New Aspects Of Drug Licensing In Japan

BY MOTOHIRO YAMASAKI, PH.D.*

The Japanese government approved amendments of the Pharmaceutical Affairs Law (PAL) of Japan last year. The amendments are the most extensive revision of the pharmaceutical regulations in Japan since the enforcement of the current PAL in 1961. The new regulations will become effective in a phased manner from 2003 to 2005. They will significantly affect business activities of drug companies and promote diversification of their business operations in the industry in Japan. To take advantages of such changes, it is worth thinking ahead over the mid- and long-term strategies of drug licensing in and for the Japanese market. This paper takes up important amendments among others that may alter the current licensing practices in the industry. The paper also views licensing opportunities in the pharmaceutical marketplace and addresses necessity of transforming conventional licensing policies into a new form of strategic co-operation in line with the changing business environment.

Change from the "Manufacturing Approval System" to the "Marketing Approval System" Similar to that in the US and Europe.

Under the current law, drugs are approved for manufacturing and hence companies have to have their own manufacturing facilities in Japan. This law will be changed to a new one, effective from April 2005, under which a new drug will be approved for marketing instead of manufacturing. The drug master file system will be also brought into effect at the same time. With these amendments, it will become possible for companies to outsource the entire production process to third parties from a drug substance to its finished product and to hold a license of its marketing approval without having their own manufacturing facilities in Japan. To market, i.e., to launch or deliver the drug on the market, the license holder must have its own presence in Japan that is capable of assuming the responsibility for quality and safety of the finished product.

Patents, know-how and trademarks are main objectives of intellectual properties for licensing in the pharmaceutical industry. However, when the marketing approval is granted to the licensor under the new law, it will become another objective for licensing. Obviously, it will play a very important role in favor of the licensor having the market approval.

The license holder will have a lot of options to choose, for example, where the product is manufactured, either outside or inside Japan, by whom it is manufactured, either itself, the licensee or any other third party contract manufacturer, and furthermore, how the final product is sold, either by itself using contract Medical Representatives (MRs) or with a partner under the currently popular co-marketing arrangement or a new business model of co-promotion*. The new law will lead to more contract manufacturing and co-promotion than ever before. The license of marketing approval will have no expiry date as long as the license holder will renew it every five years. Terms of an agreement will be more flexibly determined than now. Running royalty due for marketing approval may last even after the patent expiry. There are many other ways to capitalize on the new marketing approval system.

*Co-marketing arrangement means that the product is sold through two channels of wholesalers under one or two brand-marks with booking the sales at the two co-marketing companies. A new business model of co-promotion emerging recently in Japan is that the product is marketed by two companies through one channel under one brand-mark with booking the sales at either company.

Physician-led Clinical Trials

The current PAL states that clinical trials of an investigational drug should be conducted under the initiative of those who request the trails, namely the sponsors, limiting the sponsorship to drug companies filing New Drug Applications (NDAs). However, an amendment was made and passed in the Diet last July that is to enable physicians or medical institutions to conduct clinical trials in their sole discretion to test new investigational drugs or such drugs that are used as standard therapies in other countries but not made available in Japan by pharmaceutical companies. The intent of the amendment is to make clinically needed drugs available for official use.

In parallel with this new regulation that will be brought into effect in July 2003, the Ministry of Health, Labor & Welfare (MHLW) intends to start a large-scale clinical trial network in order to facilitate physician-led clinical trials. The data obtained from physician-led trails can be used for obtaining marketing approvals. The MHLW is also considering covering the costs of clinical trials, including those of laboratory tests and

*Dr. Yamasaki is Senior Corporate Executive Officer in charge of Corporate Strategy at Tanabe Seiyaku Co., Ltd. in Osaka, Japan.

personnel, with money from the national treasury on the condition that part of the sales will be returned after commercialization of the drugs.

The new law does not legally force drug companies to supply the drugs. It goes without saying that physicians shall observe the intellectual property rights. It is up to the drug companies whether they will supply physicians with drugs for clinical trials. In this situation, however, drug companies will take a positive role in promoting physician-led clinical trials to apply for marketing approvals of new drugs or for official approvals of off-label indications. The new regulation supported by the large-scale clinical trial network will be helpful in particular for companies to develop new drugs for rare diseases. Thanks to this, it may become worth making licensing deals of clinically highly significant drugs even if they have limited market potentials.

Diminishing License Opportunities

Mergers and acquisitions (M&As) among big drug companies have been repeatedly taking place in the US and Europe in recent years. Typical examples of these are acquisition of Warner-Lambert/Pharmacia by Pfizer and of Boehringer Mannheim/Syntex/Chugai by Roche, merger between Glaxo-Wellcome and Smith Kline Beecham, and birth of Aventis, AstraZeneca, Sanofi-Synthelabo and Novartis after respective mergers between Rhone-Poulenc Rorer and Hoechst Marion Roussel, Astra and Zeneca, Sanofi and Synthelabo, and Sandoz and Ciba-Geigy. The new companies born from such M&As are now ranked within the top 20 companies in Japan in terms of sales turnover and some of them have even larger numbers of MRs than those of the top 10 Japanese companies.

As a result, the number of pharmaceutical companies from which Japanese companies could license new drugs has decreased drastically. Recently, it has become almost impossible for domestic drug makers to license new drugs to the Japanese market from major European and American companies, because such companies born from M&As are now capable of developing and marketing their products on their own in Japan and are no longer licensing them to Japanese companies.

Furthermore, big multinational companies today take licensing-in strategies aimed at the worldwide market including Japan, as their presence in Japan becomes competitive. Therefore, when licensing new drugs into Japan from medium-sized Western pharmaceutical companies or biotechnology companies that do not yet have their presence in the Japanese market, Japanese companies are now put in severe competition not only against other Japanese companies but also against European and American big pharmaceutical companies.

Transition from Current License Strategies to a New Form of Co-operation

Market-Oriented Sector Selective (MOSS) negotiations between American and Japanese high government officials in the late 1980s paved the way for foreign companies to Japanese wholesalers that had been long controlled by major Japanese drug companies and because of that foreign firms had to depend on national drug makers for marketing in Japan. Since then, however, many foreign-affiliated companies have built their own marketing infrastructure and parted from their partners. On the other hand, major Japanese pharmaceutical companies went abroad to develop and market their new medicines by themselves instead of licensing them to Western companies.

The drug industry has seen great progress of the International Conference on Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use. It has now become possible to conduct bridging studies or simultaneous development of new drugs for registration in Europe, Japan and the United States. There is a general tendency for both Japanese and Western companies to develop and market their products by themselves in the three regions. However, it is not always best to do it alone. On the contrary, in most cases it is better for newcomers to the market to align with strong regional companies. Both Japanese and Western pharmaceutical companies are now faced with transition from conventional licensing strategies to a new form of co-operations, such as co-promotion in line with their overall business strategies.

Concluding Remarks

The switch from the current manufacturing approval to the new marketing approval system will provide the license holder with a wider range of options regarding licensing alliances. The infrastructure of large-scale clinical network under the new regulation of physician-led clinical trials will facilitate development and licensing of new drug candidates, in particular for those of orphan and niche-market drugs in Japan.

Major Western pharmaceutical companies have their subsidiaries with full functions in Japan, while Japanese ones have started building the infrastructure for development and marketing in Europe and the United States. They all need new products to expand their organization in the respective markets. Despite heavy investments made by the industry in genomic discovery research for many years, the number of new products launched on the worldwide market has not yet increased in these years, but is rather on the decline. The industry is suffering from the lack of new drugs. Under these circumstances, M&As similar to those seen in the US and Europe will inevitably occur among Japanese pharmaceutical companies more frequently in the very near future than in the past.

As recognized well, it is hardly possible for any company to constantly invent new drugs reachable to the market by its own R&D activity to the extent that the company can keep growing by double digits as expected by the stock market. To overcome this problem, a new strategy covering from R&D to marketing alliances is desperately needed. The article written by Robert A. Myers in *les Nouvelles*, (Sep., 2001) provides helpful guidance for formulating true strategic alliances.