

An extraordinary business

The pharmaceutical and biotechnology industries are undergoing challenging times. However, with the right strategies, companies can reap rewards.

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The pharma industry is often traced back to the nascent chemical industry of the late nineteenth century in Basel, Switzerland, when dyestuffs were found to have antiseptic properties. This led to the founding of family businesses, such as Roche, Ciba Geigy and Sandoz (merged as Novartis), which are now household names.

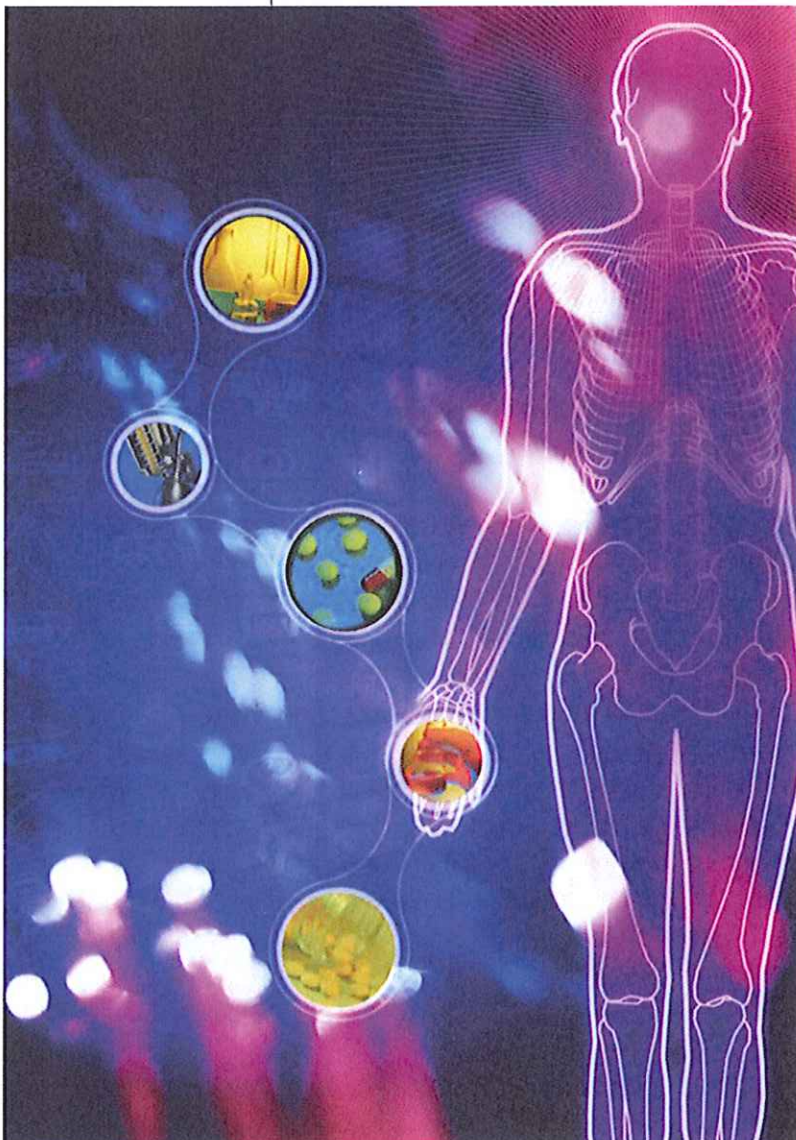
An entrepreneur's dream comes true – during the 70s to the 90s, the average profit margin of the Fortune 500 pharma companies was twice the median for all industries in the Fortune 500. Blockbusters, defined as drugs with annual sales of at least US\$1 billion, were developed and promoted with investments of just around US\$200 million.

Following pharma's footsteps is the biotech industry. Its birth probably began in the early eighties, when the US Supreme Court ruled that a genetically-modified microorganism could be patented, which triggered the formation of numerous entrepreneurial biotech companies like Genentech and Amgen to commercialize new scientific breakthroughs.

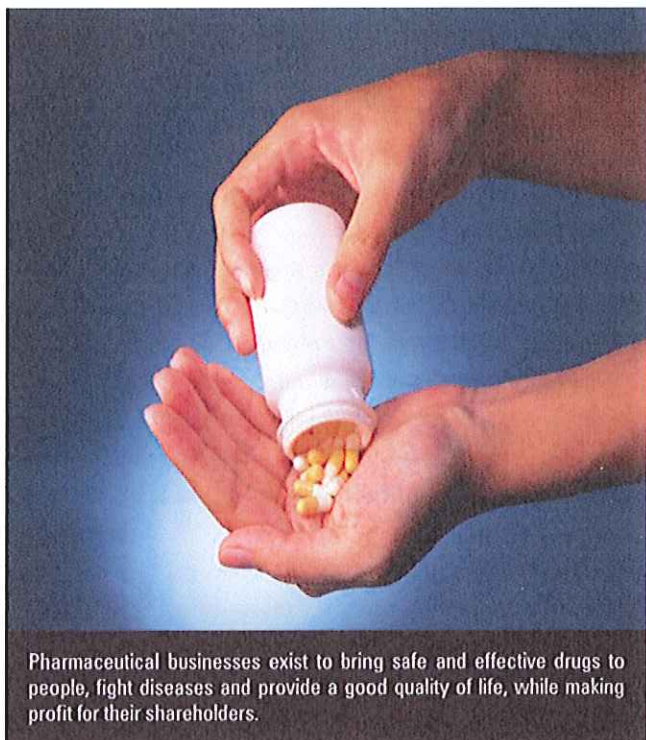
Modern biotechnology focuses on understanding the metabolic pathways related to a disease state or pathogen, and manipulating these pathways using molecular biology or biochemistry. These genetic and molecular biology scientists, supported by the venture capital community, brought their revolutionary science-focused research approaches, known as rational drug design, to enhance drug discovery.

They worked backwards from known disease biochemistry, to identify or design chemical 'keys' to fit the biochemical 'locks' of that disease. This was a radical depart from the traditional pharma medicinal chemistry approach, which discovered drugs either by isolating the active ingredient from traditional remedies or by serendipity.

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Pharmaceutical businesses exist to bring safe and effective drugs to people, fight diseases and provide a good quality of life, while making profit for their shareholders.

a profit for their shareholders. And profitable they are. The 2009 IMS data showed that the top three drugs – Lipitor (Pfizer, Astellas) to treat high cholesterol, Plavix to prevent heart attacks or strokes (BMS and Sanofi) and the biologic Enbrel to treat rheumatoid and psoriatic arthritis and plaque psoriasis (Amgen, Pfizer, Takeda) sold over US\$12 billion, US\$9 billion and US\$6 billion respectively.

Not only were they making a healthy profit, they were also dramatically improving the health and well-being of patients in almost all disease areas. We are less sick, we live longer and better than ever before, thanks to pharma and biotech innovation, and of course the all important improved screening and public education.

There are certainly cultural and operational differences in manufacturing, intellectual property landscape, and regulatory issues, but the lines between pharma and biotech companies are blurring as they merge, partner and face the same 21st century challenges. In terms of business, I often refer to them as part of the same food chain: the innovative, agile and relatively cash-strapped biotech and the heavy bureaucratic, pipeline-challenged, cash-rich pharma, needing and feeding off each other in its quest to deliver better drugs, more innovatively and efficiently.

Business models

The biopharma business model is extraordinary, nothing like what we learned at Business School 101. The requirements of heavy investments, multi-disciplinary and high level skills, high risks, as well as a timeframe of decades to obtain and present convincing, credible and robust data are mind-boggling, certainly not for the faint-hearted. Innovation and R&D, which is the heart of biotech and pharma, are exorbitantly costly, complex and time consuming, requiring a deep understanding of the rapid scientific frontiers, the market needs, the stakeholders and last but not least, the business.

In the eighties, developing and getting a drug to market took an average of 12 years and US\$200 million. Today, we are talking about anything north of US\$900 million and yet the time-lines for R&D have not decreased, neither have the success rates. More than 50 percent of all development dollars were spent on products that never reached the market, ie failures. And even if some products, after costing a billion dollars and taking 12 years of development, are approved by the regulatory agencies, there is no guarantee that the customers will agree to pay for them. Examples include Lilly's Effient, Merck's Saphris and Bridion, BMS and AstraZeneca's Onglyza. In 2009, only 29 drugs were approved for a global industry, despite the R&D spend totalling some US\$125 billion.

Another complexity is managing the intellectual property, which is key to protecting our innovation and investment. Effectively, competitors are blocked from manufacturing and marketing drugs with the same chemical composition for 20 years. However after deducting development time, there would be only eight to 10 years remaining, upon the drug reaching the market. On the other side of the same coin, what protects pharma could also keep them out of the game, hence the numerous patent litigations synonymous in our industry today.

Difficult for the average investor to comprehend, the norm in biotech is a huge, long and risky investment period, burning millions of R&D cash, while waiting (and praying) for a return on investment only at the commercialization of their drug candidate or these days, an exit through partnerships, licensing or mergers and acquisitions (M&A).

Challenging times

Nothing remains static and the industry is undergoing an unprecedented change. It is a challenging period as blockbuster

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pipelines are drying up, products are facing patent expirations and the flood of generic drugs, which cost about a tenth of the branded drugs, is threatening pharma companies' livelihood. Add a financial crisis, a stressed healthcare budget, plus the growing strength of better-informed patients and insurance payers and you get an unsurprising result of increased cost-consciousness and hence inevitable pressure on drug prices. Regulatory compliance has also played a strong role with over 15 drugs permanently withdrawn from the market due to safety concerns, tighter scrutiny on sales and marketing practices, clinical operations and post-approval safety surveillance systems, all adding up to even higher costs and higher uncertainty.

Every CEO is looking for focus to create and sustain value for shareholders. Keywords include efficiency, cost-effectiveness, organizational agility and empowerment to speed decision-making, improve productivity of R&D, encourage entrepreneurship, and continuously review market strategies to be responsive to patients and payers as well as the competitive challenges. Partnering will increase chances of success, reduce risk and boost synergies. Fashionable thoughts these days include personalised medicines to treat the right patient with the right drug, in the right manner, at the right time; and looking east towards the high potential emerging markets, and nurturing the talent that would make all these ideals happen.

Licensing and partnering

Partnerships, licensing and M&A in the industry have emerged as critical strategies to access innovation in novel areas of science, new products in different therapeutic areas and as a source of a pipeline. The search for the right licensing or partnerships has grown increasingly competitive, with deal values spiralling to dizzying heights, particularly for late stage products with blockbuster potential. More and larger deals are being made, earlier in development.

In June 2010, Forest Laboratories paid US\$50 million upfront and committed up to US\$1.1 billion in milestones for access to biotech company, TransTech Pharma's glucokinase activator (GKA) program for the treatment of diabetes. Its lead candidate TTP399 will soon start phase 2 trials with several other backups and follow-ons in pre-clinical and phase 1 studies. Common in licensing, this story has a twist in that this GKA program was developed during a six-year research pact with Novo Nordisk. Novo returned the program to TransTech in 2007, when it decided to divest its small molecule drug discovery programs. GKAs are

meant to have dual roles in the liver and pancreas, improving their control over blood glucose, while newer diabetes drugs like Merck's Januvia and Amylin's Byetta only affect the pancreas.

Interest in glucokinase as a target has waxed and waned. Roche was actively pursuing GKAs not long ago but has been silent. Clinicaltrials.gov shows that Lilly suspended work on its GKA program, which it licensed from OSI Pharmaceuticals for US\$25 million upfront in 2007, pending further toxicology testing.

As the deals have become larger, the risks have become greater and more visible to the investment community. The expectations tend to be higher when pharma or biotech evaluates an opportunity for in-licensing compared to its internal programmes. It is often easier to compile the high costs of paying a licensor upfronts, milestones and royalties than to evaluate the internal costs of salaries, travel, capital equipment, lab costs, and development budgets.



Innovation and R&D, the heart of biopharma industry, are costly, complex and time consuming.

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the West, in terms of research sophistication, talent pool and investment, but timelines are long in this industry. These so-called 'pharmerging countries' with high growth rates, genetic diversity and industrious research talent are hoping to catch up, while the ex-rich Western markets are stagnating and shrinking.

In an international survey published in 2009 by AstraZeneca, participants strongly believed that China and India will overtake the US and Japan as the most innovative countries globally. The US is still ranked as the most innovative nation by 30 percent of the 6,000 people in six countries in the survey. Japan comes in a close second with 25 percent of the vote. However, 27 percent believe China will be the place for technological innovation by 2020 while 17 percent picked India. Only 14 percent believe that the US can remain on top. These are significant numbers for the biopharma industry, which has been invest-

AstraZeneca

ing billions of dollars in building R&D operations in Asia. With intense licensing competition, companies require greater skills, creativity and flexibility, not only in their approach to securing a deal but also structuring the best deal terms. Traditional licensing agreements have evolved into the likes of option, claw-backs, co-developments, co-marketing, heavily back-ended and regional deals. Current deal-making requires not only comprehension of the underlying science, NPVs and business decisions, but also the commercial opportunity, competition, advances in science and technology, positioning against the standard of care, pricing and the emerging growth markets, bearing in mind that all these considerations would become relevant about 10 years down the road.

Datamonitor statistics show that the number of licensing deals in 2009 increased by 12 percent over 2008. It is clear that in spite of the high costs of licensing, potential licensees still look towards externalisation as a more cost effective way to access novel products than carrying out extensive in-house research.

Biotech in Singapore and the Asia-Pacific

Undoubtedly, the biotech industry has been attracting the most attention among countries in Asia Pacific over the last few years. Australia, Japan, Korea, China, Singapore, India, Taiwan, Malaysia, Hong Kong have all unveiled grand government-aided plans to grow their biotechnology industry. Asian biotech is still behind

the West, in terms of research sophistication, talent pool and investment, but timelines are long in this industry.

In biotech, the most reliable indicator of future success is the quality and depth of research undertaken in a country. Other factors of importance include availability of talented and experienced entrepreneurial leaders, scientists, business developers and resources. Commercialization of biotech research through effective industry-academia relationships, as well as industry-industry linkages is a critical success factor for the industry.

Frost & Sullivan has identified Australia, Japan and Singapore as having the highest potential ranks. The biotech companies in these countries have evolved as providers of a diverse range of biotech products and services over the last decade. The Singapore government certainly scores points for its comprehensive biotech strategies, with ample funding and concrete goals to become a regional center for life sciences, clinical trials, and drug development. **PA**

Asia Life Sciences Academy is conducting a course on "In and Out-Licensing Successfully In Biopharma Industry" from 24 to 25 Mar 2011. For more information, contact NUS Extension at <http://www.nus.edu.sg/nex/>.