HOW TO OBTAIN A PATENT FOR AN ANTIBODY PREPARATION IN JAPAN

Digest Version

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Published December 1, 2009 by SK Patent Corporation

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1. Introduction

Until now, in the pharmaceutical industry, there was a traditional innovative drug development strategy where a library of low molecular weight organic compounds was built up, and drug candidate compounds were searched for by screening. However, in the drug market of the developed nations such as Japan, the U.S. and Europe, bio-medicines and antibody drug products account for a large percentage of the new drugs which are approved, and in many cases, a different approach is used from the traditional innovative drug development strategy. So, if the innovative drug development strategy is different, then the intellectual property strategy for protecting the fruits of innovative drug research must also be different.

In the research and development of biomedicines and antibody preparations, there are many cases where a drug strategy based on the target mechanism is developed right from the beginning, rather than in the traditional method where the approach starts by screening compounds, so if a gene/protein/mechanism has been discovered at the *in vitro* level, it is important to acquire patent rights for the antibody which binds to the antigen involved with this gene/protein/mechanism as soon as possible.

But it is of course difficult to acquire pharmacological data to secure patent rights for a "pharmaceutical product claim". Therefore, how to draft a claim whereby rights can be exercised for a biomedicine/antibody preparation which is a final product based on experimental data which only suggests a mechanism of action *in vitro*, and which does not reach the level of pharmacological data, yet still smoothly secure inviolable rights, is the key to intellectual property strategy in the field of biomedicines and antibody preparations. On this point, European and American pharmaceutical companies have evolved a very skilful intellectual property strategy where some way is found of efficiently securing patent rights for candidate biomedicines and antibody preparations with a low research budget. It is true to say that in the field of biomedicines and antibody preparations, European and American pharmaceutical companies have

succeeded in obtaining an oligopoly on important patents by means of this skilful strategy.

As to exactly what the IP strategy used by European and American companies is, we have analyzed Japanese Unexamined Patent Publications and Granted Patent Publications*, and have made a study of this skilful strategy. So armed with this knowledge, we would like to describe the IP strategy that should be used to conquer the Japanese pharmaceutical product market. We fervently hope that this will greatly assist the IP divisions of European and US pharmaceutical companies to secure a leading position in Japan's domestic pharmaceutical product business.

2. Antibody Drug Products (Definition, Market, and Type)

Before going into a detailed discussion of the main points of the patent system for antibody drug preparations, I would first like to give a brief overview of antibody drug products. Those of you who already have sufficient experience can skip this chapter.

2.1 Definition of antibody preparation

Man is endowed with a defense system which protects his body. This is a mechanism (antigen-antibody reaction) in which a protein, such as a bacteria or a virus, is recognized as a foreign body (antigen), and an antibody protein attacks the foreign body.

An antibody preparation is a pharmaceutical product which makes use of this reaction that man possesses.

There are various mechanisms whereby an antibody demonstrates its curative effect, i.e.:

1) a signal by which proliferation of cancer cells is suppressed,

2) an apoptosis signal is activated, which kills cancer cells,

3) there is complement-dependent cell-mediated cytotoxicity (CDC), or

4) there is antibody-dependent cell-mediated cytotoxicity (ADCC).

ADCC (antibody-dependent cellular cytotoxicity) is one of the functions of man's immune system wherein leukocytes, such as natural killer cells and monocytes, kill target cells such as cancer cells through an antibody. Among the antibody preparations already marketed, ADCC is one of the main antitumor

mechanisms employed (e.g., Herceptin: metastatic breast cancer therapy, Rituxan: non-Hodgkin's lymphoma therapy), and the enhancement of this activity is attracting attention all over the world as next-generation antibody technology. Moreover, since it is possible to achieve a good effect at low dose, it is expected there will be major advantages in this approach such as cost-cutting and reduction of adverse drug reactions[2].

2.2 The market for antibody preparations

The market size for biomedicines in 2005 in Japan was estimated at a little over 450 billion yen, and sales of antibody preparations are thought to account for a little more than 50 billion yen. Sales of antibody preparations rapidly expanded in 2002 and thereafter, and they are expected to reach a market scale of hundreds of billions of yen in the future[4].

This is because antibody preparations have the following outstanding features not found in conventional low molecular weight compounds.

1) High effect, few adverse drug reactions

They have high specificity and affinity for the target (antigen).

They do not affect moieties other than the target.

2) They can target various reagents

They target a diversity of target molecules (antigens).

They have diversity of action.

3) They can be produced industrially

They can be modified and improved by genetic engineering.

Techniques can be evolved to design recombinant materials.

Since antibody preparations have such outstanding features, therapeutic techniques are expected to be devised soon for target molecules discovered by genome research[4].

2.3 Types of antibody preparation

Here, although there are many classes and subclasses of antibody, such as IgG 1, IgG 2, IgG 3, IgG 4, IgM, IgA 1, IgA 2, sIgA, IgD, and IgE, it is IgG 1 which is mostly used as an antibody preparation. This is because as far as concerns its half-life in blood, complement-fixation properties, Fc receptor affinity and placental transfer properties,

IgG 1 has all the features required of an antibody preparation in good balance.

Antibody preparations may broadly be classified as mouse antibodies, chimeric antibodies, humanized antibodies, and human antibodies. Of these, mouse antibodies and chimeric antibodies were used in the past, but most antibody preparations marketed these days are humanized antibodies and human antibodies[4)].

The main target of antibody preparations is cancer, and this is followed by immune system disorders and inflammation. Cancer, immune system disorders and inflammation account for more than 50% of all the antibody preparation products currently available
(PI - marketed products)[4)].

The types of antibody preparation may be broadly classified according to their mechanism of action as targeting antibodies, signaling antibodies, and blocking antibodies. In the classification of current antibody drug preparations (PI - marketed products), blocking antibodies account for over 50%. Next is targeting antibodies, and so blocking antibodies and targeting antibodies together account for more than half. The signaling antibody mechanism of action is not much used[4)].

2.4 Recent trends (Kyowa Hako's Potelligent (Registered Trademark) Technology)

In the development of future antibody preparations, Potelligent (registered trademark), an ADCC antibody production technology developed by Kyowa Hako, is now attracting attention. KIRIN BREWERY announced the purchase of Kyowa Hako at the end of the year in 2007, and in the pharmaceutical manufacturing industry, there were rumors that this was in order to acquire Potelligent (registered trademark). The feature of this Potelligent (registered trademark) technology is fucose, one of the sugar chains in the antibody. By reducing the amount of fucose, ADCC is vastly improved, and the target, e.g., cancer cells, can be very efficiently killed. In the past, there had been studies on sugar chains other than fucose, and other studies which tried to increase activity by aminoacid substitution, but the effect was apparently not very large. Kyowa Hako already found in animal experiments that the antibodies used in this technology showed an antitumor effect more than 100 times that of previous

antibodies, and that they could also contribute to the creation of anti-allergy antibody preparations.

3. Simple Overview of the Patent System

Before going into a detailed discussion of the main points of the patent system as it relates to antibody drug products, I would like to simply describe the Japanese patent system for the benefit of those not familiar with Japanese patent law. Those who already have sufficient experience of patent procedure can skip this chapter if they like.

3.1 What is a patentable invention?

The purpose of the Patent Law is defined as "Encouraging inventiveness by aiming to protect and utilize inventions, and contributing to the development of industry" (Article 1 of the Patent Law). An invention is a concept and an idea which are not visible, at least not in a form which is visible to the eye like a house or a car which can be occupied and managed. Therefore, if there is no system to adequately protect inventions, the inventor must keep his invention secret so that it is not stolen by others. However, then, not only can the inventor not use his own invention effectively, but others will try to invent the same thing, do useless research and waste investment. Hence, the patent system aims to protect an invention by giving exclusive rights known as patent rights to the inventor for a fixed time under fixed conditions, and by publishing an invention to provide an opportunity to use it, it aims to make new technology the common property of mankind, stimulate technological progress, and contribute to the growth of industry. In other words, the patent system opens (discloses) new technology to the world, while giving exclusive rights of use to the inventor, and by disclosing the invention, a way is opened to use the invention, thereby providing an incentive for improved inventions and new inventions[5)].

3.1.1 Legal inventions

In the Patent Law, an "invention" is defined as "a crystallization of technological ideas using natural laws" (Patent Law, Article 2, No. 1), and aims to protect inventions which are industrially applicable[5)]. With regard to inventions relating to "antibody preparations", such inventions are normally

deemed to be "a crystallization of technological ideas thought using natural laws", and therefore this point normally poses no problem.

3.1.2 Industrial applicability

Just because an invention has been perfected, it does not mean that it can receive a patent. In order to obtain a patent, it is necessary to satisfy the requirements for an "invention which can obtain a patent" as defined by the Patent Law. First of all, in order to be an "invention" which can obtain a patent, it must be possible to implement it industrially. This is merely because, from the viewpoint of the Patent Law which aims to stimulate "the growth of industry", it is not appropriate to protect an invention which can only be practised academically or experimentally. The "industry" meant in the Patent Law is industry in its broadest sense, i.e., not only production industries like refining, mining and agriculture, but also industries which do not produce anything like the service industry and the transport sector[5)].

Now, there are 3 categories of inventions which have no industrial application (and which therefore do not qualify as patentable), i.e.,

(1) An invention which pertains to a method for treatment of the human body by surgery or therapy, or diagnosis (medical devices and pharmaceutical products are regarded as "things"),

(2) An invention which cannot be used industrially, an invention which can only be used by an individual (e.g., method of smoking cigarettes), or an invention which can only be used academically or experimentally,

(3) An invention which is theoretically possible, but whose practical implementation is inconceivable.

An invention of an antibody preparation might correspond to (1) An invention which pertains to a method for treatment of the human body by surgery or therapy, or diagnosis thereof, so care must be taken to avoid the invention being classified this way. In other words, if it is attempted to secure patent rights for an invention relating to an "antibody preparation" in Japan, care must be taken to draft the claims so that it is not interpreted as "An invention which pertains to a method for treatment of the human body by surgery or therapy, or diagnosis".

3.1.3 Novelty and inventiveness

An "invention" which can obtain a patent must be "a new thing" which does not previously exist. This is generally referred to as "novelty." This is because granting exclusive rights like patent rights to an invention which everybody already knows, would offer no advantage to society. Under the Patent Law, the scope of an invention which does not have novelty is clearly defined, and a patent cannot be obtained in the following cases:

1) An invention which was widely known in Japan and abroad before the present application was made (e.g., television broadcasts and announcements)

2) An invention which was widely practised in Japan and abroad before the present application was made (e.g., sold in a shop or observed by unspecified persons during a manufacturing step),

(3) An invention which was disclosed in the form of a distributed publication, or which has become widely available through telecommunications circuits (e.g., patent gazettes published in Japan or abroad, research papers, in books or on CD-ROM, or published on the Internet)[5].

In addition to this, even if there is "inventiveness", a patent cannot be obtained for an invention which can easily be conceived by anybody, such as an invention which only represents a minor improvement over an invention which is already known. This is because if a patent were granted to obvious inventions which made no contribution to the progress of science and technology, even to those which did not have sufficient value to be patented and which could easily be conceived, then a whole plethora of applications would be required for technological improvements which are made every day to stop others obtaining a patent, which would be a great nuisance. In general, "it would be easy to conceive of the invention" is described as lack of "inventiveness". The decision regarding "inventiveness" is based on whether or not a person skilled in the art could easily conceive of the invention[5].

3.1.4 Important points specific to antibody preparations

In the case of inventions related to "antibody preparations", the concept of "usage invention" is often used to determine "novelty" and "inventiveness". In Japan, "usage invention" is understood to be an invention which focuses on the specific properties of a thing, and is based on the discovery of how to use it (it may be an invention of a thing or a method). Claims for a usage invention may

be claims which define a "thing limited to an application", a "method" and a "use" (however, from the viewpoint of industrial applicability mentioned above, "method" and "use" claims are not recognized for pharmaceutical applications)[10-12]. In Japanese examination criteria, if "the invention is an invention for which there is a use limitation in the claims, and the invention in the claims is based on the fact that new properties were discovered for something, due to which this thing has new uses, then since the use limitation is what specifies the invention, it is appropriate to interpret the invention so that it includes the viewpoint of use limitation". Therefore, in this case, even if the thing itself is already known, the invention relating to the claims can have novelty as a use[7].

In other words, in Japan, an invention which is recognized to be creative in that it is used for a specific purpose which was hitherto unknown regarding previous use, based on hitherto unknown properties of a certain thing, is generally considered to possess novelty as a use. This concept of usage invention is applied in technical fields where it is relatively difficult to understand how a thing is used from its structure or name (e.g., applications of compositions containing chemical substances), which is characteristic of "antibody preparations". On the other hand, in the case of machines, tools, articles and equipment, since the thing and its application are one thing, the concept of usage invention is not normally used.

3.2 What is a specification for obtaining a patent?

The protection and use of a patent under the patent system are obtained via a "specification, claims and required drawings (hereafter referred to as "specification, etc.,"), which have the functions of a technical document for disclosing the technical details of the invention, and a deed of rights for defining the technical scope of the invention. Therefore, in order to obtain a patent, it is necessary to clarify the details of the invention to the extent that a person skilled in the art can easily understand them.

In so doing, the details must be described clearly and succinctly using simple and clear wording. If these requirements are not satisfied, then a patent cannot be obtained[5].

3.2.1 Support requirement and enablement requirement

The support requirement is a requirement whereby an "invention for which it is desired to obtain a patent as specified in the claims, is described in the Detailed Description of the Invention" (Clause 36, Article 6, No. 1). In other words, an invention specified by claims must not be broader than the scope of the invention in the Detailed Description of the Invention. This is because if an invention described in the claims were not described in the Detailed Description of the Invention, it would mean claiming rights for an undisclosed invention. The support requirement is intended to prevent this[6)].

According to the examination criteria of Japan, the decision as to whether the claims comply with Clause 36, Article 6, No. 1 is made by comparing the invention as in the claims with the Detailed Description of the Invention. When making this comparison, an examination is made as to whether there is a real correspondence between the two, without being concerned by the question of whether there is compatibility with the terminology used in the Detailed Description of the Invention. This is because if it were understood to be only a matter of compatibility of terminology, rights would accrue in respect of patents which had not actually been disclosed, which is contrary to the intention of this clause. The examination as to whether there is real correspondence is performed by determining whether or not the scope of the invention in the claims exceeds that of the Detailed Description of the Invention. {Repetition!} This ensures that the problems which the invention purports to solve can be solved to the satisfaction of a person skilled in the art. If it is deemed that the scope of the invention within which the problems can be solved to the satisfaction of a person skilled in the art, has been exceeded, then it is deemed that there is no real correspondence between the invention as in the claims, and the Detailed Description of the Invention, which contravenes Clause 36, Article 6, No. 1 of the Patent Law.

On the other hand, the enablement requirement is a requirement whereby the Detailed Description of the Invention "must be sufficiently clear and detailed that a person having ordinary knowledge in the technical field to which the invention belongs can carry it out" (Clause 36, Article 4, No. 1). Namely, this requirement stipulates that the invention must be described to the extent that a person having ordinary creative ability in the technical field to which the invention belongs could, using ordinary technical means available for research and

development (documents, experiments, analysis and production), practise the invention in the claims based on the description in the specification, and the technical knowledge prevailing at the time of filing (known as the "Enablement Requirement")[6].

Therefore, when a person skilled in the art tries to implement the invention based on the disclosure of the invention in the specification and drawings and the technical knowledge prevailing at the time of filing, and cannot understand how to do it (for example, when trial and error or complicated experiments expected of a person skilled in the art are required in order to discover how to implement the invention), it is said that the Detailed Description of the Invention is not sufficient for a person skilled in the art to carry it out[6].

Stating that "this invention" can be practiced in the enablement requirement clause, means, in the case where the invention is that of a product, that the product can be manufactured and that this product can be used; in the case where the invention is that of a method, that the method can be used; and in the case where the invention is that of a method to manufacture a product, that the product can be manufactured by that method[6].

3.2.2 Requirements for claims

Among the requirements for claims, the important requirement of clarity of invention states that "an invention listed in claims for which it is designed to obtain a patent must be clearly described" (Clause 36, Article 6, No. 2). In other words, this is a requirement which stipulates that an invention for which it is desired to obtain a patent must be described so that it can be clearly understood. This is because if the invention for which it is desired to obtain a patent cannot be clearly understood, no precise judgement can be made as to the requirement of novelty or inventiveness, and it is also difficult to understand its technical scope[6].

Due to this requirement of clarity, since the invention must be described in the claims so that it can be clearly understood from claim 1, an invention which is described using various expressions by an applicant will be accepted as long as it is clear. For example, in a technical field where it is difficult to predict the structure of something from its action, function, nature or properties (hereafter, "function/properties"), since the claims specify things by their function and

properties, the scope of the invention is often unclear (e.g., inventions of chemical substances). Similar considerations apply when the claims specify something by a result which has to be achieved or by special parameters[6)].

3.2.3 Important points specific to antibody preparations

In order to satisfy the support requirement and enablement requirement, in inventions belonging to technical fields where it is relatively difficult to understand how to make something or use something from its structure or name (e.g., chemical substances), as with an "antibody preparation", it is generally necessary to provide one or more representative embodiments in the detailed description of the invention so that a person skilled in the art can carry the invention out. Moreover, in the case of a usage invention that makes use of the properties of something (e.g., a pharmaceutical product), an embodiment to back up the application is normally required. In other words, in the field of pharmaceutical preparations, it is necessary to disclose experimental data in some form or other.

3.3 What rights are granted when a patent is obtained?

A patent is a right such that "the patentee has the exclusive right to practise the patented invention commercially" (Patent Law, Clause 68). Therefore, only the patentee can carry out the patented invention commercially - others cannot carry out the patented invention commercially without giving due notice. Here, "commercially" has the broad meaning of "business", not only for profit, but also including public works and public utilities. This does not apply however when the invention is carried out privately or in the home. "Implementation" means the actions listed below specified in the Patent Law, Clause 2, Article 3.

3.3.1 Difference in rights depending on type of invention

The Patent Law (Clause 2, Article 3) broadly distinguishes inventions as an "invention of a product" or "invention of a method", and makes the further distinction of an "invention of a method to manufacture a product", from which stems the definition of "implementation" of the invention. The scope covered by the patent consequently differs depending on which of these three types of invention is involved (Patent Law, Clause 68, Article 2, No. 3).

(1) In the case of an invention of a product: the patent covers the manufacture, use, transfer, lending or importation of the product, or request to transfer or lend the product (including display for the transfer or lending).

(2) In the case of an invention of a method: the patent covers use of the method.

(3) In the case of an invention of a method to manufacture a product: the patent covers use of the method, and use, transfer, lending or importation, or request to transfer or lend a product manufactured by the method.

Therefore, to obtain a broad, strong patent, the invention for which it is desired to obtain a patent must be considered and understood from various aspects. Since the scope of a patent differs depending on the category of the invention, the best way is to make good use of the category to describe the details of the invention. Therefore, when the invention is both that of a product and that of a method, it is effective to describe it as both an "invention of a product" and "an invention of a method"[5)].

3.3.2 Technical scope of the invention

If another party's technology is used without permission, it will infringe the patent. The scope (technical scope) for which an exclusive patent is granted is determined based on the claims (Patent Law, Clause 70). For example, if there is something which is not included in the claims even if it is described in the specification, it does not fall under the technical scope of this invention. The meaning of the terms in the claims is interpreted with reference to the specification and drawings. The interpretation may also refer to the progress of the application or the technology known in the art[5)].

3.3.3 Important points specific to antibody preparations

In the case of antibody preparations, the scope of a patent is different in the case of a substance patent and a usage patent. That is, although the scope of a substance patent is broad, the scope of a usage patent is narrow by comparison. Also, in the case of a usage patent, there is a theory stating that the scope of a patent is different for a drug claim based on a mechanism of action, and a pharmaceutical product claim based on pharmacological data[10-12)].

Specifically, the technical scope of a patented invention of an antibody preparation is interpreted as follows.

Example 1: Activity suppressor ●● (D) containing (C) an antibody binding to an antigen ●● (B) having an epitope (requirement A) comprising an aminoacid sequence of sequence number ●● + E (where this antibody is a humanized antibody)

Technical scope of the invention

Component requirements

A+B+C+D

A+B+C+D (within the scope)

A+B+C+D+E (within the scope) (usage invention)

A+B+D (outside the scope)

α+B+C+D (outside the scope) (exception: equal)

How to determine scope of patented invention (Clause 70)

Example 2: In the above antibody example, unless all the requirements A-D are satisfied, they are not included in the technical scope. For example, if there is an activity promoter ●● or an activity suppressor xx instead of the activity suppressor ●●, since it is not the activity suppressor ●●, requirement D is not satisfied. Similarly, in the case of a DNA aptamer rather than an antibody (requirement C is lacking), or an epitope comprising an aminoacid sequence of sequence number xx (requirement A is lacking), this is not included within the technical scope. However, in the case of a humanized antibody, although the new element E has been added, since all the requirements A-D are satisfied, it will be contained in the technical scope.

4. Examination Criteria for Antibody Preparations

In the field of antibody preparations, as for patent applications in any technical field, the examination criteria[6)] already mentioned in "Part 1, Specification and Claims, Chapter 1, Specification and Claims Requirements"[6)], and "Part II, Patent Requirements, Chapter 2, Novelty and Inventiveness"[7)], can also be used .

However, in the special technical field of "antibody preparations", there are many cases where, if the usual examination criteria developed mainly for the machinery/electrical field were applied, it would be inconvenient. "Part VII,

Examination Criteria for Special Technical Fields, Chapter 2, Biology-Related Inventions"[8], "Part VII, Examination Criteria for Special Technical Fields, Chapter 3 Pharmaceutical Inventions"[9], and "Part II Patent Requirements, Chapter 2, Novelty and Inventiveness"[7] already cover this, but a series of "Revised Criteria for Novelty and Inventiveness" have been drawn up in recent years, which are now used in the examination procedure.

4.1 Examination criteria for biological inventions

In the examination criteria for biological inventions, the part "1. Genetic engineering" is particularly important.

At the beginning of this part "1. Genetic engineering", the following is stated: [Here, "genetic engineering" means the technology of manipulating genes artificially by gene recombination, cell fusion, etc. Inventions related to genetic engineering include those that deal with genes, vectors, recombinant vectors, transformants, syncytiums, proteins obtained by transformation techniques (hereafter referred to as "recombinant proteins"), and monoclonal antibodies. In principle, inventions related to bacteria, plants and animals obtained by genetic engineering are dealt with here][8].

4.1.1 Examination criteria for monoclonal antibody claims

In "1. Genetic engineering", the monoclonal antibody is described as follows.

"A monoclonal antibody can be specified by an antigen which the monoclonal antibody recognizes, by a hybridoma which produces the monoclonal antibody, and by cross-reactivity".

Example 1: Monoclonal antibody to antigen A.

(Note) Antigen A must be specified as a substance.

Example 2: Monoclonal antibody to antigen A produced by a hybridoma with the deposition No. ATCC HB-OOOO.

(Note) Antigen A must be specified as a substance.

Example 3: A monoclonal antibody which reacts with antigen A and does not react with antigen B.

(Note) Antigen A and antigen B must be specified as substances[8].

Here, the most important point is that "a monoclonal antibody can be specified by an antigen". That is, when a certain specific antigen (a protein or a gene

which encodes the protein) is discovered, if the mechanism has been analyzed, then the monoclonal antibody which combines with the specific antigen can also be specified by specifying the aminoacid sequence of the antigen or the base sequence encoding the antigen.

In other words, if it is desired to specify an antibody preparation containing a monoclonal antibody, it is not necessary to analyze the aminoacid sequence of the monoclonal antibody itself, and it is sufficient to merely specify the aminoacid sequence of the antigen (or base sequence which encodes the antigen). Therefore, when looking for candidate substances for pharmaceutical products, by broad, high throughput screening using a DNA chip or a protein chip, etc., if a certain specific antigen protein (or gene which encodes the protein) is discovered and its function is analyzed, it is best to not only patent the protein, gene, etc., of the specific antigen as a substance or use, but also to patent the monoclonal antibody which combines with the specific antigen as a substance or use together.

If it is desired to specify an antibody preparation containing a monoclonal antibody, it can be specified by a hybridoma that produces the monoclonal antibody or by cross-reactivity, etc., but the technical scope of the patented invention obtained by these specification methods will be very narrow.

On the other hand, if it is specified by the antigen which the monoclonal antibody recognizes, the technical scope of the patented invention obtained by these specification methods will probably be very wide. Therefore, it is advisable to draft the specification focused on the antigen which the monoclonal antibody recognizes, and to gain supplemental support by also drafting claims specifying hybridomas which produce the monoclonal antibody and its cross-reactivity.

4.1.2 Examination criteria for recombinant protein claims

In "1. Genetic engineering", the method of specifying a recombinant protein for specifying the aminoacid sequence of an antigen which is a requisite for specifying a monoclonal antibody, is defined as follows.

Specifically,

"(1) The recombinant protein may be specified by an aminoacid sequence or by the base sequence of the structural gene which encodes it.

Example 1: Recombinant protein consisting of an aminoacid sequence denoted by Met-Tyr -.... Cys-Leu

(2) The recombinant protein may be specified in an all-inclusive way by combining expressions such as "loss, substitution or addition", the functions of the recombinant protein, and, if required, the source/origin of the gene which encodes the recombinant protein. (However, the requirement of clarity, and the enablement requirement, must be satisfied).

Example 2: The following recombinant protein (a) or (b)

(a) Protein consisting of an aminoacid sequence denoted by Met-Tyr -.... Cys-Leu

(b) Protein having the aminoacid sequence (a), but wherein one or more aminoacids is missing, substituted or added, and having A enzyme activity.

(Notes)

The protein (a) has A enzyme activity.

The protein (b) is described in the Detailed Description of the Invention so that a person skilled in the art can manufacture it without trial and error or complex experiments beyond the ordinary creative ability of a person skilled in the art.

(3) The recombinant protein may be specified by its functions, physicochemical properties, source/origin and method of manufacture (however, the invention must be clear, and the enablement requirement must be satisfied"[8)].

Here, if it is desired to secure as broad rights as possible for an antibody preparation containing a monoclonal antibody, then as broad rights as possible should be secured for the aminoacid sequence of the antigen with which the monoclonal antibody combines.

Therefore, regarding the aminoacid sequence of the antigen, as mentioned above, the best plan is to attempt to secure rights not only for the specific aminoacid sequence used in experiments, but also for an aminoacid sequence in which one or more aminoacids are missing, substituted or added, and which has identical enzyme activity. In this case, apart from those sequences which have "missing, substituted or added" aminoacids, another extension may be made into sequences which have a "homology of at least ○○%", and it is prudent to use these according to the situation, or to use them in conjunction.

4.1.3 Examination criteria for gene claims

In "1. Genetic engineering", the method of specifying a gene involved in a base sequence encoding an antigen which is a requisite for specifying a monoclonal antibody, is defined as follows.

Specifically, "(1) A gene may be specified by a base sequence.

(2) A structural gene may be specified by an aminoacid sequence of a protein encoded by this gene.

Example 1: Gene which consists of an aminoacid sequence denoted by Met-Asp -.... Lys-Glu.

(3) A gene may be specified in an all-inclusive way by combining expressions such as "loss, substitution or addition", or “hybridized”, the functions of the gene, and, if required, the source/origin. (However, the requirement of clarity, and the enablement requirement, must be satisfied).

Example 2: A gene which encodes the following proteins (a) or (b)

(a) Protein which consists of an aminoacid sequence denoted by Met-Tyr -.... Cys-Leu

(b) Protein having the aminoacid sequence (a), but wherein one or more aminoacids is missing, substituted or added, and having A enzyme activity.

(Notes)

The protein (a) has A enzyme activity.

The protein (b) is described in the Detailed Description of the Invention so that a person skilled in the art can manufacture it without trial and error or complex experiments beyond the ordinary creative ability of a person skilled in the art.

Example 3: Gene consisting of the DNA of (a) or (b) below

(a) DNA having the base sequence ATGTATCGG...TGCCT

(b) Human DNA which is obtained by hybridizing DNA having the base sequence (a) with DNA consisting of a complementary base sequence under stringent conditions, and having B enzyme activity.

(Note)

The DNA encoded by protein (a) has B enzyme activity. It is assumed that the "stringent conditions" are described in the Detailed Description of the Invention.

(4) A gene can also be specified by its mechanism, physicochemical nature, source/origin, and manufacturing process (however, the requirement of clarity, and the enablement requirement, must be satisfied)[8)].

Here, if it is desired to secure rights for an antibody preparation containing a monoclonal antibody as broadly possible, it is best to specify the base sequence encoding the antigen with which the monoclonal antibody combines as broadly as possible. Therefore, as for the base sequence encoding the antigen, as mentioned above, it is best to secure rights not only for the specific base sequence used for experiments, but also for a base sequence obtained by hybridizing DNA having that base sequence with DNA having a complementary base sequence under stringent conditions, and having B enzyme activity. In this case, apart from this extension to "hybridized" type, another extension may be made into types which have a "homology of at least ○○%", and it is prudent to use these according to the situation, or to use them in conjunction.

4.1.4 Examination criteria for enablement requirement in biological inventions

Although we have said it before, in technical fields (e.g., chemical substances) where it is relatively difficult to understand how a thing is made or used from its structure or name, as with "antibody preparations", it is generally necessary to provide one or more representative embodiments in the detailed description of the invention so that a person skilled in the art can carry the invention out. Moreover, in the case of a usage invention that makes use of the properties of something (e.g., a pharmaceutical product), an embodiment that backs up the application is normally required. In other words, in the field of "pharmaceutical preparations", it is necessary to disclose experimental data in some form or other. Regarding this point, as far as concerns the examination criteria for biological inventions, in "1. Genetic engineering", the enablement requirement is described as follows.

Specifically, "Clause 36, Article 4, No. 1 notes that "the Detailed Description of the Invention...must be stated clearly and fully to the extent that a person having ordinary creative ability in the field to which the invention belongs, can practise the invention.

The meaning of this is that, the detailed description of the invention must be stated to the extent that, using the ordinary technical means in research and development (including document analysis, experiments, analysis and manufacture) in the technical field to which the invention belongs, a person

having ordinary creative ability (a person skilled in the art) can practise the invention based on the the specification and drawings, and the technical knowledge prevailing at the time of filing. Therefore, when a person skilled in the art tries to practise the invention based on the teachings of the invention as outlined in the specification and drawings, and cannot understand how to do so (e.g., trial and error and complicated experiments beyond what can be expected of a person skilled in the art are required to find out how to practise the invention), it is deemed that the Detailed Description of the Invention is not sufficiently clear for a person skilled in the art to practise it"[8)].

Specifically, to satisfy the enablement requirement for an invention of an antibody preparation, it must be written so that the antibody preparation containing the monoclonal antibody, and the aminoacid sequence of the antigen specifying the monoclonal antibody or the base sequence encoding that antigen, can be manufactured (without requiring trial and error or complex experiments beyond the ordinary creative ability of a person skilled in the art).

That is, according to the examination criteria, the invention of a "gene, vector, recombinant vector, transformant, syncytium, recombinant protein, or monoclonal antibody", must be described so that a person skilled in the art can manufacture it.

Therefore, even if there is no detailed statement about how to manufacture it, the manufacturing method must be described in sufficient detail except in the case where a person skilled in the art could manufacture it based on the specification and drawings, and the technical knowledge prevailing at the time of filing.

(1) Gene, vector, or recombinant vector

As to methods of manufacturing these, sources and origins, how to procure the vectors used or the enzymes used, the process conditions, the sampling and refining steps, and the means of verification must all be described. If genes are mentioned comprehensively in the claims,

when trial and error or complex experiments are required beyond the extent which can be expected from a person skilled in the art, the Detailed Description of the Invention must be written so that a person skilled in the art can manufacture the object of the invention in order to obtain these genes.

For example, in claims specifying a gene which was actually obtained and genes having very low homogeny with respect to it by means of function, if there are many genes that do not have an identical function to the gene that was actually obtained among the genes of very low homogeny, if trial and error or complex experiments would normally be required beyond the extent which can be expected from a person skilled in the art to select genes having an identical function to the genes obtained, then it is deemed that the invention is not sufficiently clearly stated to the extent that a person skilled in the art could manufacture the object of the invention.

Example: A gene comprising the DNA (a) or (b) below:

(a) DNA consisting of the base sequence ATGTATCGG...TGCCT

(b) A base sequence having a homology of ○○% or more with the DNA consisting of the base sequence (a), and encoding a protein having B enzyme activity.

(Note) The protein encoded by the DNA (a) has B enzyme activity.

○○% is a very low homogeny.

(Explanation)

Although (b) is specified by a function, it contains a gene having a very low homogeny with the actually acquired gene (a). When there is a large amount of DNA encoding a protein which does not have B enzyme activity in the "DNA consisting of a base sequence having a homology of ○○% or more with the DNA of base sequence (a)", then trial and error or complex experiments would normally be required beyond the extent which can be expected from a person skilled in the art in order to select the DNA encoding the protein having B enzyme activity, thus, the Detailed Description of the Invention must be written so that a person skilled in the art can manufacture the object of the invention.

(2) Recombinant protein

As regards the method of manufacturing a recombinant protein, the method of procuring a vector or host used for a gene/expression which encodes the recombinant protein, the method of introducing the gene into a host, the step for sampling/refining the recombinant protein from a transformant incorporating the gene, and means of verifying the recombinant protein, should be described. (Regarding the enablement requirement when a recombinant protein is

described comprehensively, see the above "(1) Gene, vector, or recombinant vector").

(3) Monoclonal antibody

As for production of a monoclonal antibody, the methods of procuring an immunogen and means of manufacture, immunization procedures, selection extraction procedures for antibody-producing cells and means of identifying monoclonal antibodies, should be described[8)]. Here, the practically most important consideration is that recently, the level of technology has reached the point where, as long as one can specify the aminoacid sequence of an antigen or the base sequence which encodes the antigen, a person skilled in the art who can achieve a level of technical feasibility by ordinary experimental protocols can manufacture the monoclonal antibody for that antigen.

Therefore, if a certain specific antigen (a protein or a gene which encodes the protein) is discovered and its mechanism is analyzed, the monoclonal antibody combined with the specific antigen can be produced by an ordinary experimental protocol.

That is, if it is desired to obtain rights for an antibody preparation containing a monoclonal antibody, it is sufficient if the enablement requirement is satisfied for the aminoacid sequence of the antigen with which the monoclonal antibody combines (or the base sequence encoding that antigen). Taking this to the extreme, there is no need to actually manufacture the monoclonal antibody itself, and as long as the experimental protocol for a method of manufacturing a typical monoclonal antibody is described as a sort of paper example, the enablement requirement for the monoclonal antibody will be satisfied.

Therefore, when looking for candidate substances for pharmaceutical products, by broad, high throughput screening using a DNA chip or a protein chip, if a certain specific antigen (protein or gene which encodes the protein) is discovered and its function is analyzed, if the protein or gene of the specific antigen can be patented not only as a substance or use, and in particular if the antigen can be patented as a substance, since it is completely unnecessary to actually manufacture the monoclonal antibody, it is best to also patent the monoclonal antibody which combines with the specific antigen as a substance or use.

4.1.5 Examination criteria for deposition in biological inventions

Although this was mentioned earlier, in technical fields (e.g., chemical substances) where it is relatively difficult to understand how a thing is made or used from its structure or name, as with "antibody preparations", it is generally necessary to provide one or more representative embodiments in the Detailed Description of the Invention so that a person skilled in the art can carry the invention out. Moreover, in the case of a usage invention that makes use of the properties of something (e.g., a pharmaceutical product), an embodiment that backs up the use is normally required. In other words, in the field of "pharmaceutical preparations", it is necessary to disclose experimental data in some form or other. However, in the case of a biological invention, even a person skilled in the art may not be able to implement the invention, and the enablement requirement can then be compensated for by depositing the necessary microorganism, vector, hybridoma, etc.

Regarding this point, as far as concerns the examination criteria for biological inventions, in "1. Genetic engineering", the enablement requirement is described as follows.

Specifically, it is stated that “(b) in the invention of a gene, a vector, a recombinant vector, a transformant, a syncytium, a recombinant protein or a monoclonal antibody, when the specification cannot be written so that a person skilled in the art can carry it out, a transformant (including a transformant which produces a recombinant protein) and syncytium (including a hybridoma which produces a monoclonal antibody) into which the manufactured gene, vector, or recombinant vector was introduced should be deposited, and an accession number written in the specification at the time of application.

(c) Since a hybridoma which produces a monoclonal antibody satisfying restrictive conditions (for example, monoclonal antibody which specifies compatibility with respect to antigen A by a restrictive coupling constant), is not reproducible in many cases, in an invention relating to a monoclonal antibody satisfying restrictive conditions, and an invention relating to a hybridoma which produces this monoclonal antibody, it is required to deposit this hybridoma and to write the accession number in the specification at the time of filing, except for the case where a person skilled in the art can manufacture the target based on the statements of the specification”[8)].

However, recently, the level of technology has reached the point where, as long as one can specify the aminoacid sequence of an antigen or the base sequence which encodes the antigen, a person skilled in the art who can achieve a level of technical feasibility by ordinary experimental protocols can manufacture the monoclonal antibody for that antigen. Therefore, it should be noted that if a common antigen is targeted and a common monoclonal antibody is obtained, it is no longer necessary to deposit a hybridoma. Nevertheless, as shown in (c) of the above examination criteria, in targeting a special antigen, or in aiming to obtain a patent for a monoclonal antibody which has a special structure or properties, "since the hybridoma which produces such a special monoclonal antibody is not reproducible in many cases", it is still wise to deposit the hybridoma as before.

4.1.6 Examination criteria for novelty and inventiveness in biological inventions

As was mentioned earlier, in the case of inventions related to "antibody preparations", the concept of "usage invention" is often used to determine "novelty" and "inventiveness". In Japan, usage inventions are interpreted as inventions based on the discovery of a way of using something (which may be an invention of a thing or a method), focusing on the unique properties of that thing. Claims for a usage invention may be claims which define a "thing limited to a use ", "method" and "use" (however, from the viewpoint of industrial applicability mentioned above, "method" and "use" claims are not recognized for pharmaceutical applications)[10-12].

Regarding this point, as far as concerns the examination criteria for biological inventions, in "1. Genetic engineering", the enablement requirement is described as follows regarding novelty and inventiveness.

Specifically, concerning the novelty of a monoclonal antibody, "if (1) antigen A is new, the monoclonal antibody to this antigen A usually has novelty. However, if the monoclonal antibody to a known antigen A' is known, and when antigen A is a partial modification of the known antigen A' and has the same epitope as this antigen A', the monoclonal antibody to antigen A' also reacts with antigen A. Therefore, in such a case, the invention of "the monoclonal antibody to antigen A" does not have novelty.

(2) As to an invention where the monoclonal antibody combined with antigen A is known, and "reacts with antigen A but does not react with an antigen B" specified by cross-reactivity with antigen B which is different from antigen A, when there is no special technical significance in having specified the monoclonal antibody by this cross-reactivity (when it is clear that the monoclonal antibody to the known antigen A does not react with antigen B since antigen B has few similarities of structure and function with antigen A), it is deemed that the antibody does not have novelty".

As to the inventiveness of the monoclonal antibody, "(5) when antigen A is known and it is clear that antigen A has immunogenicity (for example, when the polyclonal antibody to antigen A is known, and it is clear that antigen A has immunogenicity such as when it is a polypeptide with a large molecular weight), the invention of "the monoclonal antibody to antigen A" does not have inventiveness". However, if the invention is further specified by other features, and if the invention has an advantageous effect which could not be predicted by a person skilled in the art, it does have inventiveness[8)].

Stating the examination criteria for inventiveness the other way round, if antigen A is not known or if it is not clear that antigen A has immunogenicity (if antigen A was a new discovery, or antigen A was known previously but a new function was discovered), it is deemed that the invention of "the monoclonal antibody to antigen A" has inventiveness. However, if antigen A was known, but a new function was discovered, inventiveness will actually be difficult to recognize unless it is in the form of an "○○ activity inhibitor which contains a monoclonal antibody that combines with antigen A and inhibits the ○○ activity of antigen A".

Here, what is most important practically is that "if antigen A has novelty and inventiveness, the monoclonal antibody to this antigen A usually has novelty and inventiveness". That is, when a certain specific antigen (a protein or a gene which encodes the protein) is discovered, if the mechanism has been analyzed, novelty and inventiveness can be recognized as a substance or a use for the aminoacid sequence of the specific antigen (or base sequence which encodes the antigen), and novelty and inventiveness can be recognized as a substance or a use also for the monoclonal antibody which combines with the specific

antigen. However, as described earlier, the claims have to be drafted in a special way.

That is, if it is desired to obtain rights for an antibody preparation containing a monoclonal antibody, it is sufficient if the aminoacid sequence of the antigen with which the monoclonal antibody combines (or the base sequence encoding that antigen) has novelty and inventiveness. Therefore, when looking for candidate substances for pharmaceutical products, by broad, high throughput screening using a DNA chip or a protein chip, if a certain specific antigen protein (or gene which encodes the protein) is discovered and its function is analyzed, it is best to patent not only the protein or gene of the specific antigen as a substance or use, but also the monoclonal antibody which combines with the specific antigen as a substance or use. However, if a patent cannot be granted for the antigen as a substance, and it is hoped to obtain a patent for a use in the form of a drug claim as mentioned earlier, it is necessary to disclose experimental data showing that the monoclonal antibody has activity as an ○○ activity inhibitor.

4.2 Examination criteria for pharmaceutical inventions

At the beginning of the examination criteria for pharmaceutical inventions, it states "this chapter focuses on special decisions and handling during the examination of an application relating to a pharmaceutical invention. Here, pharmaceutical invention means an "invention of a product" which belongs to the pharmaceutical field among the applications defined in Examination Criteria Part II, Chapter 2-1.5 .2 (2)". Hence, pharmaceutical inventions are examined in a special, overlapping way based on the aforesaid idea of the usage invention[9)].

In the examination criteria of this pharmaceutical invention, the part "1. Requirements concerning the description and claims" is particularly important.

4.2.1 Support requirement for pharmaceutical inventions

First, as regards the claim support requirement of a pharmaceutical invention, it states:

"Since the regulation of Clause 36, Article 6, No.1 of the Patent Law makes it a requirement that the invention as claimed be specified in the Detailed Description of the Invention, it must not exceed what is described in the Detailed

Description of the Invention. The decision as to whether the claims comply with Clause 36, Article 6, No. 1 is made by comparing the invention as in the claims with the Detailed Description of the Invention insofar as concerns actual points of correspondence. The following are examples where Clause 36, Article 6, No. 1 would be contravened, i.e., where the content of the Detailed Description of the Invention cannot be extended or generalized to the scope of the invention as in the claims.

(1) Although an antiemetic drug which contains a component A as an active substance is claimed in the claims, there is no statement about the pharmacological test procedure which proves that component A has an antiemetic effect, nor is there any pharmacological data in the Detailed Description of the Invention, and it cannot be deduced that component A is effective as an antiemetic drug from the common general technical knowledge prevailing at the time of filing.

(2) Although a patent is claimed comprehensively for a therapeutic agent having a particular use which uses the compound defined with desired properties as an active substance in the claims, in the Detailed Description of the Invention, its usefulness as a therapeutic agent for a particular use has been confirmed only for a very few actual compounds contained in the claims, and beyond this, for most of the compounds contained in the claims, a person skilled in the art cannot deduce usefulness as a therapeutic agent in view of the common general technical knowledge prevailing at the time of filing (Tokyo High Court Decision, 15.12.26 (2003, line 104))"[9)].

Next, as regards the enablement requirement for a claim of a pharmaceutical invention, it is stated: "Since pharmaceutical inventions belong to technical fields where it is usually relatively difficult to understand how to make something or use something from its structure or name (e.g., chemical substances), it is generally necessary to provide one or more representative embodiments in the Detailed Description of the Invention so that a person skilled in the art can carry the invention out. Also, a statement about a pharmacological test result is usually called for as an embodiment which supports a pharmaceutical use". (Specific examples of a statement of a pharmacological test result which is sufficient for supporting a pharmacological action are given below).

(1) Extent of the statement about pharmacological test results

The pharmacological test result has the purpose of confirming whether the pharmaceutical invention in the claims has pharmacological action, so in principle, all of the following must be clarified: (i) which compound, (ii) in what kind of pharmacological test system is it used, (iii) what kind of result was obtained, and (iv) what kind of relevance does the pharmacological test system have to the medical application of the pharmaceutical invention in the claims.

Although in principle, pharmacological test data are given as numerical data, if due to the nature of the pharmacological test system, the results cannot be given in the form of numerical data, they may be accepted if they are stated objectively to the extent that they would be considered equivalent to numerical data, such as for example, objective observations by a doctor. As examples of a pharmacological test system that might be used, a clinical trial, an animal experiment, or an *in vitro* experiment may be mentioned.

(2) Examples where grounds for rejection are notified

(a) When there are no pharmacological test results, since it is usually difficult to predict whether a compound can be used for a specific pharmaceutical use from its name and chemical structure alone, and when there are no pharmacological test results even if an effective amount, method of administration and method of manufacture are stated at the beginning, it is difficult for a person skilled in the art to predict whether or not that compound can actually be used for the particular pharmaceutical use. Therefore, in such a case, in principle, grounds for rejection are notified to the applicant. Moreover, even if pharmacological tests are submitted later, the grounds for rejection are not cancelled. (Tokyo High Court Decision, 10.10.30 (1996 (line) 201, "Antiemetic Drug Decision", Tokyo High Court Decision 14.10.1 (2001, (line) 345), Tokyo High Court Decision 15.12.22 (2001, (line) 99))

(b) When it cannot be confirmed that the pharmaceutical product in the claims has pharmacological action because the compound used for pharmacological test was not specified

For example, if it is stated only that a compound used in the pharmacological test system in the specification at the beginning of the application is "one of a plurality of compounds", and it is not actually specified which compound is used, this corresponds to (i) being unclear in the aforesaid "(1) extent of statement about pharmacological test results", hence there are many cases where it

cannot be confirmed that the pharmaceutical invention in the claims has pharmacological action"[9)] .

Here, what is most important practically is that, if it is approved that a claim for "○○ drug which contains component A as an active ingredient" in the form of a use, is a pharmaceutical invention, a pharmacological test method and pharmacological data which support the statement that component A has ○○ action will be required. Therefore, in practice, it is necessary to prevent, as far as possible, a usage invention from being recognized as a pharmaceutical invention. In that case, the most effective method is not to make the ○○ part of the claim "○○ agent which contains component A as an active ingredient" the name of a therapy for a disease, but rather to make it the name of a mechanism of action at the *in vitro* level which is indispensable for therapy of the disease.

If this is done, since it is difficult to recognize the invention as a pharmaceutical invention, it will simply come under the examination criteria for a usage invention, thus it is no longer necessary to get past the high hurdle of pharmacological data, and a patent can be granted for a use on the basis of experimental data obtained by broad, high throughput screening using a DNA chip or a protein chip.

In this case, the part ○○ of the claim "○○ agent which contains component A as an active ingredient" is not given the name of a disease treatment, and even if it is given the name of a mechanism of action at the *in vitro* level which is indispensable for treatment of a disease, as to the question of whether or not a therapeutic agent which is a pharmaceutical invention is contained within the technical scope of the patent of this usage invention, various interpretations have been proposed, and since a clear judicial precedent does not exist, the dispute is not over[10-12)]. However, at least if the problem of interpretation can be overcome, of course, even if the part ○○ of the claim "○○ agent which contains component A as an active ingredient" is not given the name of a disease treatment, and it is given the name of a mechanism of action at the *in vitro* level which is indispensable for treatment of a disease, a therapeutic agent which is a pharmaceutical invention would be contained within the technical scope of the patent of this usage invention.

Therefore, even if the part ○○ of the claim "○○ agent which contains a monoclonal antibody combining with the antigen ●● as an active ingredient" is not given the name of a disease treatment, and it is given the name of a

mechanism of action at the *in vitro* level which is indispensable for treatment of a disease, as long as the problem of interpretation can be overcome, "xx therapeutic agent containing a monoclonal antibody which combines with an antigen ●●", which is a pharmaceutical invention within the technical scope of the patent of this usage invention, would be included.

Fortunately, if a certain specific antigen ●● (a protein or a gene which encodes the protein) is discovered, if the mechanism has been analyzed, since the monoclonal antibody which combines with the specific antigen can be manufactured by ordinary experimental protocols, if it is hoped to obtain a patent for an antibody preparation containing this monoclonal antibody, by giving the part ○○ of the claim "○○ agent which contains the monoclonal antibody combining with the antigen ●● as an active ingredient" not the name of a disease treatment, but the name of a mechanism of action at the *in vitro* level which is indispensable for treatment of a disease, it is sufficient if the enablement requirement is satisfied for the aminoacid sequence of the antigen with which the monoclonal antibody combines (or the base sequence encoding that antigen).

Taking this to the extreme, if an antigen can be patented as a substance, there is no need to actually manufacture the monoclonal antibody itself, and as long as the experimental protocol for a method of manufacturing a typical monoclonal antibody is described as a sort of paper example, in addition to the claim of a substance "the monoclonal antibody combined with antigen ●●", the enablement requirement will be satisfied if the part ○○ of the claim "○○ agent containing the monoclonal antibody which combines with the antigen ●● as an active ingredient" is not given the name of a disease treatment, but the name of a mechanism of action at the *in vitro* level which is indispensable for treatment of a disease.

Therefore, when looking for candidate substances for pharmaceutical products, by broad, high throughput screening using a DNA chip or a protein chip, if a certain specific antigen ●● (or a protein or gene which encodes the protein) is discovered and its function is analyzed, and if the protein or gene of the specific antigen can be patented as a substance or use, in particular if the antigen can be patented as a substance, since in practice it is completely unnecessary to manufacture the monoclonal antibody, insofar as concerns also "the monoclonal

antibody which combines with a certain specific antigen, then in addition to the substance claim of "the monoclonal antibody which combines with the antigen ●●", it is best not to give the part ○○ of the claim "○○ agent containing a monoclonal antibody which combines with the antigen ●● as an active ingredient" the name of a disease treatment, but the name of a mechanism of action at the in vitro level which is indispensable for treatment of a disease.

However, it should be noted that if the antigen cannot be patented as a substance, if it can be obtained as an application in the form of a drug claim, the fact that the monoclonal antibody has activity as a ○○ drug must be disclosed by experimental data.

<Column: How to deal with an examiner's unjust extension of examination criteria>

However, on the other hand, in an actual examination, if the part ○○ of the claim "○○ agent containing a monoclonal antibody which combines with antigen ●● as an active ingredient" is not given the name of a disease treatment, but the name of a mechanism of action at the *in vitro* level which is indispensable for treatment of a disease, "since any uses other than a pharmaceutical use cannot be imagined for a ○○ agent containing a monoclonal antibody which combines with an antigen as an active ingredient, there are some examiners, particularly in the bioengineering department, who base their examination on the criteria for a pharmaceutical invention". Therefore, in order to prevent unjust extension of the scope of examination criteria to a pharmaceutical invention by such an examiner, it is a very effective counterploy not to limit the application of "○○ drug containing a monoclonal antibody which combines with an antigen ●● as an active ingredient" to a drug for treatment of a disease xx, but to forcibly extend the use outside the realm of pharmaceuticals, for example by including the phrase "it may conveniently be used to enhance the growth of farm animals in husbandry , or to enhance cellular replication in the manufacture of artificial organs in regenerative medecine using IPS cells". If it is a use to manufacture artificial organs in animal husbandry or regenerative medicine targeted at mammals similar to human beings, the examiner will not be able to raise any technical objections.

Chapter 2 How to Draft a Strong Patent Specification and Claims for an Antibody Drug Product

1. What is a Strong Patent Specification and Claims?

Now, we come to the eternal problem in patents. Here, I would like to discuss the 6 requirements which, in my opinion, make for a strong patent specification.

(1) It should permit a patent to be obtained easily

Of course, it would probably be ideal if a patent examination could be made without giving rise to grounds for rejection even once, but without being so demanding, it is at least desirable that a patent is granted easily after responding to grounds for rejection only once or twice. If a patent can be granted easily, there is less chance that the patent will be subject to limited interpretation by file wrapper estoppel in the case of enforcement of the patent.

(2) It should not be quashed by an appeal for invalidation

Even if a patent is obtained easily, it is meaningless if it is quashed by an appeal for invalidation when the patent is enforced. So, probably, not being quashed by an appeal for invalidation is also a requirement of a strong patent specification and claims.

(3) It should not permit restraint by a rival company after disclosure

License negotiations are often performed after an application is filed until a patent is granted. Further, when planning research and development strategy, it is often necessary to monitor the published patent applications of rival companies, and if it is discovered that a rival company has made a strong patent application, to change the research and development strategy.

Hence, apart from the technical scope of the invention for which it is actually desired obtain a patent, the breadth of independent claims at the time of filing or disclosure, and the content of the specification, are important in order to restrain a rival company. This restraint of a rival company is an important requirement for a strong patent specification and claims.

(4) It should be able to eliminate a rival company in a lawsuit

In the final analysis, being able to effectively stop manufacture and sale of a copycat product by a rival company, and to demand high compensation in damages, is another requirement of a strong patent specification and claims. For this purpose, not only should the technical scope of the patent be broad, but

the claims and specification should be such that it is easy to discover and establish infringement.

(5) It should not reveal the company's research and development strategy

If emphasis is given to acquiring a patent easily and avoidance of being quashed by an appeal for invalidation, it may happen that the Detailed Description of the Invention and embodiments are written in too much detail. A side-effect of this is that the company's research and development strategy may be leaked, or the company's individual assay system may be leaked. In order to mitigate this side-effect, it is necessary to limit compliance with the support requirement and enablement requirement to a disclosure of the minimum plus α.

(6) It should be valid in all countries

There are now increasingly few companies doing business only in Japan, in particular in the manufacturing sector where there is increasing exposure to international competition. Therefore, it is insufficient just to acquire patent rights only in Japan, and there is an increasing need to acquire a patent in Europe, the United States and other countries including BRICS. However, it is impractical to file an application customized for all countries, and it is also not cost-effective. Hence, the know-how to draft claims and specifications which satisfy the greatest common denominator among Japan, the United States, Europe + BRICS is becoming increasingly more important.

Perhaps it is asking too much, but is it possible after all to satisfy all these six requirements in the field of antibody preparations?

Hereafter, I would like to discuss these points.

2. How Much Experimental Data is Required?

Although this is a common problem in drawing up chemical and biology specifications, how much experimental data should be disclosed when writing an antibody preparation specification? On one hand, the support requirement and enablement requirement must be satisfied, while on the other hand it is necessary to hide know-how. How can these conflicting requirements be satisfied simultaneously?

(1) The level of disclosure is different for an academic treatise and for a specification

Significance should be attached to the fact that in general, in the chemical and biotechnology fields, the level of disclosure is different for an academic treatise and for a specification. That is, in general, if the level of disclosure is that of an academic treatise, the specification would go beyond what is required to satisfy the support requirement, and there is a risk that the company's know-how would be unnecessarily divulged. Therefore, when writing a specification for an antibody preparation, it is desirable to always keep in mind that the minimum required to satisfy the enablement requirement plus α is sufficient. Specifically, in drawing up the claims, the minimum information plus α (α means that to be on the safe side, the information should be a little more detailed) necessary to be able to apply the claims, should be given.

(2) Prove only the effect of the claims of a patent application

When satisfying the support requirement and enablement requirement for a chemical or biotechnology claim, it should be borne in mind that there is absolutely no need to describe the mechanism by which the claim has its effect, and it is sufficient merely to prove the effect of the claim. In general, in the mechanical or electrical fields, experimental data is not included in the specification, and the mechanism which is theoretically deduced from the configuration is described, followed by the effect of that mechanism. However, in chemistry or biotechnology which are experimental disciplines, experiments are performed, and the results are observed. As for the mechanism to describe those results, a theory is constructed later, which is then confirmed by experiment. Therefore, although a mechanism of action corresponding to a mechanism in the mechanical and electrical fields is important academically, it is completely unimportant from the viewpoint of satisfying the support requirement and enablement requirement of an invention for which a patent is being applied. It should therefore be noted, taking this point into consideration, that there is no need to disclose a mechanism of action if it is not necessary.

Another point which should be noted is that, although it is necessary to prove an effect, this is only the effect of the invention as described in the claims, and it is unnecessary to prove the effect of a product obtained by applying the invention in the claims. For example, to satisfy the support requirement and

enablement requirement "Activity inhibitor ●● (D) containing (C) an antibody binding to an antigen ●● (B) having an epitope (requirement A) comprising an aminoacid sequence of sequence number ●●", it is sufficient to prove that this antibody has the function of a ●● activity inhibitor, and it is unnecessary to prove that as a result of the ●● activity inhibitor having this function, it has the effect of treating disease xx. It is necessary to avoid confusion over this point, so that unnecessary experimental data is not disclosed in the specification. This would lead to a leak of know-how, and delay the filing of the application until all this experimental data - although not required to obtain the patent which was originally desired for the claims - became available. As a result, it would no longer be possible to obtain the desired patent before a rival company, which would thus represent a failure.

With this in mind, we will now explain the specific techniques for drawing up a specification that does not disclose too much or too little of the required experimental data.

Technique 1: Do not disclose what tools you use for fishing

Although this has already been stated in Chapter 1, when looking for candidate substances for pharmaceutical products, by broad, high throughput screening using a DNA chip or a protein chip, if a certain specific antigen protein (or gene which encodes the protein) is discovered and its function is analyzed, It is advisable not only to patent the protein or gene of the specific antigen as a substance or use, but also to patent the monoclonal antibody which combines with the specific antigen as a substance or use together.

If, for example, a gene or protein (antigen) having a novel function is discovered,
and it is desired to obtain a patent for the antibody corresponding to this gene or protein, is it necessary to disclose the high throughput screening assay system which was used to discover this gene or protein (antigen)? The conclusion is, it is absolutely unnecessary to disclose this assay system. Disclosing such an assay system would rather result in giving precious research and development resources to a rival company for nothing, and has no advantage whatever.

In other words, the fishing tools used for genes and proteins (antigens) should not be disclosed. Therefore, broad, high throughput screening methods using a

DNA chip or protein chip employed when looking for candidate substances for pharmaceutical products, need not be disclosed. The prediction algorithm and prediction result obtained from the bioinformatics of a gene or protein need not be disclosed. Similarly, the company's original assay system for checking the function of a gene or protein at the test-tube level, which is performed to check the result of the high throughput screening, need not be disclosed.

Instead, only the result of fishing for the gene or protein (antigen) need to be disclosed.

Namely, it is necessary only to disclose data which reconfirms the function with an ordinary assay system. The best plan is to copy the protocol of a common experimental kit to describe the Materials and Methods, so that the company's experimental know-how does not leak to a rival company.

When drafting the claims, if for example a gene or protein (antigen) with a new mechanism has been discovered, it is best to describe also the method of manufacturing the antibody to that gene or protein (antigen). For example, it is required only to disclose the procedure for manufacturing an antibody from a common antigen in the case of a polyclonal antibody, a monoclonal antibody, a humanized antibody, an antibody fragment or a hybridoma. When the antibody is actually produced from the antigen, it is then decided whether or not to disclose experimental data taking the business advantages and disadvantages into consideration.

For example, in the case of a gene or protein (antigen) having a new function, if it is possible to obtain a patent for a substance (substance patent), then it is best to disclose the procedure for manufacturing the antibody and write "was easily manufactured" (if it was not actually manufactured, "can easily be manufactured") in the specification, and not to disclose the properties of the antibody obtained (particularly, experimental data for activity). This is because it is possible to patent the antibody as a substance (substance patent).

On the other hand, in the case of a gene or protein (antigen) having a new function, if it is not possible to obtain a patent for a substance (substance patent), and only obtain a patent as a use (usage patent), then since it is necessary to secure rights also for the antibody which combines with the antigen in the form of a usage patent, i.e., Activity inhibitor ●● (D) containing (C) an antibody binding to an antigen ●● (B) having an epitope (requirement A) comprising an

aminoacid sequence of sequence number ●●", it is not sufficient to disclose only the method of manufacturing the antibody, and it is necessary to also disclose experimental data proving that this antibody inhibits ●● activity by combining with this antigen.

Hence, the tactics for patenting an antigen affect the tactics for patenting an antibody, and consequently, the result of manufacturing the antibody and experimental data for the functions of the antibody also have a bearing on the preparation of the specification. In other words, the strategy for an antibody preparation is decisively affected by the tactics for patenting an antigen.

Thus, the strategy for an antibody preparation takes a cue from the "Heart Attack Theory" propounded by the famous strategist Lidell Hart of the British Empire (which was employed by Nazi Germany to invade Poland and France with great success. An IP strategy using Lidell Hart's theory is explained in detail in Chapter 3). Emphasis is placed on the tactics for patenting the antigen, which is at the heart of the rights to be acquired, and importance is attached to ensuring that, more than the antibody, the description of the antigen is as full as possible.

However, regardless of the type of antigen, what happens when an antibody with novel functions is manufactured? In this case too, it is best not to disclose the reason behind the manufacture of the antibody. It is also best not to disclose the trial and error or failures which had to be overcome before the antibody with the novel functions could be manufactured. This is because if the reason why the company embarked on research and development, or the various trials and errors were disclosed, it would make no contribution at all to satisfying the support requirement and enablement requirement, and would only give a research and development hint to a rival company. Moreover, regardless of the type of antigen, it is not necessary to disclose how the antibody exhibits its novel functions. It is sufficient to disclose only the composition and the effect of the antibody.

Regardless of the type of antigen, the composition of an antibody with novel functions - unlike that of an ordinary antibody - cannot of course be specified by the antigen. In this regard, the composition of the antibody can be specified by one of the following methods:

(1) Specifying the composition by means of a sequence, (2) specifying the composition by means of a sugar chain, or (3) specifying the composition by means of a chemical modification.

Also, regardless of the type of antigen, for an antibody with novel functions, experimental data proving the effects of the antibody must be disclosed. This is because the functions of the antigen and the functions of the antibody are not directly linked, so if the functions of the antibody are not proven by experimental data, it is not possible to satisfy the support requirement and the enablement requirement. As in the case of an ordinary antibody, regardless of the type of antigen, the mechanism by which the composition of the antibody with the novel functions exhibits its effect need not be disclosed. Further, regardless of the type of antigen, the method of manufacturing the antibody with the novel functions must be disclosed fully and in sufficient detail in order to satisfy the support requirement and the enablement requirement.

Technique 2: Hide a vital compound among dummy compounds

Although not limited to antibody preparations, there is something which applies to the whole chemical and biotechnology field, namely, it is best to prepare a large number of dummy compounds, and to hide a vital compound among them. This is due to the fact that it makes the company's strategy more difficult to be leaked to rivals. In this case, although there might be concern about a huge increase in cost due to an increase in the number of claims, if the vital compound and the dummy compounds have a common action, the cost will not increase if the claims are written as Markush-type claims.

If an office action is received stating lack of unity of invention, then the claims can be amended so that part of the company's research and development strategy is clarified (if unity of invention is recognized, the company's research and development strategy can be concealed right up to the last). If information that the rival company has started research and development of an analogue can be obtained, the remaining dummy compounds can also be separated to invite examination pendency, thus increasing the surveillance burden of the rival company, and confusing their research and development strategy.

Here, it is preferable to use a dummy compound having an identical type of activity to that of the real compound, but whose activity is weaker than that of

the real compound (because it avoids any untruthfulness, and the dummy compound can be used as a spare in research and development). Although it is rather cowardly to include a large number of dummy compounds and hide the real compound among them, it is perfectly legal, and to survive in the cutthroat world of business, there is no shame nor should there be any hesitation in making use of this ploy. In practice, a large number of dummy compounds are included in the embodiments of the specification, and an embodiment of the real compound is hidden amongst them. As a result, it is impossible to determine which one is the real compound even by reading the specification, so the company's research and development strategy will not easily be leaked to a rival company. Even if embodiments are written for a large number of dummy compounds in this way, the cost will hardly increase at all. On the contrary, by making a rival company read a specification several hundred pages thick, it will increase their surveillance burden and confuse their research and development strategy, which is a very effective ploy. To put it bluntly, the IP personnel in the rival company will definitely lose their incentive to read the whole specification. However, we recommend you to make and keep another version which specifies the real compound and the dummy compound for your own use so that the IP personnel of your company are not confused.

Although it might seem difficult to include numerous examples of dummy compounds, if broad, high throughput screening using a DNA chip or a protein chip is carried out, a large number of examples of dummy compounds can be drawn up with little effort, and since the examples with the dummy compounds can be templated, costs can be economized.

Although dummy compounds have the same activity as the real compound, it is preferable to use those which have weaker activity than the real compound (then, they are no longer a lie and they can be used as spares in research and development).

Technique 3: Disclose only experimental protocol & qualitative data

Although this is not limited to pharmaceutical preparations, and can be said to be true of the whole chemical and biotechnology field, it is best to disclose only a detailed experimental protocol and simple qualitative data. This is because the numerical data contained in experimental results for a pharmaceutical

product candidate compound is precious company know-how, and it is not desirable to disclose it to a rival company. In so doing, the detailed experimental protocol can copy an ordinary protocol such as a commercial kit. It is also best to disclose experimental data which it is not wished to disclose to a rival company only in the form of qualitative data such as +, -, ○, Δ, x without writing any numerals. However, if no digital data at all are disclosed, since some examiners may deny compliance with the requirement for clarity, the support requirement and the enablement requirement of the claims, it is best to play safe and make sure that at least reference values of qualitative data are stated clearly (+ for greater than ●●, - for less than ●●), and if an office action concerning the support requirement and enablement requirement should be received, then some kind of experimental achievement certificate should be submitted. In this case also, though it goes further than the basic value of qualitative data, if + is indicated for a dummy compound having weaker activity than the real compound, and + is indicated for the real compound also, it is still possible to conceal which is the real compound.

In so doing, provided it is within the range that could be achieved by copying an ordinary protocol such as a commercial kit, it is best to disclose the experimental protocol thoroughly in such detail that it might surprise you. If this is done, a person skilled in the art can easily implement the experimental protocol and obtain quantitative data in the same way as the qualitative data, so the enablement requirement would be satisfied. As for qualitative data, it is important to provide as many types as possible (activity, reaction rate, affinity, stability, etc.). In any case, we recommend writing down any property that can be expressed qualitatively. Further, it cannot be overstressed that reference values must be clearly given for all qualitative data.

Technique 4: Disclose experimental achievements in a report when so requested

Although this is not limited to antibody preparations, and is true for the whole chemical/biotechnology field, if a detailed experimental protocol and simple qualitative data (where reference values are clearly given for qualitative data) are disclosed in the embodiments of the specification, an experimental achievement report confirming the validity of this disclosure can be submitted.

Specifically, if an office action regarding the support requirement/enablement requirement/inventiveness is received, quantitative experimental data obtained by the same procedure as the detailed experimental protocol in the embodiments, is submitted.

In this case, provided that the reference values of the qualitative data are written in the embodiments, after receiving an office action regarding the support /enablement requirement/inventiveness, quantitative experimental data beyond the reference values may be submitted later to claim and establish the validity of the qualitative data originally written in the specification, and claim compliance with the support requirement/enablement requirement/inventiveness. At the same time, if a rival company does not obtain a file wrapper after the response to the office action, it cannot obtain quantitative data for the real compound, which increases the surveillance burden of the rival company and confuses their research and development strategy.

Also, if the specification is written cleverly, in some cases it may be possible to submit quantitative experimental data from standalone test-tube experiments for individual compounds, obtained by the same procedure as a high throughput experimental protocol using a DNA chip/protein chip written in the embodiments. This is because the high throughput experimental protocol using a DNA chip/protein chip and the quantitative experimental data protocol from stand-alone test tube experiments for individual compounds are substantially identical. Therefore, provided that the reference values for broad qualitative data which is the result of high throughput are written in the specification, after receiving an office action regarding the support requirement/enablement requirement/inventiveness, it is possible to submit quantitative experimental data carefully obtained by stand-alone test-tube experiments for individual compounds later when so requested, and claim compliance with the support requirement/enablement requirement/inventiveness.

In this case also, if a rival company does not obtain a file wrapper after the response to the office action, it cannot obtain quantitative data carefully obtained by stand-alone test-tube experiments for the real compound, which increases the surveillance burden of the rival company and confuses their research and development strategy.

Technique 5: When a mechanism of action should be disclosed, and when it should not

Although this is not limited to antibody preparations, and is true for the whole chemical/biotechnology field, if the effect of a real compound (antigen/antibody) is novel, it is not necessary to disclose the mechanism of action as described above.

Moreover, in the case where the effect of the real compound (antigen/antibody) is known and its mechanism of action has been discovered for the first time, it is best to draft claims for a use of its mechanism of action. Specifically, if a mechanism of action is specified for the "●● part of "a ●● drug containing the real compound", it is easy to draft claims as a use of the mechanism of action. Then, it is necessary to disclose the mechanism of action in the embodiments. In this case, regarding an effect which was already known (1st pharmaceutical application), it is understood that any patent rights, after obtaining a patent for an application of the mechanism of action which was discovered, do not extend to this effect. However, regarding an effect which was unknown (2nd pharmaceutical application), do patent rights for an application of a mechanism of action extend to this effect?

There are some cases where even if the effect of the real compound (antigen/antibody) is novel, it is advantageous to obtain a patent also for an application of the mechanism of action. Specifically, when the novel effect is a 1st pharmaceutical use which is a mechanism of action downstream of a metabolic pathway, if a patent is obtained for a use of the mechanism of action, it may be possible to exercise rights for a second pharmaceutical use. This is because if a patent is obtained for a use of an upstream mechanism of action leading to a mechanism of action downstream in the metabolic pathway, it may be possible to exercise rights as a use of a midstream mechanism of action. A similar way of thinking to that of metabolic pathway appears to exist with regard to signal transmission.

Technique 6: When pharmacological data should be disclosed, and when it should not

Although this is not limited to antibody preparations, and is true for the whole chemical/biotechnology field, when there is sufficient experimental data for a

mechanism of action of the real compound (antigen/antibody), but there is hardly any certainty about pharmacological data, then if a patent can be obtained as a use of a mechanism of action, since it is possible that patent rights may be recognized also for a pharmaceutical product, there is no need to disclose pharmacological data if it is not available.

In this case, if sufficient pharmacological data subsequently becomes available, another application can be filed for the first pharmaceutical application (preferably before the filing date of the application for the mechanism of action), and by disclosing sufficient pharmacological data with this other application, adequate protection can be obtained together with the previous application for mechanism of action, so there is no particular disadvantage.

On the other hand, if there is sufficient experimental data for the mechanism of action of the real compound (antigen/antibody), and sufficient pharmacological data is also available, it is best to obtain a patent as a use of a mechanism of action for the real compound, and obtain a patent also as a first pharmaceutical use based on this mechanism of action.

In that case, it is necessary to disclose experimental data for both the mechanism of action and pharmacological data in the embodiments. As mentioned earlier, both the experimental data for the mechanism of action and the pharmacological data may be disclosed as a detailed experimental protocol and simple qualitative data (reference values must be clearly given) in the embodiments of the specification.

3. How to Draft a Claim having Novelty and Inventiveness

(1) Which is better, a compound claim, a drug claim or a pharmaceutical product claim?

When drafting a claim for a pharmaceutical preparation, which is better, a compound claim, a drug claim or a pharmaceutical product claim? In the world of pharmaceutical preparations, the Ministry of Health, Labour and Welfare has absolute authority as regards approving new drugs. Hence, even if wonderful results are obtained for a new drug in basic research, unless the drug clears clinical tests, it cannot be commercialized, so there is a trend to pay more attention to the downstream area than in other industries.

However, in the patent system, a much stronger patent can be secured by patenting the results of basic research than by patenting the results of applied research. In other words, and this is true not only of pharmaceutical preparations but also of the whole chemical and biotechnology field, if an antibody preparation can be patented, it is best if a patent can be obtained as a claim for a compound. This is because since a compound claim is a "substance patent", the most extensive rights can be obtained which is an advantage.

Moreover, although it is a claim for a compound with functional limitation, "an antibody with a function", it is a substance patent, so it is understood that patent rights can extend even to an application using this antibody unrelated to its function, and those rights are stronger than a drug claim or a pharmaceutical product claim.

At the same time, while not limited to antibody preparations and generally true of the whole chemical and biotechnology field, a drug claim is a sort of usage patent, so the scope of the patent is narrower than that of a compound claim. This is because, even if a patent is obtained for a drug claim with limited function, "a ●● drug containing an antibody having a ●● function", it is understood the patent can be applied only to activities using this antibody in the ●● use (corresponding to mechanism of action) (however, there is academic disagreement as to whether the patent can be applied to a pharmaceutical product based on its mechanism of action).

And while not limited to antibody preparations since it is generally true of the whole chemical and biotechnology field, a pharmaceutical claim is a sort of final usage patent, so the scope of the patent is narrower than that of a compound claim or a drug claim.

This is because, even if a patent is obtained for a pharmaceutical claim limited by a 1st pharmaceutical application, "a pharmaceutical product for the purpose of therapy of ●● containing ●● antibody", it is understood the patent can be applied only to activities using this antibody in the ●● application (1st pharmaceutical application) (because, in many academic circles, it is interpreted that the patent cannot be applied to a pharmaceutical product with a 2nd application based on the same mechanism of action).

(2) Is it better to make a distinction on the basis of composition, mechanism or effect?

Although not limited to antibody preparations and generally true of the whole chemical and biotechnology field, it is best to make a distinction on the basis of composition. This is because, if a patent is obtained for "an antibody having … composition", it can be applied to all antibodies having this composition.

On the other hand, there are also some cases where, depending on how the claims are drafted, it is better to make a distinction on the basis of action rather than composition.

This is because, if a patent is obtained for "an antibody having ●● function", it can be applied to all antibodies having that function.

It may be noted that even if a distinction is made on the basis of action, if a patent is obtained as "a ●● drug containing an antibody having ●● function", the patent can be applied only to activities using this antibody for the ●● application relating to its function.

Further, if a distinction is made on the basis of effect, it is difficult to obtain a patent as "an antibody showing a ●● effect" (it becomes a sort of wishful claim which is too vague).

However if, in order to avoid a wishful claim, a patent is obtained for "a ●● drug containing an antibody having a ●● function", the patent can be applied only to activities based on this function (the function must be limited in order to avoid making it too vague), which use this antibody for the ●● application relating to its effect.

Moreover, if a patent is obtained as "a ●● drug containing an antibody having a ●● composition", it can be applied only to activities using this antibody for the ●● application relating to its effect based on this composition (the composition must be limited in order to avoid making it too vague).

Now, keeping the above points in mind, we should like to describe the specific techniques needed to draw up claims which are bound to satisfy novelty and inventiveness.

Technique 1: Making a distinction according to difference in composition of the antibody/composite

Although this is not limited to antibody preparations and is generally true of the whole chemical and biotechnology field, it is a positive advantage to make a distinction on the basis of the composition of the antibody/composite.

For example, if it is a matter of a technique for modifying an antibody so that it has a novel function unrelated to the antigen, such as Kyowa Hakko's Biowa, Roche's Glycart or Genentech's Xencor, a clear distinction can be made from the prior art. Therefore, if a patent can be obtained, it will be an extremely strong patent (the most important fact is that patent rights can be exercised regardless of the type of antigen).

Technique 2: Making a distinction by specifying a biochemical action *in vitro*

Although this is not limited to antibody preparations and is generally true of the whole chemical and biotechnology field, if a distinction can be made by specifying an *in vitro* biochemical action, this can also become a quite powerful patent.

For example, the type of antigen (gene/protein) with novel function can be specified, and a distinction made by specifying according to the binding affinity with the antigen.

Of course, if a new enzyme is discovered which inhibit/activates the antigen by binding to it, and a specification is drawn up based on this function, an even more powerful distinction can be made.

Technique 3: Making a distinction by specifying a physiological action in the cell

Although not limited to antibody preparations and is generally true of the whole chemical and biotechnology field, if a distinction can be made by specifying a physiological action in the cell, a fairly strong patent can be obtained.

However, in this case, it is also common for the distinction to be made by specifying the kind of antigen (gene/protein) for which a new mechanism has been discovered, and specifying the binding affinity to that antigen at the test-tube level. It would appear that in most cases, experiments are carried out at the cellular level in view of the results obtained *in vitro*, as a result of which the physiological action in the cell becomes clear. Therefore, this is often combined with the technique of making a distinction by specifying the physiological action *in vitro* described earlier.

Technique 4: Making a distinction by specifying a physiological action in a tissue, organ or individual

Although not limited to antibody preparations and generally true of the whole chemical and biotechnology field, if a distinction is made by specifying a physiological action in a tissue, organ or individual, it will usually be a distinction at a level close to that of a final application, so the scope of the patent will not be so broad.

There are very few cases where experimental data for physiological action in a tissue, organ or individual is obtained at the same time as experimental data at the test-tube level and cellular level. Therefore, there appear to be many cases where a patent application is filed first for experimental data at the test-tube level and cellular level, and then another patent application is filed which makes a distinction by physiological action in a tissue, organ or individual before the first application is disclosed.

Technique 5: Making a distinction by specifying a disease, symptom or patient where there is an effect

Although not limited to antibody preparations and generally true of the whole chemical and biotechnology field, if a distinction is made by specifying a disease, symptom or patient where there is an effect, it will usually be a distinction at a level close to that of a final application, so the scope of the patent will not be so broad.

There are very few cases where experimental data for a disease, symptom or patient is obtained at the same time as experimental data at the test-tube level and the cellular level. Therefore, there appear to be many cases where a patent application is filed first for experimental data at the test-tube level and the cellular level, and then another patent application is filed which makes a distinction by specifying a disease, symptom or patient where there is an effect before the first application is disclosed.

There also appear to be many cases where, in order to extend the actual life cycle of a pharmaceutical drug before the patent expires, a patent application is filed after discovering a disease, symptom or patient where there is an effect as a result of research on a second pharmaceutical application. It can also happen that a patent application is filed when a doctor in a university hospital for

example discovers an unexpected effect after applying a medication to patients outside the scope for which it was originally intended.

Technique 6: How to draft claims when pharmacological data is available, and when it is not

Although this is true not only of antibody preparations but of the whole chemical and biotechnology field, there is actually no great cause for concern even if there is no pharmacological data. This is because if a novel mechanism of action has been discovered at the test-tube level or cellular level, a patent can be sought in the form of a usage patent relating to a novel mechanism of action, like "a ●● drug containing a ●● antibody".

Although this is true, even if a claim is drafted in the form "a ●● drug containing a ●● antibody", some examiners may actually demand pharmacological data as with a pharmaceutical invention, so it is expedient to avoid expressions that would cause the invention to be treated as a pharmaceutical invention. It should be noted that, even if sufficient pharmacological data is available, if a novel mechanism of action has been discovered, it is desirable to draft not only pharmaceutical product claims, but also drug claims for a usage invention related to this mechanism of action. This is because if a patent can be obtained as a drug claim related to a mechanism of action, then patent rights may also be exercisable for a second pharmaceutical application.

4. A convincing argument for the strength of a usage patent

(1) Actually, there are not so many strong arguments for usage patents, but here we should like to describe a strong argument for the advantage of a "functionally limited drug claim".

The only argument regarding the advantage of patenting a "functionally limited drug claim" that we know of is that mentioned on p.135-137, "Patents in the Pharmaceutical Industry" (Vol. 2) by Kenichi Sugita.

An invention relating to an application specified by a mechanism is, for example, a usage invention wherein the use is specified by a function of a compound (here, an inhibitory effect against an enzyme Y), e.g., "an agent having an inhibitory effect against enzyme Y containing a compound X as active ingredient", and expressed in the form of a drug product.

If the enzyme Y has an important function in its relation to some disease, although compound X is a useful medication for these diseases since it was found to have a novel inhibitory effect against the enzyme Y, it is the usage invention of "an agent active against enzyme Y having compound X as an active ingredient" which should of course be patented. In this case, the specific use of the enzyme Y inhibitory agent is the treatment of a disease related to the enzyme Y.

So, are diseases related to enzyme Y at the time of filing the only ones to be considered?

In view of this, the protection afforded by the patent would appear to be weak, because the point of the invention is that compound X was discovered to have the novel enzyme Y inhibitory action. However, at the time of filing, the inventor has not even disclosed anything about diseases related to enzyme Y that might be discovered in future, and there are some who are of the opinion that the inventor should have extensive rights within this scope.

We believe the courts have not yet ruled on this point, but what does the reader think?

Well, concerning an invention related to a use specified by a mechanism, there is something else that must be considered. For example, assume that prior to the filing of the above patent application, it was known that compound X had therapeutic activity against a disease P, although the mechanism was not known. Then, let us assume a patent was granted for "an enzyme Y inhibitory action having a compound {X} as active ingredient". Now, what problems can arise? If there is no connection at all between the enzyme Y inhibitory effect and disease P, even if a third party uses compound X for disease P, it does not make use of the enzyme Y inhibitory effect, so there would be no problem. But if there was a connection with the enzyme Y inhibitory effect and the therapy of disease P, it gets complicated. In other words, this is when disease P is one of the diseases for which the inhibitory effect against the enzyme Y can be considered.

In this case, the rights devolving from "an agent active against enzyme Y having a compound {X} as active ingredient" have an effect on the actions of a third party using compound X for disease P. However, the use of compound X

for disease P was known before the filing date of the present application, so the invention could have been conceived by anybody.

In other words, summing up, the invention of "an agent active against enzyme Y having a compound {X} as an ingredient" does not have novelty.

However, the point of the invention is that an inhibitory effect against enzyme Y was discovered for compound X. Does this mean that, in view of the fact that the therapeutic action of compound X on disease P was known, it is not necessary to protect the invention?

No. Thanks to this invention, it became possible to use compound X for diseases thought to be connected with enzyme Y. In other words, there is great value in protecting the invention.

Hence, in the above case, if the expression "agent active against enzyme Y containing compound X as active ingredient" (excluding its use as a therapeutic agent for disease P) is adopted, novelty is supported, and a usage invention of diseases connected to enzyme Y other than disease P can be protected.

(From p.135-137, " Patents in the Pharmaceutical Industry" (Vol. 2) by Kenichi Sugita (the parts underlined were modified by Okuno)).

(2) As mentioned above in the explanation by Sugita, if there is a connection between the enzyme Y inhibitory effect and the therapeutic effect on disease P, the rights of a claim for "an agent active against enzyme Y containing compound X as active ingredient" also affect a third party using compound X for disease P.

If the use of compound X for disease P was known before the filing date of the present application, it is then part of the public domain (an invention that anybody could carry out), so the rights of the invention do not extend to the use of compound X for disease P.

Nevertheless, even in this case, since a disease connected with enzyme Y other than disease P (a "second pharmaceutical use") is not within the public domain (an invention that anybody could carry out), the rights of the invention are deemed to extend to "the use of compound X for diseases related to enzyme Y other than disease P". In other words, it is considered that the effect of a usage invention (functionally limited drug claim) in principle extends to a first pharmaceutical use and a second pharmaceutical use. Even if the first

pharmaceutical use was already known, at least it is considered to extend to the second pharmaceutical use.

Hence, if novel functions are discovered for known genes and proteins in the course of drug design of biomedicines, antibody preparations and nucleic acid preparations based on the full analysis of the human genome after the year 2000, patenting a usage invention specified by a mechanism for these functions may hold great economic potential for the future.

5. Concept of 'Universal Drafting'

The technique of drawing up one document so that it fits all countries is known as universal drafting (a term coined by Mr. Okuno). The greatest advantage of this is that, (1) the cost of drawing up the patent application can be economised), and (2) the cost of translating the patent application documents can be economised.

Of course, in fact, it is desirable to customize the claims and specification for each country when making an overseas application, but it is practically impossible to draw up a patent application document in such a way that it is customized for all countries. In particular, now that the proportion of PCT applications is increasing, this technique is no doubt exceedingly in demand. Universal drafting must have the following two features.

(1) Patent specification and claims for Japan, EU and the United States

In universal drafting, a patent specification and claims must be prepared which can comply with the requirements of Japan and the United States. In particular, and this does not apply only to antibody preparations, but to the whole of the chemical and biotechnology field, the concepts of substance invention, usage invention and pharmaceutical product invention are different in Japan, EU and the United States. Consequently, regarding the claims, (1) it is most practical to draw up at least (1) a substance claim, (2) a functional limitation substance claim, (3) a functional limitation drug claim, and (4) a pharmaceutical product claim, and to have the local agent modify them in response to office action (if they are customized for Japan, it is too troublesome, and since there are many countries with laws that require using a local agent, it is expedient to customize the claims locally overseas). Regarding method claims and usage claims, it is difficult to draw these up in Japan from the viewpoint of industrial applicability,

so, in addition to describing the action of (1) a substance claim, (2) a functional limitation substance claim, (3) a functional limitation drug claim, and (4) a pharmaceutical product claim, it is probably best to claim priority when the application is filed in Japan by incorporating corresponding points in the specification.

Also, in universal drafting, the requirement of novelty and inventiveness must be satisfied in the developed nations. This is not limited to pharmaceutical preparations and is true of the whole chemical and biotechnology field, but there are many cases where, if a detailed experimental protocol and simple qualitative data are disclosed in the examples of the specification, an experimental achievement report (including a declaration) to establish the truth of the disclosure, is submitted to claim inventiveness.

Further, in universal drafting, the assay system must not be disclosed in the specification to rivals in the developed nations. This is not limited to antibody preparations and is true of the whole chemical and biotechnology field, but if a detailed experimental protocol including an ordinary kit protocol and simple qualitative data are disclosed, it is not necessary to disclose the company's assay system to rival companies (in any case, confirmatory experiments must be performed using an ordinary kit, so nothing is lost if experiments have to be repeated).

In universal drafting, a candidate compound must not be revealed in the specification to rival companies in the developed nations. Again, this is not limited to antibody preparations and is true of the whole chemical and biotechnology field, but if many examples using dummy compounds are written in the examples of the specification, and the example with the real compound is hidden amongst them, it is not necessary to give the real compound to a rival company. Also, there are many cases where, if a detailed experimental protocol and simple qualitative data are disclosed in the examples of the specification, an experimental achievement report (including declaration) to establish the truth of the disclosure may be submitted to claim inventiveness, so there is not much problem.

(2) Patent specification and claims to comply with the requirements of BRICS

In universal drafting, the support requirement and the enablement requirement must be satisfied in the developing countries including BRICS. In particular, while this is not limited to antibody preparations and is true of the whole chemical and biotechnology field, there are many cases where, if a detailed experimental protocol and simple qualitative data are disclosed in the examples of the specification, an experimental achievement report (including declaration) may be submitted to establish the truth of the disclosure, and claim compliance with the support requirement and enablement requirement. However, the experimental protocol must be described in the fullest detail possible (of course, company know-how should not be leaked, which may be accomplished by incorporating the description of an ordinary kit as well). There are many cases where submission of the experimental achievement report is viewed quite leniently (if the local agent is requested to negotiate with the overseas patent office, this is usually accepted).

Also, in universal drafting, the specification should be written so that it incorporates a difficult manufacturing method for the benefit of rival companies in the developing countries including BRICS. In particular, while this is not limited to antibody preparations and is true of the whole chemical and biotechnology field, the specification may mention the name of an experimental kit or piece of analytical equipment which can only be acquired in Japan and is difficult to procure elsewhere, and the experimental conditions such as temperature may be company settings (measured by the ●● mode of a ●● device manufactured by Shimazu Laboratories). If this is done, a company in a developing country will find it difficult to implement, which is an advantage. If possible, a manufacturing protocol may be described using equipment which is no longer sold, which makes it very difficult to implement (if an office action regarding the support requirement or enablement requirement is received, a copy of the operating manual for the device and its translation may be submitted). In this way, while making it practically difficult to implement, it is possible to satisfy the support requirement and enablement requirement.

(3) Ideal universal drafting to comply with the requirements of Japan, EU, US and BRICS

Unfortunately, such a wonderful tool does not yet exist. However, if a model for universal drafting is drawn up in the company, and is modified on the basis of

instructions obtained each time an office action is received from each country, a natural, ideal model for universal drafting can probably be created. And there are some patent offices which have already drawn up such a model for universal drafting, so an available option is to ask one of these offices (e.g., SK Intellectual Property Law Firm).

Chapter 3: Patent Mining Strategy for Antibody Drug Products

We should now like to describe patent mining strategy, which is a kind of intellectual property strategy actually used by large pharmaceutical companies in Europe and the United States. Patent mining, originally known as patent troll (patent mafia) in IT and software industries in the US, is an intellectual property strategy started by venture companies which focus on research and development or acquisition of intellectual property, and do not actually engage in product development, manufacture and sales.

In IT and software industries in the US, there was a business patent bubble around the year 2000, along with which novel business ideas using the Internet, for example, were built into software inventions, and as a result of which a myriad of venture businesses which filed patents sprang up like flowers after the rain. These venture businesses would jump into any promising business opportunity and patent anything at random, and if anybody else wanted to start such a business, then they would approach them, demand a settlement a little lower than a lawyer's fees for infringing their rights, and make a profit. This was the business model they chose.

However, although it was not mentioned much by the mass media, this patent mining strategy was not limited to the IT or software field, and actually, in the biotechnology field also, many bioventures in the US adopted this patent mining strategy.

In fact, although it was hidden in the shadow of the IT bubble, around the year 2000, another enormous scientific revolution was taking place with the completion of the human genome project in Japan, the US and Europe, and reading of the human genome by cellular genomics created by Dr. Craig Venter. With high speed DNA sequencers, it was becoming possible to read a large number of DNA sequences in a short time as long as sufficient money was invested. Further, with the progress in bioinformatics, it was becoming increasingly easy to extract gene candidate sequences such as ORF (Open Reading Frame) from DNA sequences read by DNA sequencers. And, using technologies such as the DNA chip developed by Affymetrix, it was becoming possible to analyze the expression of large numbers of target gene candidate sequences at a stretch.

Under these conditions, although it was hidden in the shadow of the IT bubble, from about the year 2000, a large number of bioventures in the US read DNA base sequences wherever they found them using high-speed DNA sequencers, extracted promising gene candidate sequences using bioinformatics technology from among these DNA sequences, and broadly analyzed the expression of the extracted gene candidate sequences by high throughput screening using DNA chips. Bioventures like this, who did patent mining, and put in patent applications for large numbers of gene inventions, protein inventions and antibody inventions based on this broad analysis of functions, sprang up like flowers after the rain.

Hereafter, we will explain the patent mining used by American bioventure firms step-by-step in detail.

STEP 1: High throughput screening using DNA chip and protein chip

Now that the human genome has been elucidated - and except for living organisms for which the genome has not been fully revealed - when searching for pharmaceutical drug candidates using mammals such as humans, mice and rats, firstly, in general, bioinformatics is used to narrow down the target, and then high throughput screening is performed using a DNA chip or protein chip for this target. For example, if it is desired to develop a therapeutic drug for pancreatic cancer, a search is carried out for genes and proteins that are greatly overexpressed or under-expressed in pancreatic cancer cells using a DNA chip or protein chip

STEP 2: Functional analysis of genes/proteins from broad *in vitro* experimental data

Once a gene has been found that is greatly overexpressed or under-expressed in pancreatic cancer cells, the functions of that gene or protein are analyzed by broad *in vitro* experimental data. In this case, for example, assume that the mechanism of pancreatic cancer is understood, and that it is known that ●● enzyme plays a key role. For example, the binding properties of these genes (translation products)/proteins to ●● enzyme may be investigated using a protein chip. As a result, when it is understood that the gene (translation product)/protein binds to ●● enzyme, then it can be examined whether or not

these this gene (translation product)/protein inhibits or promotes the activity of ●● enzyme using an enzyme activity assay system. After that, it is a good idea to manufacture a model antibody to this gene (translation product)/protein. This monoclonal antibody then binds to this gene (translation product)/protein, and it is attempted to find out how the inhibition/promotion of the enzyme changes to narrow down antibody preparation candidate substances.

STEP 3: Embedding a mining patent for an analyzed mechanism

When the functional analysis is complete, an application for the analyzed function is filed in respect of this gene/protein/monoclonal antibody. Now that the human genome has been fully revealed, it is often difficult to obtain a patent for a gene/protein/monoclonal antibody which was searched and whose functions were analyzed by high throughput screening. Hence, a mechanism of action type functional analysis can be performed at the *in vitro* level, so it is best to find a novel function, and file an application for this function ○○. At this time, it is understood that the technical scope of the usage patent based on this functional analysis of mechanism at the *in vitro* level, includes a final pharmaceutical application downstream (in the sense of signal transduction or metabolic pathway) of the mechanism of action at the *in vitro* level (at least, there are no cases of judgement where this has been refuted). So there is no doubt it has a powerful damping effect on a rival company. Here, it should be noted that since the gene/protein/monoclonal antibody was searched by high throughput screening, then there is a possibility that a large number of genes/proteins/monoclonal antibodies having identical functions may be discovered. In this case, one application may be filed for a plurality of genes/proteins/monoclonal antibodies. Since these genes/proteins/monoclonal antibodies have identical functions, one application may be filed by making use of a Markush claim.

STEP 4: Division and continuation

After an application has been made for multiple genes/proteins/monoclonal antibodies, it is wise to go on dividing, and continuing. Now, due to a revision of the law, for new applications filed after April 1, 2007, an application can be divided even after a patent has been obtained (patent examination), so it is a

good idea to divide it again and keep on making new applications. Because in this case, "anticipation" described later is possible, and the surveillance burden of a rival company can be increased.

STEP 5: If a rival company starts developing a new product, start drafting a mining patent

After filing one application for multiple "genes/proteins/monoclonal antibodies", if this application is divided and continued, a rival company must be continually watched to see whether or not they appear to be starting development (or manufacture and sales) of a new product related to a mining invention. If it was found that the rival company has started developing (or manufacturing or selling) a new product, the relevant claim is immediately amended, and replaced by a claim which includes the new product that the rival company is trying to develop (or manufacture or sell). Also, efforts are made to patent this claim as soon as possible, send a warning letter to the rival company, and demand compensation.

If this is done, the research and development/commercialization of the rival company can be halted, and in some cases, if for example it is known that ●● enzyme is the key to pancreatic cancer, it is even possible to put a stop to the development of biopharmaceuticals and antibody preparations related to ●● enzyme. Then, the company will have plenty of time to carry out research and development of biopharmaceuticals and antibody preparations related to this ●● enzyme, and if the rival company is allowed to pursue research and development, a higher license fee of several tens of % can be exacted from them, which is just like enjoying the fruits of their efforts to make money without actually doing anything yourself.

STEP 6: Building an improvement patent on a rival company's application for a pharmaceutical patent

If, as described above, after watching the moves of a rival company, it is found they have started development (or manufacture and sales) of a new product related to a mining invention, it is best to immediately amend the claims of the relevant application, rewrite them to include the new product which the rival company was trying to develop (or manufacture and sell), and anticipate a mining patent. An application is then made for an improvement patent

embodying the optimum form of the new product over the rival company's patent application for the new product.

To build this improvement patent, it is sufficient to read the rival company's patent specification, optimize blending compositions, numerical ranges, drug forms, crystal structures, functional groups, other agents used concurrently, methods of administration, dosages and dosing intervals, and put them in the form of claims. It does not matter whether, depending on the extent of optimization, there is no inventiveness if the rival company's application is cited. If possible, it is better to optimize various factors from various viewpoints. Even if the modified invention is rejected in the examination of an improvement patent, for applications after April 1, 2007, this new application can be divided after it was rejected (rejection examination), so it can be divided and continued each time it is rejected.

Anyway, it is important that an improvement invention can be filed on top of the rival company's patent application. If this is done, a new product which a rival company wishes to develop (or manufacture or sell) can be attacked from above and below by "anticipating a mining patent" and "building an improvement patent". Of course, the rival company will try to quash the "mining patent" and " improvement patent" above and below their new product by providing information or grounds for invalidation, but since there will always be one application above and below still in the process of examination, there will always be a new "mining patent" and "improvement patent" which cannot be quashed, so eventually the rival company will never be to develop its new product in peace.

STEP 7: Gentlemanly license negotiations, warnings, and exercise of rights after securing an advantageous position

Thus, it is a good plan to conduct gentlemanly license negotiations, warnings, and exercise of rights after pushing the rival company into the mire where it cannot move. This is just like Lidell Hart's indirect approach - scattering a large number of mining patents around by high throughput screening, watching a rival company and then stopping the rival company by "mining patents" and "improvement patents". In this way, your company's portfolio is given far higher priority than that of the rival company, and then, by gentlemanly license

negotiations, warnings, and exercise of rights, you "win without a fight". Indeed, this shows how great was the strategy of Liddel Hart, who loved the Chinese philosopher "Sun Zi" so much.

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