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New opportunities in Asia: a focus on India and China

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IBC's Drug Discovery Technology Asia conference
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The IBC's Drug Discovery Technology Asia conference held 18–20 October 2004 in Mumbai, India, provided a good overview of some of the key challenges facing countries in the Asia–Pacific (AP) region, particularly in India and China, and the rapidly growing move into drug discovery and clinical trials.

Business models in Asia

The conference was kicked off with a keynote presentation from Lorenz Ng (Eli Lilly Asia, China) summarizing the state of play for companies focussing on drug discovery in the AP region. Following a period of brain drain largely to the US, AP countries are now seeing a reverse brain drain and Ng suggested that there should be a focus on a 'brain game' where the key pockets of knowledge are identified and maximized.

Currently, outsourcing is the main domain in AP because of its ease of execution, and the fact that it is not intellectual property- (IP-) critical and is rule-based work with defined deliverables. However, as countries such as India, Singapore, Taiwan, China and Korea start to increase their activity in the pharma marketplace, they need to become global where their capabilities are yet to be demonstrated and to do this will require significant collaboration.

Generally, partnerships in Asia currently fall into two categories: academic–government partnerships and industry partnerships (such as molecule-specific collaborations, joint collaborations with shared risk, or capacity outsourcing e.g. WuxiPharmatec). The essential features for innovation in these countries include a government policy that provides the necessary environment: IP protection (e.g. trade policies and judicial systems), finance (macroeconomic stability and tax/fiscal incentives), and existing industry and human resources.

Ng suggested one of the most obvious future models for the AP pharma industry is to persuade US companies to offload their assets (lead compounds) to an AP partner for co-development. There are various ways of doing this including: (i) the Train and Transfer model (TNT), where an entire team is trained in the US in discovery research and then transferred back to the AP country; (ii) the Trans-continental Straddle Model, where start-ups are founded by returnees to the AP country who maintain business relationships with US start-ups; and (iii) the e-R&D model, for example Eli Lilly's Innocentive, where problems are outsourced to the Web for other researchers to find the answer, which means that you offload your risks. Interestingly, the majority of scientific talent exists outside the US (70%), whereas the majority of R&D spending is in the US (80%; source: PhRMA).

There was a lot of interest and concern from AP companies on how to avoid the big brother syndrome when partnering with very large multinationals such as Pfizer. Abhijit Banerjee (Pfizer, USA) commented that experience from partners with small companies in the US have shown Pfizer that they need to understand the partners' needs and manage their expectations. Ravi Sodha (Novartis Pharma AG, Switzerland) explained that companies in China, India and Korea, for example, have been selling drugs for many years so they know how to do this but it is the research area where they need western expertise.

Government initiative in India

R.A. Mashelkar (Director General of the Council of Scientific and Industrial Research, India) provided a valuable summary of India's largest public-private partnership (PPP) – The New Millennium Indian Technology Leadership Initiative (NIMITLI), which aims to develop new technologies through consortia of academics and R&D departments. The NIMITLI has already had early successes with Biosuite which developed a new drug within 18 months at a cost of only US$5M and is due to launch in the US in June 2005, and further successes have been seen with psoriasis and TB therapies.

Financial investment in Asia

Sarath Naur from APIDC Venture Capital (VC) (India), one of the first biotech-focussed VCs in India, stated that, in the past 18 months in India, there has been >$1B VC investment in technology and US VCs are making a total of 30–100% IRR on their portfolios. Indian VCs are not far behind, with big success stories such as Biocon. There has been an exponential growth in patentable technologies, with more

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than half the US patents granted originating in India. However, although building IP is an important first step, it is noteworthy that >90% of patents are yet to be monetized.

Naur did voice concern that there is too much money around in AP biotech currently, and VCs are in reactionary mode, forgetting the lessons learned from the dotcoms. Funding opportunities for AP companies are therefore mainly focussing on enabling companies to structure proactively and to cross-border early-stage deals to make the most of the large pool of highly trained health workers and the patient base in India, as well as the plant biodiversity, chemistry skills and IT.

Sanjay Sehgal, Schroder Capital Partners (Asia) Pte Ltd (Singapore) said that portfolio building is still more important than building excellence in management in AP, and good scientific talent in India and China is still difficult to tap into. Countries such as Australia, Japan, Taiwan and Singapore are in the lead, although China, India, Hong Kong and Korea are catching up in terms of entrepreneurial spirit, infrastructure and clusters, IP protection, talent pool, and investor community. Biotech companies in Asia are small: 3.2% of global revenues are from AP, with 1.2% of global R&D expenses, but 5% of global employees from AP. Meanwhile, AP has 19.6% of private companies and 14.2% of public companies globally (Ernst & Young, Global Biotechnology Report 2004).

IP in Asia

One of the issues raised by almost every speaker was IPR and the need to have effective laws to enforce patents. John Thottathil (Abbott Laboratories, USA) pointed out that countries must be careful to ensure they respect and adhere to international law, safeguard IP of others entrusted to them, embrace the GATT Treaty and stay clear of others' IP as it is very hard to erase a bad reputation.

A panel discussion around this thorny issue of patents brought up some interesting statistics. Li Chen from Roche R&D (China) said that, while there had been 260M patents filed in the US last year, 300M patents were filed in China and this is growing at 20% per year, with companies in Korea and Japan also actively filing in China. However, these applications tend to be of low quality through a lack of basic understanding of patent law. Chinese generic companies are also learning quickly from the success of patent challenges. For example, there are numerous companies in China now producing generic versions of Viagra, although these are still being challenged by Pfizer.

Chen did explain that notable revisions have been made to Chinese patent law since 1985, when the law was first developed, including an extension of patent lifetimes to 20 years, providing law enforcement of patent rights protection, and development of patent coverage for small molecule drugs, biopharmaceutical and TCM definitions for patents. In India, where patent law is much further behind, Ajit Dangi (OPPI, India) confirmed that the new patent laws are planned for discussion in the winter session of 2004, which should then bring India in-line with international patent law.

Multinationals setting up research centres in Asia

China is the sixth largest market for drugs and has a large talent pool with 580,000 students having gone abroad between 1978 and 2002, of which 150,000 have returned home. Estimates from the *Financial Times* in 2003 showed that, if present growth rates in China continue, the country will be the world's largest drug market by 2020; currently there are 6,700 pharma enterprises. The biggest challenge faced by multinationals in China is pricing pressure exerted through government-mandated reductions. Although China's 2003 National total investment in science and technology was 15B RMB (Renminbi – Chinese currency), this is still a small amount compared with a company such as Pfizer. Government sponsorship is being targeted towards a few key research institutes and a few biotech parks are emerging, such as Beijing Zhongguancun Life Science Park and Guangzhou Biotech Hub. Technology platform centers have also been developed: the National HTS Center, the National Drug Safety Center and the National NMR Center. Chen suggested that drug discovery research in China is starting to bear fruits, with 60 Class I NDAs filed during 2000–2002.

Chen felt that the slow progress in China is a symptom of the lack of incentive to engage discovery research: a modern research environment has yet to be formed, there is a lack of knowledge of target-oriented drug discovery, it is difficult to create drug discovery teams as there is still a focus on individual goals within academic environments, and they often tend to be slow to reach out to partners, leaving most pharma groups in China engaged in marketing and drug development rather than research. However, China has excellent resources and internationally trained biomedical scientists, and Roche has decided to create an R&D centre in Shanghai. In 2004–2005, this centre will be staffed with 40 scientists in discovery chemistry and then grow to be a fully staffed discovery research centre in 3–5 years with integration of chemistry, biology and pharmacology.

Although India has many similarities with China, Lars Walan (AstraZeneca, Sweden) felt there are still too many question marks for India. In terms of discovery research, Indian researchers are generally are very good at synthetic, process and natural product chemistry as well as pharmaceuticals, but it should be equally recognised that they are generally poor at computational and medicinal chemistry, and at pharmacology. However, India does have strong biology skills that are largely underused, and there is a keenness to learn with good team spirit, and much improved communication and partnering skills.

Clinical trials in India and China

Swati Piramal, from Nicholas Piramal India Ltd (India), discussed some of the opportunities and challenges around companies conducting clinical trials in India. Nicholas Piramal is one of the largest pharmaceutical companies in India grown through numerous acquisitions including Boehringer Mannheim, Hoescht Research Centre and Roche Products Ltd. The key advantage of conducting clinical trials in India is that it is much cheaper and easier to find the required patient populations even for trials with complicated inclusion/exclusion criteria due to the lack of multitherapy in India compared with many western countries. There is already a strong base of international CROs in India and additional support infrastructure is emerging. The key current limitations in India are that the laws do not allow Phase I trials to be conducted in India of

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drugs discovered outside of the country, so as to avoid becoming 'guinea-pigs'. Furthermore, there are not enough regulators in the country to decide which Phase I trials are appropriate. However, Piramal emphasized that this law must change if India is to progress.

In an enlightening keynote, Walan provided a frank description of the problems of setting up a base in either China or India. AstraZeneca decided in Jan 2002 to explore the potential for accessing new clinical investigators and patient populations in Asia. Some of the key business considerations involved in this decision included the fact that AstraZeneca sales in China are higher than in India and have the fastest growth rate. Another significant factor was that patent protection is present in China, whereas progress in IPR in India has been slow and importantly, there is also no data protection in India.

However, India does have the advantage that many facilities work in English, but China is more developed in terms of health and welfare indications, has lower infant mortality, and higher life expectancy. The final decision was made to set up a clinical research unit in Shanghai but to investigate the possibilities in India for off-shoring biostatistics and data management.

After moving to China, AstraZeneca discovered several other areas that should be considered when making such a decision, for example: (i) the long time required for clinical trial approval in China precludes participation in many global trials (by comparison, approval can be between 2 weeks and 3 months in USA; 2 weeks guaranteed including approval by the ethical committee in Singapore; but up to 12 months in China); and (ii) the level of information the Chinese SFDA require exceeds EU and US requirements: submissions must be translated into Chinese and the government laboratories recheck the quality of all study drugs. Furthermore, strict regulations on export of genetic material (such as blood, biopsy specimens) can prove a big problem and there are concerns about quality assurance during courier delivery of study drugs. Also, in some therapeutic areas, the number of centres with government approval to conduct clinical trials can be very limited. However, Walan commented that it proved easy to attract highly competent medical professionals to the pharma industry in China and they have an impressive knowledge and facility in English. The staff and investigators have proved very hardworking and motivated, and it is possible to obtain reasonably rapid approval (e.g. 2 months) for clinical trials in China once the NDA has been filed. There is also a sign of willingness of the drug regulators in China to change the situation of slow approval times, although realistically this is likely to take a couple of years before it matches the US.

Conclusion

The general feeling is that although there are still many outstanding issues that must be addressed (especially by countries such as India and China) to be able to attract substantial western investment and partners, significant progress in this direction has already been made. There appears to be a strong commitment by both governments and the companies within these countries to ensure that rapid progress is made on the key issues such as patent law and regulation, language barriers, broad scientific expertise, business expertise and good partnering skills. The key problem areas that were raised by some of the western multinational companies that have already taken a step to work in Asia were fully embraced by the respective countries and there is a real energy to ensure that investment and partnerships with western multinationals and investors are forthcoming and prove successful.

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Chemical Grues and Little Willies

A thought-provoking tonic on the lighter side

Column by Raymond C. Rowe, AstraZeneca, UK

Please note that these are the personal opinions of the author and do not necessarily represent those of AstraZeneca.

A grue is simply a comically sadistic and grisly little poem of four lines. The term was originally coined by Robert Louis Stevenson (1850–1894), the author of the well-known romantic adventure stories *Treasure Island* and *Kidnapped*. Stevenson was also a poet whose poems, although not showing the highest poetic genius, were skilful and original, often written with children in mind. The word 'grue' is a Scottish word with roots in old Swedish ('grua') and Danish ('grue') meaning to feel horror or fear, hence the more common derivative 'gruesome'.

A contemporary of Stevenson, Harry Jocelyn Clive Graham (1874–1930), wrote a collection of grues under the pseudonym Colonel D. Streamer entitled *Ruthless Rhymes for Heartless Homes* [1]. Originally published in 1899, this book was an immediate success and has been reprinted several times over the intervening years. An example from Graham's collection illustrates the basic structure of the grue:

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