BioProcess™ INTERNATIONAL

Reprinted with permission from BioProcess International 3(9):20-24 (October 2005)

SMW Strategic Manufacturing Worldwide

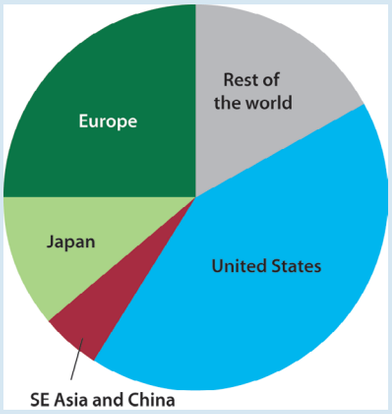
Bioprocessing in Asia

Now and the Next Five Years

by Scott M. Wheelwright

Both Asia and biotechnology are often in the news. Many Asian governments are looking to life sciences to propel their continued growth. This article is an overview of the outlook for biotechnology and bioprocessing in various regions of Asia. Bioprocessing in Asia is driven by the worldwide pharmaceutical industry, the regional economy relative to the world economy, and country-specific actions related to biotechnology. After reviewing each of these factors, I highlight specific opportunities and issues for bioprocessing in the region.

Figure 1: Worldwide pharmaceutical market share shown as percentage held by each country or region (2003 data) (2)



The Pharmaceutical and Biotech Industries

Starting with the numbers: The worldwide pharmaceutical market in 2004 was estimated at $550 billion dollars (1). In 2003 the US share of the worldwide pharmaceutical market was 42%, Europe 25%, Japan 11%, Southeast Asia and China 5%, and the rest of the world had 17% (Figure 1) (2). The worldwide market for pharmaceuticals has increased by 50% in the past five years and can reasonably be expected to grow as the amount spent on healthcare expands in developing countries such as India and China.

Overall, it's no secret that the biotechnology industry is alive and doing very well. In 2004 the United States had estimated revenues of $58 billion and employed 146,100 people. The industry in Europe had revenues of $7.5 billion in 2003 and employed 32,470 people (2).

Economic Comparisons

As a rising tide lifts all boats, a rising economy generally has a positive effect on the companies located within it. Therefore, companies in the pharmaceutical and biotechnology industries are affected by the economies of the countries in which they are located. Figures 2–3 and Table 1 compare various countries, including China and India, by different measures of performance. If we looked back 10 or 20 years, China and India would rank very differently on these lists. The fact that they are now so close to the top indicates huge advances made in recent years.

JOEY CHUNG (WWW.ISTOCKPHOTO.COM)

The consequence for the pharmaceutical and biotech industries is tremendous. Large numbers of investments are being made in the developing countries of Asia from both within and outside them. Indian companies are investing in China, and Chinese countries are investing in India. Both are investing in

neighboring countries as well as in European and US companies.

As the economies of China and India continue to expand, the neighboring countries will also experience growth at varying levels. The growth that occurs in the economies of Asia will produce growth in the pharmaceutical and biotech industries in this region in two ways: economic expansion of all industries and expansion due to an increase in the number of consumers capable of paying for improved health care.

Country-Specific Actions Related to Biotechnology

Almost all advanced and rapidly advancing countries in the world have designated biotechnology and life science as focal points for growth in the coming decades. Governments in these countries have established task forces and committees to support life science research and advance the biotechnology capabilities within the country.

Competitiveness: In the past decade we have witnessed a capitalist revolution in Asia. The communist countries of China and Vietnam and the heavily socialist India, for example, have made complete turnarounds and embraced private ownership of property as a key to economic prosperity. Many enterprises that were owned and operated by the government have been converted to private ownership and management. Government, academic, and business leaders recognize that the most efficient distribution of scarce resources comes through free-market operations. They also recognize (though they have found the reality harder to implement) that rule of law is key. Only when the means of production are controlled by individuals who are rewarded for their risk are the incentives of workers aligned with the needs of customers. Thus, private ownership is essential.

No single individual or group has sufficient knowledge to determine the value of a material to others. However, the free market allows each of us to bid the price that reflects the value of something to us. This allows materials and other resources to be used by those who value them the most, rather than by those with political connections. Free trade always benefits both seller and buyer; otherwise they wouldn't freely trade. The rule of law — under which everyone is held to the same legal rule and no one obtains exemption from complying with the law — protects against abuse by those in power or authority and reduces the risk of entering into a contract because both parties know it can be enforced.

The consequence of this revolution in thought has been spectacular economic growth in many parts of Asia. China and India now each contain a middle class that rivals that of the United States in size. Along with economic growth has come increased purchase power and increased economic investment. The pharmaceutical industry has benefited, with more people able and willing to spend money on healthcare products and more money invested in plants and operations to produce those products.

Regulatory Adjustment: China has actively deregulated its domestic pharmaceutical market as part of its agreement for joining the WTO. The State Food and Drug Administration (SFDA) is also revising regulations to harmonize with international standards. China adopted ICH guidelines for Good Clinical Practice in 1998. The country's Drug Administration Law that took effect on 1 December 2001 requires drugs to be produced in compliance with GMP (**3**).

The revised Pharmaceutical Affairs Law in Japan, which took effect in April 2005, allows filing of Drug Master Files by foreign companies seeking product licenses in Japan (**4**). This revised law also allows contract manufacturing of finished dosage forms. Both changes are expected to allow greater flexibility to manufacturers desiring to market their products in Japan and have the potential to increase the efficiency of production.

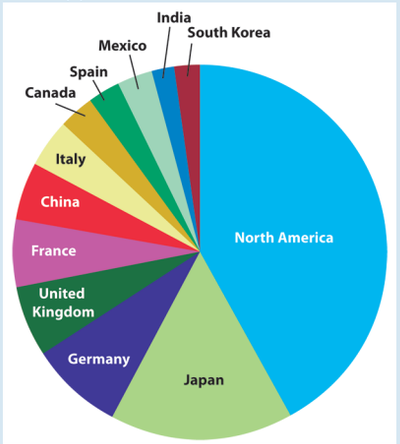
In India, cGMP compliance has been embraced by the industry and is well accepted (**5**). The Indian pharmaceutical industry is noted for providing guidance and counsel to its members regarding compliance. That is reflected in the number of sites in India approved by the FDA — 72 approved in 2004 (**6**). The Indian pharmaceutical industry benefits from several advantages, which include English language use, a well-trained and educated labor force, and supporting industry associations. Pharmaceutical companies in India are growing at a compound annual rate of 15.4% each year. Indian colleges graduate 135,000 students with pharma-related degrees annually.

Table 1: Percentage of worldwide exports by country/area (biggest exporters) (**9**)

Rank	Country	% of total*
1	Euro area	17.2
2	United States	13.6
3	Germany	9.1
4	United Kingdom	6.6
5	Japan	6.1
6	France	5.2
7	China	4.1
29	India	0.9

*% of total world exports

Figure 2: The 12 biggest economies of the world (**9**)



One consequence of the increased competition between pharmaceutical and API manufacturers in China and India has been failure of many companies to sustain profitable businesses. As in all industries, when the pharmaceutical and biopharmaceutical industries mature, some companies will disappear and others will be acquired to build stronger and more capable enterprises.

Intellectual Property: Drug patents have undergone a major change in India. The Indian Patents Act of 1970 abolished the recognition of foreign drug patents in India. Although spark plugs, CD players, and other technologies received patent protection, no drugs were protected. One consequence was that in

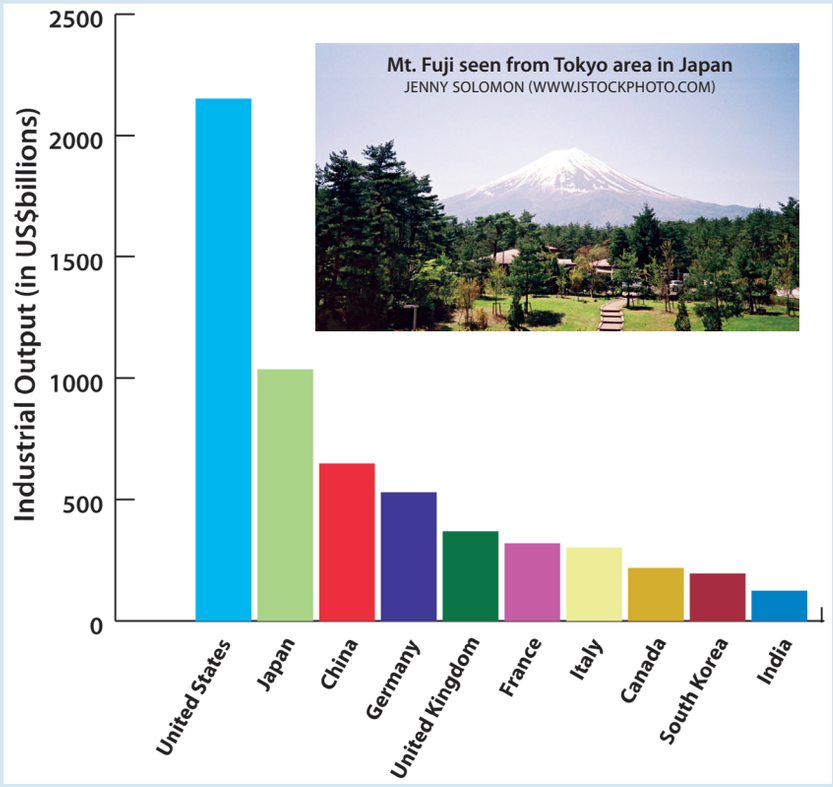
India major pharmaceutical products were widely available at low prices. A colleague informed me that seven different Indian manufacturers sold atorvastatin (Lipitor) for cholesterol reduction. However, since the January 2005 adoption of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) treaty, the situation has changed. Medicines invented after 1 January 2005 and those protected by patents outside India since 1 January 1995 will be protected by TRIPS (7). With these changes, drug makers will enjoy the same 20-year monopoly they enjoy in other countries. Although the changes in India reflect a movement toward the international standard of patent protection for pharmaceuticals, the change is not complete and will probably take several more years to settle down.

China is also tightening its patent protections for pharmaceuticals. Although much fuss was made in the United States of the rejection by China of the patent for Viagra, few articles mentioned that previous to China's rejection, Europe had also rejected the patent for Viagra (albeit for different reasons). Some observers suggest that the reasoned procedure followed by China in evaluating and then rejecting the Viagra claims are indicative of a patent system that has grown strong and continues to grown strengthen.

Generic Pharmaceuticals: India's generic industry includes more than 60,000 generic brands in 60 therapeutic categories. In 2004 India had claimed 4% of the $16 billion US generics market. Estimates suggest the share of the US market taken by Indian manufacturers may reach 10% by 2008, out of a total market of $22 billion (7). India had 20,000 drug companies worth $4.5 billion in 2002, and it is expected to grow 8–9% annually. The country ranks fourth in pharmaceutical sales volume and 13th in value internationally. India is projected to move from niche and commodity APIs to dosage forms and finished generics (8). China is expected to move from production of basic building-block chemicals and commodity APIs to custom intermediates and niche APIs.

China and India together have a near-monopoly on products with expired or nearly-expired patents. Essentially all US generics companies have partnerships with companies in China and India. The share of fine chemicals outsourced to China and India could be as high as 30% by 2007 (8). The fine chemicals business developed in India and China in the 1960s as a result of government pushing for self-sufficiency. Since then, China has been increasing value-added products, while India focused on APIs to sell locally without patent protection. Both countries have used the skills and technology they developed in fine chemicals to move into APIs and to now move beyond bulk APIs to more complex niche materials.

Figure 3: Industrial output by country (9)



Mt. Fuji seen from Tokyo area in Japan
JENNY SOLOMON (WWW.ISTOCKPHOTO.COM)

Bioprocessing and Biopharmaceuticals

Bioprocessing in the United States, Europe, and Japan is well established as a tool for the manufacture of biopharmaceuticals. Bioprocessing in Asia has a long history but is less well developed. In previous years a severe shortage of foreign exchange led to the use of alternative separation methods, including precipitation and centrifugation instead of chromatography. In recent years, however, foreign exchange has been less of an issue, and investment funding has become limiting. The availability of supplies has greatly increased, and the major suppliers of laboratory consumables now stock materials in regional warehouses and provide deliveries within a few days. The following description of the local scene in various countries is provided as an indication of the situation, but because the information is based on interviews rather than a survey of market sales, the data may be subject to bias.

In Japan, the sales of biopharmaceuticals has been flat for the past few years, though approvals for antibody therapeutics and vaccines produced in cell culture are anticipated to support an increase of 5–10% in 2006. Major changes to the Pharmaceutical Affairs Law have altered the complexion of the manufacturing scene in Japan, but they have not significantly changed the volume of materials made (4). The changes to the law have slowed the review of applications, though the Ministry of Health, Labor and Welfare has recognized this and is taking measures to improve the situation.

Charminar monument in Hyderabad, India
ARAVIND TEKI (WWW.ISTOCKPHOTO.COM)

In China, the production of biopharmaceuticals has grown at a rate of 5–10% over the past few years and is expected to continue to expand at about 10% per year. Growth in bioprocessing is limited by the number and quality of new products in the pipeline. Local investment has been slow because of the long payback times for biopharmaceuticals, and many companies are pursuing the same products, so competition limits the return for all. In addition, the movement of products from academic institutions is hampered by the absence of established channels for technology transfer. This situation is expected to improve as the intellectual property laws are strengthened. The pharmaceutical business previously experienced higher popularity, but many companies that entered the field subsequently failed. As the market continues to develop and mature, and as Chinese personnel gain experience in biopharmaceutical product development, the industry expects to benefit from an improving business environment.

In India, the situation is similar. One observer estimates the industry has been growing at 25% for the past three years and expects the industry to double from the current $800 million over the next three years. Growth in large part has been due to the production of pediatric vaccines by a number of companies that have met international standards for cGMP and become qualified to sell their products to the WHO. This in turn has allowed them to develop expertise in biologicals manufacturing. There is also a trend towards products with a local relevance, such as vaccine for bird flu, therapies for tropical diseases, and development of products based on indigenous medicines. The former patent situation also led to several companies making copycat versions of popular biopharmaceuticals, which supported the growth of the bulk biologicals industry and also has led to growth in product (fill and finish) manufacturing.

India and China have also developed local manufacturers of equipment, such as autoclaves and lyophilizers, and foreign companies have established operations for the production of fermentors and other equipment. I have seen equipment manufactured in India by a European company to European specifications that is indistinguishable from European-made vessels.

Outlook

Differences between the costs of operation in less-developed Asia and developed countries (United States, Europe, and Japan) are immense. Salaries in developing countries are one-seventh to one-tenth those in the developed countries for equivalent skill levels. Even with lower efficiencies, a company can lower its labor costs by a factor of three by moving operations to a lesser-developed country. And the lower labor rates translate into lower capital costs because the expense of facility construction and equipment contains a significant labor component.

Many operations in the development of biopharmaceuticals have moved to Asia. Clinical development and drug discovery are expanding rapidly. A comparison of preclinical costs in the United States and China indicates a factor of five difference. In other words, a preclinical program that costs $300,000 in the United States costs only $60,000 in China (**2**). We have not seen large transfers of bioprocess development and analytical methods development to lesser developed countries, but this will undoubtedly change in the next decade. The world is filled with opportunities for new products, new services, and new ways to deliver both.

References

1 Special Report: The Drugs Industry. *The Economist* 19 March 2005: 73–75.

2 Burrill & Co. *China Is Partnering*. 2005. www.burrilldatacenter.com.

3 Drug Administration Law of the People's Republic of China. Order of the President of the People's Republic of China No. 45, 28 February 2001. www.sfda.gov.cn/eng/.

4 Wheelwright SM, Kosaku H. Changes to the Japanese Pharmaceutical Affairs Law. *BioProcess International* 3(1) 2005: 14–16.

5 Rutledge CR. India: A Dominant Player. *Contract Pharma* 3(1) 2005: 56–61.

6 Meredith R. Lupin's Unsexy Bet. *Forbes Magazine* 13 December 2004.

7 Mayer R. A Passage for India. *MedAdNews* 24(8) 2005: 4, 62, 64.

8 Polastro ET. Asia Outlook: Chinese and Indian Markets. *Contract Pharma* 2(10) 2004: 82–89.

9 Pocket World in Figures, 2005 Edition. *The Economist*, 2004.

***Scott M. Wheelwright, PhD,** is president of Strategic Manufacturing Worldwide, Inc., 13119 Glen Brae Drive, Saratoga, CA 95070, 1-408-420-5352, info@smwbiotech.com*