

Global Environments: Navigating the Perfect Storm

Emile Bellott, a consultant in drug development, discusses opportunities, challenges and competitive strategy in the global pharmaceutical and biotech industries

Today's pharmaceutical and biotech industry sectors are largely a product of the late 20th century. In the post-industrial era, manufacture and provision of pharmaceutical drugs have been organised and have prospered as fully integrated business units. One of the trends of today is the formation of new enterprises on a geographically dispersed virtual business model. Historically, there have been the chemistry-based pharmaceutical companies and the biology-intensive biotech companies. The distinction between pharma and biotech businesses is becoming increasingly blurred, as the pharmas build out biotech-focused business units, either organically, or by mergers and acquisitions (M&A). In fact, all the major pharmaceutical manufacturers are pursuing biotech products.

The global reach of the pharma and biotech companies of today – both large and small enterprises – is enabled by general advancements in commerce, technology, and government. Globalisation of the industry is a double edged sword, presenting the obvious opportunities for markets and suppliers, but also placing increasingly stringent demands on recognising and exploiting the sources of competitive advantage.

For the past two decades, the industry buzz has been about 'pipeline productivity'. The well-known graphic showing exponentially increasing drug R&D expenditures by the pharmaceutical industry, in parallel with level or declining new drug approvals, year-by-year, has been a popular talking point at industry meetings and conferences.

With many current drugs going off-patent, competition from generics manufacturers is increasing. The observation of a pipeline drought is a harbinger of industry profitability and competitiveness of the major players. This recognition has stimulated the search for new tactical approaches to discovery and development: outsourcing, new technology, revision of regulatory approaches, and appeals to government protection.

Lagging R&D pipeline productivity is a legitimate cause for concern because it

reflects an imminent drop in value creation and return on investment from the largest industry players. That said, it is only one indicator of the perfect storm in which the pharmaceutical and biotechnology industries are struggling to navigate in order to continue to prosper and expand in relation to global healthcare needs.

Other elements of the current industry environment include:

- Globalisation and virtualisation of the drug development enterprise
- Social concern for basic healthcare in the developing world
- Cost containment pressure from the marketplace
- The high cost of developing a new drug
- Outsourcing of R&D, production and testing activities
- Availability of capital
- Protection of intellectual property

In the aggregate, every factor contributing to business success has undergone a sea change: basic science, capital markets and sources, government regulation, IP protection, competition and markets.

This article presents an overview of the pharma and biotech situation in a business strategy context and discusses the issues and approaches involved in maintaining

and enhancing competitive business advantages, in this global, science-based industry. Several examples of pitfalls and opportunities in the new global environment are discussed within the general framework of 'competitive advantage', which was first enunciated by Michael Porter, of the Harvard Business School (1).

FACTORS AFFECTING VALUE CREATION

In the modern environment, it is not sufficient to have a good, effective product. Nor will an efficient and productive company guarantee success. In the Porter analysis, the most successful enterprises are those that most strategically deal with the factors that influence their ability to capture and create value, namely: barriers to entry; suppliers; customers; product substitutes and enhancements; competitive rivalry; and government. In addition, for purposes of the present discussion we add: regional clusters; capital markets and sources; skilled workforce; and science and technology base (see Figure 1).

The generalities of business strategy in a competitive environment are well understood. However, several factors are worth mentioning here, due to their unique affect on the pharma and biotech sectors

Figure 1: Strategic factors that contribute to the enterprise's ability to capture and create value



in constraining and defining business strategy options for these enterprises.

THE EMERGENCE OF INDUSTRY CLUSTERS (REGIONAL ADVANTAGE AND SYNERGY)

In recent years, economists have come to view the interplay of business enterprises, academia, government, customers and workforce as a complex ecosystem. While this is not completely surprising, the recognition of synergies and historic legacy have led to the emergence of such regional concentrations. These provide for easy mobility and re-allocation of the human talent pool, an efficient venue for technology transfer, and critical mass for formation of new businesses through entrepreneurship and reorganisation. Successful clusters are also characterised by a high level of access to suppliers, capital, lawyers, communications, higher education, and transportation infrastructure. They enjoy practical proximity to markets of commercially viable size, such as San Francisco, Boston, NY-DC corridor, London, Germany, Switzerland, Milan and Tokyo.

Even in the decentralised, virtual business model that has gained prevalence in the past decade, such companies and their suppliers and collaborators appear to co-locate in one or more new clusters which serve their purposes. Examples of these

include clinical CROs – eastern Europe and India; pharmaceutical manufacturing and R&D – Bangalore, Mumbai, Hyderabad, Shanghai, and Beijing.

Governmental activities are also aimed at creating and nurturing new clusters and even attempting to build them *de novo*, as with Ireland, Korea and Singapore.

GLOBAL AND TRANSNATIONAL NATURE OF THE BUSINESS MODEL

The global nature of the marketplace and transnational reach of individual business enterprises (both large and small) means that pharma and biotech companies are increasingly partnering with suppliers in other countries to reduce costs and to gain access to technology and pools of skilled labour. In the first instance this was an expedient for cost reduction. It is now supplanted by a trend of collaborations and alliances with firms in low-cost geographic areas.

In addition, a broader tendency towards outsourcing from established companies, particularly the larger industry players, has led to the formation of new regional clusters, particularly in South Asia and India. These new enterprises are not just skilled, low cost suppliers, but future competitive players in the industry. Both national and regional governments see the immediate employment advantages, the

opportunity to seed the formation of their own indigenous innovator pharmaceutical and biotech companies, and the opportunity to rationalise their international trade payments (2).

This approach has been highly effective in areas where there is a relatively modern communications infrastructure and a large contingent of scientists and engineers, either educated in the west or educated to world-competitive standards, such as China and India. Globally, pharmaceutical exports are estimated to be growing at 10 to 15 per cent annually (3) and skilled bioscience jobs offer a premium over the average industrial wage – as much as double in the US (4).

English has become the *lingua franca* of international business. It is even more so in a science-based industry, where communication of discoveries and results through the worldwide scientific community is mainly in English-language conferences and journals. In this regard India, China, and most other industrial countries emphasise foreign language fluency in their educational programmes as an important foundation of international competitiveness. China and India enjoy the benefits of a domestic commitment to higher education, supplemented by a large pool of US- and EU-trained scientific talent.

THE HEAVY FOOTPRINT OF NATIONAL GOVERNMENTS

Governments are active in almost all aspects of the competitiveness landscape. The industry is heavily regulated and relies on governments for freedom to operate and product approval, as well as to provide a level competitive playing field and reliable IP protection.

Due to the fundamental societal benefit derived from healthcare and therapeutics, governments have become increasingly involved in constraining prices, fostering regional industrial development agendas, providing incentives and funding for basic science, and dismantling certain monopolistic aspects of the business – all in the course of seeking to serve their citizens and national interests.

Globalisation of the business model, particularly in relation to regulatory

surveillance of the supply chain and regulatory approval of human and veterinary therapeutic drugs, has led to initiatives for harmonisation of government standards. This not only allows for transnational outsourcing of manufacturing, preclinical and clinical development phases of pharmaceutical projects, but greater ease of attaining marketing approval in all of the world's major healthcare markets. As events have shown in the past year, lax standards in manufacturing and analytical methods in individual companies in China can lead to an adverse, if temporary, impact on reputation and development of business relationships.

Governments establish and maintain patent systems to secure the right and opportunity to profit from their inventions for inventors and innovators. The integrity of the patent systems as a protection of IP is paramount in an industry like this, where ownership of IP and clear delineation of its scope provides a stable framework to market products profitably and without interruption. Not surprisingly, the major world patent systems are harmonising, in terms of priority date, publication, and patent life span.

We are in a new era, in which the major international players respect the legal basis for IP rights and patent protection. But, less than three decades ago in India, for example, companies routinely violated patents to produce knock-off pharmaceutical drugs, at low cost, to serve the developing world's needs. The situation has been reversed, in part to assure the continued economic gains of a pharmaceutical sector that is now a trusted collaborator and supplier to the rest of the world (5).

THE IMPACT OF SCIENCE AND TECHNOLOGY

The pharmaceutical and biotechnology industries are comprised of science-based businesses. The impact of this observation goes beyond the mere fact of using scientific knowledge to conduct business operations and to invent products. As noted by Pisano, they are commercial enterprises that "attempt to both create science and to capture value from it... The science based business actively

participates in the process of advancing and creating science" (6).

The underlying science base is undergoing continuous change. Approaches to drug discovery have evolved from folklore and trial and error, to understanding of molecular structure, cellular biochemistry, molecular biology and genomics. In the post-genomic era, we are only now seeing the difficulties in exploiting the wealth of new targets. At the same time, we see the path to new opportunities through systems biology and genomics, and unexpected new biological mechanisms, for example, in RNA interference and stem cells (7). The advancement of science not only opens up markets for new products but for product enhancements as well, as with genomics-based 'personalised medicine' and diagnostics, for example.

The rapid advance of basic and applied science has major implications for the industry. Scientific knowhow, particularly in specialised areas of biology, is the lifeblood of the industry. In the past, chemists could be redeployed in order to synthesise other drug candidates. However, exploiting new biological target classes and therapeutic paradigms may require discovery and development activities involving new skill sets. Thus the universities where scientists are trained have adopted a significantly greater commercial focus. Major research universities are active in industry collaborations, patenting, licensing, and establishment of startup companies.

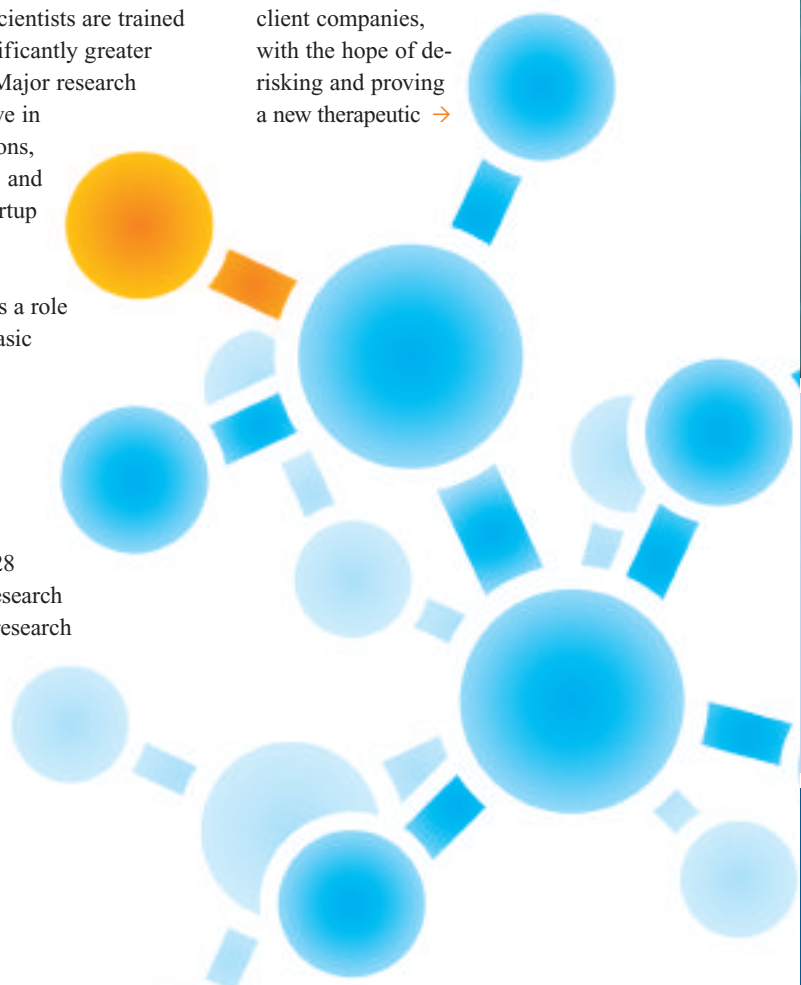
Government also has a role to play in funding basic scientific research and educational infrastructure. For example, the US National Institute of Health funds approximately US\$28 billion per year in research grants to academic research institutions in the US and worldwide. In recognition of the collaborative nature of research, the NIH is targeting

up to US\$500 million per year to have 60 academic research centres working cooperatively as a consortium to advance medical research (8). More recently, the Indian Government's Department of Biotechnology has established a partnership with the Wellcome Trust to award 700 biomedical research fellowships over 10 years (9).

CAPITAL MARKETS AND SOURCES

Development of innovative new therapies is capital intensive. First, there is the high cost of a skilled labour force. In addition, the costs of scientific discovery, testing, manufacturing, and regulatory compliance have pushed the cost of developing a new drug from discovery through to marketing to as much as US\$1.3 billion (10). In a profitable established firm, these costs are provided for by product sales.

Emerging innovative companies and startups are said to operate more efficiently. Development funding for these emerging enterprises is provided largely from private sources – either networks of private equity investors (venture capitalists) or the venture capital arms of established pharma/biotech companies. In essence, these venture capital sources are funding a portfolio of risky development programmes in their client companies, with the hope of de-risking and proving a new therapeutic →



concept or drug sufficiently, in order to realise a higher value.

With the public capital markets effectively shut off to emerging enterprises, the likely end-game is the licensing of the programme to a larger market-driven pharmaceutical and biotech company, or outright acquisition by the larger firm. For the past decade, mergers and acquisitions activity has increased year on year, both in number and size of deals (11).

Recognising the advantage of early involvement in order to shape the scientific agenda and gain early options to participate or form new ventures, industry-academic partnerships are an emerging phenomenon on the business landscape (12). All the major US, European, and Japanese pharmaceutical companies have also established venture capital departments, in order to make strategic investments in emerging companies, thus gaining control, or a window, on new technologies at an early stage (13).

Such business models provide pipeline opportunities for the larger integrated companies and a vibrant marketplace in new science-based ventures. In addition, given the focus on lean operations and eschewing 'brick-and-mortar', the new ventures spawn further opportunities for outsourcing and innovative forms of collaboration with other industry and academic colleagues.

Finally, charitable foundations have entered the capital mix with goals informed by social consciousness. These sources have an agenda of research programmes and activities targeting the underserved disease indications and broader health needs of the developing world such as the Wellcome Trust, Gates Foundation and the Michael J Fox Foundation. They are also a significant source of grant funding for research and training.

A BRIEF PROFILE OF THE INDUSTRY

In general, the industry has been profitable over the decades, with a return on equity exceeding the average of industries in general. Annual industry turnover has increased at around seven per cent per year as the prices of these

products increased in relation to their value, more products in more therapeutic categories were developed, and pharmaceutical products were sold into increasing segments of the worldwide population. In recent decades, the lure of entrepreneurial success in the emerging biotech and drug companies has attracted additional investment capital for startups and M&A.

The worldwide market for pharmaceuticals is currently estimated at US\$700 billion in global sales. Sales are distributed amongst world markets approximately as follows: US – 45 per cent; EU, including the UK – 23 per cent; Japan – 10 per cent; and rest of world – 22 per cent. Global pharmaceutical exports are estimated at 45 per cent of global sales, and are growing at about 10 per cent per annum. Within the developed world, the cost of pharmaceuticals consumed varies from 1.5 to 2 per cent of annual per capita GDP, depending on country.

The industry is concentrated. It consists of a first tier of multi-billion dollar corporations. All of the top 10 firms are US or EU-based corporations. The top 10 pharma combined account for approximately 55 per cent of global pharmaceutical sales. In addition, there are thousands of smaller enterprises ranging in size from one to a few hundred employees. The enterprises are geographically clustered, for reasons of historical legacy, proximity to factor inputs, and market location. The average R&D spending of the large pharmaceutical companies is 15 per cent of revenues, although in strictly biotech enterprises, R&D expenditure is closer to 50 per cent of revenues.

Patent activity and research are similarly concentrated in developed countries. Eight of the top 10 research universities are located in the US. Biotech patent ownership of the top 20 institutions is dominated by US universities. The top four worldwide biotech patent holders are: Japan Institute of Science and Technology – 1,022; University of California – 543; US Government (NIH) – 443; and Genentech – 421. The three most cited and influential patents are owned by MIT and Harvard University (14).

DEVELOPING A COMPETITIVE STRATEGY IN THE GLOBAL ENVIRONMENT

Development and implementation of a competitive strategy involves synchronicity. It requires the simultaneous recognition of the opportunity and the existence of enabling trends in the business environment. Early attempts to address the pipeline drought in the major integrated pharmaceutical companies sought improved profitability through cost cutting and/or increased revenues.

Cutting Costs through Outsourcing
Drug development and production costs were squeezed through the time-honoured methods of trimming bureaucracy and substituting tactical outsourcing for in-house capability. This led, initially, to the development of major US and European contract manufacturing organisations and the gradual dismantling of pilot-scale production within the pharma themselves. It was clear that key intermediates and APIs could be manufactured in Eastern Europe, China or India at a fraction of the US or EU cost.

To be sure, this was accomplished in stages, as the new partners demonstrated capability, reliability and respect for IP. This major shift was also facilitated by an adequate pool of skilled scientists in the target countries – often educated in the US or Europe – and the harmonisation of regulatory requirements. As experience was gained on both sides, a comfort level has been reached so that outsourcing of discovery and preclinical development activities (high IP content) and clinical trials (high regulatory content) in China, India, Eastern Europe, and Russia are now regarded as mainstream.

Capturing Value as a Service Provider
The outsourcing activity targeted to India and China was initially intended as a tactical means of cost reduction by the client. Over time, with the expansion of the outsourcing business model, a cadre of scientifically capable service providers were established and began to thrive in their own biotech and pharmaceutical clusters in Hyderabad, Mumbai, Bangalore, Shanghai and Beijing. From their own perspective, these companies sought to move up the value chain and to capture more of the value inherent in

pharmaceutical and biotech work. At this early stage, they did not participate in the upside of the programme, nor did they share the risk.

Recently, as both trust and working relationships have expanded, most of the major pharmaceutical companies have established collaborations that go beyond the original fee-for-service model; India – GSK, Lilly, Amgen, Forest, Merck; and China – Lilly, Sanofi-Aventis, Novartis, Pfizer, AstraZeneca. Typical scenarios include partnering targets and leads, co-development, and co-marketing (5).

The success of this strategy is facilitated by strategic economic development initiatives by the governments of India and China, and the fact that there are a large number of US- and European-educated nationals involved on both sides of the partnership equation. For example, presently over 2,500 employees at life sciences faculties at US research universities are native Chinese, and 10 to 20 per cent of the scientists in the labs of US drug and biotech companies (15).

One other unanticipated aspect of the move up the value chain deserves mention: access to capital. Service providers do not typically fit the investment profile of VCs and private equity sources. By transforming themselves into ‘drug development’ companies, the outsource providers may have made themselves more attractive to sources of capital in the long run.

Breaking into New Markets

Large pharmaceutical companies are already setting up corporate research centres in China and India, not only at a lower cost, but in order to gain a better understanding of the needs of these countries. The original pharmaceutical and biotech companies gain access to an emerging pharmaceutical market in these countries and access to a new and innovative talent pool, as well as a lower cost source for their development activities.

The nations gain a foothold in important high-value and long-term industry as a prelude to developing their own indigenous integrated pharmaceutical companies. Placement of critical operations in these locations cements

their position as regional pharma/biotech clusters, with potential for spin-offs.

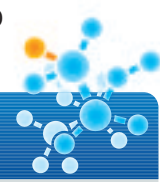
Increasing Revenues

In public companies, one way to increase revenues (and simultaneously cut costs through synergies) is through mergers and acquisitions (M&A). The industry has gone through many rounds of M&A, realising efficiencies for the surviving organisation and making redundant thousands of experienced staff engaged in various phases of development. Some of the largest integrated pharmaceutical companies of today are comprised of the residual operations of as many as a dozen competitors, as can be

seen in the lineage of Pfizer, GSK, or AstraZeneca.

M&A as a Route to New Markets

Another aspect of M&A involves access to new markets. This is particularly true in the case of the Japanese pharmaceutical companies that wish to sell their products into the larger market in the US and potential new opportunities in India and China, thus becoming global players. Recent examples include Takeda’s US\$8.8 billion acquisition of Millennium Pharmaceuticals, Daiichi-Sankyo’s pending US\$4.6 billion merger with India’s generic manufacturer, Ranbaxy Laboratories, and Mitsubishi Pharma’s establishment of a US\$100



The Future

The perfect storm that surrounds the pharma and biotech industrial sector represents the concatenation of social, economic, technological, regulatory and political factors. The strategic forces that have defined the business environment for decades are shifting. Executing strategies to deal with the problems and opportunities posed by them will determine corporate (and national) success.

- Pace of scientific advancement – new basic discoveries with therapeutic potential arise more quickly than the market lifecycle of existing products. They arise mainly from academic laboratories.
- Cost of drug development and approval – recently estimated at \$1.3 billion (US) and increasing historically at 7.6 per cent per annum (10).
- Pipeline productivity – NCE approvals are flat or declining over the past decade, despite increasing R&D expenditures. In many individual companies, patents on large-revenue products are expiring, with insufficient prospective pipeline candidates to backfill.
- Global capital markets – IPOs are a less likely means of return on investment for small and start-up enterprises. Large capital transferred to the developing world,

(through trade imbalance) is seeking local and international investment opportunities.

- IP protection/patents – IP protection outside the developed world has improved in recent years.
- Generic drugs – increasing use of generics in the developed world. Rapid growth of successful global generic companies.
- Pricing pressure – pressure on drug pricing by payers and price regulation by national authorities. Large under-served markets with limited ability to pay.
- New therapeutic targets and approaches – implications for academia, industry infrastructure, and cost of drug development.
- Regional economic development and emergence of clusters – Government as a player in industry location and incentives. Geographic location as an element of competitive strategy.
- Large underserved world markets – need for therapeutic drugs (HIV, malaria, TB and parasites) but implications for IP protection, location of manufacturing operations, and dispersion of know-how.

million new venture fund in the US.

In the case of Ranbaxy-Daiichi-Sankyo merger, Ranbaxy derives 60 per cent of its sales from US and EU markets; D-S is the 15th largest drug maker in the world and the only one that specialises in producing both new drugs and generics.

In-Licensing

Another way to increase revenues is to launch new products. Supposing for the moment that internal pipelines are not sufficient, this can be accomplished by licensing-in new products from other innovator pharmaceutical and biotech companies and from universities. This mode recognises opportunities where the innovator may have excess pipeline candidates or programs and IP that are strategically unsuitable for their own business model.

One contemporary consequence of the in-licensing model is a burgeoning marketplace in technology transfer and licensing deals. This is consistent with the growth in popularity of the 'virtual' company business model. Secondly, licensing is now an explicit part of the business plan exit strategy for innovative startup companies launched with private capital backing, and who would, in any event, not have the resources to carry their first drug through human clinical trials and marketing approval.

Finally, the appetite for licensing opportunities and recognition of the value discount, at earlier stages, has prompted small and large pharmaceutical and biotech companies to license inventions from universities, with preliminary efficacy data and strong scientific rationale. This is the basic 'bread and butter' for VC funded biotech startups, and may often involve proactive involvement of the VC in identifying the opportunity and assembling a team.

As is often the case, business opportunities lead to a 'land-rush'. The case of pharmaceutical and biotech companies is not different. There is currently a great impetus amongst these companies towards proactively funding multi-million dollar and multi-year research collaborations with major research universities. Generally, the programmes are loosely directed, if at all. The universities gain a new source of major research funding, while the

companies gain a preview of important new areas of discovery, a potential place in line for licensing opportunities, and a long-run enhancement of the talent pool (12). For example, major multi-year deal have been announced between large pharmaceutical and biotech companies and major research universities: GSK – Harvard; Alnylam – MIT; AstraZeneca – Columbia University; and Pfizer – UCSF (16,17).

CONCLUSION

In seeking to capture and create value, a successful pharma and biotech enterprise must consider both the forces shaping the global, transnational environment, as well as the realities on the ground that characterise the regional business ecosystem in which it hopes to thrive. Thus it needs to adapt to the realities of the marketplace in which it operates and which it serves, and the constraints imposed by regional disparities in pricing power, societal infrastructure, capital markets and work force. Actions by governments and other competing enterprises create additional opportunities and threats to the success of the business.

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