prop up profits, big pharma is presently utilizing two principal strategies. Firstly, companies are reducing costs by extensively restructuring and by making record numbers of redundancies [15]. There are even rumors of big pharma mega-mergers to enhance economies of scale (defined as the decrease in cost per unit as production increases). Secondly, drugmakers are strategically maximizing sales from current blockbuster medicines by gaining approvals for new formulations, additional indications and, when patent loss is imminent, follow-on compounds that are simply purified forms – single isomers or active metabolites – of the original drug. These strategies, however, offer only a limited, short-term solution.

In the longer term, drugmakers have the incredible opportunity to discover innovative products by exploiting the largely untapped potential of biotechnology and pharmacogenomics. These groundbreaking fields cannot, however, replace mainstream drug development, so pharmaceutical firms must also intensify their efforts in the traditional arena. Big pharma will also benefit from the chance to treat more patients as the world population increases and becomes disproportionally older, as many chronic diseases rise in prevalence, and as the emerging markets, such as China, India, and Brazil, spend more on healthcare.

Biotechnology

Traditional drugs are small, simple chemical molecules, synthesized, essentially, by combining substances in an ordered process. By contrast, biotech products (biologics) are protein-based, structurally complex, and produced within genetically modified microorganisms and animal cells. So why should big pharma pursue biotech drugs? There are three key reasons.

Firstly, biologics offer pharmaceutical companies an excellent way to replenish their pipelines to again discover innovative medicines, with superior efficacies, safety profiles and cost-to-benefit ratios. During the past decade, big pharma has concentrated heavily on producing me-too drugs—products that are fourth or fifth in a particular therapeutic class. They are easier and cheaper to discover than first-in-class medicines but offer only limited additional benefits. Therefore, once the original products in a pharmacologic class lose patent protection, doctors will commonly switch patients from pricey me-too drugs to cheaper generic ones. This practice is guaranteed to increase, as governments worldwide control rising healthcare costs by advocating cost-effective prescribing.

Secondly, the biologics sector is experiencing robust growth. Last year, global biotech sales grew at double the rate of pharmaceutical sales (up 12.5% to US$ 75 billion vs. up 6.4% to US$ 712 billion) [4]. The number of billion dollar-plus biologics has increased from only six in 2002 to a prominent 22 in 2007 [16]. In fact, biotech drugs now account for a fifth of all blockbuster products [4]. Biologics have classically been developed by small, start-up firms, but big pharma is increasingly realizing that biotech drugs will also be crucial to its future success. Therefore, drugmakers are vigorously adding biologics to their pipelines by acquiring biotech firms, by in-licensing biological products and by building their own biotech facilities.

Thirdly, biologics are currently protected from generics in the USA, which accounts for 56% of the global biotech market [4], because no regulatory pathway exists for the FDA to approve generic copies, called 'biosimilars' or 'follow-on biologics'. Even once a pathway is created, biologics will still, almost certainly, have two major advantages.

Biologics are expected to be granted 12–14 years of data exclusivity [17], defined as the period of time after approval of a drug during which the FDA cannot license a generic that relies on any of the original product's data. This will effectively keep biosimilars off the market for this substantial duration as generics depend on the innovator drug's data to minimize their own approval costs.

It is also anticipated that the process of gaining FDA approval for biosimilars will be considerably harder than that for traditional generics. Why? Biologics are almost impossible to replicate because each is intimately dependent on the cell line and manufacturing process used. Extremely minor changes in a biosimilar from the original product can significantly alter the efficacy and side effects profile. To rule out any differences, biosimilars need to be completely characterized, but existing laboratory-based analytical technologies are unable to do so because of the highly complicated composition of biological drugs. Therefore, generic manufacturers will be required to conduct costly and lengthy clinical studies to confirm that a biosimilar is sufficiently comparable to the innovator biologic in terms of efficacy and safety. Such trials are not required for traditional generics.

As a result, whereas traditional generics are priced up to 80% cheaper than branded products, biosimilars are predicted to be discounted by only 15–35% [18]. This will reduce the incentive to prescribe them, particularly if concerns linger about their comparability.

It is imperative that any FDA pathway provides an adequate period of protection for biologics from generics, so that manufacturers can recuperate their costs and make a fair profit. But an unnecessarily prolonged period before generic entry will be detrimental: Patients will be unfairly forced to continue to pay high prices, and drugmakers will be able to rest on their past successes; hence, decreasing the incentive to aggressively pursue new opportunities.

Pharmacogenomics

People respond differently, and often unpredictably, to a particular drug because of their unique genetic profiles. Consequently, commonly prescribed drugs work in only ~40–60% of patients and serious side effects are alarmingly common, causing 100 000 deaths in the USA alone each year [19]. Pharmacogenomics is a new discipline which seeks to determine how variations in genes between people affect their response to drugs. It forms the basis of personalized medicine which is an approach that aims to select the 'right' drug – having maximum efficacy and minimum side effects – for a patient based on their DNA. It will decrease the inefficient trial-and-error approach to prescribing; hence, cutting healthcare costs. It will also become increasingly possible to test individuals to determine their genetic predisposition to common diseases, and consequently implement preventative strategies, such as lifestyle modifications or prophylactic drugs.

In the USA, political will for personalized medicine is growing: In 2002, the Secretary of Health and Human Services created the *Secretary's Advisory Committee on Genetics, Health, and Society* (www4.od.nih.gov/oba/sacghs.htm) to consider issues relating to personalized drugs. In 2006, Senator Obama introduced the *Genomics and Personalized Medicine Act* to aid progression in this field [19]. This year, President Bush signed the *Genetic Information Nondiscrimination Act* into law [20], which prevents employers and health insurers from discriminating against people on the basis of their genetic predisposition to disease. The fear of this happening had previously been a key barrier to progress in pharmacogenomics. This legislation is also positive for personalized drug development because, in the past, people were understandably apprehensive about participating in medical research which entailed genetic data being collected [21].

How will personalized medicines work? Firstly, gene variants associated with a particular disease or drug side effect will be identified. Secondly, biomarkers, such as proteins, will be used to stratify the population into subgroups. Thirdly, the best treatment for each subgroup will be determined.

But why should big pharma bother to pursue this field? Screening participants, using biomarkers, before clinical trials begin could be used to exclude people anticipated to respond inadequately to the experimental agent or predicted to be at high-risk of side effects. This would drastically reduce product failure rates later on. Fifty percent of Phase III experimental drugs are presently unsuccessful [3], which is incredibly costly to manufacturers from a financial and public image standpoint. Also, drugs that would have been abandoned because of efficacy or safety problems in the general population could be approved for specific patient subgroups, in whom the drug is beneficial or does not cause serious side effects. Additionally, personalized drugs will be instantly distinguishable in an increasingly crowded marketplace, giving them a competitive advantage. Finally, healthcare payers may encourage the prescribing of personalized drugs because they have a higher chance of working.

To realize the full potential of personalized medicine, big pharma must shift its mindset from the blockbuster model, which aims to produce drugs for the mass population, and accept that personalized products will inherently be for smaller patient groups. Companies also need to focus on producing biomarker tests for drugs to identify the patient group in which a particular drug will be beneficial. Drugmakers therefore need to build up their own diagnostic businesses or to form partnerships with or acquire diagnostic companies.

Concluding remarks

The pharmaceutical industry currently faces considerable challenges. Drugmakers should accept that the era of blockbuster and me-too products is coming to an end. In the future, new drugs will almost certainly need to demonstrate a clear benefit over medicines already on the market to obtain approval. Big pharma must refocus its energy to discover superior drugs that will genuinely help sick people. This will entail companies departing from their comfort zones and entering uncharted territory. Biotech and personalized drugs offer an ideal platform to do this. Traditional drug development must also continue, but must be targeted very much towards finding medicines that add real value. Each new pursuit will not bring success, but companies must not be deterred and should remain resolute to reap the rewards of their endeavors in the end. Governments must also shoulder responsibility for spurring on pioneering drug research for the good of society, and healthcare policies must reflect this by providing incentives for drugmakers to pursue new horizons.

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