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Pharmaceutical and Biotechnology Companies

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Strategic Manufacturing Worldwide



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Recently enacted changes to pharmaceutical law in Japan provide significant opportunities for non-Japanese companies to increase their market presence in the country and provide manufacturing services to its pharmaceutical industry. Two changes in particular are important: the rules for submission of Drug Master Files (DMFs) by non-Japanese companies and the freedom of Japanese manufacturers to outsource all aspects of their manufacturing. Additional minor changes related to physician-sponsored INDs may also be of interest.

Enacted in 1948, the Pharmaceutical Affairs Law (PAL) was intended to assure the quality of drugs marketed in Japan (1). Major revisions in 1961 were immediately followed by the thalidomide scare, so safety was quickly brought under the umbrella of the law. That corresponds with passage in the United States of the Kefauver–Harris drug amendments in 1962 (2). Good manufacturing practices (GMPs) were established for Japan in 1975 under an administrative guidance system. Corresponding regulations were established for the United States in 1975 covering blood and blood components and in 1978 covering drugs and medical devices (3, 4).



Tokyo at dusk (WWW.PHOTOS.COM)

As with the US Food, Drug and Cosmetic Act, the PAL provides a basic structure for review and approval of drugs before marketing. This structure resides in the Japanese Ministry of Health, Labor, and Welfare (MHLW, or *Koseirodosho* in Japanese, known locally by the syllable-acronym *Koroshō*). Over the years, changes have been enacted and the law modified in response to a changing industry and regulatory environment. On 25 July 2002, further revisions were made that affect, in particular, the role of

foreign companies in the Japanese pharmaceutical market. These changes are scheduled to go into effect in April 2005 (5).

### DRUG MASTER FILES

Under the new regulations a foreign company's DMF may be submitted directly to MHLW, whereas previously all manufacturing and controls information was provided as part of the new drug application (NDA) submitted by a Japanese partner. This change is significant because it allows manufacturing and testing methods and data to be kept secret, not divulged to the partner.

Submission of an NDA in Japan requires an in-country (domestic) caretaker who is held responsible for the accuracy of the data and all submission documents. Until now, such caretakers have been required to submit all that information together in an integrated package — including chemistry, manufacturing, and controls (CMC) data. No provision was made for separating confidential data relating to raw materials into a separate DMF. Now information relating to raw materials, active pharmaceutical ingredients (APIs), excipients, and other additives may be filed separately under the newly amended law.

Importantly, providers of materials who wish to keep their

manufacturing or characterization details confidential can do so now. They can maintain full control over their proprietary information, whether dealing with a joint venture partner, subsidiary, or distributor as caretaker. For example, if the Japanese affiliate is a joint company with representatives from both a US or European and a Japanese organization, and the non-Japanese partner has a proprietary position on the manufacture of the active ingredient, that manufacturer may choose to keep related information proprietary to avoid sharing industrial secrets with the Japanese partner. Similarly, there may be reasons for keeping detailed manufacturing information from a local affiliate.

An ability to file a separate DMF may be even more important in dealing with distributors, and not only because companies have less recourse to remediation when working through one. Under the amended law, there may be substantial financial incentives to use a DMF.

An opportunity arises now for providers of both APIs and inactive ingredients to develop new formulations designed specifically for Japanese consumers. So a non-Japanese provider can file a DMF to allow export of material to Japan for use in Japanese products. That manufacturer may then contract with a Japanese formulator to develop new products targeted and marketed specifically to Japanese physicians and consumers. That way, a product line can be extended without the risk of losing proprietary information. Material can be used in multiple different formulations aimed at particular market segments, and a single DMF is referenced by multiple parties for different applications. Filing a DMF will also be an attractive option for raw material suppliers, such as manufacturers of chromatography resins, who have long relied on DMFs for doing business in other countries.

Filing a DMF will require technical help from a Japanese company, but such help can be provided independently from the local marketer of the product. Several contract research organizations (CROs) can provide capable service in Japanese regulatory affairs and supply translated documents for submission to the government. Although differences between the *Japanese Pharmacopoeia* and those of other countries still exist, Japan is a signatory to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). As such, it accepts the common technical document (CTD), and with translation of some sections, a CTD can be used as the basis for a DMF.



(WWW.PHOTOS.COM)

### **OUTSOURCING**

Another important regulatory change allows Japanese manufacturers to outsource their entire manufacturing operations. Previously, such manufacturers were required to own their manufacturing facilities. Under the new revision, a company with adequate quality control systems is no longer required to manufacture products in its own facility, but instead can contract out the whole process to a qualified supplier.

That provides opportunities for non-Japanese contract manufacturing organizations (CMOs) to provide an increased level of service to Japanese pharmaceutical and biotechnology companies. The change was anticipated by the Japanese pharmaceutical industry because of its potential for reducing costs of manufacturing. Realization of such

cost benefits — and increased contract business — will depend on the capability of parties on both sides of a given project to effectively transfer technology and to provide the desired services.

This change will also enable research and development (R&D) companies, including venture-backed organizations, to move products further through development on their own without having to invest in expensive facilities. Because the law is set to change in April 2005, some Japanese companies are already talking to outside CMOs about moving product manufacture offshore. Another possible consequence may be the split-off of manufacturing divisions from Japanese drug companies as separate entities, such as has occurred in both Europe and the United States.

Any factory manufacturing drugs for sale in Japan, wherever it's located, must have a Japanese pharmaceutical manufacturing business license and comply with Japanese cGMP requirements. The MHLW certifies overseas plants that supply drugs to Japan, and it is ministry policy to inspect such plants before that certification. As a signatory to ICH, Japan is working with EMEA and FDA committees to harmonize regulations, but this work is not yet complete. Its rules, however, are no more onerous than those under which most companies currently operate — and given that opportunities are opening up with this change in the law, compliance with those features unique to Japan may be well worthwhile.

### **A TIMELY OPPORTUNITY**

Other changes in the PAL, not covered here, relate specifically to medical devices, to postmarketing safety monitoring, and to the organization of the Japanese reviewing body. One additional change of note, however, is a revision that will allow pharmaceutical companies to supply drugs directly to physicians for physician- and medical-institution-sponsored clinical trials.

This system is very similar to a US investigational new drug (IND) application procedure for clinical investigators.

All these changes to the Japanese licensing law go into effect in April 2005. Although the MHLW is still working out some details (for example, detailed guidelines for filing DMFs are currently being prepared in Japan), now is the time to move forward and take advantage of the business opportunities resulting from the revisions. The timing is right to begin preparation of DMFs and to negotiate manufacturing contracts.

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## FOR FURTHER READING

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