

# WINDS FROM JAPAN

The Licensing Executives Society Japan

## Life Cycle Management of Drugs and Patent System in Japan

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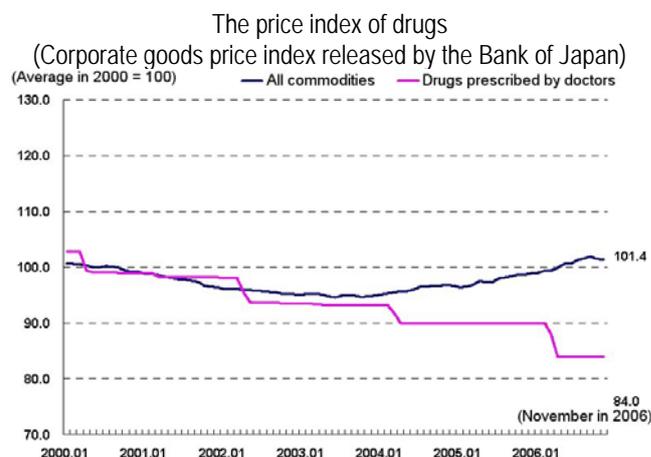
### 1. Japanese Pharmaceutical Market

The size of the Japanese pharmaceutical market was US\$56.7 billion in 2006, which accounted for about 9% of the global market (US\$643 billion), second only to the US market. On the other hand, though the size of the global market for drugs expanded to US\$601 billion in 2005, from US\$280 billion in 1995, the size of the Japanese market has changed little. Accordingly, the Japanese share of the global market has halved over the last ten years.

Japan provides a public medical insurance system, which is carried on as a social insurance system covering all citizens. Through this insurance system, about 30% of the nation's medical expenses are covered by public funds, and all prices for medicine, including medical compensation for doctors and prices for new drugs are substantially controlled by the Japanese government. Recently, because the nation's medical expenses are expected to increase along with the aging of Japanese society, policies for constraining the nation's medical expenses have been adopted, which have significantly affected Japan's pharmaceutical market.

The Japanese government determines prices reimbursed by public medical insurance for each of preparations and standards of all drugs prescribed by doctors. The reimbursement price of each drug is reviewed every two years and almost all reimbursement prices of drugs are

reduced, including those of new drugs immediately after their release onto the market. This system is called the "Drug Pricing System" and under the system, expenses for drugs covered by medical insurance are constrained and as a result, the size of the Japanese pharmaceutical market has been kept at a certain level in recent years. On the other hand, among major advanced nations, only Japan has a system in which the prices of new drugs immediately after their release onto the market are reduced through political action. The price index of drugs over the past several years has deviated from the general average price index and over the long term the trend has been downward.



(Reprinted from Future Vision of Pharmaceutical Industry, released by Office of Pharmaceutical Industry Research, 2007)

Despite such drug price constraint policies, it is a concern in Japan that public financing of medical insurance will worsen. As a countermeasure, the government is making an effort toward the promotion of generic drug use. The market share of generic drugs is 16.8% in Japan (on a volume basis, 2004), which is significantly lower than that in the United States (56% in 2005), Germany (41% in 2004), and the UK (49% in 2004). The government has adopted a policy of expanding the market share of generic drugs by revising the form of prescriptions issued by doctors in 2006 and 2008 and aims at increasing the market share of generic drugs to 30% on a volume basis by 2012.

There are often debates in terms of constraining the nation's medical expenses as relate to policies for the domestic drug market. On the other hand, pharmaceutical companies are of the opinion that under the present drug

pricing system, which determines the prices of new drugs without regard to market price, the value of innovation through research is not properly evaluated, and this obstructs the securing of adequate profits and resources for research and development to create an innovative new drug. The government has revealed its opinion in a report "New Vision for the Pharmaceutical Industry" released in 2007, which is available in English translation via the homepage of Ministry of Health, Labour and Welfare, that it is necessary to consider, in terms of promotion of the pharmaceutical industry, a mechanism in which pharmaceutical companies can enjoy returns corresponding to the risks of research and development and innovation during the patent term of new drugs in order to properly evaluate innovation through research. The report, at the same time, refers to importance of steadily implement replacement with generic drugs as a term of patents and reexamination period under the Pharmaceutical Affairs Law expire, in order to secure sustainability of public finances for medical insurance.

## 2. Life Cycle Management of Drugs

The life cycle of drugs can be recognized as having four stages: an introductory period; a growth period; a maturation period; and a declining period, similar to a general product life cycle. Drugs which hit the market after authorization by the government shift to a growth period, during which sales expand. After sales promotion activities during the introductory period and after passing the profitability point, they enter a maturation period in which they acquire profits to recoup research and development costs. Thereafter, due to the entry of generic drugs, they enter a declining period and sales decrease due to a drop in market share and price.

In the life cycle management of drugs, it is important to obtain maximum gross sales during the life cycle of the drugs. For that purpose, in addition to strategies for accelerating the start of sales during the introductory and growth periods, measures for delaying the entry of generic drugs and thereby delaying the advent of a declining period should be considered. Generic drugs are allowed to enter the market after the reexamination period has elapsed under the Pharmaceutical Affairs Law, and after expiry of the patent term covering the drugs. What is critical is how to extend the term of patent rights protecting drugs to delay the advent of a declining period as life cycle management.

Reexamination System under the Pharmaceutical Affairs Law and Patent Term Extension System, which are closely related to life cycle management of drugs, will be explained hereinafter.

## 3. Patent Term Extension System

A patent term may be extended up to five (5) years upon application for registration of an extension if the patented invention could not be worked for the necessity of obtaining an approval of a drug. In this regard, not only the term of drugs but also the patent terms of pesticides may be extended in Japan. However, medical equipment, food additives and artificial colors are not eligible for extensions.

The features of the term extension system of Japan are summarized below.

(1) Applicants are limited to patent owners. In addition, patent owners and exclusive licensees or registered

ordinary licensees must obtain approval for manufacturing under the Pharmaceutical Affairs Law.

(2) The period for application is prior to the expiry of the patent term of which an extension is applied and within three (3) months of the date of approval. In this regard, if it is not expected that approval for manufacturing under the Pharmaceutical Affairs Law can be obtained by the day previous to the date six months prior to the expiry of the patent term, application for registration of an extension may not be accepted after six months prior to an expiry of the patent term unless the prescribed form has been submitted by the day previous to the date six months prior to the said expiry.

(3) The term to be extended shall be the period during which the patented invention could not be worked, and it shall be the period from either the date of commencement of clinical tests or the date of registration of establishment of the patent right, whichever comes later, to the date of approval. It shall be calculated by year, month, and date, and may not exceed five (5) years.

If clinical tests were conducted overseas and then the drug was subsequently approved as a result of conducting of clinical tests or bridging tests in Japan, the date of commencing clinical tests overseas can be regarded as the date of commencing clinical tests.

Therefore, as there are cases where it is advantageous that patent rights should be obtained as early as possible for obtaining a longer extended term, for that purpose, it is recommended that expedited examination be requested. It generally takes two or three years from filing of a request for examination for a first office action to be issued, but if expedited examination is requested, it may take as little as three (3) months.

### (4) Subject of Registration of Extension

(4-1) Where there are multiple patents corresponding to one disposition, for any of the patent rights, registrations of term extensions may be approved individually. For example, if there are a patent for a chemical compound which is the active ingredient of an approved drug, a use patent for applying the active ingredient to an approved medical use and a process patent for the manufacturing process of the active ingredient, any of the said patent rights may be registered for extension individually. Further, a patent invention of formulations may be subject to registration of extension. As stated above, registration of extension is allowed under a broader scope in Japan than in the United States or Europe.

(4-2) If there are multiple dispositions corresponding to one patent right; for example, if multiple approvals different in efficacy and effect are given to a patent right for compounds which are the active ingredients of drugs, or multiple approvals are given to different compounds in a patent right which claims multiple compounds, multiple registrations of extension may be accepted based on these approvals.

(4-3) An application for patent term extension based on a later approval of a pharmaceutical with active ingredient and efficacy/effect both identical to those specified in another earlier approval (e.g., differing only in dosage form or manufacturing process) shall be refused.

Therefore, under current examination standards, where the approval under the Pharmaceutical Affairs Law has

already been obtained for a certain substance and usage, if the patent right is effected based on the dosage forms, etc., the said patent right is treated as not being eligible for registration of extension. Since new drugs are difficult to develop, pharmaceutical companies generally attempt to extend registration of a new patent of formulations. In the case where Takeda Pharmaceutical Company Limited requested extension of the formulation patent of Leuplin, an anticancer drug the invention of which is named "long sustained-release microcapsule," the Intellectual Property High Court upheld the decision which refused application for registrations of extension of the patent right based on the reasoning that it was not recognized that it was necessary to obtain the approval for manufacturing under the Pharmaceutical Affairs Law for practice of the patent invention in terms of the object (active ingredients) and usage (efficacy and effect). (Intellectual Property High Court (Administration Ke), No. 10311, 2006, judgment as of July 19, 2007)

(4-4) For an object which is actually the same as an object approved for drugs, if usage is equal to that which was already subject to disposition, application for registrations of extension shall be refused. For example, if there is a patent right in which a compound and its salts are claimed, and the drug, whose active ingredients are the sodium salt of the compound, has already been approved, the registrations of extension based on the approval of the drug, whose active ingredients are potassium salt of the compound and whose efficacy and effect is equal, is not accepted.

(4-5) Patent rights related to intermediates, or catalysts and manufacturing devices used for manufacturing of final product are not subject to extension.

(5) Validity of patent rights related to drugs whose term was extended covers only cases where a patent invention is practiced for the drugs subject to approval of manufacturing under the Pharmaceutical Affairs Law, and does not cover other cases.

For details of application for registrations of extension, please refer to the following website of the Patent Office in English.

[http://www.jpo.go.jp/cgi/linke.cgi?url=/tetuzuki\\_e/t\\_tokkyo\\_e/1312-002\\_e.htm](http://www.jpo.go.jp/cgi/linke.cgi?url=/tetuzuki_e/t_tokkyo_e/1312-002_e.htm)

Examination Guidelines for Patent and Utility Model in Japan

Part VI: PATENT TERM EXTENSION

#### 4. Reexamination System under the Pharmaceutical Affairs Law

Test data supporting efficacy and safety, which are required to be submitted to administrative authorities for application for approval of new drugs, are provided for in TRIPs as an intellectual property right (Article 39, paragraph 3). In the United States and the EU, to protect test data submitted by manufacturers of new drugs, such test data are not allowed to be used for examination of approval of generic drugs for a certain period of time after approval of the new drugs.

On the other hand, in Japan, the balance of interest between manufacturers of new drugs and generic drugs is actually regulated by the reexamination system under the Pharmaceutical Affairs Law, which inherently aims at reconfirming the efficacy and safety of drugs, not by a data protection system concerning intellectual property rights.

Under this system, a party whose new drugs have received approval is obliged to have the new drugs undergo reexamination after the elapse of a certain period of time from the start of commercial availability (Re-examination Period) to confirm the safety of the new drugs (Article 14-4 of the Pharmaceutical Affairs Law). On the other hand, application for approval of generic drugs is not allowed until the Reexamination Period elapses. Therefore, entry of generic drugs is blocked for a certain period of time, producing a result similar to that under the data protection system, and manufacturers of new drugs can secure a period for recovering development costs for new drugs.

Under the reexamination system in Japan, in addition to new drugs whose active ingredients are new, for pharmaceuticals whose active ingredients were already approved, if the administration route is new, dosage and formulation is new or efficacy is new, a Reexamination Period is granted.

Reexamination and Data Protection Period

Subject Drugs	Japan	U.S.A.	EU
New active ingredients	8 years (10 years for rare disease drugs, etc.)	5 years	8 years (+ two years reversed for marketing)
Formulation for new administration route	6 years	3 years	None
New dosage, new formulation	4 to 6 years	3 years	None
New efficacy	4 to 6 years	3 years	1 year (only the efficacy is treated as a benchmark)

Reexamination Period of drugs whose active ingredients are new had previously been six (6) years, in general, but the Reexamination Period of drugs whose active ingredients are new, which was approved after April 2007, was extended to eight (8) years in general on request for extension of a Reexamination Period from new drug manufacturers. As a result of two years extension of the period for generic drugs to enter the market after the approval of new drugs, it is expected that additional new drugs which are not protected by patents will be commercially profitable and able to be developed. In particular, it is expected that there will be an increase in introduction of new drugs which have not been sold in Japan as they are not protected by patents, although they are sold in the United States and Europe, and that such increase will contribute not only to the promotion of the pharmaceutical industry but also to enhancement of choices at the site of medical treatment.

Application for approval of manufacturing generic drugs is made after the elapse of the Reexamination Period, and the drug price is listed after the approval is obtained, and then sales will commence. Price listing of generic drugs was made annually, but it took nearly one year to commence sales of drugs depending on the timing of obtaining approval, which was regarded as a problem. To improve this problem, price listing of generic drugs twice a year has been in effect in July and November since 2007. In this regard, the timing of price listing of generic drugs will be changed to May and November in 2009.

#### 5. Patent Applications for Pharmaceutical Inventions

##### (1) Life cycle of drugs and pharmaceutical inventions

Research of a drug targeted on a specific disease usually commences by establishment of a screening system.

Thereafter, a leading compound is selected and various derivatives thereof are subjected to screening for optimization. In common practice, a compound having good pharmacological activities is obtained to proceed with the filing of a patent application covering them. In most cases, it is expected to take 10 to 18 years from the

commencement of research of a drug to the marketing launch after the approval for manufacturing is obtained, including the period of the above-described screening.



For example, if the marketing of a drug is launched 15 years after an initial patent application, only a period of five years remains during which a drug can be marketed exclusively based on the patent right. It is, therefore, difficult to secure sufficient profit and resources for research and development for continuing the development of desired new drugs. Under the Japanese patent law, an extension of the patent term up to five (5) years can be obtained as a countermeasure.

On the other hand, there is a case where a compound including a certain enantiomer, a pharmaceutically acceptable salt and a solvate such as a hydrate, which has superior properties as a pharmaceutical, is found in the scope of the claims of an initial application during the development period after the initial application. In such a case, a separate patent application should be filed for such a compound as a selective invention, if the invention has a remarkable effect. A patent right may be granted even where it is filed after disclosure of the initial application. A patent right having a late filing date also has a late patent expiration date, which may contribute to a substantial extension of the term during which a drug can be exclusively marketed. Similarly, evaluation should be made for possible patent applications for respective inventions covering a new medicinal use of a development compound, a process for preparation, a crystal form, a combination use with other drugs, and a special formulation. Under the Japanese patent practice, each patent covering a drug for which approval for manufacturing is newly obtained may be subject to registration of a patent term extension of up to five (5) years (refer to “3. Patent Term Extension System” stated hereinbefore).

It is difficult to obtain patents for these pharmaceutical applications as the filing date is delayed, because the number of relevant prior art documents increases. It is preferable to file an application before issuance of the publication of the first application in view of patentability of the later application.

## (2) Medicinal use invention

There is a case where a new indication, a specific administration method and a remarkable effect resulting from a combination with other drugs may be found in clinical trials of a development drug. In such a case, a patent application may be filed to cover a medicinal use invention resulting from the above findings. According to the Examination Guidelines for Patent and Utility Model in Japan issued by the Japanese Patent Office (referred to as “Examination Guideline” hereinafter), there is provided a paragraph for medicinal inventions as examination

guidelines for specific technical fields, an English translation of which is available at the website of the JPO: ([http://www.jpo.go.jp/tetuzuki\\_e/t\\_tokkyo\\_e/1312-002\\_e.htm](http://www.jpo.go.jp/tetuzuki_e/t_tokkyo_e/1312-002_e.htm); Part IV, Chapter 3: Medicinal Invention). The Japanese patent practice related to medicinal use inventions will be described below.

### a. Claim drafting for medicinal use invention

The Japanese Patent Office does not grant any patent for an invention regarding “a method of surgical operation for humans, treatment and diagnosis” because it is regarded as an invention of medical activities which are not industrially applicable (the principal clause of Article 29, Paragraph 1 of the Japanese patent law), and this patent practice has been supported by judicial precedent (Case of claiming the revocation of appeal decision No. 65, Administration Ke, 2000). On the other hand, an invention of product such as a pharmaceutical composition, which is to be administered to humans, is recognized as an industrially applicable invention. Medicinal inventions specified by a combination of two or more drugs or a method of treatment such as a dose interval and dosage are also handled similarly, as long as they are “inventions of products.” For example, the following claim drafted in a format of “method for treatment” which is admissible under U.S. patent practice may be handled as an industrially applicable invention if it is rewritten as a pharmaceutical composition (invention of product).

[Medical treatment claim]

**A method for treatment of hepatitis C in a patient having  $\alpha$ -type genotype, comprising administering compound A to the patient at an initial dose of 5.0mg/kg to 10.0mg/kg, followed by a dose of 0.3mg/kg to 0.5mg/kg on alternate days.**

[Pharmaceutical composition claim]

**A pharmaceutical composition comprising compound A as an active ingredient for treatment of hepatitis C in a patient having  $\alpha$ -type genotype, which is administered to provide the patient with compound A at an initial dose of 5.0mg/kg to 10.0mg/kg, followed by a dose of 0.3mg/kg to 0.5mg/kg on alternate days.**

In addition to such a pharmaceutical composition claim, a claim reciting an agent or a kit as a subject matter is generally accepted as a format of drafting a medicinal invention. One example is shown below.

**An agent for treating or preventing disease Z, comprising compound X as an active ingredient.**

**A kit for treating disease Z, comprising compound X in a dosage form for oral administration; and compound Y in a dosage form for injection.**

On the other hand, regarding a claim drafted in a format of “compound for a specific use,” the Examination Guidelines in Japan state that the phrase “for a specific use” shall not be interpreted as definition of an invention (Chapter 2, Section 1. 5. 2 (2)). For example, regarding the following claim in which a compound X is a known compound: “A compound X for use as a medicament in the treatment of disease Z” under the current examination practice in Europe, the format of the claim can be used for reciting a second medicinal use invention of a known compound. However, under Japanese examination practice, it is interpreted as a compound without restriction of use.

A claim intended for “use of compounds in the preparation of medicament” (a so-called Swiss-type claim; “e.g. A use of compound X in preparation of a medicament for treating disease Z”) is interpreted as “an invention of use method” and as “an industrially applicable invention” under Japanese patent practice. Many applications including a Swiss-type claim are patented. On the other hand, some examiners in Japan have stated that a claim drafted in such a format is not sufficiently clear. Further, so far there has been found no example of any actual enforcement of a Swiss-type claim. Therefore, it is considered that a patent application covering the second medicinal use should include at least one claim reciting “invention of product” such as a pharmaceutical composition, in view of stability of patent right.

#### b. Disclosure of pharmacological test results in specification

As an enablement requirement of a medicinal use invention under the Japanese patent practice (Article 36, Paragraph 4, item No.1 of the Japanese patent law), it is required to disclose, in an original specification, pharmacological test results which support a medicinal use as one or more representative examples (Examination Guidelines, Chapter 3, Section 1. 2. 1). According to the Examination Guidelines, as pharmacological test results, the specification shall disclose the following matters: (i) a specific compound used in the test, (ii) full explanation of a pharmacological test system used in the test, (iii) the test results specifically shown in terms of values or the like, and (iv) the relationship clarified between a medicinal use to be claimed and the pharmacological test system used. The Examination Guidelines also state that when the subject specification fails to disclose any pharmacological test results, rejection for failure to meet enablement requirement will not be overcome even if pharmacological test results are submitted after application. The Japanese Patent Office has applied the Examination Guidelines strictly to the enablement requirement, thereby making the requirement more strict than that of the US and EP.

[Judicial precedent 1]

The case of claiming the revocation of appeal decision No. 10312, Administration Ke, 2005 (plaintiff: Astellas Pharma Inc., defendant: Commissioner of the Japanese Patent Office)

The claim in Japanese Patent Application No. H08-532341 (corresponding to PCT application: WO96/33715) recites as follows:

**An agent for preventing and/or treating dialysis-induced hypotension and/or hypotension after dialysis, which comprises 1-[3-(2-phenyl-pyrazolo [1,5-**

**a]pyridin-3-yl)acryloyl]-2-(carboxymethyl) piperidine or a salt thereof as an active ingredient.**

An appeal decision was issued by the JPO, rejecting the application on the grounds that the subject specification did not meet the enablement requirement. In the case for seeking revocation of the decision, the judge supports the original decision and states as follows:

“The subject specification describes, in addition to the compound recited in the claim, that the compound is an active ingredient of a therapeutic agent for the disease recited in the claim. Further the specification discloses to some extent an effective amount, an administration route and formulation of the therapeutic agent. However, it is clear that there is neither pharmacological data supporting the usability of the compound as the therapeutic agent for treating the disease recited in the claims nor any description equivalent to such pharmacological data. The subject specification merely describes, to some extent, an effective amount, the administration route and formulation of the therapeutic agent. However, such descriptions are not sufficient for a person skilled in the art to understand whether or not the agent is actually effective in the use claimed. This is also the same as the judgment made for the original appeal decision.”

Incidentally, the EP application and the US application corresponding to the application concerned have each been granted a patent for broader claims (refer to EP 0823254B1 and US 6232324B).

Further, where there is no description of pharmacological test results in the specification, rejection for failure to meet support requirement (Article 36, Paragraph 6, item No.1 of the Japanese patent law) may also be notified. Still further, to argue the inventive step of a medical use invention (Article 29, Paragraph 2 of the Japanese patent law), significant effects provided by the subject invention are often asserted on the basis of pharmacological test results disclosed in the specification. Under the current Japanese practice, it is preferable that the maximum possible pharmacological test results are disclosed in the initial specification.

[Judicial precedent 2]

The case of claiming the revocation of trial decision No. 10459, Administration Ke, 2005 (participant: Zepharmia Inc., defendant: Commissioner of the Japanese Patent Office)

Regarding Japanese Patent No. 3264301, the patentee demanded a trial for correction to introduce the following amended claim:

**A pharmaceutical formulation for nasal drops, which comprises sodium cromoglycate (1%), chlorpheniramine maleate (0.25%) and naphazoline hydrochloride (0.025%).**

However, the trial decision was issued by the Japanese Patent Office to dismiss the demand for correction on the grounds that the invention recited in the amended claim lacks inventive step. In the lawsuit for revocation of the trial decision, the patentee asserted the significant effects of the invention (peak effects) in addition to difficulty in reaching the combination of the ingredients. In this regard, this judgment points out that the subject specification includes clinical test results of patients with allergic rhinitis but does not include a specific protocol of the clinical test, specific data supporting individual improvements in various symptoms of allergic rhinitis and

the specificity of the claimed concentration of the ingredients; and concludes that “neither the peak effect provided by the invention of the amended claim nor remarkable improvements in nine symptoms asserted by the participant cannot be confirmed specifically by referring to a description in the subject specification.” Consequently, the court dismissed the demand of the participant.

[Judicial precedent 3]

The case of claiming the revocation of appeal decision No. 10389, Administration Ke, 2005 (plaintiff: Kowa Company Ltd., defendant: Commissioner of the Japanese Patent Office)

The Japanese Patent Office made an appeal decision rejecting Japanese Patent Application No. H10-341452 on the ground of lack of inventive step. The application claims the following invention:

**An antipyretic antiphlogistic analgetic agent comprising ethenzamide and tranexamic acid.**

In the case for seeking revocation of the appeal decision, the judge stated, by referring to a citation, that “at the subject filing date, a use of an antipyretic antiphlogistic analgetic agent in combination with tranexamic acid was considered as providing a synergistic effect and as a combination for improving a therapeutic effect. To assert a remarkably significant effect in judging the patentability of the subject invention, it is not sufficient to indicate simply a synergistic effect. However, it is necessary to indicate an inherent effect, which cannot be obtained in combination with a salicylate-related anti-inflammatory agent that is an antipyretic antiphlogistic analgetic agent other than ethenzamide”, and recognized that “the subject specification does not include grounds necessary for assessing the claimed combination, and as a result, no remarkably significant effect can be recognized in the subject invention.”

Further, the plaintiff submitted additional test data showing that no enhanced antiphlogistic effect is found in combination of tranexamic acid with other antipyretic antiphlogistic analgetic agents such as acetaminophen, and argued that the enhanced antiphlogistic effect obtained only in combination of ethenzamide with tranexamic acid should be recognized as a remarkably significant effect. In response to this argument, the judge stated that “the subject specification does not include a description suggesting that the use of ethenzamide provides such a significant effect as compared with the use of a salicylate-related antiphlogistic agent other than ethenzamide and, therefore, the assertion of the plaintiff is not based on the description in the subject specification”, and consequently supported the appeal decision originally made by the JPO.

(3) Selective invention relating to pharmaceuticals

There is a case where after an application is filed for covering the resulting compounds of screening in a first phase of drug development, favorable pharmacological properties are found in a compound which falls within a scope of the claims but is not specifically disclosed in the specification of the application. There is also a case where favorable properties are found in a novel crystal form of a development candidate compound. Such a compound and a crystal form having excellent properties may be granted a patent as a selective invention.

Under the pharmaceutical legislation of the EU, even where a formulation contains a derivative (salt, ester, isomer and the like different from an active ingredient of an original drug) of an active ingredient of the original drug, the derivative is considered as the same active ingredient as long as no significant difference is found in safety and efficacy. Therefore, the formulation is approved as a generic drug.

On the other hand, for a generic drug to be granted approval for manufacturing under Japanese practice, it must contain the same active ingredient as that of an original drug. For example, if active ingredients of an approved original drug are a specific salt, an ester and a hydrate, the generic drug is also required to contain a salt, an ester and a hydrate, which are chemically identical to those of the original drug. Therefore, in Japan, there is a case where a patent right on a specific salt and a hydrate of an active compound may play an important role in life cycle management of a drug in which they are contained as an active ingredient.

However, where an application covering a selective invention is filed after publication of related applications, it is usually required during examination to indicate a remarkably excellent effect of the subject invention, as compared with the inventions disclosed in the related prior applications. This point must be taken into account in preparing the specification of the application.

Further, there are cases that a patent has been granted to a specific optical isomer, even if a racemic form is publicly known. On the other hand, there is a judicial precedent stating that each of the optical isomers is substantially disclosed due to the fact that a racemic form has been disclosed (Case of claiming the revocation of appeal decision No. 8, Administration Ke, Tokyo High Court, 1991). Where a patent application is filed for a selective invention relating to a specific optical isomer, it is preferable to include a medicinal use claim in the application, for example: “A pharmaceutical composition for treating disease X, which comprises R-enantiomer of compound X at enantiomeric excess of 80% or more.”

[Judicial precedent 4]

The case of claiming the revocation of appeal decision No. 62, Administration Ke, 2003 (plaintiff: Aventis Pharma Societe Anonyme, defendant: Commissioner of the Japanese Patent Office)

This is a case for seeking revocation of an appeal decision by the JPO rejecting Japanese Patent Application No. H04-504006, (corresponding to WO 92/12980), which claims the following invention:

**A pharmaceutical composition for improving quality and/or length of sleep, which comprises a dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperadiny)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrolo[3,4-b]pyrazine or a pharmaceutically acceptable salt thereof in combination with one or more pharmaceutically acceptable diluents or adjuvants.**

In the judgment, the judge stated as follows: “the plaintiff has asserted a remarkably significant pharmacological effect of the subject invention on the ground that one of the optical isomers (dextrorotatory isomer) claimed as the subject invention has an activity more than twice higher than that of a racemic form, and such a high activity of the subject invention is beyond expectation of a person skilled in the art. However, such

a value of activity of twice corresponds to a value obtained in a case that one of the optical isomers is active, while the other is inactive (no activity). It has been previously stated that a chemical compound having optical isomers is diverse in exhibiting pharmacological activities. Exhibit B-2 points out that there is a case where one of the optical isomers may act as an antagonist on pharmacological activities of the other isomer, and Exhibit B-1 also describes that “one of the isomers not only fails in exhibiting any activity but also gives competitive inhibition to an effective enantiomer, thus resulting in a drastic decrease in bioactivity of the racemic body to 1/2 or less as compared with an active enantiomer, and this situation has often been experienced in the research and development of pharmaceuticals,” suggesting a possibility that one of the optical isomers may have an activity more than twice higher than that of the racemic form. With these facts taken into account, such an effect asserted by the plaintiff for the subject invention that a dextrorotatory isomer of zopiclone has a sleeping activity more than twice higher than that of the racemic form should be recognized as one embodiment of differences in pharmacological activity among optical isomers, and therefore the effect cannot be considered as a remarkable effect beyond expectation of a person skilled in the art.” Consequently the judge denied an inventive step of the subject invention.

[Judicial precedent 5]

The case of claiming the revocation of appeal decision No. 10271, Administration Ke, 2006 (plaintiff: Merck & Company Incorporated, defendant: Commissioner of the Japanese Patent Office

This is a case for seeking revocation of an appeal decision by the JPO, rejecting the Japanese Patent Application No. H11-507368 (corresponding to WO99/01444), which claims the following invention:

**A polymorphic form of the compound 2-(R)-(1-(R)-3,5-bis(trifluoromethyl)phenoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine designated Form I, essentially characterized by an X-ray powder diffraction pattern with key reflections as 12.0, 15.3, 16.6, 17.0, 17.6, 19.4, 20.0, 21.9, 23.6, 23.8, and 24.8° (2 theta).**

The plaintiff estimates, based on the difference in solubility between these crystals, that the crystal of the subject invention (I-type crystal) is more stable than a known crystal (II-type crystal) by 0.2Kcal/mol, and asserts that “since there is found the above difference in stability, it is clear for a person skilled in the art that a significant improvement is obtained in various respects such as the homogeneity of a pharmaceutical formulation, the bioavailability and the stability.” In response to the assertion, the judge stated that “there is not sufficient evidence indicating that the difference in the free energy will directly provide practical superiority of the I-type crystal in stability (e.g. stability in storage at room temperature), compared with the II-type crystal. Therefore, the thermodynamic stability of the subject invention is not approved as a significant effect which is beyond expectation,” and denied an inventive step of the subject invention.

## 6. Lawsuit for Injunction against Generic Drugs

(1) Procedures of application for approval of generic drugs and patents

An application for approval of generic drugs must be submitted to the regulatory authority (Ministry of Health, Labor and Welfare) after termination of the re-examination period of an original drug (refer to “4. Reexamination System under the Pharmaceutical Affairs Law” stated hereinbefore), and the authority confirms during examination that there is neither substance patent nor pharmaceutical use patent, which impede production of the generic drug. Where an application for approval of a first generic drug is filed, it is required to attach information on a substance patent (and use patent) of an active ingredient of the original drug. On the other hand, an original drug company can submit in advance information on patents for their original drugs to the regulatory authority. The submitted information shall not be disclosed to any third party. The regulatory authority confirms that there is no patent, which became a problem for producing the generic drug, on the basis of the submitted information, before issuance of approval. On the other hand, the authority announces that they only make a decision on the patent matter when such a decision can be clearly made. Namely, the examination is made mainly for a substance patent, while it is made for a use patent only when a clear judgment can be made.

In a judicial decision made by the Supreme Court in 1999 (the judicial decision made at the second petty bench of the Supreme Court on April 16, 1999), an act of conducting various tests necessary for an application for approval for a generic drug during the term of a patent right held by an original drug company is recognized to fall within “implementation of a patented invention for test or research” as stipulated in Article 69, Paragraph 1 of the Japanese patent law, and the judgment stipulates that no effect of patent right is enforceable.

(2) Case of lawsuit for injunction against generic drugs

When there is a patent which will pose problems in examining approval for a generic drug, a manufacturer of generic drugs has to invalidate the patent, by demanding a invalidation trial before the Japanese Patent Office prior to the examination of approval. On the other hand, the regulatory authority will not evaluate all patent rights held by a manufacturer of original drugs. Thus, a case may arise where a generic drug may be approved despite the fact that the generic drug infringes a patent right owned by an original drug company. For the original drug company one course of action would be to file a lawsuit seeking injunction against marketing of the approved generic drugs.

[Judicial precedent 6]

The case of seeking the injunction against patent right infringement No. 19162, Wa, 2005 (plaintiff: Astellas Pharma Inc., defendant: Taiyo Pharmaceutical Co., Ltd.)

Injunction against the manufacture and marketing of a product of the defendant was demanded on the ground of infringement of the patent right of the plaintiff (Japanese Patent No. 1943842, Japanese Patent Application No. S63-202527). The product of the defendant is a generic drug manufactured and marketed by the defendant, which contains cefdinir as an active ingredient. Claim 1 of the subject patent covering a crystal of cefdinir reads as follows:

**A crystal of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamide]-3-vinyl-3-cephem-4-carboxylic acid (syn-isomer), characterized by an X-ray powder**

**diffraction pattern with peaks near the following diffraction angles: 14.7, 17.8, 21.5, 22.0, 23.4, 24.5 and 28.1°.** (Hereinafter, the crystal of the invention concerned is referred to as “A-type crystal”).

The plaintiff obtained the pharmaceutical formulation of the defendant, conducted X-ray powder diffraction, confirmed that the active ingredient of the pharmaceutical formulation of the defendant exhibited peaks at diffraction angles recited in claim 1, and submitted the results as evidence.

The defendant asserted that the crystal disclosed in Example 16 of the prior art document (Japanese Patent Domestic disclosure No. S59-89689) is the A-type crystal, by showing experimental results that an X-ray powder diffraction pattern of the crystal obtained by their follow-up experiments in accordance with the method described in the document coincides with that of the A-type crystal. Further the defendant asserts that the subject patent lacks novelty and should be invalidated.

The plaintiff asserted that since a solid obtained in Example 16 of the prior art document is significantly different in IR spectrum indicated in the document from that of the claimed crystal, the solid is not the crystal of the patented invention. Further, the plaintiff pointed out that in the experiments conducted by the defendant, the deposit of a target substance occurred in a step of concentrating a solution prior to a step of crystallization by pH adjustment, and asserted that such procedures are not reasonable and the experiment conducted by the defendant does not exactly correspond to the method disclosed in Example 16 of the prior art. In addition, the plaintiff conducted separately their own experiments in line with Example 16 and submitted results of a follow-up experiment indicating that no A-type crystal is obtained.

First, the judge admitted that the pharmaceutical formulation of the defendant belongs to the scope of the subject patent.

Regarding the defendant’s assertion of invalidation of the patent, first of all, the judge stated that the solid described in the prior art document is not the A-type crystal, since its IR spectrum is different.

Further, the judge indicated criteria for the decision:

“an invention disclosed in a publication distributed in Japan or abroad or an invention made publicly available through electric communication lines before a patent application is not patented (Article 29, Paragraph 1, Item No. 3 of the Japanese patent law). However, “the invention disclosed in a publication” includes not only an invention, the content of which is described in the publication but also an invention which can be induced from matters described in the publication, in light of common technical knowledge at the time of filing of the application. Therefore, an invention, the content (technical idea) of which could be easily implemented by a person who has ordinary knowledge in a technical field to which an invention belongs (a person skilled in the art) on the basis of the content described in the publication and common technical knowledge at the time of filing of the application, cannot be patented.”

Regarding the result of the follow-up experiments submitted by the defendant, the judge stated that such an experimental step that a target compound starts to deposit in mid-process of concentration cannot be regarded as a follow-up experiment conducted exactly in line with the description in Example 16 of the cited publication, and further stated “it is not considered that a method of manufacturing the A-type crystal of Cefdinir is disclosed to such an extent that a person skilled in the art could easily implement the method.” and recognized that no reason is found for the invalidation of the patent concerned asserted by the defendant.

In conclusion, the court ruled in favor of an injunction against the manufacture and marketing of the product of the defendant. The conclusion of this judgment was also backed by the appeal court (case of appeal for seeking the injunction against patent right infringement No. 10034, Ne, 2007).

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## **An informative joint meeting was held in Tokyo by Life Sciences Sector Members of LES USA/Canada and LES Japan**

**By Ichiro NAKATOMI\***



Major benefits of LES membership include personal and professional growth that come from interacting, networking and learning from each other about licensing. An excellent example of that happened in a January meeting, in Tokyo, by Life Sciences Sector members from LES USA/Canada and LES Japan. The event was an “opportunistic” meeting that took place following the BIOAsia conference. It allowed members of the LES Japan Healthcare Working Group to have a first-hand review and discussion of the landmark LES USA/Canada “BioPharmaceutical Royalty Rate and Deal Terms Survey”



Last summer, Mr. Chikao Fukuda, the past-President of LESI, led a tour of delegates from LES USA/Canada to conduct a series of business development and licensing seminars in Argentina, Brazil and Chile. One segment of the seminars was a presentation of the “BioPharmaceutical Royalty Rate and Deal Terms Survey”. It was during this tour that Chikao met Mr. Jim McCarthy, who served as the survey chairperson and led the development and execution of this landmark LES USA/Canada survey. Jim is Senior Vice-President, Corporate Development for EGEN, Inc, a biotechnology company in the U.S., specialized in nucleic acid delivery and therapeutics. Jim has been a long term LES member of USA/Canada and has thirty years of life

sciences professional experiences, which include corporate business development and licensing roles doing projects and deals in over 30 countries. When he visited Tokyo for BIOAsia, a travel change put him in Tokyo for an extra day and he kindly offered to share with the LES Japan Healthcare Working Group the current survey results. I got his proposal through Chikao Fukuda on January 15, 2009, and immediately announced to our Healthcare Working Group members that a meeting and presentation would be held in my office at NanoCarrier on January 22. As we all know, licensing professionals know how to organize a team quickly and make good things happen!

In spite of a short notice, approximately one third of group members responded to attend the meeting. In fact ten members from LES Japan and four members from LES USA/Canada jointly attended. Our LES Japan healthcare members are composed by mainly business people working on licensing deals related to Pharmaceutical and Biotech companies and University. I should not forget that Mr. Leslie Pryce, living in Nagoya and serving as a consultant of pharmaceutical deals, also came to visit the meeting by an invitation from Jim at the BIOAsia conference.

The goal of the survey was to provide LES member with current data from deals in the past three years that is not available from other sources. It was a survey by LES members, for the benefit of LES members. An important point for LES members is that the names of companies that participate and the products involved are kept confidential. The survey data provided by Jim was summarized, as follows.

1. Total 155 biopharmaceutical deals from Academic, Biotech and Pharma, comprised of recent deals completed in 2005–2007.
2. Fixed royalties are more occasional than Tiered Royalty for early stage deals.
3. In preclinical deals, more than 80% of fixed royalty rate deals had a fixed royalty rate of less than 5%.
4. Tiered royalty rate deals generally had a higher royalty rate: ~5% royalty rate in preclinical deals, ~7% in pre POC deals and a ~14% rate in post POC deals.
5. Higher milestone payments were observed in tiered royalty rate deals.
6. NPV was computed in only 19% of total deals etc.

The complete survey and data are available only to LES members and is available on the LESI web-site (see <http://www.lesi.org/>).

There was a reception party after the meeting, and we got together to discuss many topics about licensing and doing deals in our industry today. Jim described the event as “a wonderful joint meeting of LES USA/Canada and LES Japan, on behalf of LES International, that was an example of the global nature of our business and how we came together as licensing professional with much in common”. He announced that LES USA/Canada Life Sciences Sector is working with the LESI Life Sciences Sector to conduct the next survey on a global basis in the 4<sup>th</sup> quarter of 2009 with the survey results published for LES members in 2010. The goal is to get the participation of all LES societies and have a landmark global biopharmaceutical royalty rate survey that has not been before. Such a survey could only be done by a group of professionals like LES.” Currently, a global LES survey committee, led by Jim, is planning the next survey. The committee is seeking members from other countries and a special invitation was provided to LES Japan members to help recruit and encourage LES Japan member to participate when the survey is launched later this year.

LES Japan appreciated Jim reaching out to LES Japan members to share the information that made the event possible. I would like to continue many more such joint meeting for LES Japan in the future. I also thank all the LES Japan members who changed their schedules on such a short notice and came to the meeting. Lastly, Leslie Pryce was so impressed and excited by this group, that he had become a member of LES Japan. Adding new members is always an excellent result.

The best way to summarize the meeting is that it was an example of “LES in action” and the benefits LES provides to members with professional information, networking and many new friends.

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*\*President and CEO, Ph.D., NanoCarrier Co. Ltd.*

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## IP News from Japan

**By Shoichi OKUYAMA \***

### Copyright Law to be Amended

A bill to amend the Copyright Law of Japan was introduced in the current Diet session after the Cabinet approved the bill on March 10, 2009. The bill covers three major areas: (1) use of copyrighted materials on the Internet, (2) prevention of unlawful dissemination of copyrighted materials, and (3) improved access to information for the visually or mentally impaired. With regard to item (1), for example, information search service providers will be allowed to make copies without authorization of copyright holders, and caching for efficient transmission will be exempted from copyright

infringement. Also, secondary use on the Internet of old broadcast programs is allowed under certain conditions even if it is not possible to locate the copyright holder. The National Diet Library will be allowed to make electronic copies of documents it has. Furthermore, in connection with item (2), the act of downloading a digital music or image file knowing that the file has been made available illegally will be prohibited even if it is done for private use only, although no criminal penalty will be provided. The personal copying of copyrighted materials by an individual is allowed for private or home use under Article 30 of the Copyright Act. Unauthorized uploading of copyrighted materials has already been prohibited. For item (3), exceptions to copyright infringement will be

expanded to provide the visually or mentally impaired with better access to information. The bill is expected to become law soon.

Many of these changes are clearly too late. Since Japan does not adopt the American-style "fair use" approach, each exception to copyright infringement has to be prescribed in the statutes. This turned out to be a deterring factor for IT business such as search engines in Japan because legislation always lags technological or business developments. Pros and cons of the fair use doctrine have been discussed in Japan, but it may be a Pandora's Box for Japan, where legal certainty is valued.

#### **Tokyo District Court Orders Injunction on "Magicon"**

Fifty five Japanese companies including Nintendo sued five China-related companies including Kanenka Kabushiki Kaisha in order to stop sales and importation of what is commonly known as "Magicon" (for magic control), which makes it possible to run bootleg game software on Nintendo's game machines "DS" and "DS Lite," for violation of Article 2(1)(x) of the Unfair Competition Prevention Act. Item (x) of this Article, which was added when the law was amended in 1999, defines sale or importation of a device or a computer program that interferes with access-control or copy-protection functions of software or other audio-visual products as an act of unfair competition. The Plaintiffs did not seek any damages. The product the Defendants sold was called "R4 Revolution for DS" and made it possible for a user to run game software copied from authentic software sold by the Plaintiffs. The authentic software includes specific signals that interact with the

software stored in the "DS" and "DS Lite" machines so as to allow authentic software to run on the machine and not its copied versions. According to news reports, the damages the Plaintiffs suffered amounted to the equivalent of several billion US dollars. The Tokyo District Court, on February 27, 2009, issued an injunction blocking the sale and importation of the Defendant's products and also ordered the destruction of the products.

#### **The Japanese Patent Law Will Be Entirely Rewritten**

The Commissioner of the Japan Patent Office, Mr. Takashi Suzuki, who took the post in July 2008, has decided that the entire Japanese Patent Law should be rewritten in about three years. This year marks the fiftieth anniversary of the current Japanese Patent Law, and numerous amendments have made the Patent Law an ugly and complicated patchwork. The Commissioner has set up a "Study Group on the Patent System" to study general outlines of the new Patent Law. This Group has one IP High Court judge, six professors, four corporate managers, two attorneys-at-law (one of whom is a former IP High Court judge), one U.S. attorney-at-law (former JPO examiner), and one patent attorney. The first meeting was held on January 26, 2009 and ten to twelve meetings will be held over the next twelve months or so. This writer is a member of the Study Group.

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*\*Editor, WINDS from Japan  
Patent Attorney, Ph.D., Okuyama & Co.*

## **Editors' Note**

We trust that the articles included in this issue will prove useful in providing you with up-to-date information on a variety of IP issues in Japan. For your information, 2009 Annual Meeting of the LES Japan will be held at Kyoto Kokusai Hotel in Kyoto on July 3 and 4, 2009. Please visit the web site at:

[http://www.lesj.org/contents/english/06\\_1meet.html](http://www.lesj.org/contents/english/06_1meet.html)  
for detailed information on registration of a meeting and accommodation.

If you would like to refer to any back issues of our newsletter, they can be accessed via the URL as follows:

<http://www.lesj.org>

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### **WINDS from Japan Editorial Board Members, 2009**

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