DNA Hepatitis B Vaccine: International Vaccine Institute, Korea

Intellectual property as a barrier to market entry is examined through a study of the development and introduction of recombinant DNA (rDNA) hepatitis B vaccine (HBV) in developing countries. The most widely used vaccines in the mid-1980s were produced by Merck and GlaxoSmithKline, which were the first two companies to introduce the rDNA HBV. Almost a decade later, Korean and Indian manufacturers entered the rDNA HBV vaccine market. However, the price remained relatively high (>US$7 per dose) until the Global Fund for Children's Vaccine (today amalgamated with the GAVI Alliance) was established with seed funding from the Bill and Melinda Gates Foundation. With this funding the price dropped to less than US$0.30 per dose. This study sought to identify factors that affected supplying low-cost vaccine to the public sector.

Merck and GlaxoSmithKline licensed three key patents assigned to Institut Pasteur, Biogen, and the University of California. These patents were filed in the United States, Europe, and a few other developed countries. The companies stated that licenses to more than 90 other patents relating to manufacturing processes such as isolation and purification were also needed.

The Korean companies pursued collaborations or joint ventures but chose not to focus on the United States and European markets mainly due to regulatory and market entry costs. These companies sought World Health Organization prequalification for their production facilities and approval for the vaccine from several governments in Asia and other countries in the developing world.

A Korean company, LG Chem, formed a joint venture with Chiron. Chiron had a license from the University of California (key scientists at Chiron were inventors on the University patent). Through the joint venture, LG scientists could learn how to make the vaccine. Korea Green Cross entered into a joint venture with Rhein Biotech, which had developed and patented its own method for making the vaccine. Having surveyed globally for a partner to exploit its technology, the German company chose Korea because of the low cost of production achieved by Korea Green Cross. The Korean company Cheil Sugar also sought to enter the market for the vaccine and attempted to develop its own technology. After nearly 20 years of effort, Cheil Sugar (now CJ Corp.) abandoned the effort.

These LG Chem and Korea Green Cross alliances were formed in an environment that was supportive of biotechnology innovation. The Korean government accorded high priority to R&D in biotechnology and provided strong support for overseas training and domestic research. The biotech industry received the backing of private sector investment, and domestic and export markets were encouraged by the government. High priority was given by the Korean government to hepatitis B immunization thereby ensuring an initial market for the companies.

This case study concludes that intellectual property was not a major barrier to market entry. Korean companies took several years to enter the market because of lack of resources, including a small cadre of scientific staff, the need to improve national regulatory systems, and, importantly, the small size of the global market. The international public sector market remained underdeveloped in part because of its low priority for large pharmaceutical companies, lack of demand by

Mahoney R. 2007. DNA Hepatitis B Vaccine: International Vaccine Institute, Korea. In *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (eds. A Krattiger, RT Mahoney, L Nelsen, et al.). MIHR: Oxford, U.K., and PIPRA: Davis, U.S.A. Available online at www.ipHandbook.org.

Editors' Note: This case study was originally presented at the MIHR conference Using Intellectual Property for Improved Health in Developing Countries: An Evidence-Based Approach to Good Practice, Bellagio, Italy, June 14–18, 2004.

developing countries, and little procurement by international donor agencies.

Each company sought to secure intellectual property in order to bring its vaccines to market, but patents did not hinder developing the vaccine because the companies focused on markets in countries where the three key patents were not filed. Intellectual property had some affect on access but was much less important than regulatory and manufacturing issues, and market development. However, the situation might be different post-2005 when most developing countries are required to be TRIPS compliant. In the TRIPS era, patents may be routinely filed in many countries such as Brazil, China, India and Korea thereby making it more difficult for second comers to produce in and sell to those large and important markets.

FEATURES OF THE CASE

Types of agreements

Merck and GlaxoSmithKline obtained licenses to three key patents assigned to Pasteur Institute, the University of California, and Biogen. These patents were filed in the United States, Europe, and a few other developed countries. Both companies obtained licenses to numerous other patents having to do with manufacturing processes, including isolation and purification. The Korean companies took three different routes. Cheil sought to develop the technology on its own. LG Chem (previously Lucky Gold Star) formed a joint venture through which it obtained know-how for the production of the vaccine. Korea Green Cross entered into a joint venture with a foreign company, Rhein Biotech of Germany, which had developed an alternate production method.

Patent and IP rights decisions

Merck and, to a lesser extent, GlaxoSmithKline were primarily interested in markets in developed countries and obtained all necessary licenses to patents filed in those countries. The Korean companies opted not to pursue the same markets as Merck and GlaxoSmithKline because of the costs of obtaining regulatory approval and establishing a market presence associated with those markets. LG Chem decided to proceed simply by obtaining know how and relying on its low cost of manufacture and aggressive marketing skills. Korea Green Cross and Rhein Biotech formed a joint venture in which they exploited the Rhein Biotech patent for a manufacturing method different from that used by Merck and GlaxoSmithKline. Cheil sought to develop its own proprietary technology but eventually abandoned this effort.

Policy implementation

All five companies complied with the laws and regulations applicable in their legal jurisdictions. Each company sought a clear IP path to marketing the vaccines. To the author's knowledge, no infringement lawsuits were brought against any of the companies.

EXTERNAL FACTORS THAT AFFECTED DECISION MAKING

Key factors that affected decisions made by the Korean manufacturers were the costs of regulatory compliance with respect to and market entry into the United States and Europe. In addition, the Korean Food and Drug Administration had been undertaking certain improvements, and until those improvements were completed, the Korean manufacturers could not supply United Nations agencies. The Korean manufacturers also had to obtain World Health Organization prequalification for their production facilities, which LG Chem and Korea Green Cross succeeded in accomplishing in the late 1990s. The key factor in allowing the Korean manufacturers to supply low-cost vaccine to the public sector was the establishment of a market through the Global Fund for Children's Vaccine, initially funded by the Bill and Melinda Gates Foundation.

LESSONS LEARNED AND HEALTH-ACCESS ISSUES

Intellectual property was an important issue for all the companies involved in the DNA hepatitis B vaccine project, but IP issues did not significantly impede the pace at which the Korean manufacturers were able to enter the market. The key factors were (in approximate order of importance):

- requirement for a global market
- need to meet international regulatory standards
- need to undertake in-house R&D or obtain know-how from a joint-venture partner
- time it took to construct and improve production facilities that would meet WHO requirements

Further, the ability of Rhein Biotech and Korea Green Cross to exploit the Rhein Biotech patent on an alternate production method provides support for the argument that it is easier to develop and market vaccines in a complex IP environment than it is to develop and market new defined chemical entities that have been patented. Vaccines are complex biological products that can be made through a diversity of procedures while defined chemical entities are single molecules that may be easy to produce only through one process. ■

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