Trilateral Comparative Study of Functional Definitions for Medical Compounds－Study of patentability and validity of medical use claims defining effective ingredients by function*

The Second Subcommittee, Biotechnology Committee

(Abstract)

Three years have passed since the publication of a report of trilateral comparative study on reach-through claims. During these three years, many examination decisions were made with regard to reach-through claims. In this connection, we conducted a comparative study on how claims for function-defined medical uses have been examined since then and discovered that the judgment on patentability differs greatly between an application claiming a publicly-known target or an active ingredient that is partially well-known or publicly-known and an application claiming both new target and function-defined medical use at the same time.

(Contents)

1. Introduction
2. Examination guidelines of Japan, the United States, and Europe and the trilateral project B3b
   2.1 Examination guidelines of Japan, the United States, and Europe
   2.2 Trilateral Project B3b
3. Example cases of examination of claims defining medical compounds by function
   3.1 Method of the study
   3.2 Findings of the study
   3.3 Example cases where a patent was granted in Japan, the United States, or Europe
   3.4 Example cases where a patent application was rejected in Japan, the United States, or Europe
4. Judgments on the patentability of the claims defining medical compounds by function
   4.1 Precedents in Japan
   4.2 Precedents in the United States
   4.3 Precedents in Europe
5. Observation
6. Conclusion

1. Introduction

In November 2001, the patent offices of Japan, the United States, and Europe adopted a comparative study report (hereinafter referred to as "trilateral comparative study report") on the patentability of "reach-through" claims (claims for an invention that may be made in the future based on the invention currently disclosed). Reach-through claims are a type of medical use claims defining active ingredients by function (hereinafter referred to as "function-defined medical use claims"). Since the publication of a trilateral comparative study report, three years have passed. During these three years, many examination decisions were made with regard to function-defined medical use claims. We decided to conduct a trilateral comparative study on how the function-defined medical use claims have been examined since the publication of the trilateral comparative study report.

The members of the Second Subcommittee, Biotechnology Committee 2004 who took part in this study were as follows: Shizuo AO (Chairperson of the Subcommittee, Banyu Pharmaceutical Co., Ltd.), Emiko YANO (Vice-

* "*CHIZAI KANRI*" (Intellectual Property Management), Vol. 56, No.1, pp. 95-114 (2006)

chairperson, Yamanouchi Pharmaceutical Co., Ltd.), Tsutomu UCHIYAMA (Eisai Co., Ltd.), Kazuo OKUBO (Asahi Glass Co., Ltd.), Kaori SHIMA (Ajinomoto Co., Inc.), Hideki TAKEDA (Fujisawa Pharmaceutical Co., Ltd.), Mikio TOMISHIMA (Mitsubishi Chemical Corporation), and Amane TOMOMOTO (TANABE SEIYAKU Co., Ltd.).

2. Examination guidelines of Japan, the United States, and Europe and the trilateral project B3b

2.1 Examination guidelines of Japan, the United States, and Europe

The Japanese Patent Act has three provisions regarding function-defined medical use claims as follows: Section 36(4) (Enablement Requirement), Section 36(6)(i) (Support requirement), and Section 36(6)(ii) (Claim Clarity). These claims are explained with examples in the section entitled "Description Requirements of the Specification and Claims" in the Japanese patent examination guidelines.

In Europe, the European Patent Convention (hereinafter referred to as "EPC") has two provisions related to function-defined medical use claims as follows: Article 83 (Enablement Requirement) and Article 84 (Support Requirement and Claim Clarity). While the European examination guideline do not present any specific examples about functional claims, Paragraph 107[1)] of the Examination Guidelines for Patent Applications relating to Medical Inventions in UK that corresponds to the EPC points out that support must be considered for the claims functionally defining an invention of the second medical use of a group of compounds.

In the United States, 35USC§112 ¶1 (hereinafter referred to as §112, ¶1: Enablement requirement and support requirement: written description requirement) and 112 ¶2 (hereinafter referred to as §112, ¶1: Claim definiteness) specify function-defined medical use claims. As the scope of functional claims tends to be wide, functional claims are required to comply with written description requirement[2)], quite strict these days, in order to be permitted.

Table 1 Related provisions in Japan, the United States, and Europe

	JP	EP	US
Enablement requirement (Sufficiently clear and complete)	Section 36(4)*	EPC Article 83	35USC §112¶1
Support requirement	Section 36(6)(i)**	EPC Article 84	
Claim Clarity	Section 36(6)(ii)***		35USC §112¶2

* Revised in 1994 from "state the purpose, structure, and effect of an invention" as specified in the former Section 36(4)
** The former Section 36(5)(i)
*** Revised in 1994 from "state only the matters indispensable for the structure of the invention" as specified in the former Section 36(5)(ii)

2.2 Trilateral Project B3b

In the Trilateral Project B3b, the JPO, USPTO, and EPO have been conducting a comparative study on the examination of biotechnology-related applications since 1995. In November 2001, they adopted a comparative study report on the patentability of reach-through claims. In the report, a comparative study conducted on tentative cases revealed that the JPO, USPTO, and EPO share the view on the utility of and description requirements for reach-through claims. The findings of the comparative study are available on their websites.

In the Case 4 of their study, function-defined medical use claims were analyzed.

The summary of the specification is as follows: The specification discloses that a new receptor that was isolated is useful for the treatment of obesity. In addition, the specification describes that the agonist compounds of this receptor, namely, X, Y, and Z, were identified by use of the disclosed screening procedure. Furthermore, the pharmacological mechanism involved in the treatment or inhibition of obesity by the activation of this receptor is described theoretically in the specification. The test data confirms that at least compound X is able to activate this receptor when administered to a host animal and such administration results in a reduction in total body weight of an art recognized model for obesity. However, the specification provides no chemical structures of compounds other than X, Y, or Z.

A study was conducted on the function-defined medical use claims that were identified as "Composition comprising a receptor agonist for use in treating obesity wherein said receptor agonist is identified by the method of claim 2 (Screening method), as an active ingredient"

The three Offices concluded that the claims do not comply with enablement, and clarity requirements, etc., except for those regarding X, Y, and Z by saying "The claims encompass a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function have not been defined. (Omitted) It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity."[3)] Moreover, the three Offices concluded that the enablement, and clarity, requirements, etc., are not satisfied in the example case of function-defined medical use claims regarding the compounds that affect the targeted new receptor.

3. Example cases of examination of claims defining medical compounds by function

3.1 Method of the study

In order to study the medical use claims defining compounds by function, we searched for patent applications for which a patent was granted in Japan, the United States, or Europe in and after January 2002 in the classification of IPC A61K45/(Medicinal preparations containing active ingredients not provided for in groups A61K31/00-41/00: This means that the compounds contain unspecified active ingredients and are usually included in this classification.). Then, we selected the applications claiming functionally defined compounds.

Similarly, we also selected the applications for which a patent was granted in Japan, the United States, or Europe in and after January 2002 in the field of genetic engineering and medical purposes (C12N and A61K) because those applications could contain medical use claims about the screening results. Regarding applications filed in Japan, we searched for applications containing claims about proteins and peptides and in the field of genetic engineering (C07K and C12N15) and made a comparison between the claims at the time of publication and those at the time of registration in order to select the application in which any claim containing functional definitions was deleted in the course of examination. We also examined foreign correspondences of these selected applications.

3.2 Findings of the study

The findings of the study are shown in Figure 1 below. We selected 48 patents and applications that the patent offices examined in and after January 2002 and determined whether to grant a patent for and that contain a medical use claim defining compounds by function. We then analyzed the examination procedure of those 48 cases. While there may be other cases that should be subject to this study, we consider that those 48 cases are sufficient to identify the examination trends. Figure 1 classifies the cases as follows. The upper half of the table shows the cases where targets such as the receptor affected by active ingredients are already known to the public, whereas the lower half shows the cases where those targets are new. Regarding the columns of the table, regardless of whether an experiment has been conducted for confirmation or not, each of the columns, in the order from left to right, is dedicated to the cases where the specification does not state the substance affecting the target, where the specification is clear enough to state an antibody or antisense, where the specification states several compounds, and where the specification states many compounds with cited patent numbers and so on.

3.3 Example cases where a patent was granted in Japan, the United States, or Europe

This Subcommittee have analyzed the examination procedure of some patent applications. The following are the summaries of representative cases. The functional definitions in the claims are underlined.

Case 3-1 (Patented)
[Patent Number] JP3638289
[Filing Date] August 13, 1997
[Registration Date] January 4, 2005

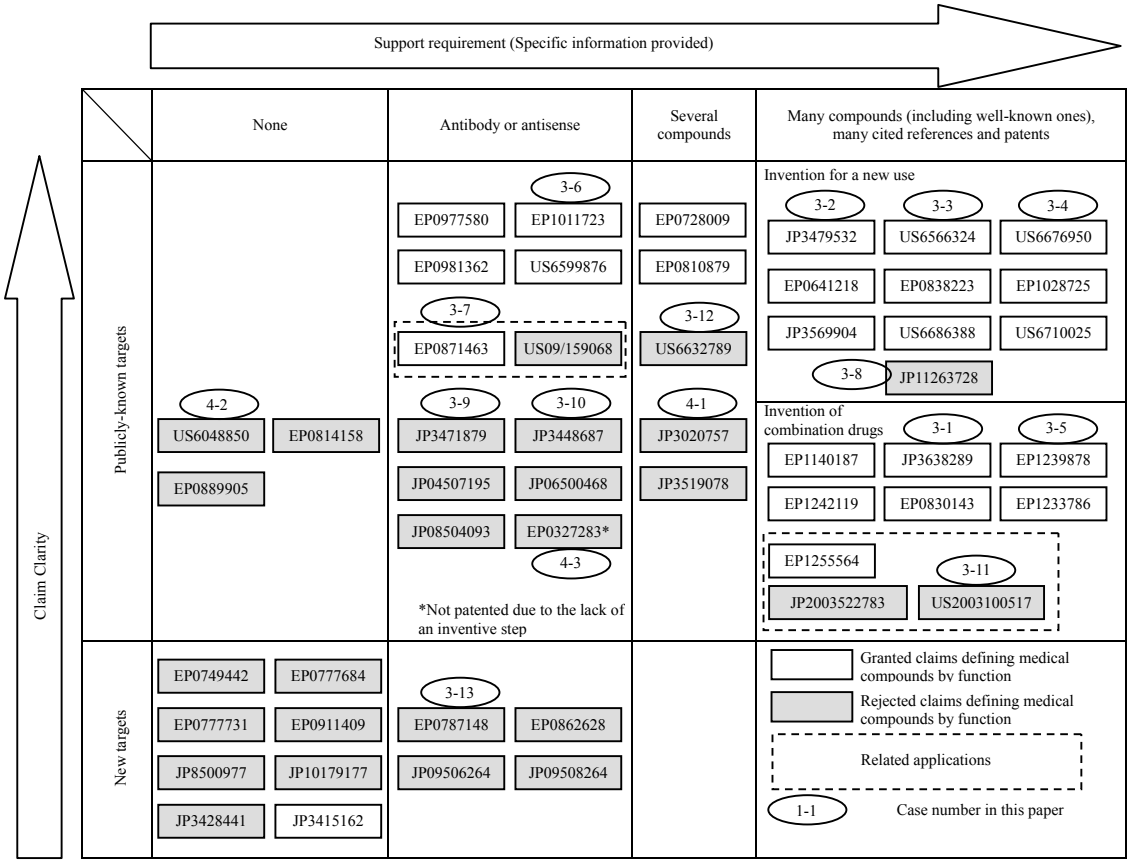

Figure 1 Research Results

[Name of the Invention] Treatment of Upper Airway Allergic Responses with a Combination of Histamine Receptor Antagonists

[Permitted Representative Claim] A pharmaceutical composition containing histamine H3 receptor antagonist that is capable of creating a sufficient amount of a histamin H3 receptor antagonist to provide a nasal decongestant effect when an antihistaminic effect amount of a histamine H1 receptor antagonist exists simultaneously.

[Summary of the Case] This is a case where a function-defined medical use claim was permitted by presenting drug efficacy data on the combinations of either of the two types of publicly-known H1 receptor antagonist and either of the two types of H3 receptor antagonist (three combinations in total).

In this case, it was found that the simultaneous use of at least one publicly-known histamine H1 receptor antagonist, together with sufficient amounts of at least one well-known histamine H3 receptor antagonist reduces nasal airway resistance.

The examiner refused the application by stating the reasons for refusal set forth in Section 29(1) and (2) in the notification of reasons for refusal because the combined use of H1 receptor antagonist (Pyrilamine) and H3 receptor antagonist (Burimamide) was more effective than the use of only one of them in the test to measure the nasal airway resistance and also because the fact that Burimamide also functions as an H3 receptor antagonist had been known to the public by the priority date of this application. Since the cited reference was about the effect of local administration, this application focused only on systemic administration. In this way, the applicant successfully removed the reasons for refusal.

The examiner also notified the applicant of the reasons for refusal specified in Section 36(4) by saying that it is obvious from the working examples that any compound that exhibits low binding affinity does not have a desired effect even if it is an H3 receptor antagonist. In response, the applicant specified the binding affinity and successfully removed the reason for refusal.

The specification lists publicly-known an-

tagonists as H1 receptor antagonists and H3 receptor antagonists. No notification of reasons for refusal has been issued in connection with the enablement, clarity, and support requirements of any antagonist other than those disclosed in the specification.

A patent has been granted for neither US counterpart nor EP counterpart of this application.

Case 3-2 (Patented)

[Patent Number] Patent No.3479532

[Filing Date] March 30, 1990

[Registration Date] October 3, 2003

[Name of the Invention] Treatment of AIDS Dementia, Myelopathy and Blindness

[Permitted Representative Claim] A pharmaceutical composition for reducing death of CNS neurons in a human patient infected with a human immunodeficiency virus, which comprises ------ the compound capable of reducing the gp120-responsive rise in free Ca<++> ion concentration in the CNS neurons of said patient, being a calcium channel antagonist.

[Summary of the Case] The Office issued the decision of refusal by stating that the claims contained a functional definition that could cover a wide range of compounds whose effect had not been confirmed by working examples. The applicant later obtained a patent through appeal proceedings by focusing on the compounds based on the function shared by the compounds described in the working examples and submitting the documents after the filing of the application which show the relations between those compounds and the drug efficacy.

This application was filed for a discovery that the central nervous system damage caused by HIV infection is attributable to a rise in the free Ca<++> ion concentration that responds to HIV coat protein gp120.

The specification describes a calcium channel antagonist as a compound that is capable of reducing the gp120 (publicly-known target)-responsive rise in free Ca<++> ion concentration in the CNS neurons and lists many well-known antagonists by citing references. The working examples show death of neurons caused by gp120, a rise in Ca<++> ion concentration by the addition of gp120, reduction in death of neurons and prevention of the rise in Ca<++> ion concentration by the addition of well-known calcium channel antagonists (nifedipine and nimodipine).

The notification of reasons for refusal and the decision of refusal[4)] did not mention the issue of clarity but pointed out a violation of Section 36(3) (currently (4)) by holding " The specification is not sufficient to prove that a person skilled in the art cannot confirm the said effect of the compounds other than nimodipine and nifedipine" (Enablement requirement).

In response, the applicant explained the efficacy of calcium channel antagonists for central nervous system diseases caused by HIV infection. In the course of appeal procedure, the applicant submitted several documents after the filing of the application to prove that many other calcium channel antagonists other than those described in the working examples are effective in treating central nervous system diseases caused by HIV infection.

Consequently, the Patent Office asked the applicant to make an amendment to the claims by adding the phrase "the compounds are calcium channel antagonists" and granted a patent after the amendment.

A patent was granted for an EP counterpart and a US counterpart of this application before the publication of the trilateral comparative study report with maintaining the functional definition which was unacceptable in Japan (without the restrictions of "the compounds are calcium channel antagonists").

Case 3-3 (Patented)

[Patent Number] US6566324

[Filing Date] February 26, 2001

[Registration Date] December 23, 2002

[Name of the Invention] Preventing airway mucus production by administration of EGF-R antagonists

[Permitted Representative Claim] A method of treating hypersecretion of mucus --- effective amount of an epidermal growth factor receptor (EGF-R) antagonist that binds the EGF-R.

[Summary of the Case] This is a case where a new use of an "antagonist" was patented in response to the applicant's opposition to the Office's view that the functional definition of the "antagonist" might be a violation of §112, ¶ 1 (Support requirement) because the "antagonist" has a publicly-known substance for a publicly-

known target.

The specification explains the discovery that the airway secretion results from the degranulation of goblet cells, the proliferation of which is promoted by stimulation of EGF-R and that inhibition of the activity of EGF-R provides a means for preventing excessive formation of mucus in pulmonary airways. The working examples present a detailed analysis of the mode of action by describing two tests to confirm the effects of two specific compounds and one antibody. The specification also lists and explains many publicly-known low-molecular compounds, antibodies, antisense molecules, and many other substances as EGF-R antagonists.

The examiner initially rejected this application for the reason that the definition of "EGF-R antagonists" violates §112, ¶ 1. However, the applicant removed the reasons for refusal by explaining in detail the publicly-known "EGF-R antagonists" and the specification describing their functions in this case, by presenting a detailed analysis of the mode of action, and by pointing out that efficacy tests were conducted on three specific EGF-R antagonists.

A patent has not been granted for an EP counterpart and a JP counterpart of this application.

Case 3-4 (Patented)

[Patent Number] US6676950

[Filing Date] February 15, 2002

[Registration Date] September 10, 2003

[Name of the Invention] Neurokinin receptor antagonists and methods of use thereof for inhibiting HIV infection

[Permitted Representative Claim] A method for inhibiting HIV infection … comprising the administration of at least one antagonist specific for the neurokinin receptor family in an effective amount to said patient.

[Summary of the Case] This is a case where a patent was granted to an application in the claims for a functionally-defined method for inhibiting HIV infection by use of NK receptor antagonists. All the NK receptors from 1 to 3 are publicly-known. The antagonists used in the working examples are CP-96345 as an NK1 receptor-specific antagonist, CP-96344, which has a similar structure and lacks antagonist activity, and R-113281 as an NK receptor-nonspecific antagonist. In addition, the substance P of physiologic ligand and its antibody were also used. No office actions for rejection has been issued in relation to NK receptor antagonists, which are defined by function in this application.

Case 3-5 (Patented)

[Patent Number] EP1239878

[Filing Date] December 19, 2000

[Notification Date of Rule 51(4)] July 25, 2003

[Name of the Invention] Formulations of adenosine A1 agonists and 5HT1 agonists

[Permitted Representative Claim] Use of an adenosine A1 agonist --- and 5HT1 agonist --- for the treatment of conditions associated with pain and the alleviation of symptoms associated thereof.

[Summary of the Case] This is a case about a combination of two substances defined as "agonist" wherein a patent was granted for the second medical use described in the use claim and the first medical use described in the composition claim.[5] While all the claimed "agonists" contain a publicly-known or well-known compound, the examiner did not find this functional definition problematic.

The specification states that adenosine A1 agonists has analgesic action by citing references (14 patents) and provides detailed explanation on a compound described in one of those references by presenting its general formula. In the specification, four specific compounds are mentioned. Regarding 5HT1 agonists, on the other hand, while the specification lists many compounds including citations from references, no detailed explanation about the compounds described in the references and their pharmacological effects are provided.

The working examples shows only the examples of synthesis of specific compounds explained as representative compounds of adenosine A1 agonists and describes neither specific cases of combined use of adenosine A1 agonists and 5HT1 agonist nor the effect of such combined use.

The examiner initially rejected the application not for the reason that the definition of "agonist" violates Article 83 or 84 but for the reason that the failure to prove the synergetic effects of these compounds violates Article 56 (Inventive step) and not Article 84 (Support requirement). In response, the applicant submitted

a written opinion containing examples of efficacy tests and obtained a patent by subsequent validation. No opposition has been raised so far.

While a JP counterpart and a US counterpart of this application was filed, neither of them has been patented.

Case 3-6 (Patented)

[Patent Number] EP1011723

[Filing Date] May 22, 1998

[Notification Date of Rule 51(4)] January 23, 2003

[Name of the Invention] 88 k da tumorigenic growth factor and antagonists

[Permitted Representative Claim] A pharmaceutical composition comprising a GP88 antagonizing agent and a pharmaceutically acceptable carrier

[Summary of the Case] This is a case about the discovery of publicly-known protein GP88's ability to stimulate tumor cell proliferation, which can be inhibited by antisense and anti-GP88 antibody, wherein both medical composition claim (the first medical use), which contains such functional definition as GP88 antagonist, and use claim[6] (the second medical use) were permitted.

In this case, the working examples of GP88 antagonist indicate antisenses and antibodies only. The definition of GP88 antagonist in the claims did not constitute a reason for refusal. A patent was granted to three US counterparts of this application. These applications each claimed a diagnosis method and antisense. No claim containing a definition of antagonist has been granted. There is no JP correspondence of this application.

Case 3-7 (Patented)

[Patent Number] EP871463

[Filing Date] June 5, 1996

[Notification Date of Rule 51(4)] March 19, 2002

[Name of the Invention] Regulation of eating behavior

[Permitted Representative Claim] The use an antagonist of MCH in the preparation of a medicament for a method of inhibiting eating appetite, or the gain of weight ---

[Summary of the Case] This is a case wherein a patent was granted for the use of MCH (melanocyte concentrating hormone) antagonist for the production of a pharmaceutical to inhibit weight gain and the use of MCH agonist for the production of a pharmaceutical that promote weight gain although no information was disclosed regarding the specific structure of nonpeptide agonist and antagonist and the confirmation of the effects.[7]

In this case, it was found that MCH itself, a publicly-known peptide, can be used for a new purpose, which is to promote eating behavior.

The specification explains that the antagonists are unrelated by amino acid homology to MCH or which are not polypeptide. The specification also describes the minimal sequence to elicit an equipotent response of activity, a MCH analog (reduced ring analog of partial peptides), and partial peptides that are preferable as agonists or antagonists by citing references. However, the specification does not state the specific structure of any nonpeptide agonist and antagonist.

The examiner did not issue a notification of reasons for refusal pointing out a violation of Article 83 and 84 (Enablement, clarity, and support requirements) and granted a patent for this application.

After the grant of the patent, three companies filed an opposition to the patent grant and the grounds included the patent application violates Article 83. This dispute is still pending.

A patent was granted for a US counterpart of this application for the method of promoting the gain of weight in a subject comprising administering an effective amount of an agonist of MCH, wherein the agonist of MCH is a peptide analog (US5849708).[8] The method of inhibiting weight gain by administering MCH antagonist not limited to peptide was rejected for the reason that the application fails to satisfy the enablement and written description requirements and therefore violates §112, ¶ 1. The applicants did not respond to the final notification of refusal (2004.1.8) and is therefore considered to have abandoned the application (Ser. No09/159,068).[9] In the notification of reasons for refusal, it is pointed out that the claim is similar to a single means claim, that the application fails to provide guidance about the structure, that the application fails to disclose nonpeptide pharmaceuticals, making it impossible to confirm that the applicant possesses the claimed invention. No comments were given about the claim definiteness. A

divisional application with claims covering the MCH agonist and antagonist is currently pending (2004-0242487 A1).

3.4 Example cases where a patent application was rejected in Japan, the United States, or Europe

Case 3-8 (Rejected)

[Publication Number] JP11-263728

[Filing Date]November 18, 1994

[Date of Decision of Refusal] May 21, 2004

[Name of the Invention] Therapeutic Agent for sexual dysfunction

[Rejected Representative Claim] A pharmaceutical composition for curative or prophylactic oral treatment of erectile dysfunction in human , which comprises cGMP PDEv inhibitor or its pharmaceutical acceptable salt ----------.

[Summary of the Case] This is a case where the Office issued the decision of refusal, pointing out the violations of the support requirement with regard to the pharmaceutical composition containing an enzyme inhibitor that is a publicly-known target while this case was ended by the applicant's withdrawal after filing a request for the appeal procedure.

This application was filed for compounds that are effective in treating sexual dysfunction.

The specification lists several well-known compounds as example compounds and states the identification of enzyme cGMP-specific PDEv from human corpus cavernosum. However, the specification mentions very briefly that the compound has inhibitory activity of cGMP PDEv and that the compound is effective in treating sexual dysfunction. The specification discloses neither the contents of the pharmacological test nor the name of a specific compound whose effectiveness for sexual dysfunction has been confirmed.

The Office issued a notification of reasons for refusal, pointing out the applicant's violations of Section 36(4) and other provisions by saying "The applicant is required to submit pharmacological data or give a theoretical explanation in the specification if the active ingredient is defined by function and contains compounds with various chemical structures," "The application fails to clarify the pharmacological test method and pharmacological data," "A person skilled in the art would have to conduct undue experimentation to obtain the active ingredient necessary to carry out the invention." (Enablement requirement). In response, the applicant argued that the specification included theoretical and clear explanations and that many therapeutic drugs containing the above-mentioned enzyme inhibitor as an active ingredient for sexual dysfunction were developed after the publication of the application. The applicant failed to remove the reasons for refusal and appealed.

However, the applicant did not defend his position but withdrew the application (January 25, 2005). A divisional application of this application is still pending (Patent Application 2004-270721).

As the compounds, the Office permitted second medical use claims for the well-known compounds cited as specific examples in the parent application.

With regard to the foreign counterparts of the parent application, second medical use claims for the enzyme inhibitor were permitted in Europe and the United States before the publication of the trilateral comparative study report.[10] However, regarding the EP counterpart, the United Kingdom decided to invalidate the patent on the grounds of nonobviousness (Judgment of the Court of Appeal No.A3/2000/3811 of January 23, 2002). In addition, a trial against the decision of revocation made in response to an opposition is still pending. On the other hand, the US counterpart is under reexamination procedure wherein the Office issued a notification of reasons for refusal, pointing out the application's violation of Section 102 and other Sections (Feb.10, 2005). As of today, the applicant has not responded to the notification.

Case 3-9 (Rejected)

[Patent Number] JP3471879

[Filing Date] January 20, 1994

[Registration Date] August 26, 2003 (Decision of registration through pretrial reexamination)

[Name of the Invention] Method of Inhibiting Serine Kinase Activity, ------ and Inhibitor for PI3-Kinase Activity

[Rejected Representative Claim] The antagonist ------ of PI3-kinase, ------ when bonded, ------ inhibits PI3-kinase activity and has the amino-acid sequence that corresponds to the

neutralized DRHNSN sequence

[Summary of the Case] The specification only gives a general explanation about an antibody as antagonist and agonist. The Office rejected the claims that define the antagonist and agonist only by amino-acid motif and not by molecule, pointing out the noncompliance with the enablement requirement. The applicant appealed against the examiner's decision of refusal and made an amendment to restrict the antagonists to particular molecules. Consequently, a patent was granted to the applicant through pretrial reexamination.

This application was filed with regard to the two subunits (p110 and p85) of PI3-kinase, a publicly-known protein, to seek a patent for a new discovery of the phosphorylated part of the subunit (p85) and the interacting region among the subunits related to the modulation of kinase activity.

The specification only generally defines as antagonist and agonist the antibody that recognizes the interacting region among the subunits and the antibody related to the phosphorylated part of the amino acid. However, the specification discloses neither specific low-molecular compounds nor information about the functions, efficacy, and specific antibodies. In the working examples, the bonding domain of the two subunits was identified. In addition, the enzyme active motif of the subunit (p110) was confirmed.

During the examination procedure, the Office issued a several notifications of reasons for refusal by saying "Undue experimentation would be necessary to obtain such compounds," "The detailed description of the invention presented in the claims fails to state the purpose, structure, and effect of the invention to such an extent that a person skilled in the art can easily carry out the invention (Section 36(4))," and "The claims are unclear because they do not disclose specific compounds (Section 36(6)(ii))." While having deleted the claims regarding agonists, the applicant refused to amend the claims regarding antagonists and continued defining antagonists only by the said amino-acid motif without defining molecules. Consequently, the Office issued a decision of refusal, pointing out the application's noncompliance with the enablement requirement. In the course of appeal procedure against the examiner's decision of refusal, the applicant amended the Representative Claim as follows: "The ------ antagonist of PI3-kinase, ------ while functioning as a p110 subunit that contains a neutralized DRHNSN sequence." In this way, the applicant restricted antagonists to the p110 subunit, which is a specific molecule, and obtained a patent through pretrial reexamination.[11] No foreign counterparts of this application were filed.

Case 3-10 (Rejected)

[Patent Number] JP3448687

[Filing Date] November 26, 1991

[Registration Date] May 1, 2003

[Name of the Invention] A Novel Protein Tyrosine Kinase

[Rejected Representative Claim] An agonist (antagonist) to the protein tyrosine kinase-like molecule according to any one of claims 1[12] to 10.

[Summary of the Case] As this application did not provide any information about an agonist or antagonist of a new protein, the Office issued a notification of reasons for refusal by pointing out the noncompliance with the enablement requirement. In response, the applicant deleted the claims containing a functional definition.

This application was filed for the novel protein tyrosine kinase, JAK1 and JAK2.

The specification did not disclose the agonist and antagonist at all. There were working examples regarding the JAK1 and JAK2 molecules in the specification, wherein the examples were gene cloning, sequence determination, protein expression, antiserum preparation, domain structure analysis and so on. However, the specification only mentioned the general roles of publicly-known protein tyrosine kinase in intracellular transduction and simply mentioned that the JAK1 and JAK2 molecules were unique since it possessed more than one protein kinase catalytic domain.

The examiner issued a notification of reasons for refusal on the grounds that the claims regarding an agonist and antagonist did not meet the enablement requirement. In reply to the office action, the applicant submitted an amendment to delete the claims without counterargument against it. The application was granted to the claim regarding a screening method to determine whether a certain substance is an agonist or antagonist.[13]

While an EP counterpart and a US coun-

terpart of this application were filed, neither of them has been granted to the claims regarding an agonist and antagonist.

Case 3-11 (Rejected)

[Publication Number] US2003-0100517

[Filing Date] October 9, 2002

[Registration Date] March 3, 2005

[Name of the Invention] Pharmaceutical composition

[Rejected Representative Claim] A pharmaceutical composition comprising a squalene epoxidase inhibitor in combination or association with a macrolide T-cell immunomodulator or immunosuppressant, together with at least one pharmaceutically acceptable diluent or carrier.

[Summary of the Case] In this case, the applicant claimed many publicly-known compounds defined by function in order to seek a combination patent. The application was initially rejected based on the grounds that it does not satisfy the requirement specified in Section 112, para. 2, but registered after an amendment was made to specify a part of the structure.

The patent granted is a composition patent for a combined use of a squalene epoxidase inhibitor, a publicly-known target, and macrolide immunomodulator. The specification lists many compounds for each compound group and cites patent documents related to those compounds, respectively. The working examples confirmed a synergetic effect of a combined use of a macrolide immunomodulator (Three ascomycin-like compounds and tacrolimus) and a squalene epoxidase inhibitor (Terbinafine), and the lack of such a synergetic effect of a combined use of a macrolide immunomodulator and antifungal (Fluconazole). The application has no statements about the relationships between squalene epoxidase and its lower-level compounds and between macrolide and its lower-level compounds.

During the examination proceedings, the Office issued a notification of reasons for refusal three times on the grounds that the application does not satisfy the requirement specified in Section 112, para. 2 (Claim Definiteness) by saying in the notification "Claims are drawn to compositions and methods comprising the use or inclusion of 'a squalene epoxidase inhibitor' and a 'macrolide T-cell immunomodulator or immunosuppressant' together with a carrier, which is seen to be missing a critical element. The claim fails to particularly point out the identity of the active agents (the compounds) to be used in the composition instantly claimed. The current claim language is drawn to compositions and methods which are not described structurally/ formulaically/ nomenclatorially; but rather by the active agent's mode of action, function, or effect requisite to an activity produced by the composition. The claims are missing the critical element, which is the particular or distinct identity of the active agent to be used in the composition. Defining the agent structurally, formulaically, or nomenclatorially would be more preferable way to define the subject matter claimed, instead of the current functional description." After receiving the first notification of reasons for refusal, the applicant argued, without making any amendment, that the definitions are sufficiently clear by pointing out the part of the specification that lists a group of compounds. However, the applicant failed to remove the reasons for refusal. In the final notification of reasons for refusal, the following reason was stated in addition to the above-mentioned reason: "The metes and bounds of the claim cannot be determined by the use of the current functional language. The language which describe the compounds intended to be used in the compositions and methods potentially includes thousands of compounds, those which are known and unknown, those which are known to possess said activity and those are not known to possess said activity." Furthermore, in response to the applicant's argument that the specification gives clear definitions, the Office rejected the argument by saying "The examiner has not questioned support requirement, which is a §112, ¶ 1 issue, and no such support issue has been set forth. However, the specification states 'a squalene epoxidase inhibitor is for example, a thiocarbamate antifungal such as ---'. It is noted that exemplification is not an explicit definition of anything. If applicants are relying on the specification for definition, the specification must clearly set forth the definition explicitly and with reasonably clarity, deliberateness, and precision." As the applicant responded without amending the functional definitions, the Office issued an advisory action in which a CAFC judgment was cited as follows in addition to the above-mentioned reasons: "In claims involving chemical materials, generic formulae usually

indicates with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is."[14)]

Thereafter, the applicant made an amendment to limit a squalene epoxidase inhibitor to a thiocarbamate antifungal, or an aryl- or heteroarylmethylamine antifungal, and also limit a macrolide immunomodulator to a ascomycin or rapamycin including a lactone or lactam moiety and finally obtained an allowance.[15)]

Counterparts of this application were filed with the EPO and the JPO respectively. The EPO only requested the deletion of a claim about the medical treatment method and did not reject the application under Article 83 or 84. Consequently, a notice was sent to the applicant under EPC Rule 51(4).[16)] The JPO issued a notification of reasons for refusal on the grounds that the claim regarding the medical treatment method fails to comply with the requirements specified in the body of Section 29 and Section 36(4) (Enablement requirement) and (6) (Claim clarity).[17)] In response, the applicant made an amendment similar to that made to the US counterpart but has not received any response from the JPO as of April 2005.

Case 3-12 (Rejected)

[Patent Number] US6632789

[Filing Date] April 29, 1994

[Registration Date] May 19, 2003

[Name of the Invention] Methods for modulating T cell responses by manipulating intracellular signal transduction

[Rejected Representative Claim] A method for modulating a response by a T cell expressing a cell surface receptor which binds a costimulatory molecule, comprising contacting the T cell with an agent which modulates production of D-3 phosphoinositides in the T cell.

[Summary of the Case] This application was filed for a method to modulate a response by a T cell expressing a cell surface receptor which binds a costimulatory molecule, comprising contacting the T cell with an agent which modulates production of D-3 phosphoinositides in the T cell. In the course of the examination and appeal procedure, the examiner issued a notification of reasons for refusal by pointing out the noncompliance with the requirements specified in §112, ¶ 1 and ¶ 2. An applicant restricted "an agent which modulates production of D-3 phosphoinositides" and "a cell surface receptor" to a specific compound stated in the specification, "CD28 receptor," respectively and was consequently granted a patent.

The specification discloses "the fungal metabolite wortmannin or the bioflavenoid quercetin, or derivatives or analogues thereof (e.g LY294002)" as an example of an agent which inhibits production of D-3 phosphoinositides in a T cell. Furthermore, the working examples show the inhibition of D-3 phosphoinositide production induced by the contact of wortmannin with a CD28 receptor and the inhibition of IL-2 production (Inhibition of T-cell activation) induced by the contact with CD28. The specification discloses a CD28 receptor as a T-cell receptor in charge of a costimulatory signal. Similarly, in the working examples, the description is restricted to the production inhibition induced by CD28 as described above.

The examiner noticed a non-final rejection that a cell surface receptor should be restricted to a CD28 receptor because only a CD28 receptor could meet the enablement requirement (§112, ¶ 1) and that, since the specification only described in vitro modulation and did not disclose any in vivo action such as an administration method, which made it difficult for persons skilled in the art to distinguish "in vitro" from "in vivo" in the claims, the claims should be restricted to "in vitro" (§112, ¶ 1 and ¶ 2). Although the applicant submitted a communication to amend the description of an agent as "--- an agent which acts intracellularly to modulate production of D-3 phosphoinositides---" in reply to the office action, a final rejection that was maintained the same reasons as the one stated in the previous office action was noticed. The applicant appealed and amended the claims in the course of the appeal procedure and finally obtained a patent.[18)]

A JP counterpart of this application was filed and has been still pending. An EP counterpart was granted a patent without restricting the receptor to a CD28 receptor after the applicant restricted the agent to "an intracellular agent" in the claims[19)].

Case 3-13 (Rejected)

[Publication Number] EP787148

[Filing Date] October 26, 1995

[Notification Date of Rule 51(4)] September 30, 2003

[Name of the Invention] AL-1 neurotrophic factor, a ligand for an Eph-related tyrosine kinase receptor

[Rejected Representative Claim] An AL-1 antagonist preferential for AL-1 activity for use in the preparation of a medicament for modulating angiogenesis associated with a disease.

[Summary of the Case] This application was initially rejected on the grounds that the specification does not disclose any specific low-molecular compound as an AL-1 antagonist and that the use claims regarding the AL-1 antagonist (A method of modulation angiogenesis associated with a disease condition, comprising administering ------ an AL-1 antagnonist) is unclear and lacks the support of the specification, and also that the reach-through claims are unacceptable. In response, the applicant deleted these claims and obtained a patent.

This application contains not only a substance claim for AL-1 and its genes based on the discovery of a new protein, AL-1, and its function and efficacy but also a medical use claim for an AL-1 antagonist targeted at this new protein (An amendment was made to the original claim regarding a treatment method when the application moved into the domestic phase of examination),

The specification describes soluble AL-1, a neutralizing anti-AL-1 antibody, an AL-I receptor (REK7), chimeric protein of an AL-1 receptor, and a soluble AL-1 receptor as AL-1 antagonists, but fails to disclose any specific low-molecular compound as AL-1 antagonists. The specification also lists the functions and efficacy of AL-1 as well as the efficacy of AL-1 antagonists. The working example shows that soluble AL-1 has an antagonist activity in the cell culture system.

The examiner issued a notification of reasons for refusal stating "In particular, the claims concerned with general AL-1 antagonists are lack the clarity and (technical) support by the description" (Claim clarity and support requirements) under Article 84. In response, the applicant amended the claim to a second medical use claim while maintaining the functional definition (for modulating angiogenesis associated with a disease condition). The examiner maintained the same reasons for refusal based on Article 84, saying "The claim is not directed to a specific disease condition" (Claim clarity). As the applicant responded without making any amendments to the claim, the examiner once again gave the same reasons for refusal and instructions under Article 84, saying "Applicant is requested to delete the claim since this is a reachthrough claim. The substance used to treat angiogenesis is not properly technically defined. Hence, the scope of the claim is unclear as is the status of known medication for treating angiogenesis with respect to AL-1 binding and antagonism, thus making assessment impossible." (Claim clarity). Finally, the applicant deleted the second medical use claim containing the functional definition and obtained a patent. No notification of reasons for refusal has been issued related to the enablement requirement. A divisional application of this application was filed and is still under examination. As the divisional application has not been publicized yet, its claims are unknown.

A US counterpart and a JP counterpart were filed in connection with this application. The USPTO has not permitted the claim regarding a treatment method[20] that administers an "antagonist" in the course of the treatment, while having already granted many patents on the claims directly related to AL-1. The JPO has not given any instructions as of April 2005.

4. Judgments on the patentability of the claims defining medical compounds by function

4.1 Precedents in Japan

[Case Number] Tokyo High Court, 2003(Gyo-Ke) No.104

[Date of the Judgment] December 26, 2003, Case wherein the plaintiff demanded cancellation of the decision to revoke the patent[21]

[Name of the Invention] New Medical Use of Tachykinin Antagonist

[Rejected Representative Claim (After the correction)] A medicament for use in the treatment of emesis whose active ingredient is a tachykinin antagonist, which is an NK1 receptor antagonist

[Summary of the Case] This is a case wherein the Office, which decided to revoke a patent granted for a medical use claim defining an active ingredient by function, received an opposition against the decision and defended the appropriateness of the decision before the court. After the grant of a patent for "a medicament for use in the treatment of emesis whose active ingredients are tachykinin antagonists, including substance P antagonists and other neurokinin antagonists," two oppositions were filed in connection with the grant of the patent. Having received a notification of reasons for the revocation, the applicant deleted Claim 1 in order to restrict the tachykinin antagonists to an NK1 receptor antagonist.

In the specification, only one compound is confirmed to have the properties of an NK1 receptor antagonist and of a medicament for use in the treatment of emesis.

The Patent Office decided to revoke the patent on the grounds that the patent was granted for the revised claims for the invention 1 to 7 and 9 defining the active ingredients by function and a wide range of general formulas in violation of Section 36(4), (5), and (6) (2002.11.7).

The Tokyo High Court upheld the Patent Office's decision and judged that the grant of the patent has violated Section 36(4), (5), and (6) by holding that the application cannot be considered to state the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art because the specification fails to prove the efficacy of an NK1 receptor antagonist as a medicament for use in the treatment of emesis except for the compound that has been confirmed to have the properties of an NK1 receptor antagonist and of a medicament for use in the treatment of emesis and also holding that the invention described in the specification is different from the one portrayed in the detailed description of the invention because the invention stated in the specification is beyond the scope of invention confirmed by the detailed description of the invention and that the specification cannot be considered to disclose only the indispensable constituent features of the invention.

In view of the following part of the judgment, it seems that the Tokyo High Court would not refuse the patentability of the invention if the relationship between the activity that defines the active ingredient and the therapeutic activity for a specific disease can be objectively recognized by persons skilled in the art.

"The detailed description of the invention presented in the specification cannot be regarded to be clear and complete enough for a person skilled in the art to carry out the invention of a medicament for use in the treatment of emesis because its active ingredients, namely NK1 receptor antagonists, have not been proven to be effective in treating emesis except for one of those antagonists, (2S,3S)-3-(2-methoxybenzylamino)-2-phenyl piperidine, that has been proved to be effective in such treatment. A patent would have been granted if the detailed description of the invention presented in the specification had been considered to be clear and complete enough for a person skilled in the art to objectively recognize a property of an NK1 receptor antagonist as a medicament for use in the treatment of emesis. Such level of clarity and completeness of description could have been achieved if it had been confirmed that a considerable number of substances with NK1 receptor antagonism that are structurally dissimilar to one another are effective in treating emesis."

4.2 Precedents in the United States

[Case Number] 358 F.3d 916, 69 USPQ2d 1886, Case No.03-1304

[Date of the Judgment] February 13, 2004

[Name of the Invention] Method of inhibiting prostaglandin synthesis in a human host

[Rejected Representative Claim] A method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a nonsteroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human host in need of such treatment.

[Summary of the Case] The US6048850 Patent ('850 patent)[22] was granted for a new-generation anti-inflammatory drug without gastrointestinal side effects. The patent claimed a pharmaceutical "method for selectively inhibiting PGHS-2 activity in a human host" in which "the activity of PGHS-1 is not inhibited." This case attracted a great deal of public attention as "Rochester Case."

PGHS-1 (COX-1) and PGHS-2 (COX-2) are important enzymes that produce prostaglandins. The inventors discovered that the compound

that it would be possible to reduce inflammation without gastrointestinal side effects if a method could be found for selectively inhibiting the activity of PGHS-2 without inhibiting the activity of PGHS-1. The specification discloses a screening method for PGHS-2 selective inhibitors but fails to specify the PGHS-2 selective inhibitors obtained by this screening method.

[District Court Judgment[23)]] The '850 patent was issued on April 11, 2000. On the same day, the University of Rochester filed a lawsuit for an injunction and damages against G.D. Searle with the District Court for the Western District of New York. The defendant requested the district court to hand down a summary judgment to invalidate the patent on the grounds that the patent does not satisfy the written description requirement (§112, ¶ 1) because the '850 patent application fails to disclose specific PGHS-2 selective inhibitors and that the patent does not fulfill the enablement requirement (§112, ¶ 1) either because any person skilled in the art who try to practice the invention would be required to carry out undue experimentation.

Citing the *Enzo Biochem*,[24)] the district court concluded that the functional features will be considered to comply with the written description requirement if a relationship between the functions and the structures is known to the public or disclosed in the specification. The court judged that the '850 patent application fails to fulfill the written description requirement because it only describes the desirable functions of the compounds and does not specify the relations between the functions and the structures of the compounds.

The court also judged that the patent fails to satisfy the enablement requirement either because the invention imposed undue burden on the defendant who had to spend about eight months for the identification of PGHS-2 selective inhibitors, carrying out a screening test on more than 600 compounds.

Dissatisfied with the district court's decision of invalidation of the '850 patent, the plaintiff appealed to the Court of Appeals for the Federal Circuit (CAFC).

[CAFC Judgment] In response to the argument of the University of Rochester that the written description requirement should invoke only to a case with priority issues of the invention. The CAFC judged that the written description requirement serves a teaching function, as a quid pro quo in which the public is given meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time. Therefore the written description requirement must be fulfilled independently. The CAFC upheld the summary judgment of the invalidation of the patent handed down by the district court by holding that the written description requirement should apply regardless of the type of the invention and should not be considered to be satisfied without the description of the structure of the compound.

[Demand for a retrial before the CAFC en banc[25)]] The CAFC dismissed a request of the University of Rochester for a retrial before the CAFC en banc on the interpretation of the written description requirement. While there are differences among the judges in the interpretation of the scope of application of the written description requirement and the enablement requirement specified in §112, ¶ 1, the differences have not been discussed en banc. The CAFC maintained the recent interpretation that the written description requirement must be fulfilled.

4.3 Precedents in Europe

Case 4-3

[Decision Number] T0182/00[26)]

[Date of the Decision] January 7, 2004

[Date of the Opposition] December 9, 1999

[Name of the Invention] Method of reducing immunoglobulin E responses

[Rejected Representative Claim] A pharmaceutical composition for reducing an immunoglobulin E response in humans comprising an effective amount of an antagonist to human interleukin-4 and ---.

[Summary of the Case] In the opposition and appeal decisions, the Office decided to invalidate the patent because the patent does not involve an inventive step specified in Article 56 based on the results of an in vitro test conducted by use of mouse antibodies were regarded as a prior art. In response, the patent owner sought the appeal procedure at the office but saw his request dismissed by the Office. While the

Office did not consider Article 83 and 84 as issues related to its decision, the Office admitted that the reason for the decision on the opposition related to Article 83 was convincing. For your reference, the judgment of the Opposition Division on the form of expression of "antagonist" is outlined below. The Opposition Division stated that the opposition was filed in connection with Article 83 and was not filed based on Article 84 while the opposition appears to be related to Article 84 at the first glance. The decision of the Opposition Division is as follows:

"Referring to medical dictionary, "antagonist" is an accepted technical term having the meaning of '…a substance that tends to nullify the action of another substance…' Together with the definition of the technical solution proposed (reducing IgE secretion by blocking IL-4), skilled person would appear to perfectly know what is meant by "antagonist" in Claim 1, namely any substance which inhibits the IgE enhancing activity of human IL-4 by any conceivable mechanism. Monoclonal antibodies would appear to be preferred, but other antagonists are immediately apparent, even if they may not yet have been provided. Any method which uses a molecule which inhibits IL-4 from exerting its IgE-enhancing activity is considered to fall under the scope of Claim 1; in the opposition division's view, the use of the term "antagonist" does in no way endanger the feasibility of the claimed invention. (Omitted) As claims 1-10 for all Contracting States therefore comply with Article 83 EPC, the opposition formulated under Article 100b) EPC is rejected."

Case 4-4

[Decision Number] T0241/95[27)]

[Date of the Decision] June 14, 2000

[Name of the Invention] Use of R-Fluoxetine as selective serotonin IC-receptor ligands

[Rejected Representative Claim] The use of (R)-fluoxetine, that is (R)-fluoxetine substantially free of (S)-fluoxetine, --- for treating a mammal suffering from or susceptible to a condition which can be improved or prevented by selective occupation of the 5-HTIC receptor.

[Summary of the Case] The examiner considered that the application violates Article 54. In addition, the definition of the target disease by function was regarded to be a violation of Article 84. While the applicant filed a request for the appeal procedure, the Office dismissed the request. Upon the second auxiliary request, the application was remanded for review. While this case does not provide an example of judgment regarding a functional definition in the form of an antagonist, the decision handed over in this case is often cited in other cases where the applicability of Article 84 needs to be determined with regard to the functional definitions used in the claims. For your reference with regard to the applicability of Article 84, the decision is cited as follows:

"The functional terms used to define the condition to be treated are acceptable as long as the claim still meets the requirements of Article 84 EPC. According to decision T 68/85, cited by the appellant, the requirement of clarity demands not only that the skilled person be able to understand the wording of the claim but also that he be able to implement it. In other words, the functional feature must be accompanied by instructions which are sufficiently clear for the expert to reduce them to practice. This implementation of the invention implies that means must be available to the skilled person, either from the patent application or from the common general knowledge at the relevant date of the application, to recognize and evaluate the technical effect of the functional definition. When the claim is directed, according to the usual wording, to a further therapeutic application of a medicament and the condition to be treated is defined in functional terms, such as those in the claim under consideration, the skilled person must be given instructions, in the form of experimental tests or any testable criteria, allowing him to recognize which conditions fall within the functional definition and accordingly whether or not the therapeutic indication representing the heart of the invention falls within the scope of the claim. (Omitted) Under these circumstances, the Board is of the opinion that at the filing date of the application no means involving testable criteria existed to assist the skilled person in assessing whether or not a "condition" improved or prevented by (R)-fluoxetine was comprised in the functional definition of the claimed subject-matter. For these reasons, the Board holds that claim 1 does not meet the requirements of Article 84 EPC."

5. Observation

As specified in the trilateral comparative study report and the Japanese examination guidelines,[28] the USPTO, EPO, and JPO assume that undue burden would be required to obtain the active ingredient if chemical structural information is not disclosed. Based on this assumption, overall claims are considered to violate the enablement requirement except for those related to a compound whose structure is disclosed in detail. Under this assumption, even if the gene and protein as a target of a pharmaceutical and some of the agonists or antagonists affecting the target are well-known, the situation is the same in that overall claims are generally considered to violate the enablement requirement. However, the examiners' decisions as to whether the enablement requirement was fulfilled or not differed greatly.

Before the publication of the trilateral comparative study report, there were some cases that the USPTO examined a patent application for an invention related to new genes and proteins and permitted its reach-through claims without questioning the compliance of the enablement requirement despite the fact that the application did not provide any working examples concerning agonists of the proteins, etc.[29] As far as the cases covered in this paper are concerned, no reach-through claims in the applications for an invention of new genes and proteins were permitted. It might be reasonable for the Office to have rejected, on the grounds of the noncompliance with the enablement requirement, all the applications that failed to obtain the compounds (excluding antibodies and peptides) that function as an agonist or antagonist of the proteins and other substances in question and failed to confirm their therapeutic effects. This reflects the tightening examination standards of the USPTO since before the publication of the trilateral comparative study report.

On the other hand, a patent was granted in many cases, especially in Europe, because the Office did not issue a notification of reasons for refusal on the grounds that the enablement requirement cannot be satisfied due to the difficulty to obtain the compounds covered by overall claims (Case 3-1, 3-2, 3-4, 3-5, 3-6, and 3-7, etc.). In some cases where the genes or proteins as targets were publicly-known, however, the applications were rejected on the grounds of noncompliance with the enablement requirement.

In Europe, the examination standards to determine whether the functional definitions in a claim comply with the requirements specified in Article 83 and 84 are applied to actual cases in a relatively relaxed manner. One of the reasons for this would be the EPO's practice of regarding the issue of expressing as an agonist and antagonist not as a violation of Article 83 (Enablement requirement) but rather as an issue related to Article 84 (Support and claim clarity requirements) (Case 4-3) and also its practice of considering that the claim clarity requirement specified in Article 84 is satisfied as long as whether the compound defined by function is included within the claims or not is obvious from general knowledge, the working examples understandable by any person skilled in the art, or from the instructions stated in the specification that clarify the judgmental standards (Case 4-4).

As shown in the case of tachykinin antagonist (Case 4-1), Japan, in comparison with Europe, tends to judge the compliance with the enablement requirement from the perspective of whether all the compounds defined by function have the same action (therapeutic effect) in addition to the perspective of whether the compounds defined in the specification can be produced by any person skilled in the art. In contrast, the examination procedures at the EPO and the USPTO are not so strict in this respect. In some cases, especially in the cases of applications involving a combination of drugs, the Office did not issue a notification of reasons for refusal even if the application failed to confirm that all the compounds defined by function have the same action (therapeutic effect) because the therapeutic effect claimed in the specification was confirmed based only on the results of a test conducted on a small number of such compounds (Case 3-1, 3-5, and EP counterpart of 3-11).

According to the Japanese examination guidelines, an applicant whose patent application has been rejected may remove the reason for refusal if he can prove that a compound whose function is generally defined has a similar action (therapeutic effect).[30] In fact, the reason for refusal was remove in this way in Case 3-2.

It is inappropriate to permit such way of granting a patent by allowing an applicant to

submit additional data later to supplement his application that failed to prove the essential elements of the invention, i.e., the relationship between a specific function and a specific action (therapeutic effect).

As mentioned in the Japanese examination guideline concerning the description requirement,[31] the examination procedure that strictly applies the description requirement (Support requirement) would be able to prevent from granting a patent for applications that fail to sufficiently disclose the essential elements of their respective inventions as those mentioned above. However, in reality, the lack of attention paid to this issue as described earlier resulted in the grant of a patent in some cases (Case 3-2).

In Japan, the scope of an invention is considered clear if the substance that functions as an active ingredient is well-known at the time of filing of a patent application for the invention.[32] If the target is novel, the JPO considers that the specification lacks clarity.[33] However, any applicant who sufficiently proves in his specification submitted on the application filing date the essential elements of the invention, i.e., the relationship between a specific function and a specific action (therapeutic effect), is considered to comply with the clarity requirement under the examination guidelines.[34]

In most cases, a function-defined medical use claim does not restrict the active ingredient to a compound that is well-known as of the filing date of the application. Regardless of whether some of the compounds that function as active ingredients is well-known or not, it would be rare that all the compounds covered by the language of the claims are well-known. Therefore, it might be inappropriate for examiners to differ in how strictly the clarity requirement as well as in the enablement requirement is applied to each case.

6. Conclusion

This case study revealed that the examination standards for the patentability differ greatly between applications for a target that is publicly-known or for an active ingredient that is partially well-known and applications that claims both a new target and a function-defied medical use. The examiner needs to figure out how much undue experimentation would be necessary to obtain active ingredients that are not specifically disclosed in the specification and how the extent of undue experimentation is affected by the fact that the target has been publicly-known since before the application filing date. Both types of applications are the same in that the language of their claims includes structurally dissimilar compounds that will be obtained in the future. Thus, it should not be appropriate for the examiners to differ in the strictness of applying the enablement requirement and clarity requirement. The same shall apply to the case where the active ingredient is partially well-known. We consider it appropriate to grant a patent for an application that specifically discloses an active ingredient in the specification and proves the essential elements of the invention in the specification, i.e., the relationship between a specific function and a specific action, even if the target or the compound that functions as an active ingredient is not known at the time of the application filing date. In short, such an application should be granted in the same way as an application for a target that is publicly-known or for an active ingredient that is partially well-known.

Notes:

1) Examination Guidelines for Patent Applications relating to Medical Inventions (March 2004), The UK Patent Office Homepage, http://www.patent.gov.uk/patent/reference/medig uidlines/ second.htm
2) Synopsis of Application of Written Description Guidelines, United States Patent and Trademark Office Homepage, http://www.uspto.gov/web/ menu/written.pdf
3) The claims encompass a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function have not been defined. (Omitted) The skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

4) The representative claim rejected in Case 3-2
A pharmaceutical composition for reducing death of CNS neurons in a human patient infected with a human immunodeficiency virus, which comprises the compound capable of reducing the gp120-responsive rise in free Ca<++> ion concentration in the CNS neurons of said patient in a concentration effective to cause such reduction.
5) The composition claim granted in Case 3-5
9. A pharmaceutical composition which comprises an adenosine A1 agonist or --- and a 5HT1 agonist or --- .
6) The use claim granted in Case 3-6
13. Use of a GP88 antagonizing agent wherein said agent inhibits the production or biological activity of GP88 in the manufacture of a medicament for treating diseases associated with increased expression of GP88.
7) The antagonist use claim in Case 3-7
1. The use of MCH, or an agonist or fragment thereof, in the preparation of a medicament for a method of promoting eating appetite, or the gain or maintenance of weight, in a subject comprising administering an effective amount of MCH, or an agonist or fragment thereof, to said subject.
8) A US counterpart patent in Case 3-7 (EP871463)
(Patent Number) US5,849,708
(Filing Date) June 6, 1995
(Registration Date) June 25, 1998
(Permitted Representative Claim) A method of promoting any of eating, the gain of weight, or maintenance of weight, in a subject comprising administering an effective amount of melanocyte concentrating hormone (MCH), or an agonist of MCH, wherein the agonist of MCH is a peptide analog having one to five amino acid residues --- .
9) A US counterpart patent in Case 3-7 (EP871463)
[Patent Number] US 09/159,068 (Divisional application)
[Filing Date] September 23, 1998
[Date of Final Refusal] January 8, 2004
[Rejected Representative Claim] A method of inhibiting appetite, or the gain of weight, in a subject comprising: --- administering an effective amount of an antagonist of melanocyte concentrating hormone (MCH) to said subject, wherein the antagonist binds an MCH receptor.
10) An EP counterpart patent of the parent application in Case 3-8 (JP11-263728)
[Patent Number] EP702555B
[Filing Date] May 13, 1994
[Notification Date of Rule 51(4)] March 14, 1997
[Permitted Representative Claim] The use of a cGMP PDE inhibitor, or ---, for the manufacture of a medicament for the curative or prophylactic oral treatment of erectile dysfunction in man.
A US counterpart patent of the parent application in Case 3-8 (JP11-263728)
[Patent Number] US6469012
[Filing Date] May 13, 1994
[Registration Date] May 22, 2002
[Permitted Representative Claim] A method of treating erectile dysfunction in a male human, comprising orally administering to a male human in need of such treatment an effective amount of a selective cGMP PDEv inhibitor, or ---..
11) The representative claim granted in Case 3-9
The separating antagonist of PI3-kinase, as a ligand binding to the p85 subunit of PI3-kinase, when bonded with the said p85 subunit, inhibits the phosphorylation of serine 608 and thereby reduces PI3-kinase activity, while functioning as a p110 subunit that contains a neutralized DRHNSN sequence
12) The claim 1 of Case 3-10
An animal protein tyrosine kinase (PTK)-like molecule comprising a polypeptide having multiple protein kinase catalytic domains but no SH2 domain.
13) The claim for the screening method permitted in Case 3-10
A method to determine whether a substance is an agonist or antagonist of the animal protein tyrosine kinase-like molecule according to Claim 1 which comprises: contacting the cells expressing the said animal protein tyrosine kinase-like molecule with the said substance under the preferable conditions for the phosphorylation of the substrate by the said animal protein tyrosine kinase-like molecule and determining whether the said substance is an agonist or antagonist by comparing the phosphorylation conducted in the presence of the said substance with the phosphorylation conducted in the absence of the said substance.
14) *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398
15) The representative claim granted in Case 3-11
A pharmaceutical composition comprising a combination of a squalene epoxidase inhibitor selected from a thiocarbamate antifungal or an aryl- or heteroarylmethylamine antifungal and a macrolide T-cell immunomodulator or immunosuppressant which has a macrocyclic compound structure including a lactone or lactame moiety and is an asco- or rapamycin, as active ingredients, together with at least one pharmaceutically acceptable diluent or carrier, wherein said squalene epoxidase inhibitor and said macrolide T-cell immunomodulator or immunosuppressant of said composition can be administered substantially the same or in combination.
16) An EP counterpart patent in Case 3-11 (US2003-0100517)
[Patent Number] EP1255564
[Filing Date] February 16, 2001
[Registration Date] May 5, 2003

[Permitted Representative Claim] A pharmaceutical composition comprising a squalene epoxidase inhibitor in combination or association with a macrolide T-cell immunomodulator or immunosuppressant, together with at least one pharmaceutically acceptable diluent or carrier.

17) A JP counterpart patent in Case 3-11 (US2003-0100517)
[Publication Number] JP2003-522783
[Filing Date] February 16, 2001
[Date of Notification of Reasons for Refusal] July 27, 2004
[Representative Claim That Constituted a Reason for Refusal] A pharmaceutical composition comprising a squalene epoxidase inhibitor in combination or association with a macrolide T-cell immunomodulator or immunosuppressant, together with at least one pharmaceutically acceptable diluent or carrier.

18) The representative claim granted in Case 3-12
A method for inhibiting a response by a T cell expressing a CD28 cell surface receptor which binds a costimulatory molecule, comprising contacting the T cell with an agent which acts intracellularly to inhibit production of D-3 phosphoinositides in the T cell, wherein the agent is selected from the group consisting of quercetin and LY294002, and derivatives or analogues thereof.

19) An EP counterpart patent of the parent application in Case 3-12 (US6632789)
[Patent Number] EP758232
[Notification Date of Rule 51(4)] October 30, 2003
[Permitted Representative Claim] A method for inhibiting a response by a T cell expressing a cell surface receptor which binds a costimulatory molecule, comprising contacting the T cell with an intracellular agent in vitro which inhibits production of D-3 phosphoinositides in the T cell.

20) The treatment method claim in Case 3-11 (EP787148)
A method of modulating angiogenesis associated with a disease condition, comprising administering to a mammal an angiogenicallymodulating effective amount of an AL-1 antagonist.

21) Case 4-1
[Patent Number] JP3020757
[Filing Date] September 18, 1992
[Registration Date] October 25, 1999

22) Case 4-2
[Patent Number] US6048850
[Filing Date] June 7, 1995
[Registration Date] September 9, 1999

23) *University of Rochester v. G.D. Searle & Co.,* 249 F. Supp. 2d 216(W.D.N.Y. 2003)

24) *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 963 (Fed. Cir. 2002)

25) *University of Rochester v. G.D. Searle & Co.,* 375 F.3d 1303, 71 USPQ2d 1545, Case No. 03-1304 (Fed. Cir., Jul. 2, 2004)

26) Case 4-3
[Patent Number] EP0327283
[Filing Date] January 30, 1989
[Notification Date of Rule 51(4)] July 7, 1992
[Permitted Representative Claim] 7. Use of an antagonist to human interleukin-4 for the preparation of a therapeutic composition useful in reducing an immunoglobulin E response in humans.

27) Case 4-4
[Patent Number] EP0449562
[Filing Date] March 26, 1991

28) Part I, Chapter 1, 5.3 Examples on Enablement Requirement (Section 36 (4)(i)) (Case 3-4)

29) "Study on the patentability of functional and characteristic claims for biotechnology-based inventions and on the interpretation of the patents" Intellectual Property Management(*Chizaikanri*), Vol.52, No. 12)

30) Part I, Chapter 1, 5.3 Examples on Enablement Requirement (Section 36 (4)(i)) (Case 3-7)

31) Part I, Chapter 1, 5.1 Examples on Actual Relationships (Section 36 (6)(i)) (Case 1-1)

32) Part I, Chapter 1, 5.2 Examples on Clarity of Invention (Section 36(6)(ii)) (Case 2-2)

33) Part I, Chapter 1, 2.2.2.1 Typical Examples of Violation of Section 36(6)(ii), (6)(ii), Part I, Chapter 1, 5.2 Examples on Clarity of Invention (Section 36(6)(ii)) (Case 2-1)

34) "When a person skilled in the art cannot conceive a concrete product with such function or characteristics, etc., even by taking into consideration the common general knowledge as of the filing, since the concrete matters pertaining to the invention cannot be understood, the scope of the invention usually cannot be deemed clear. However, even when a concrete product can not be conceived, if the invention disclosed in the specification or the drawings cannot be properly identified unless defining the product by its function or characteristics, etc., it is not appropriate to determine that the scope of the invention is unclear only on the basis of the ground that a concrete product can not be conceived. In this case, if the relation between the product with the function or characteristic, etc., concerned and the technical standard as of the filing can be understood, the scope of the invention should be treated as being clear." (Part I, Chapter 1, 2.2.2.1 Typical Examples of Violation of Section 36(6)(ii), (6))

(Date manuscript received: July 4, 2005)