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Recent changes concerning regulatory protections for pharmaceutical companies in Japan

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This article examines the following two significant recent changes to the regulatory regime in Japan relating to the business of originator pharmaceutical companies and generic pharmaceutical companies:

- The extension of the study period for drugs with new active ingredients.
- The new permissibility of partial applications and approvals.

These changes directly impact certain legal protections (such as the re-examination system and patent term extensions) in Japan for pharmaceutical companies that produce original drugs. These protections are increasingly important in the light of governmental steps to increase the historically low market share of generic drugs in Japan.

BACKGROUND

According to the Japan Generic Medicines Association (JGA) (comprised of the major generic pharmaceutical companies in Japan), the market share of generic drugs in Japan increased from 16.8% in 2004 to 17.6% in 2008 (based on the number of units sold) and from 5.2% to 6.8% (based on the cash amount of sales over the same period). According to statistics of the Ministry of Health, Labour and Welfare of Japan (MHLW), the market share of generic drugs (based on the number of units sold) as of September 2009 was 20.2%. Due to generic drugs' low market share, the MHLW is now focusing on the promotion of generic drugs in order to achieve its goal of making the market share of generic drugs (based on the number of units sold) at least 30% by 2012. Legal protections for pharmaceutical companies that produce original drugs are increasingly important in light of this governmental promotion.

In Japan and most other pharmaceutical markets, patent rights are a fundamental legal protection for originator pharmaceutical companies. Europe and the US have also developed data exclusivity and marketing exclusivity systems, respectively, to provide certain protections for originator pharmaceutical companies. These systems aim to ensure that originator pharmaceutical companies have the exclusive right to market the original drugs for a certain period of time by preventing health authorities from relying on the originator's clinical data to approve applications for generic drugs.

In Japan, however, there is no established system similar to either the data exclusivity or marketing exclusivity systems that would explicitly prohibit the MHLW from relying on the originator's clinical data. Nevertheless, the Pharmaceutical Affairs Act of Japan (PAA) does provide a re-examination system and, although its primary purpose is to ensure the efficacy and safety of newly approved drugs, in practice it functions in a manner similar to the data exclusivity or marketing exclusivity systems.

In addition to the re-examination system, the patent term extension, as set out under the Patent Act of Japan (PA), also gives market protection in Japan for originator pharmaceutical companies. Unlike in the US, under the PA, a patent term extension can be made multiple times for one patent covering an original drug.

Recently though, important changes have taken place regarding such protections for originator pharmaceutical companies in Japan. One change in relation to the re-examination system is the extension of the study period. Another change to the patent term extension is in relation to the permissibility of partial marketing approvals (MAs) for generic drugs.

RE-EXAMINATION SYSTEM

When an MA is granted, the new drug is designated by the Minister of the MHLW (Minister) as a drug for which the active ingredients, quantities, dosage, administration, and indications are clearly different from those of drugs which have already been approved for marketing (*Item 1, Paragraph 1, Article 14-4, PAA*).

Although an applicant for the MA of a new drug must submit to the Minister clinical data supporting the safety and efficacy of the drug, the scope and the number of clinical cases examined in the MA approval process are limited. Accordingly, an additional review concerning the safety and efficacy of the newly approved drug is necessary even after the marketing of the drug has begun. The purpose of this re-examination system is to ensure the safety and efficacy of a newly approved drug by imposing on the MA holder the obligation to gather clinical data during a certain period after the MA is granted so that the Minister has the opportunity to re-examine the safety and efficacy of the drug.

An MA holder for a new drug must apply for a re-examination by the Minister within three months after the expiration of a certain period of time (the study period), based on the category of the drug (*Item 1, Paragraph 1, Article 14-4, PAA*).

Study period

The study period for each new drug is determined by the category of the drug (*Notification No. 725 of the Director-General of the Pharmaceutical Affairs Bureau, 25 August 1993 and Notification No. 0401001 of the Pharmaceutical and Food Safety Bureau, 1 April 2007*):

- Orphan drugs: ten years from the date the MA was granted.
- Drugs with a new active ingredient, excluding orphan drugs: eight years from the date the MA was granted.
- Drugs for which only the indications clearly differ from those of drugs which have already been approved for marketing: four to six years from the date the MA was granted.

The Minister can extend the study periods in the second and third cases after hearing, but not necessarily following, the opinion of the Pharmaceutical Affairs and Food Sanitation Council (a consultative panel for the MHLW), and when the Minister confirms that the extension is necessary to perform a proper re-examination of the new drugs (*paragraph 2, Article 14-4, PAA*). However, any such extended study period cannot extend to more than ten years from the date on which the MA was granted.

Post-marketing study

During the study period, the MA holder must perform a study of the new drug subject to re-examination and report the results of the study to the Minister in accordance with the Ordinance for Enforcement of the PAA (*paragraph 6, Article 14-4, PAA*).

Application for re-examination

An MA holder for a new drug must apply for a re-examination by the Minister within three months after the expiration of the study period, and include clinical data on the new drug. The clinical data must be gathered and produced in accordance with the relevant ordinances, such as the:

- Good Post-marketing Study Practice ordinance.
- Good Laboratory Practice ordinance.
- Good Clinical Practice ordinance.

If the MA holder fails to apply for re-examination, the Minister may revoke the MA for the new drug or order a partial change of the MA's details.

In the re-examination, the Minister examines whether the new drug falls under one of the categories of the approval refusal reasons given in Article 14, paragraph 2, Item 3 of the PAA, such as a lack of efficacy or a harmful side effect that outweighs its efficacy.

Result of re-examination

If after the re-examination the Minister has found that the new drug falls under one of the categories of the approval refusal reasons, then after hearing (but not necessarily following) the opinion of the Pharmaceutical Affairs and Food Sanitation Council, the Minister revokes the new drug's MA. If it is possible, however, to avoid the drug falling under any of the approval refusal reasons by partially changing the particulars of the MA (for example, the quantities, dosage, administration or indications), the Minister orders a partial change in the MA in accordance with the results of the re-examination.

If the Minister determines that the new drug does not fall under any of the categories of the approval refusal reasons, the Minister does not take any action, and the MA holder can continue marketing the drug.

Protection for originator pharmaceutical companies

The primary purpose of the re-examination system is to secure the safety and efficacy of newly approved drugs. In practice, however, the re-examination system protects originator pharmaceutical companies in a way that is similar to the data exclusivity and the marketing exclusivity systems in the EU and the US.

Data to be submitted with an application for an MA

An applicant for an MA for a new drug with new active ingredients must submit extensive data with its application. In contrast, an applicant for an MA of a generic drug with the same active ingredients and quantities, dosage, administration and indications as an approved original drug must submit much less information. Due to this lessened requirement, generic pharmaceutical companies enjoy a reduction in time and costs for the application for an MA, although only after the expiration of the original drug's study period.

When a pharmaceutical company applies for an MA for a generic drug during the original drug's study period, however, the pharmaceutical company must file the same or more extensive data than was attached to the application for the MA of the original drug (*Notification No. 0331015 of the Pharmaceutical and Food Safety Bureau, 31 March 2005*). This is to ensure the safety and efficacy of the generic drug, whose active ingredients, quantities, dosages, administration, and indications have not yet been re-examined after the MA. Therefore, when a generic pharmaceutical company applies for an MA of a generic drug during the study period of the original drug, it does not enjoy the advantages of time and cost reduction; hence, in practice, the re-examination system thereby serves as a protection for originator pharmaceutical companies in a manner similar to the data exclusivity or the marketing exclusivity systems.

This protection for originator pharmaceutical companies during the study period is established by a notification by the MHLW. This notification, however, is not, and does not have the force of, legislation. Therefore, protection based on the re-examination system can be rescinded or amended by another notification from the MHLW without any resolution of the Diet of Japan.

Recent changes

Historically, the study period for drugs with new active ingredients was, in principle, six years. In 2007, this period was extended to eight years by Notification No. 0401001 of the Pharmaceutical and Food Safety Bureau dated 1 April 2007. This extension strengthened the protection for originator pharmaceutical companies under the re-examination system and was a long-held demand from originator pharmaceutical companies in Japan. In addition, the Japan Pharmaceutical Manufacturers Association, which is comprised of major originator pharmaceutical companies in Japan, announced on 14 March 2007 that it will seek a further extension making the study period for drugs with new active ingredients ten years, the longest period allowed under the PAA.

PATENT TERM EXTENSION

One of the important protections for originator pharmaceutical companies is a patent right for an original drug. In principle, the Minister will not approve any generic drugs as long as the patent right that covers the active ingredients of the original drug is valid. This is to avoid a situation where the original drug patentee makes a claim for an injunction against the generic drug manufacturer to cease the sale of the generic drugs, and the stable supply of the generic drugs cannot be maintained due to such dispute.

The duration of a patent is 20 years from the filing date of the patent application; however, a patentee in the field of pharmaceuticals must commonly wait for a considerable period of time to use its patented invention for business purposes, due to the requirement that pharmaceutical products must be approved by the governmental health authority (that is, an MA be received). In light of this erosion of the patent term, the PA has established the patent term extension system to compensate patentees (the originator pharmaceutical companies) for time lost while awaiting an MA.

If there is a period during which a patentee cannot use its patented invention for a drug product because it is waiting for the MA for the drug product, the duration of the patent right can be extended (*paragraph 2, Article 67, PA*). The extended term is based on the period in which the patentee was unable to use the patented invention, after the patent was granted, due to obtaining an MA.

Unlike in the US, multiple patent term extensions can be granted under the PA for one patent if two or more MAs have been granted for different indications of the drug covered by the patent. The maximum duration of each extended term is five years.

The effect of a patent term extension does not cover all of the patent rights. Only the use of the patented invention for the specific drug product that was the subject of the MA triggering the patent term extension is covered (*Article 68-2, PA*). That is, if the MA covers a specific usage of the drug product the patent term extension is limited to that specific usage.

When a patentee holds a patent right on a new chemical substance, and when an MA has been granted for a new drug that contains that substance as an active ingredient for a specific indication, a patent term extension can be registered for the patent. This extension covers only the use of this substance for this specific indication. Therefore, after the original expiration date (that is, 20 years after the filing date of the patent application), anyone can use the patented substance except for use for this specific indication.

If, however, another MA is granted for a second indication, a second patent term extension can also be registered for the patent right for the substance. The duration of the extension is based on the period for obtaining the additional MA. Therefore, the duration of the second extension can be longer than that of the first.

For example, if the duration of the first extension is two years and that of the second is four years, between the expiration date of the first (two years after the original expiration date) and the second (four years after the original expiration date), third parties can use the drug in relation to the first indication but not the second indication.

Recent changes

In principle, the Minister will not approve any generic drug when a patent right prevents the generic drug from being marketed.

When two patent term extensions of different lengths are registered for the same drug but for different usages, such partial approval of the generic drug can be problematic for the period when one is in force and the other is not. The relevant question is whether generic pharmaceutical companies can apply for and be granted an MA for a generic drug only for a specific indication when the patent right for the underlying substance is still valid in relation to a second indication due to a second extension.

If partial approvals (*mushi-kui sho-nin*) or partial applications (*mushi-kui shin-sei*) are allowed, generic pharmaceutical companies can market generic drugs containing a patented substance only for the first indication without infringing the extended patent right covering the use of the substance for the second indication.

Partial approvals can therefore be said to cause some inconsistency between the approved indications for the original drug and those of the generic drugs. Accordingly, the Pharmaceuticals and Medical Devices Agency of Japan, which conducts reviews of applications for MAs by working together with the MHLW, has not historically permitted partial approvals or partial applications on the grounds that generic drugs should be interchangeable with original drugs and should be the same as original drugs not only in terms of their active ingredients but also in relation to their indications. It follows that partial approvals or partial applications should not be allowed.

Consequently, if some of the indications of original drugs were protected by a patent term extension, a partial approval for the unprotected indications could not previously be granted. There was, however, an exception in that when the protected indications were subject to re-examination, a partial approval for the unprotected indications could be allowed.

The practice of not granting partial approvals was changed in 2009. Under Notification No. 0605014 of the Evaluation and Licensing Division in the Pharmaceutical and Food Safety Bureau dated 5 June 2009, partial approvals for indications not covered by a patent subject to a patent term extension became possible.

Accordingly, since 5 June 2009, generic pharmaceutical companies have been able to obtain partial approvals after the expiration of the patent term extension corresponding to the basis indications (that is, the indications which are the basis of the original MA) even though a patent term extension corresponding to an indication for which an additional MA granted is valid. The JGA calls these newly allowed partial applications "applications for basis indications" (*kihon kou-nou shinsei*).

As in the case of the protection based on the re-examination system, the permissibility of partial applications and partial approvals is also based on a notification by the MHLW, not legislation approved by the Diet of Japan. Accordingly, the practice concerning partial application and partial approvals can be amended or rescinded in the future by another notification of the MHLW without any resolution of the Diet.

SUMMARY

While the extension of the study period strengthened the protection for originator pharmaceutical companies, the permissibility of partial applications or partial approvals allows generic pharmaceutical companies to launch generic drug business earlier than was previously possible. Therefore, these important changes seem to conflict with government policy on the protection of the business of original drug manufacturers against generic drug manufacturers.

These two changes were both made by notifications of the MHLW and are not based on any amendment of any legislation approved by the Diet of Japan. As such notifications can be amended easily, compared with passing an amendment of legislation approved by the Diet, it is possible that the situation will change again in the future.

In light of these recent changes and the conflict between the policies regarding the promotion of generic drugs and the protection for originator pharmaceutical companies, it is important for pharmaceutical companies conducting or contemplating doing business in Japan to carefully monitor and follow future regulatory changes which will be made not only by the Diet but also by the MHLW in connection with the areas of pharmaceutical law and patent law in Japan.

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