Biologics Regulation in Asia

by Ames Gross

Asia's market for medical products is one of the world's largest markets. Japan is the second largest market in the world for pharmaceutical products, and China is catching up. In 2002, Japan's pharmaceutical market was worth US$53 billion, and China's was worth approximately $23 billion (Table 1). Asia's medical devices markets are also growing. Even smaller countries such as Thailand, Singapore, and Malaysia had medical device markets worth $500 million, $410 million, and $300 million, respectively, in 2002 (Table 2). In general, the Asian medical markets are growing more than 10% per year.

The size and growth of Asia's medical products markets has inspired many Asian governments to realign their regulations to ensure higher quality products and to further comply with international standards. One medical product area currently undergoing regulatory change in Asia is the biologics market, which is growing.

Foreign companies and investors have begun entering Asia to tap into that growth. Here I provide an overview of the biological products market in Asia and discuss some recent regulatory changes in the region.

US Central Intelligence Agency (www.cia.gov)

Japan

Because it is the second largest in the world, the Japanese medical products market has long attracted foreign companies and investors. The biologics market in Japan is no exception.

For example, in October 2003, Crucell NV (Leiden, The Netherlands) and Gene Medicine Japan, Inc. (GMJ, Kobe, Japan) announced that they had entered a licensing agreement for Crucell's proprietary PER.C6 production technology. The PER.C6 process is used to produce safe, scalable cell lines for biologics such as recombinant proteins and monoclonal antibodies. Crucell will provide manufacturing technology to GMJ to produce biopharmaceutical products, including vaccines and antibodies. Production in GMJ's facilities is scheduled to begin in June 2004.

Regulatory Obstacles: Although many foreign companies are

interested in entering Japan, complicated government regulation is a major obstacle. In recent years, however, the Japanese government has attempted to revise its regulations to provide more transparency and compliance with international regulations. For example, as part of extensive pharmaceutical affairs law (PAL) revisions in Japan, the Japanese government consolidated safety measures for biological products in July 2003.

Under the revised PAL, biological products are defined as "products including ingredients derived from human or biological (excluding plants) source materials (such as cell, tissue, blood, etc.), which should be subject to particular attention from the public health point of view" (1). Examples of these products include blood products and plasma derivatives, vaccines, recombinant proteins (cell cultured), cellular and tissue-based products, and gene therapy vectors. Major characteristics of biological products as defined by the Japanese PAL include:

- The inability to rule out potential risk from infectious agents derived from source materials
- Dependence on the donor profile of unspecified persons or animals from which source materials are collected for the safety of individual products
- A limited ability to inactivate infectious agents in a product while maintaining its integrity and function.

Regulatory Changes: Revisions in the Japanese PAL include a classification system for biological products based on risk factors and a delineation of duties and roles for manufacturers, health professionals, and government agencies involved with biological products. A revised approval and licensing system has been put in place to enhance the introduction and safety of products and to bolster postmarketing safety measures. The revisions also include a system to retain records for traceability of infections as well as an Infection Relief Fund to assist persons infected by biological products. Manufacturers will contribute to the fund. Victims will be compensated based on the severity of infection. The Infection Relief Fund should be operating by April 2004.

Table 1: Size of Pharmaceutical Markets in Asia (2002)

Country	Market Size (US$)
China	23 billion
Hong Kong	1.5 billion
Philippines	300 million
Indonesia	350 million
Japan	53 billion
Malaysia	210 million
Singapore	400 million
South Korea	6.3 billion
Taiwan	2.5 billion
Thailand	1.5 billion

Source: Compiled from various sources by PBI

Table 2: Size of Medical Device Markets in Asia (2002)

Country	Market Size (US$)
China	2.2 billion
Hong Kong	500 million
Philippines	70 million
Indonesia	150 million
Japan	23 billion
Malaysia	300 million
Singapore	410 million
South Korea	1.1 billion
Taiwan	700 million
Thailand	500 million

Source: Compiled from various sources by PBI

In recent years, concern has been growing about the safety of blood products in Japan. In the summer of 2003, the Japan Red Cross found that 37 units of blood for transfusion — out of 6400 examined — tested positive for hepatitis B. Sources say the contaminated blood was probably used (2). In December 2003, it was discovered that a person contracted HIV through a contaminated blood transfusion, the first such case since Japan introduced the ultrasensitive nucleic acid amplification test in 1999 (3). The Japanese Health Ministry is advising all recent recipients of transfusions to follow up with the Japan Red Cross and seek testing. It is also encouraging the Red Cross to improve its blood screening methods to prevent future incidents.

China

Many companies are vying to market their biological products in China and compete with local state owned enterprises (SOEs) manufacturing similar products. As a result, many SOEs are merging to create larger, more formidable companies. In September 2003, for example, China Science Equipment Import & Export merged with China Biological Products to form a new biological products company, China Biotechnology. The newly formed company seeks to integrate modern biological product development and other relevant industries as well as alternate between the production of traditional Chinese medicines and new products.

Major multinational pharmaceutical companies including GlaxoSmithKline (GSK), Aventis Pasteur, and Merck and Co. have entered China's biologics market. Chiron Corporation and PowderJect Pharmaceuticals (a wholly owned subsidiary of Chiron) are also following in their footsteps. On 6 November 2003, Chiron announced the opening of a new state-of-the-art blood-screening laboratory in China. It will test for HIV and hepatitis C in donated blood. The lab opened as part of the celebrations for the 50th anniversary of the Beijing Blood Center. In the future, the lab will also be used as a clinical trial site for product registration in China.

Vaccine Market Issues: However, even with those major multinational players entering China's biologics market, experts predict that it will still be difficult for foreign companies to overtake the local market because of the competitive pricing, technology, and production costs of China's domestic biologics companies. For example, in the

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vaccines market, the Chinese government has placed price restrictions on certain vaccines to protect consumers and keep the market competitive. The price for hepatitis A vaccines is limited to 17.5 RMB (US$2.10). Hepatitis A vaccines in the United States are sold for approximately US$50–$70. This considerable price difference prevents some foreign vaccine manufacturers from entering the Chinese market because of a lack of forecasted revenues and profits. However, for other foreign companies, the size and potential of the market in China is enough to overlook short-term costs and hurdles.

A major obstacle to the Chinese vaccine market will soon be removed when private companies are allowed to distribute commercial vaccines beginning in 2004. The government has decided to open up this sector to help meet the growing demand for vaccines. During the SARS (severe acute respiratory syndrome) outbreak in early 2003, the Chinese government recognized a need for greater resources to quickly distribute vaccines for infectious diseases during times of emergency.

So sometime this year, government public health organizations will move out of the vaccines distribution sector to permit the entry of private distribution companies. Vaccines distribution is an area public health organizations monopolized for decades. Although its abandonment will mean lost income for those organizations, in the long run the government believes this course of action will best protect the health of the Chinese public.

The Chinese vaccine market is huge and sees an annual growth rate of approximately 15% a year. According to the *China Pharmaceutical News*, this is considerably higher than the global vaccine market's growth rate of 10% a year (4). In 2002, China administered more than 6 million injections of the flu vaccine. Also, about 15 million babies are born each year in China, and they all require vaccines.

Like Japan, China has problems with tainted or contaminated blood products. According to statistics released in 2003 by Shanghai's Center for Disease Prevention and Control, approximately 6.5% of the city's 886 HIV carriers and AIDS patients contracted the virus through contaminated blood products (5). Blood donation centers did not perform sufficient testing to determine whether diseases or viruses were in blood. As a result, those receiving donated blood were not well protected. To combat blood products contamination, the Chinese government has announced a plan to spend $272 million to establish and upgrade 459 blood banks in the central and western parts of the country (6). The Chinese government also plans to crack down on the illegal plasma trade to better control the quality of blood products.

SOUTH KOREA

The Biologics Evaluation Department is a branch of the Korean Food and Drug Administration (KFDA) in charge of biologics regulation and quality evaluation. The department reviews specifications and test methods, conducts lot release tests, and establishes the national standards for biological products. Divisions of the department cover the bacterial products, viral products, biotechnology, and blood products. All applications for biological pharmaceutical products approval in South Korea are handled by the Biologics Evaluation Department on behalf of the KFDA.

Recently, foreign companies have been entering South Korea to tap the growth potential of the biologics market. In November 2003, Emerson Process Management (St. Louis, Missouri) announced its partnership with Celltrion (Incheon, Korea) to help automate its first large-scale biopharmaceutical manufacturing facility in South Korea. John Berra, president of Emerson Process Management, said, "We are proud to be selected as a partner to provide automation and validation services for what will be one of the largest and most technologically advanced biologic manufacturing facilities in Asia" (7).

The 215,000-ft^2 plant will contain bioreactor systems for clinical- to commercial-scale production of protein-based pharmaceuticals. The facility, in Incheon's Songdo New City Technology Park, will be used to produce VaxGen AIDS vaccines and other licensed biopharmaceutical products.

TAIWAN

Taiwan's government has long been known to support industries with high potential for growth, and the biologics industry is one area it is eager to promote. In August 2003, GSK signed a cooperation memorandum with Chen Chien-jen, Taiwan's health minister, for clinical cooperation in vaccine research and development. In September 2003, GSK President Russell Greig visited Taiwan for talks with Premier Yu Shyi-kun on establishing a vaccine R&D center in Taiwan, which would be a first for GSK in Asia. They also spoke of building a vaccine mass production facility in Taiwan. Although still in discussions, both sides feel confident that the planned facilities will be established soon (8).

SINGAPORE

Singapore's Health Sciences Authority (HSA) and China's State

Table 3: Cultural Differences

Western Approach	Eastern Approach
Make a deal	Build relationships
Maximize short-term profits	Establish long-term foundations
Assess competitive capabilities	Assess integrity and trust
Be frank	Don't deliver bad news
Make changes fast	Move when ready

Source: Pacific Bridge, Inc.

Food and Drug Administration (SFDA) have signed a memorandum of understanding (MOU) formalizing their agreement to strengthen cooperation between them. The areas of cooperation include the exchange of information and expertise on biological products.

On 12 September 2003, representatives of the two agencies signed the MOU at the HSA building in Singapore. Dr. Tan Chor Hiang, chief executive officer of the HSA, said, "There is no doubt that by working closely with our overseas strategic partners in our regulatory work, which is based on a risk management approach, our ability to closely manage the risk associated with the products we regulate will be greatly improved. We are confident that the MOU will create the best opportunities for the HSA and the SFDA to ensure good health outcomes" (9).

As a result of the MOU, information and expertise will be exchanged between the HSA and the SFDA on medical products such as biological products, traditional Chinese medicines, chemical drugs, and medical devices. The MOU has begun the formation of a joint Committee of Coordination and Liaison to facilitate bilateral exchanges between the countries.

Government Support for Biologics: The measures Singapore's government is taking to aid the biologics industry are indicative of its desire to nurture a strong base for the development of biological products in the country. Singapore is already home to innovative scientists seeking to improve biological products and their methods of delivery.

For example, an associate professor from the Biological Sciences Department of the National University of Singapore, Gong Zhiyuan, is currently researching methods of delivering hepatitis B vaccines through the consumption of genetically modified fish. Gong successfully transferred genes into a zebra fish, allowing it to produce hepatitis B vaccines. He hopes to also be able to transfer the genes to other more popular fish such as salmon. Fish with the transferred genes can create hepatitis B proteins in their muscles and can produce up to 27 grams of protein. Humans or animals consuming the fish will automatically receive the hepatitis B protein and would be spared painful injections of the vaccine. However, Gong cautions that the edible vaccine is still in its early stages of development and will require many more years of clinical trials before it could be approved for human consumption. Nonetheless, this first step in developing such an alternative form of biological vaccine indicates Singapore's expertise in the biologics industry.

Be Aware of the Differences

Growth in the biologics industry in Asia has attracted the attention of many foreign companies and investors. Growth of the vaccines industry in Asia is particularly notable. However, those who choose to venture into Asia must be aware of the current environment in the industry. Foreign companies must also be knowledgeable about the relevant regulations and recent changes to them that are occurring in Asia.

In addition to understanding the business factors of penetrating the Asian biologics market, foreign companies must realize the cultural differences that exist. Cultural differences also exist among Asian countries. The region is not homogenous. Therefore, companies interested in entering Asian countries must be aware of cultural differences. For example, Japanese culture varies greatly from Chinese culture. However, one universal factor is that relationships are key in Asia (Table 3). To build a successful business, foreign investors must focus on building trusting and solid relationships. By understanding business, regulatory, and cultural aspects of countries in Asia, foreign companies will be well equipped to successfully and profitably penetrate the Asian biologics market.

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