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Hirotaka Nonaka

FTO (Freedom to Operate) in the Pharmaceutical Industry

Nomos

MIPLC Munich Intellectual Property Law Center
Augsburg München Washington DC

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I. Introduction

When a company intends to place a new product or service on the market, it must understand the risk of infringing the third parties' intellectual property. It is a common practice for the company to conduct a Freedom-to-Operate (FTO)[1] search to determine and reduce the risks of potential patent infringement prior to launching a new product or service. The FTO search is performed to find relevant third parties' patents that may cover the new product or service. The FTO is also called "Patent Clearance". If the company completely neglects the FTO search, and then, later on, the product is found to infringe a third parties' patent, it is most likely that the company would be sued by the patentee as an infringement of the patent. As a result of losing the infringement case at the court, the company has to stop selling its product and to compensate the damage that the patentee suffered from. Therefore, the FTO search is indispensable to perform prior to placing the new product or service on the market. Even if the company finds some relevant patents as a result of the FTO search, the company should not necessarily give up marketing the product because the company still has a chance to obtain a license from the patentee. With this licensing-in activity, the company can operate its business freely in the market. Therefore, this activity is called "FTO-licensing".

In part II of this paper, I would like to focus on the FTO-licensing in the pharmaceutical industry. There are many characteristic aspects in this industry that are never seen in other industries, which makes the FTO-licensing in the pharmaceutical industry very special. These characteristic aspects roughly consist of the following four points. First, the economical scale of the market in the pharmaceutical industry is incomparably large, with an estimated 716 billion Euro at ex-factory prices in 2015 in the

1 "Freedom to Operate (FTO) is the ability to proceed with the research, development and/or commercial production of a new product or process with a minimal risk of a new infringing the unlicensed intellectual property (IP) rights or tangible property (TP) of third parties" (Stanley P. Kowalski, *Freedom to Operate: The Preparations,* ipHandbook of Best Practices (last visited September 5, 2016), http://www.iphandbook.org/handbook/ch14/p02/).

world.[2] This market is still growing rapidly in some highly populated countries. Second, the cost of a research and development (hereinafter referred as "R&D") for a new drug is very expensive. One of the reasons for the high cost is clinical trials, which would cost approximately 2 billion Euro according to the recent survey.[3] Third, in spite of such an expensive R&D cost, success rates are extremely low. It is reported that the total success rate is calculated to be 0.01%.[4] For this characteristic, R&D for a new drug is a highly risky business. Fourth, a duplication of the drug made by another company is quite easy compared to conducting R&D for a new drug on its own. Accordingly, patent protection in the pharmaceutical industry is much more essential to recoup R&D investment than that in other industries. In order to recoup the investment, pharmaceutical companies in general wish to monopolize the marked and sell the drugs rather than to conduct licensing-out because selling the drugs in the monopolized market is the most profitable way. Taking into account this low probability of obtaining a license from another company, a pharmaceutical company must conduct a thorough FTO search at the beginning.

Because of the above-mentioned obligation, the part III of this paper focuses on how to achieve the FTO in the pharmaceutical industry. I would like to describe not only the characteristic points regarding the FTO in the pharmaceutical industry but also an FTO in general. It should be noted that even if 99% of an FTO is conducted properly, the other uncompleted 1% could ruin the whole FTO search because that 1% might contain the relevant third parties' patent which covers the technology that the pharmaceutical company intends to include in its product/service. To perform a thorough FTO, it is important to first describe how to build an FTO team, how to search relevant patents, how to interpret potentially adverse patents and how to deal with adverse patents, especially pointing out the characteristic features about the FTO in the pharmaceutical industry.

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2 European Federation of Pharmaceutical Industries and Associations (hereinafter referred as "EFPIA"), *The Pharmaceutical Industry in Figures, 2016 Edition* 14 (last visited September 5, 2016), http://www.efpia.eu/uploads/Modules/Documents/the-pharmaceutical-industry-in-figures-2016.pdf.

3 *Id.* at 6.

4 M. Dickson, J.P. Gagnon, *The Cost of New Drug Discovery and Development* (June 20, 2009), http://www.discoverymedicine.com/Michael-Dickson/2009/06/20/the-cost-of-new-drug-discovery-and-development/.

In part IV of this paper, I would like to describe two issues with regard to FTO-licensing, and analyze them. The first one is the issue on FTO-licensing and EU competition law. When a pharmaceutical company wishes to license-in, it concludes a license agreement which includes the obligation on royalty payment. Basically, the parties of a technology license are free to determine the amount and nature of royalty payments. But in some cases, the license will have the risk of being interpreted to be anticompetitive. Royalties on products produced without using licensed technology is one of these cases. I analyzed the TTBER and the Guidelines, taking into account the characteristic features in the pharmaceutical industry, then I pointed out the possibility that the Guidelines should not be applied to the royalty on drugs. The second one is the issue on FTO-licensing between a bio-venture company and a pharmaceutical company. Recently, an increasing number of pharmaceutical companies have mapped out the strategy to license-in the technology of a bio-venture company mainly because they want to diminish the risk of R&D failure. These companies tend to license-in or buy a promising candidate for a new drug regarding certain type of disease. And nowadays there are many bio-venture companies that are willing to license-out their technologies to pharmaceutical companies. However, the reality of licensing-in/out is contradictory to their high expectations. After analyzing the situation, I proposed some solutions.

II. Key features of innovation in the pharmaceutical industry

A. Huge and growing market

The world pharmaceutical market was estimated to be around 716 billion Euro at ex-factory prices in 2015. The bigest three markets in the world pharmaceutical markets are US, EU and Japan. The market share of these three regions are estimated to be around 48.7% (349 billion Euro) in the US, 22.2% (159 billion Euro) in EU and 8.1% (58 billion Euro) in Japan, respectively.[5] In addition to this market share, it should be noted that there is a rapid growth in the market and R&D environment in highly populated emerging markets such as Brazil, China and India. The Brazilian and Chinese markets grew by 14.0% and 7.0%, respectively. This growth is rapid, compared with an average market growth of 5.9% for the EU market and 8.5% for the US market.[6]

B. High R&D investment

The development of a new drug requires a substantial investment of capital, human resources, and technological expertise. Even if a pharmaceutical company successfully finds a promising candidate for a new drug, it has to tackle the next obstacles of strict adherence to regulations on testing and manufacturing standards before a new drug is used in real life. All these requirements become the factors to increase the cost of R&D for a new drug.[7] According to the survey in 2016, the cost of R&D for a new drug is estimated to be nealy 2 billion Euro.[8] This survey shows that the cost has been increasing since 1970 at the rate of becoming double in ten years.[9] The pharmaceutical industry is known as the sector with the highest ratio of R&D to net sales. The survey investigated the overall R&D

5 EFPIA, *supra* note 2, at 14.
6 EFPIA, *supra* note 2, at 4.
7 Dickson et al., *supra* note 4.
8 EFPIA, *supra* note 2, at 6.
9 EFPIA, *supra* note 2, at 9.

percentage of net sales in many industries[10] and found that the Pharmaceutical and Biotechnology sector ranks the highest with the percentage of 14.4%. It is followed by Software & Computer Services (10.1%) and Technology Hardware & Equipment (8.0%). And the average of all 41 industries is 3.4%.[11] This number clearly shows how outstanding the R&D cost in the pharmaceutical industry is.

One of the reason for this costly R&D mainly lies in increased regulatory requirements.[12] Before a pharmaceutical company puts a new drug on the market, it has to survive long and costly clinical trials. These clinical trials require more participants and longer period of trials than before because the trends in the type of new drug development have recently changed. It is also reported that recent R&Ds for new drugs are shifting to the treatment of chronic diseases, which needs a prolonged period of time for curement. Thus, the clinical trials would accordingly take a longer period to examine medical safety than drugs for other diseases. Therefore, for developing a new drug, one survey indicates that it would take an average 12.8 years currently, which shows significant increase from an average only 7.9 years in the 1960s.[13]

C. High Failure rates

One of the characteristic features in R&D for a new drug is very high failure rate. R&D for a new drug is roughly classified into two stages. The first one is the laboratory stage. The researchers try to examine many candidate chemical sibstances that they believe to be promissing. They usually obtain these substances by the extraction from naturally occuring products, the artificial organic synthesis or the combination of both methods. The process of extracting and synthesizing chemical substances takes a lot of investment, labor and time because the molecular structures of effective

10 Data relates to the top 2,500 companies with registered offices in the US (829), EU (608), Japan (360) and the rest of the world (703), ranked by total worldwide R&D investment (with R&D investment above 17.9 million EURO).

11 European Commission, EU R&D Scoreboard (The 2015 EU Industrial R&D Investment Scoreboard) 53, http://iri.jrc.ec.europa.eu/scoreboard15.html. The table 3.2 (Ranking of the top 11 industrial sectors by overall R&D in the 2015 Scoreboard.) shows these figures in the first column “Global R&D intensity (%)”.

12 Dickson et al., *supra* note 4.

13 Dickson et al., *supra* note 4.

drug components are nawadays so complex that it often includes many steps before final chemical substances are obtained. Then they conduct screening experiments using animals for all candidates in order to check characteristics including effectiveness and toxity. The successful rates for the candidates to survive the first stage is considered to be significantly low. If they are lucky enough to obtain good results, they will go on the second step; the clinical development, which is the experimental step involving human to check effectiveness and side effect on human body. There are several phases (Phase I, II and III) that should be passed until a pharmaceutical company finally obtains final approval. According to the survey in recent ten years,[14] the overall likelihood of approval from Phase I for all developmental candidates was reported to be only 9.6 %.[15] Chronic diseases are the hard category to obtain final approval with its overall likelihood of approval being 8.7 %.[16] For calculating total successful rates, it is necessary to multiply these two stages. It is reported that on the average only about one of every 10,000 (0.01%) chemical substances researched will successfully become a marketable drug,[17] and behind one successful project there are at least 9 unsuccessfull projects which nonetheless must have been financed.[18] Since a successful drug has to produce enough profit of R&D for next future drugs, this situation is put in very clear words by Sir R. Jacob: "The few winners must pay for all the losers."[19]

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14 The survey was conducted by Biotechnology Innovation Organization that is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. It analyzed individual drug program phase transitions for ten years, from January 1, 2006 to December 31, 2015. Its world largest database includes 7,455 clinical drug development programs, across 1,103 companies.

15 Biotechnology Innovation Organization, Clinical Development Success Rates 2006-2015 (June 2016), https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf.

16 *Id.* at 16.

17 Dickson et al., *supra* note 4.

18 Tudor I. Oprea, Current trends in lead discovery: *Are we looking for the appropriate properties?* 16 J. Comp.Mol.Des. 325, (2002).

19 Robin Jacob, IP and Other Things: A Collection of Essays and Speeches 233 (Oxford and Portland, Oregon 2015).

D. Significance of patents as safeguard of innovator's profits

As described above, the development of a new drug is cost intensive and highly risky business for pharmaceutical companies, requiring them to invest high R&D cost and take a risk of high failure rates. On the other hand, the duplication of the new compound is a simple technical matter. This is an especially important issue in the pharmaceutical research because the development of a new drug involves the long lag time from discovery of a novel compound to marketing.[20] A pharmaceutical company as an innovator needs to exclude the following third party who tries to copy its invention from the market until they recoup their investment and make enough profits for further innovation. That's the reason why it always needs patent protection for a new drug. Patent is the legal protection that is the exclusive right for a limited period of time regarding the new and inventive invention. This patent protection allows a pharmaceutical company to have enough time to recoup their significant investment in R&D. Without patent rights, competitors can simply copy biopharmaceutical innovations as soon as they are proven safe and effective, offering their own versions in the market without investing the time and money to develop the drug. Innovators in the pharmaceutical industry could lose the ability to recoup their substantial investment in a new drug development, making it more challenging to find funding. In this way, patent protection in the pharmaceutical industry is significant as safeguard of innovator's profits.

20 Dickson et al., *supra* note 4.

III. How to achieve freedom to operate (FTO)

A. Overviews of FTO analysis preparations

We have already found how unique the key features of innovation in the pharmaceutical industry are, and accordingly how significant patents are for pharmaceutical companies to recoup their investments. Therefore, pharmaceutical companies are much more desperate to monopolize the market compared with companies in other industries. In case of finding the patent infringing activities by third parties, a pharmaceutical company would take all possible measures to exclude them from the market. This means when a pharmaceutical company would like to start researching and marketing its new drug, the pharmaceutical company must make sure that it would not infringe other pharmaceutical companies' patents. Discontinuance of the project for developing a new drug due to patent infringement of third parties must be avoided by any means possible because it could be almost amount to the failure of the project. Therefore, examining third parties' patents and making sure that the new drug is totally free from patent infringement is very important.

The procedure for assessing whether the product/process is free to sell or not is called an FTO analysis.[21] As much of the money and time is invested in one project in the pharmaceutical industry, it is absolutely indispensable for a pharmaceutical company to carry out intensive research on the FTO analysis from the very early stage of its R&D.

B. Building up the multidisciplinary FTO team

Ideally, an FTO team leader should have special expertise of pharmaceutical product and process because comprehensive and sophisticated understanding of its own product and process is essential for the team leader to

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21 Stanley P. Kowalski, *Freedom to Operate: The Preparations,* ipHandbook of Best Practices, at 1329 (last visited September 5, 2016), http://www.iphandbook.org/handbook/ch14/p02/

accomplish intensive FTO analysis.[22] Additionally, the FTO team leader must have considerable expertise in IP-related issues, such as a technology transfer professional officer, intellectual property practitioner like a patent agent, a scientist who has participated in various IP rights and technology transfer courses, workshops, or seminars.[23] In this way, the FTO team leader must be capable in two different professional fields since an FTO analysis is conducted in the domain where science and law overlap.

Other than the team leader, the FTO members should include scientists who had supervised the project, technology transfer personnel, and technicians/support staff.[24] A participation of technicians/support staff is very important because they know what exactly happened during the product research, development, and commercialization. It is also helpful to include business personnel (depending on the stage of commercialization) and possibly administrative staff to the FTO team. They might have information on relevant communications, documents, and agreements.[25]

One important thing when building up the FTO team is to make constituent team stuffs multidisciplinary. Opinions from several points of view and discussions would make their FTO analysis more precise and in-depth.

C. The FTO search

The FTO search is normally conducted by a competent professional searcher[26]. The searcher will normally use the patent clasification codes and keywords in order to narrow the scope of the third parties' relevant patents and patent application. This FTO search is extremely important and must be conducted in the most deliberate manner. The FTO team will examine and pick up most relevant patents and patent application among the search result. If the searcher fails in picking up even one relevant third parties' patent, the FTO team will not able to find it in later procedure no matter how intensively the FTO team conducts FTO analysis. It should be noted that just one patent could kill whole one pharmaceutical project.

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22 *Id.* at 1331.
23 *Id.* at 1331.
24 *Id.* at 1332.
25 *Id.* at 1332.
26 H. Jackson Knight, Patent Strategy 158 (3rd ed. Wiley 2013).

One should carefully bear in mind that the FTO search is totally different from a patentability search.[27] The purpose of a patentability seach is to find relevant prior arts which could destroy the subject patent or patent application. These prior arts basically need to disclose concrete example in order to destroy the broad claim of the subject patent or patent application. This is as we call "Species/Genus anticipation rule", which means that species anticipates genus, but genus does not necessarily anticipate species.[28] On the other hand, the purpose of the FTO search is to look for patents and patent applications which might have a great impact on the legal practice of the invention. Therefore, the searcher must look for patents and patent applications that have broad claim that might cover the product/process a pharmaceutical company is going to market, even though the invention is not specifically mentioned.[29] There are many patents and patent applications that look irrelevant to the product/process at first sight, but nevertheless it is likely that the claims of which are described broadly enough to cover them. In other words, it is quite common that the claims of relevant patents and patent applications don't contain keywords to specify the product/process at all. For example, when you would like to conduct the FTO search for your newly developing drug with a new chemical entity X, the typical keywords for finding relevant patents and patent applications could be chemical structure of X, molecular name of X and characteristic functioning group of X. However, you have to pay attention to numeric value patents, functional patents and product by process claim patents, all of which might not contain typical keywords for X but still cover X within the scope of the claims. This makes the FTO search very difficult to conduct accurately. The searcher must accurately predict what kind of wordings are used in the claim of possible relevant patents and patent applications.

D. Pharmaceutical Technical Considerations

The FTO team should consider pharma-product/process-specific components.[30] First, the FTO team has to take into account the compounds them-

27 Id.
28 Janice M. Mueller, Patent Law 176-177 (4th ed. Wolters Kluwer 2013).
29 Knight, *supra* note 26.
30 Kowalski, *supra* note 22, at 1335.

selves including the form of the compounds (ex. crystalline form, amorphous form), the steric structure of the compounds (ex. enantiomers), and the components which will be produced by metabolic process in human body (ex. metabolites, prodrugs). Second, the type of pharmaceutical compositions (ex. delivery system, vehicles and adjuvants) must also be considered. Third, the methods, steps, and components involved in the product synthesis are also critical. Drug synthesis normally consists of many steps. In each step, the reagents, the intermediates, purification techniques, and handling techniques of the third parties' patented invention might be involved. Fourth, downstream considerations (ex. method of use, modes of treatment, dosimetry, and limiting side effects) are also important to keep in mind.

In case of vaccines, there are additional FTO analytical considerations specific for vaccine research, development, manufacture and deployment, including expression systems, fusion partners, immunostimulators, adjuvant systems, excipients, and delivery devices.[31]

These pharma-product/process-specific considerations are very complicated. But an interview with technicians/support staff would greatly help the FTO search because they are the PHOSITA (Person Having Ordinary Skill In The Art) who might have information on "dangerous or safe" technique for patent infringement.

E. Pharmaceutical Patent Information

In addition to the standard patent search tools and resources, pharmaceutical patent search needs to check specific patent resource materials. The Orange book, the Merck Index and the actual file wrapper search are typical examples.[32]

The FDA[33] publishes a list of all drugs approved for marketing in the US under the title "Approved Drug Products with Therapeutic Equivalence Evaluations", which is also called "Orange Book". Orange Book is

31 Kowalski, *supra* note 21, at 1336.
32 Kowalski, *supra* note 21, at 1340.
33 U.S. Department of Health and Human Services, Food and Drug Administration

daily updated and can be readily accessed via the Internet.[34], [35] The FTO team can obtain information about approved drug products with therapeutic equivalence, as well as the expiration dates of patents on therapeutic small molecules and on approved indications and compositions[36].

The Merck Index is a one volume encyclopedia of chemical, drugs and biologicals that contains more than 10,000 monographs, which lists patents and publications on older drugs and reagents.[37] The Merck Index is available as a printed edition or online.[38] One of the advantages of the Merck Index Online is its accurate search ability by the chemical formula. It is risky to rely on only keyword patent searching because in pharmaceutical patents, a claim often contains a chemical formula to define the scope of the claim. And this chemical formula cannot normally be found only by keyword patent searching. The FTO team can easily and accurately search the patents by the chemical formula of the product.

It is prudent that the FTO team actually goes to the patent office to examine the boxes containing patent prior arts.[39] This is sometimes necessary to know the differences in nomenclature used by various patent drafters since some of differences might not be readily identified and sorted out in electronic searching.[40] As described above, there is the possibility that relevant patents and patent applications use a different nomenclature in the claims from the ones the FTO team grasps and include as the keywords. One of the purposes of examining patent prior arts filled in the patent office is to obtain the information on other possible nomenclatures. There are many ways to describe only one chemical entity. For example, an alcohol, which is contained in beer and has simple chemical structure, could be described either as “alcohol”, “drinking alcohol”, “ethanol”, “ethyl alcohol”, “1-ethylalcohol”, ”C_2H_6O”, “C_2H_5OH”, “CH_3CH_2OH”,

34 Orange Book, *Approved Drug Products with Therapeutic Equivalence Evaluations* (last visited September 6, 2016), http://www.accessdata.fda.gov/scripts/cder/ob/.
35 John R. Thomas, Pharmaceutical Patent Law, 418 (Bna Books 2005).
36 Kowalski, *supra* note 21, at 1340.
37 Kowalski, *supra* note 21, at 1340.
38 The Merck Index Online (last visited September 6, 2016), https://www.rsc.org/merck-index?e=1.
39 This is the case in the US. In other countries like Japan, the patent office provides this type of information online for free of charge (Japan Patent Office (last visited September 6, 2016), https://www.jpo.go.jp/).
40 Kowalski, *supra* note 21, at 1340.

"Et-OH", and "^OH"[41]. Normally, the structure of a new drug component is much more complicated, and therefore the nomenclature of which is fairly diverse.

F. Period of silence

The FTO team must recognize that patent applications are not available until they are published. In Europe and Japan, this period of silence is 18 months[42] after the earliest effective filling date. This means that there may be pending patent applications still below the surface, but nonetheless relevant to the FTO analysis.[43] This is called "period of silence". The FTO team has to keep searching for this secret patent application for at least 18 months to secure that there is no relevant patent applications. In US, historically, all pending patent applications were maintained in secrecy unless and until they are issued as patents. But after the American Inventors Protection Act of 1999, the default rule is that a regular U.S. utility patent application will be automatically published 18 months after its effective filling date.[44] It is worth noted that even under the current law a purely domestic patent application can avoid 18-months publication.[45] But with regard to pharmaceutical patent search, the FTO team can practically ignore this secret US patent application because there is substantially no pharmaceutical company that files patent application only in US.

G. Interpreting potentially adverse patents

When the search ends with relevant patents or patent applications which might have potential impact on the legal practice of the invention, the analysis then should be conducted as a next step. This analysis should be conducted by or with the help of an intellectual property professional[46] like qualified patent counsel because the claim will be often stated in an am-

41 "^OH" is the expression representing only carbon skeleton and functioning group.
42 In Europe: EPC Article 93(1)(a), and in Japan: JPA Article 64.
43 Kowalski, *supra* note 21, at 1341.
44 Mueller, *supra* note 28, at 65.
45 35 U.S.C. § 122(b)(2)(A)(ii), (iv)
46 Knight, *supra* note 26, at 159.

biguous manner, and interpretation of patents needs the help of specialized expertise with experience. The analysis is done by carefully and objectively reviewing the claim of the patents or the claim and description of the patent application.

1. Difference of analysis between patent and patent application

It should be noted that the FTO team has to clearly differentiate the way of reviewing between patents and patent applications. The biggest difference between them is whether patents are finally granted or not. Patent applications are the pending state before patents are granted. Accordingly, patent applications have chances of claim amendment in the future.

a) The scope of possible amendment

In case of patents, the scope is determined by the claim, and the description and drawings is used to interpret the claim.[47] The claim may not be amended in such a way that the claim is extend from the original claim.[48] Accordingly, the FTO team basically can review the claim as the maximum scope of the invention. On the other hand, in case of patent applications, applicants can amend the claim unless the amendment contains new subject-matter which is not included in the content of the application.[49] This means that until the patent application is granted, it is possible that the scope of the claim can be freely extended within the disclosure of the patent application, which is known as "claim up amendment". This is called so because applicants can claim the inventions that are stated only in the description. Accordingly, the FTO team should take into account not only the current claims but also possible future claims that could appear from the invention disclosed only in the description.

47 In Europe: Article 69 EPC, in Japan Article 70(1)(2) JPA.
48 In Europe: Article 123(3) EPC, in Japan Article 126(6) JPA.
49 Article 123(2) EPC, in Japan Article 17bis(3) JPA.

b) Patentability

In case of patents, they normally meet the requirements of patentability since they survived the review of patentability by an examiner at the patent office although the validity of patents is sometimes challenged and some of patents disputed are actually revoked. Therefore, the FTO team should examine the claims of patents on the condition that they are valid. On the other hand, in case of patent applications, since they are not yet reviewed and patents are not granted, the FTO team should first of all review validity of the claim. In practice, patent drafters tend to draft claims in a very broad manner which might even lack inventive step from prior art with the purpose of obtaining as broad claim as possible. If the applicant received an office action from the patent office, then he is able to amend the claims to the minimum extent which is necessary to circumvent the cited prior art. With this drafter's IP strategies in mind, the FTO team should predict how the claims would be amended to meet patentability requirement under prior arts that are considered to be cited by the patent office in the future. In this way, this process requires deep insight and experience in IP field.

2. File wrapper

It is also important to consider the information provided by the applicant to the patent office, which is called "prosecution history" of the patent.[50] An applicant, in an effort to obtain the patent, usually tries to differentiate the claimed invention from prior art found by an examiner. For this purpose, the applicant amends the claim and/or submits statements on interpretation of the claim. In many jurisdictions, it is prohibited to adopt patentee's assertion in the patent infringement case which contradicts the assertion made in the prosecution history (prosecution history estoppel). Therefore, in case of an interpretation of the claim, the FTO team should examine this prosecution history to check relevant amendment and/or statement which might narrow the scope of the claim. Ideally, the file wrapper should be searched and analyzed only by qualified patent counsel because searching file wrapper is part of claim interpretation. A patent

50 Knight, *supra* note 26, at 159-160.

counsel will use the contents of the file wrapper (claim amendments or disclaimers etc.) in order to interpret the precise meaning and scope of the claim wordings.[51] If the patents or patent applications are filed globally, it might help the FTO team to examine file wrapper in another countries because file wrapper could be helpful on worldwide-base.

It should be noted that in some countries such as Germany and UK prosecution history is not taken into account or not so directly relevant when the court examines the scope of the claim. In these countries, the FTO team can simply skip or spend less time to examine file wrapper.

3. Doctrine of equivalents

Even if it is clear that the product/process does not literally fall within the scope of the claim, the FTO team should not easily eliminate that patent from the watching list because the product/process still carries significant risk of infringing that patent under the doctrine of equivalents. The Doctrine of equivalents is a judge-made law that extends the scope of the claim beyond literal wording of the claim. Each country has developed its own requirement for the doctrine of equivalents, and the extent to which the scope of the claim extends differs in each jurisdiction. Accordingly, when the FTO team conducts patent searching in one country, the FTO team staff should familiarize themselves well enough with the infringement under the doctrine of equivalents there. This examination for the doctrine of equivalents is as difficult as that of literal infringement, and even more difficult in many cases. Therefore, final examination should be conducted by IP professionals.

4. Status searches

Once relevant patents and/or patent applications are found, the FTO team should keep an eye on their latest status because the published documents only show the information at the date of publication. It is normal that they will change their status later on. As for patents, the FTO team might find that one patent is not in force anymore because the patentee did not pay

51 Kowalski, *supra* note 21, at 1340.

maintenance fee,[52] or that the claim of another patent is amended[53] in a manner which excludes the subject product/process from the scope of the claim. As for patent applications, the FTO team might find that one patent application is deemed to be withdrawn without being requested to examine.[54]

5. Patent term extension

One unique feature for patents in the pharmaceutical industry is the patent term extension system. The FTO team should be aware of this system in each jurisdiction in terms of the term extension and the scope of the extended patent.

a) Term extension

The period of patent extension shows clear difference between Europe and other major jurisdictions (US and Japan). By paying attention to this difference, the FTO team can anticipate when exactly the relevant patent will expire, and accordingly its pharmaceutical company can be free to operate the invention.

In Europe, Council Regulation of 1992 concerning the creation of a Supplementary Protection Certificate (hereinafter referred as "SPC") was approved and came into effect in 1993, which provides different protection from patent law.[55] The European SPC aims to improve the protection of innovation in the pharmaceutical industry, and it intends to provide a uniform solution at the European Community level. As is set out in the Recitals (1) to (5) of the European Regulation, the purpose is to give sufficient incentive for the pharmaceutical industry to carry out the long and costly research necessary to bring new medicinal products to the market.

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52 Knight, *supra* note 26, at 160.

53 Philip W. Grubb, Peter R. Thomsen, Patents for chemicals, pharmaceuticals and Biotechnology: Fundamentals of Global law, Practice and Strategy 371 (Oxford University 5th ed. 2010)

54 In Europe: Article 94(1)(2) EPC, in Japan Article 48ter(4) JPA.

55 Ryoko Iseki, *Patent term extension in Japan: an academic and comparative perspective*, *in* Pharmaceutical innovation, Competition and Patent law 188 (Josef Drexl & Nari Lee eds., Edward Elgar Pub 2013).

The period of patent term extension by the SPC ranges from the date on which the application for a "basic patent" was lodged to the date of the first authorization to place the product on the market in the Community, reduced by a period of five years.[56], [57] This period is quite unique to Europe and different from the ones in US and Japan. Here, the time when the patent right is registered is not an issue. Even if the patent right registration comes after the date of marketing approval, it is still possible to add the period from the date on which the application is filed to the date of marketing approval.[58]

In US and Japan, the purpose of the system is to restore the effective period of the patent right that was lost due to the waiting period. According to the provision under US Patent Act, the extension term shall be the same with the time equal to the regulatory review period for the approved product for the period that occurs after the date on which the patent is issued.[59] Thus, in case that the regulatory review period occurred before the issue date, the extension term would become zero in the US. This is the same in Japan.

b) The scope of the extended patent

The extent of protection of the patent is normally determined by the claims.[60] However, when the FTO team examines the scope of the extended patent, it should be aware that the extent of it is determined in the different manner. In order to acquire patent extension, a pharmaceutical company must obtain a certificate that proves the period for which the pharmaceutical company can't place the drug on the market because of waiting the authorization. The scope of the extended patent shall not cover the

56 Article 13,1 of the Council Regulation (EEC) No. 1768/92 of 18 June 1992.

57 Iseki, *supra* note 55, at 192.

58 Matsui, S. and T. Aoki, *"Tokkyoseido no kokusaiteki seigouka to iyakuhinbunya no tokkyoken kikan enchoseido ni mirareru hiseigou (International Harmonization of the Patent System and Disconformities in the Patent Right Term Extension System in the Drug Field)"*, AIPPI, 2008, 53(6), 2 and 14.

59 35 U.S.C. § 156(c).

60 § 69(1) European Patent Convention in EU and § 70 Japan Patent Act in Japan. In US there is a case law with regard to the extent of the protection and it is the claim that basically determines it.

whole claims, but shall cover only the drug[61]. But, this interpretation is really difficult because it is totally different from the interpretation of normal claims and there are not so many cases in the past that can show the criterion for that. Therefore, the FTO team has to understand the uncertainty of this type of scope interpretation.

H. Dealing with Adverse Patents

If the intense review of potentially adverse patents by an IP professional unfortunately brings the FTO team the conclusion that the proceeding with making, using, or selling an invention constitutes an infringement of the patent, there are several options to be considered.

1. Legal / IP management strategies

a) License-in / Cross-license

One of the options is obviously to obtain a patent license from the patent owner, that is, the permission to use the patented invention in exchange for royalty payment. Although a licensee will become harder to make a profit from selling its licensed product due to royalty payment to a licensor, it is nevertheless advantageous to obtain a patent license because the licensee can completely eliminate the risk for injunction of its product in the market and troublesome patent infringement in the future.

However, the patent owner is generally not obliged to give a patent license. Even if the patent owner accepts to give a patent license, the licensing terms would probably involve a very large sum of money.[62] In the pharmaceutical industry, it is rarely seen to obtain a reasonable patent license under normal circumstances because the patent owner is also desperate to recoup the investment, and monopolizing the market with no licensee is the best way to achieve it.

The FTO team should then think of several IP strategies to make the patent license negotiation advantageous for its pharmaceutical company. One of the IP strategies is to create the circumstance under which the

61 § 4 SPC in EU, and § 68 bis Japan Patent Act.
62 Knight, *supra* note 26, at 160-161.

patent owner can't refuse the offer for licensing. That is to find the patent owner's weak points and attack them.[63] The key is the patents of the FTO team's pharmaceutical company.

It is highly recommended that the FTO team's pharmaceutical company owns various types of patents prior to license negotiation in order to obtain better license condition. These patents are roughly classified into two categories; "aggressive patent" and "defensive patent". "Aggressive patent" is the one that is used to overcome the weak point of the FTO team's pharmaceutical company. The FTO team can use this "aggressive patent" to conduct a patent license negotiation advantageously. "Aggressive patent" does not necessarily have to do with the technologies that the FTO team's pharmaceutical company is developing and marketing. Rather, "aggressive patent" should be aimed to attack the negotiating partner, whose patent is covering the technologies that the FTO team's pharmaceutical company. "Aggressive patent" is designed to cover the technologies that the competitors (therefore, future negotiating partner) would use now or in the future, rather than the FTO team's pharmaceutical company itself. As described above, it is the patent aimed to conduct the patent license negotiation advantageously.[64] Filling and obtaining "aggressive patent" is one of the IP strategies. It's not something the FTO team can prepare just before a patent license negotiation, but the pharmaceutical company always has to bear that in mind and continue filling patent applications to obtain in the future. On the other hand, "defensive patent" is the one that is used to protect the business and most important right for technology-based companies. The company should not allow the third party to infringe this "defensive patent" right and should not license out "defensive patent" to the third party. If "defensive patent" is infringed, the company should enforce the right and let the third party stop it by all means.[65]

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63 Giichi Maruyama, Chitekizaisan Sennryaku, gijyutu de jigyou wo tsuyokusurutame ni (The IP Strategy: Strengthening the Business by means of the Technology) 123 (Diamond sya 2012). The author has 40 years' of experience at IP department in Cannon Inc., Japanese Electronics Company selling camera, video, printer, photocopying machine and so on. He is well known in Japanese IP industry as one of the successful IP managers who performs skillful IP strategies. Some say that one of the reasons Cannon Inc. survived very competitive electronics industry was his ingenious IP strategies.

64 *Id.* at 123.

65 *Id.* at 113.

In case of the pharmaceutical company that carefully considers this IP strategy for "aggressive patent", the first thing that the FTO team should examine would be whether or not the negotiating partner is infringing one of "aggressive patents". If the FTO team is lucky enough to find that the negotiating partner is likely to infringe one of its "aggressive patents", then the negotiating partner would be substantially obliged to license out the patent at issue in the patent license negotiation since the negotiating partner would otherwise be accused of the infringement of "aggressive patent". The content of this "aggressive patent" could be anything as long as it covers the negotiating partner's act. It is not limited only to the one about drugs. If the negotiating partner develops other business, for example apparatuses for medical operation and chemical products, and the FTO team's pharmaceutical company also develops the business and hold patents, it is worth while checking the possibility that the negotiating partner's infringement in those products because even such the patent can work as "aggressive patent" in a patent licensing negotiation for a drug. In this way, "aggressive patent" would give the FTO team a great chance to successfully conclude advantageous patent license agreements.

In addition to the above, there is the further advantage of having "aggressive patent".[66] For example, imagine the circumstance where the FTO team's pharmaceutical company (X) has the risk of infringing patents B_1 and B_2 (hereinafter referred as "problematic patents") of the third party negotiating partner (Y) according to the FTO survey. But, at the same time, X finds that some of Y's activities also have the risk of infringing X's patents, A_2 ("aggressive patent"). Here, the patents A_1 and B_1 are the core technologies for X and Y respectively. Thus both X and Y don't want to license out these technologies unless they are obliged to do so. The patents A_2 and B_2 are non-core technology, which can be licensed out depending on the condition of the licensing agreement (See Table 1). Here, we assume that X's product has not been put on the market yet because it is still at the early stage of the development. Accordingly, Y does not know it. Y is not infringing X's patent A_1 but Y will probably assess it as very attractive technology that should be included in Y's product if Y could somehow succeed in licensing it in.

66 *Id.* at 127-128.

[Table 1]

		Patents	License
X	Core technology	A_1	X does not wish to license out.
	Non-core technology	A_2 = ”aggressive patent”	X can license out with good condition.
Y	Core technology	B_1 = problematic patent	Y does not wish to license out.
	Non-core technology	B_2 = problematic patent	Y can license out with good condition.

Under this circumstance, X sends a warning letter to Y, making the case that Y's product is infringing X's patent A_2 (“aggressive patent”) and X is prepared to license it out to Y in return for concluding cross license agreement in which Y will license out Y's patents B_1 and B_2. Y has no choice but to accept X's offer for cross license in order to continue Y's business. Good thing for X is that X does not have to license out patent A_1 on X's core technology (Table 2).

[Table 2]

	Patents relevant to their activity.	Patents they wish to license in	Actual cross license
X	A_1, A_2, B_1, B_2	B_1, B_2	License in: B_1, B_2 License out: A_2
Y	A_2, B_1, B_2 Y does not use A_1 but wishes to use it if possible.	A_1, A_2	License in: A_2 License out: B_1, B_2

However, if the X's product has already been put on the market, the patent license negotiation could have been totally different. In this case, Y knows X's weak point, that is, X can't continue its business on X's product unless X obtains the license for Y's patents B_1 and B_2. Therefore, Y can strongly insist that X should license out not only patent A_2 but also patent A_1 on X's core technology in cross license agreement. X has no choice but to accept Y's offer in order to continue its business. In this way, the license negotiation with “aggressive patent” before X puts its product on the market is really advantageous for X. Therefore, the FTO team should be

aware of the importance of obtaining as many "aggressive patents" as possible in advance and using them for the license negotiation before the FTO team's pharmaceutical company puts its product on the market.

b) Oppose / invalidate third-party patents

Since granted patents survived the review by examiners with regard to patentability, they are basically valid. But patents can be challenged even after they are issued. A successful challenge will invalidate a patent claim, and sometimes the entire patent.[67] One drawback of these procedures is the cost. But if a pharmaceutical company ignores the patent in question and continues to sell its product, it is likely to end up with patent infringement law suit that cost is much more expensive than the one for opposition or invalidation procedures. Another drawback is that this procedure might trigger and accelerate patent holder's actions for finding a possible infringer and filing a law suit.

c) Seek compulsory license

Article 31 of TRIPS (the Agreement on Trade-Related Aspects of Intellectual Property Rights) provides the issuing of compulsory licenses to national producers in national emergencies. This provision has been adopted by most countries, and is mainly aimed to the pharmaceutical industry. Although the applicable case is very limited, it is worthwhile examining this compulsory license.

67 Anatole Krattiger, *Freedom to Operate, Public Sector Research, and Product-Development Partnerships: Strategues and Risk-Management Options*, ipHandbook of Best Practices 1323 (last visited September 6, 2016), http://www.iphandbook.org/handbook/ch14/p01/

2. R&D strategies

a) Modify product

An alternative to patent license is to change the product specifications. This is possible only if (1) the FTO analysis is performed at the early stage of the development and (2) there is an alternative technology for modification in the public domain that would work at least as well as the prior product. Otherwise this strategy is not a good idea because many years' of works and a lot of investment would be lost, and a license negotiation might be a better solution.[68]

b) Invent around

Invent around is the option in which the pharmaceutical company seeks alternative ways to develop the product. This would delay product development, but could lead to significant benefits in terms of new patents for cross license, and perhaps even better products.[69] As described above, "aggressive patents" can work as a strong weapon for advantageous cross license. The drawback would be very high costs.

3. Business Strategies

a) Wait-and-see

With regard to business strategies, the simplest option for the pharmaceutical company is to commercialize the product in question and wait to see if the patent holder contacts you for a license.[70] It would be still possible to come to a licensing agreement. However, the pharmaceutical company should understand that it is very dangerous option because the company would be sued as a patent infringement once the patent holder refuses the licensing-out, causing the pharmaceutical company to give up its business. What's worse is, in US, if it can be proven that the infringer willfully in-

68 *Id.* at 1324-1325.
69 *Id.* at 1325.
70 *Id.* at 1325.

fringed the particular patent of the third party, then a court may assess damages three times higher than the patent holder's actual lost revenue.[71] For the pharmaceutical company that has to minimize the risk of business failure, this option is not recommended at all.

b) Merge and/or acquire (M&A)

Instead of the option for licensing-in, the pharmaceutical company can acquire, through mergers and acquisitions, the company that owns relevant patent in order to enable the pharmaceutical company to operate patented invention.[72] Contrary to the licensing option which is to "borrow" the technology, this option is substantially to "buy" the technology. But there are some downsides of M&A. First, in the M&A procedure, both a buyer and a seller usually require the resolution of general meeting of stockholders regarding this M&A transaction. This is not easy as you may imagine. Second, buying a company means accepting the all legal liability that a seller might have in the future. Proper due diligence is indispensable prior to M&A.

71 *Id.* at 1325.
72 *Id.* at 1325.

IV. Structure and operation of FTO-licensing markets in the pharmaceutical industry

A. FTO-licensing and EU competition law

1. Licensing and technology transfer in general

When a pharmaceutical company finds that the product or the process it wishes to sell or develop appears to be covered by the third party's patent rights, basically it has to obtain a license from the patentee in order to be free to go ahead. In general, licensing helps to spread innovation and enables licensee to develop new products and services. It also gives licensee an incentive to recoup the cost and further investment for next R&D. In this way, licensing plays an important role in economic growth and consumer welfare.[73] Therefore, licensing is in most cases pro-competitive. However, it could sometimes harm competition. The anticompetitive agreements are prohibited by Article 101 of the Treaty of the Functioning of the European Union (TFEU). As for the regime of licensing and technology transfer, it provides better guidance other than Article 101 of TFEU.

One is the Technology Transfer Block Exemption Regulation (TTBER), which exempts certain licensing agreements from antitrust rules, creating a safe harbour for licensing agreements concluded between companies that have limited market power and that respect certain conditions set out in the TTBER. Such agreements are deemed to have no anticompetitive effect or, if they do, the positive effects outweigh the negative ones. The other is the Technology Transfer Guidelines, which provide further guidance on the application of the TTBER as well as on the application of EU competition law to technology transfer agreements that fall outside the safe harbour of the TTBER.[74]

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73 European Commission press release, *Antitrust: Commission adopts revised competition regime for technology transfer agreements* (Mar. 21, 2014), http://europa.eu/rapid/press-release_IP-14-299_en.htm.

74 *Id.*

2. Royalty obligations in general

The parties to a technology license are normally free to determine the amount and nature of royalty payments without being caught by the Article 101 of the TFEU.[75], [76] It is in principle permissible in the agreement that the payment by the licensee is a lump sum, a minimus royalty,[77] a fixed amount for each product produced using the licensed technology, or a percentage of the selling price, or (in the case of software) an amount per user or machine, or a combination of these. Where the licensed technology relates to an input in the final product, the Guidelines indicate that royalities may be based on the price of the final product, provided that it incorporates the licensed technology.[78]

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75 The Guidelines § 184: "The parties to a license agreement are normally free to determine the royalty payable by the licensee and its mode of payment without being caught by Article 101(1) of the Treaty. This principle applies both to agreements between competitors and agreements between non- competitors. Royalty obligations may for instance take the form of lump sum payments, a percentage of the selling price or a fixed amount for each product incorporating the licensed technology. In cases where the licensed technology relates to an input which is incorporated into a final product it is as a general rule not restrictive of competition that royalties are calculated on the basis of the price of the final product, provided that it incorporates the licensed technology. In the case of software licensing royalties based on the number of users and royalties calculated on a per machine basis are generally compatible with Article 101(1)."

76 Jonathan D.C. Turner, Intellectual property and EU competition law 243 (2nd ed. Oxford 2015).

77 The Guidelines § 183(e): "This section does not deal with obligations in license agreements that are generally not restrictive of competition within the meaning of Article 101(1) of the Treaty. These obligations include but are not limited to: (e) obligations to pay minimum royalties or to produce a minimum quantity of products incorporating the licensed technology".

78 The guidelines § 184.

3. Previous view on royalty obligation based on the price of the final product

a) Case: Windsurfing International v Commission of the European Communities

There is the CJEU case in 1986 that held it anticompetitive to impose obligations to pay royalties on products produced without using the licensed technology, that is, Case C-193/83 *Windsurfing International v Commission of the European Communities.*

Windsurfing International Inc. is a US-based company which develops and sells "sailboards", an apparatus composed of a "board" (a hull made of synthetic materials equipped with a center-board) and a "rig" (an assemblage consisting essentially of a mast, a joint for the mast, a sail and spars) which makes it possible to combine the art of surfing with the sport of sailing. The company's turn over derives partly from the proceeds of the sale of "sailboards" which it manufactures, and partly from the income arising out of licenses which it has granted to other undertakings. In the 1970's Windsurfing International Inc. extended its operations to Europe, where it initially submitted patent claims in certain member countries of the European Community, namely the United Kingdom and Germany.[79] Under the Article 1 of the licensing agreement between Windsurfing International Inc. and German undertakings, among many obligations on the licensees, there was the obligation on the licensees to pay royalties for "rigs" manufactured under the German patent only on the basis of the net selling price of a complete "sailboard".[80] The Commission held that a number of clauses in licensing agreements which were concluded prior to 1981 with certain German undertakings, including the method of calculating the royalties infringed Article 101 of the TFEU. Accordingly, Windsurfing International Inc. brought an action for annulment before the CJEU against the Commission decision.[81]

Under these facts, the CJEU concluded that the method of calculating the royalties Windsurfing International Inc. had adopted was anti-competi-

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79 Paragraph 2, *Case C-193/83 Windsurfing International v Commission of the European Communities*.

80 *Id.* paragraph 9(3).

81 Ariel Ezrachi, EU Competition Law: An Analitycal Guide to the Leading Cases 346 (4th ed., 2014).

tive, holding that "As for the agreements providing that the royalty must be calculated at least on the basis of the price of the complete sailboard, it must first of all be noted that this is not one of the cases which, according to the commission, justify such a method of calculation, namely where 'the number of items manufactured or consumed or their value are difficult to establish separately in a complex production process, or . . . there is for the patented item on its own no separate demand which the licensee would be prevented from satisfying through such a method of calculation'. The rig is not incorporated in the board and, as was seen earlier, there was a separate demand for rigs. Those considerations also apply to the board, whose value is in any event much higher than that of the rig.",[82] "Nevertheless it must also be pointed out that the royalty levied on the sale of rigs on the basis of that calculation proves not to have been higher than that laid down for the sale of separate rigs in the new agreements, since the licensees acknowledged that it would be equitable to accept a higher rate of royalty once the licensor' s remuneration was to be calculated on the price of the rig alone. It follows that that method of calculation did not have as its object or effect a restriction of competition in the sale of separate rigs.",[83] and then "In the light of those considerations, it must be held that the method of calculating the royalties based on the net selling price of a complete sailboard was of such a nature as to restrict competition with regard to the separate sale of boards, which were not covered by the German patent, but not the sale of rigs.".[84]

b) The previous Guidelines: Commission Regulation (EC) No. 773/2004

The previous Guidelines on technology transfer agreements was Commission Regulation (EC) No. 773/2004 which include reference to above *Windsurfing International case*. With regard to the calculation of royalties, the paragraph 81 of the previous Guidelines noted that "The hardcore restriction contained in Article 4(1)(a) also covers agreements whereby royalties are calculated on the basis of all product sales irrespective of whether the licensed technology is being used. Such agreements are also caught by Article 4(1)(d) according to which the licensee must not be re-

82 *Windsurfing, supra* note 80 paragraph 65.
83 *Windsurfing, supra* note 80 paragraph 66.
84 *Windsurfing, supra* note 80 paragraph 67.

stricted in his ability to use his own technology. In general such agreements restrict competition since the agreement raises the cost of using the licensee's own competing technology and restricts competition that existed in the absence of the agreement. This is so both in the case of reciprocal and non-reciprocal arrangements. Exceptionally, however, an agreement whereby royalties are calculated on the basis of all product sales may fulfil the conditions of Article 81(3) in an individual case where on the basis of objective factors it can be concluded that the restriction is indispensable for pro-competitive licensing to occur. This may be the case where in the absence of the restraint it would be impossible or unduly difficult to calculate and monitor the royalty payable by the licensee, for instance because the licensor's technology leaves no visible trace on the final product and practicable alternative monitoring methods are unavailable."

c) License

As described above, it was once considered to be anti-competitive to base a royalty on the price of the whole product whrere only part of it is protected by the licensor's rights, unless it is impractical to base the royalty on the value of the protected part, or there is no separate demand for the protected part on its own, or the basis used would make no practical difference to the royalty charged.[85]

4. Royalties on products produced without using licensed technology

a) Issues

Patent licenses are subject to competition laws, as are other business relationships. In EU, technology licensing and similar agreements, often referred to as "technology transfer", are the subject of the technology transfer block exemption in Regulation 316/2014 of the European Union, which identifies certain provisions in a patent license that are considered to have an impact on competition, and identifies provisions that would be

85 Tuner, *supra* note 76, at 242.

regarded as being anti-competitive[86]. The types of provisions in a patent license which need a consideration of competition law concern are price restrictions or price minimums, market division, export restrictions, product quantity limitations, and compulsory assignment of improvements from a licensee to a licensor[87].

In the pharmaceutical industry, when the parties need FTO-license, they often include many patents even though they are not sure to use all patents because they want to secure their freedom-to-operate in the future. The issue here is whether or not royalties on products produced without using licensed technology are anti-competitive.[88] As described above, in some early cases so far including *Windsurfing International case*, the courts held it to be anti-competitive when a licensor obliges a licensee to pay royalties on products produced without using the licensed technology.[89] And the previous Guidelines basically followed these cases.

b) TTBER and the Guidelines on the issue

Article 2 of the TTBER (Exemption) provides the safe harbour to the technology transfer agreements. But in contrast, Article 4 of the TTBER (Hardcore restrictions) provides certain types of agreements with which the exemption in Article 2 shall not apply. There are many types of the agreements listed in Article 4, the relevant article in this issue is Article 4.1(a) and (d).[90] With regard to this issue, the current guidelines, Guide-

86 Philip Mendes, *Licensing and Technology Transfer in the Pharmaceutical Industry* 26 (last visited September 7, 2016), http://www.wipo.int/export/sites/www/sme/en/documents/pdf/pharma_licensing.pdf

87 *Id.* at 26.

88 Tuner, *supra* note 76, at 243.

89 *Windsurfing, supra* note 79.

90 Article 4 of the TTBER (Hardcore restrictions) reads: 1. Where the undertakings party to the agreement are competing undertakings, the exemption provided for in Article 2 shall not apply to agreements which, directly or indirectly, in isolation or in combination with other factors under the control of the parties, have as their object any of the following: (a) the restriction of a party's ability to determine its prices when selling products to third parties; (d) the restriction of the licensee's ability to exploit its own technology rights or the restriction of the ability of any of the parties to the agreement to carry out research and development, hereunless such latter restriction is indispensable to prevent the disclosure of the licensed know-how to third parties.

lines on the application of Article 101 of the Treaty on the Functioning of the European Union to technology transfer agreements (2014/C 89/03) (Hereinafter referred as "the Guidelines") provides several relevant paragraphs: § 101[91], 116[92], and 185[93].

According to TTBER and the Guidelines, it is clear that royalties on products produced solely with the licensee's own technology are regarded

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91 § 101 of the Guidelines reads "The hardcore restriction contained in Article 4(1)(a) TTBER also covers agreements whereby royalties are calculated on the basis of all product sales irrespective of whether the licensed technology is being used. Such agreements are also caught by Article 4(1)(d) according to which the licensee must not be restricted in its ability to use its own technology rights (see point (116) of these guidelines). In general such agreements restrict competition since the agreement raises the cost of using the licensee's own competing technology rights and restricts competition that existed in the absence of the agreement (58). This is so both in the case of reciprocal and non-reciprocal arrangements."

92 § 116 of the Guidelines reads "According to Article 4(1)(d) the licensee must also be unrestricted in the use of its own competing technology rights provided that in doing so it does not make use of the technology rights licensed from the licensor. In relation to its own technology rights the licensee must not be subject to limitations in terms of where it produces or sells, the technical fields of use or product markets within which it produces, how much it produces or sells and the price at which it sells. It must also not be obliged to pay royalties on products produced on the basis of its own technology rights (see point (101)). Moreover, the licensee must not be restricted in licensing it own technology rights to third parties. When restrictions are imposed on the licensee's use of its own technology rights or its right to carry out research and development, the competitiveness of the licensee's technology is reduced. The effect of this is to reduce competition on existing product and technology markets and to reduce the licensee's incentive to invest in the development and improvement of its technology. Article 4(1)(d) does not extend to restrictions on the licensee's use of third party technology which competes with the licensed technology. Although such non-compete obligations may have foreclosure effects on third party technologies (see section 4.2.7), they usually do not have the effect of reducing the incentive of licensees to invest in the development and improvement of their own technologies."

93 § 185 of the Guidelines reads "In the case of licence agreements between competitors it should be borne in mind (see points (100) to (101) and (116) above) that in a limited number of circumstances royalty obligations may amount to price fixing, which is considered a hardcore restriction (see Article 4(1)(a)). It is a hardcore restriction under Article 4(1)(a) if competitors provide for reciprocal running royalties in circumstances where the licence is a sham, in that its purpose is not to allow an integration of complementary technologies or to achieve another pro-competitive aim. It is also a hardcore restriction under Article 4(1)(a) and 4(1)(d) if royalties extend to products produced solely with the licensee's own technology rights."

as hardcore restrictions in agreements between competitors[94]. However, with regard to the royalties on products produced without using the licensed technology in other circumstances, the Guidelines does not clarify anything further.

c) Analysis on Article 4(1)(a) and relevant Guidelines

According to the Guidelines § 101[95], 185[96], the royalties on products produced without using the licensed technology are considered to restrict the ability to determine its prices. This might sound persuasive at the beginning because one intuitive approach for determining the price of products is to calculate it from the actual manufacturing cost. One simple way of calculation is to keep a cost percentage below 30%. If this calculation is actually taken in practice, it is true that it would restrict the ability to determine its prices because the payment of royalties is definitely extra cost the manufacturer has to pay additionally.

However, the cost is not a dominant factor at all to influence the price of products. The manufacturers will always think to maximize their profit. If there are people who are willing to pay at high price, the manufacturer would charge the high price regardless of how much the actual manufacturing cost is. In general, there is no direct connection between the payment of royalties and the prices charged for products, particularly in a competitive product market.[97] In addition to that, in the pharmaceutical industry where the determining price of a new drug is special and complex, there are many other factors that could have more influences on a drug price except for the payment of royalties.

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94 The Guidelines § 101, 116, 185, TTBER Article 4(1)(a) and 4(1)(d). Especially in § 185 of the Guidelines: "It is also a hardcore restriction under Article 4(1)(a) and 4(1)(d) if royalties extend to products produced solely with the licensee's own technology rights."

95 The Guidelines § 101: "The hardcore restriction contained in Article 4(1)(a) also covers agreements whereby royalties are calculated on the basis of all product sales irrespective of whether the licensed technology is being used."

96 The Guideline § 185: "It is also a hardcore restriction under Article 4(1)(a) and 4(1)(d) if royalties extend to products produced solely with the licensee's own technology rights."

97 Turner, *supra* note 76, at 243.

According to Forbes article[98], the factors that should be taken into account are so many and complicated: uniqueness of a drug, competitors drug price, the benefit that a drug offer over existing therapy, the cost of current treatment for the disease a drug targets, a drug's possibility for changing practice of medicine such that patients will no longer have to pay costly hospital procedures, and whether a drug save or extend lives or not. This article goes on further regarding how people feel about that price of a drug. If it costs too highly, doctors and patients might be reluctant to prescribe it because it is likely that they think the drug too little benefit for the added cost. If it provides a discount price to an existing therapy, it is likely that they might avoid it because the cheap drug would not work better than existing therapy.[99]

One study conducted on determinants of launch price of a drug points out the following factors.[100]

(i) Competitors Prices

First of all, if there is a competitor's drug in the similar category and in the same market, the launch price of a drug would be significantly influenced by that competitor's drug.[101] If there is a local pharmaceutical company that sells a generic drug, that cheap price would definitely have an influence on the drug price.

(ii) Launch Timing and Sequence

The launch price of a drug will generally decline with time elapsed since global launch.[102] Therefore, if the timing of the launch of a drug in the market is delayed, the pharmaceutical company of the drug would be vir-

98 John LaMattina, *What Is The Rationale For The Pricing Of New Drugs?* (Sep. 10, 2012, 11:55AM), http://www.forbes.com/sites/johnlamattina/12012/09/10/on-the-pricing-of-new-drugs/#500d64ed4b8e

99 *Id.*

100 Patricia M. Danzon, Andrew J. Epstein, Working Paper Series: Effects Of Regulation On Drug Launch And Pricing In Interdependent Markets 35-40 (Working paper 14041, National Bureau of Economic Research 2008).

101 *Id.* at 35.

102 *Id.* at 35.

tually obliged to set a cheaper price than the first one put on the global market. The entry of the following drugs could also have an impact on the launch price of a drug. As for sequence, drugs are classified as two categories in the study; superior products and inferior products, and then they analyse that in case of inferior products first or second entrants appear to receive premium price compared to the other inferior drugs although in case of superior products first several drugs are likely to enjoy premium price.[103]

(iii) Cross-national spillovers

Since drugs can be exported internationally, pharmaceutical companies have to take into account the lowest price of their own drug that was already put on the market in other countries. In the study they analyse that for both superior and inferior products launch prices will be influenced by the lowest price previously received in other high-price EU countries, whereas effects of launch in low-price EU countries is insignificant. In case of superior products the lowest price in non-EU countries is significant, but that is not significant in case of inferior products because they are less likely to launch in high-price non-EU countries such as US and Canada.[104]

(iv) Products Characteristics

The characteristics of a drug (package size, drug forms etc) should also be taken into account. If the drug is sold as the pack with many units all together and the price of a drug is determined by the pack, it would have a negative effect on the price of the drug. For example, a drug with pack size over 100 units will be purchased in large quantities by pharmacists to dispense them to patients from large packs. The price per dose for injectable and non-oral forms (liquids, creams etc) is significantly higher than that of the oral solid formulations.[105]

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103 *Id.* at 36.
104 *Id.* at 37.
105 *Id.* at 39.

(v) Country Fixed Effects

The country where a drug is going to launch is a big factor on its price. In case of superior product, the price is significantly higher in the US and Japan than that in Germany.

Taking into all these factors above, interestingly enough, the cost of manufacturing a drug is not counted as important factor in this paper. I assume that this shows small influence of the cost on the price of a drug. Here, I would like to introduce one typical example of "Soliris" to show that the cost of manufacturing a drug has little to do with the price of products. Soliris is the drug for rare diseases manufactured by Alexion, which is often referred as an orphan drug. Solaris is used for treating two types of diseases: a rare kind of anemia and an more rarer kidney disease known as aHUS (atypical hemolytic uremic syndrome). It is estimated that there are only a few thousand patients around the world who use Soliris. Nonetheless, Soliris anually earns $1.1 billion in sales in 2012. This is because Soliris costs $440,000 per patient per year, being known as the most expensive drug in the world.[106] The reason why the price of Soliris is so high is not known to the public since Alexion refuses to clarify it regardless of NICE[107]'s inquiry. Accordingly, it is totally unknown whether or not Alexion pays royalty, and if so, the extent to which that royalty has an influence on the price of Soliris. But I assume it is quite likely that even if Alexion pays royalty, the amount of the royalty would not be comparable to Soliris's extraordinary expensive price. The influence of the royalty on the price of Soliris would be almost negligible.

As described above, according to the Guidelines § 101, 185, the royalties on products produced without using the licensed technology are considered to restrict the ability to determine its prices. Therefore, such royalties must be regarded as hardcore restrictions. However, I think this guidance by the Guidelines is not appropriate especially for the pharmaceutical industry with the reasons discussed above.

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106 Pharmaphorum, *Alexion must 'explain' high cost of Soliris, says NICE* (Mar. 4, 2014), http://pharmaphorum.com/news/alexion-must-explain-high-cost-of-soliris-says-nice/.

107 NICE (The National Institute for Health and Care Excellence) is an executive non-deparmental public body of the Department of Health in the United Kingdom.

B. FTO-licensing between a venture business company for innovative drug development and a pharmaceutical company

1. Introduction

As described above, developing a new drug from zero to marketing is becoming more and more difficult these days. Accordingly, it is significantly important option for a pharmaceutical company to build an alliance with a venture business company for innovative drug development.[108]

2. Reasons for the growing interest for licensing-in/out the pharmaceutical industry

Recently, there are quite a few numbers of larger pharmaceutical companies developing new drugs that adopt the IP strategy with which they are willing to license-in the technology of a venture business company.[109] The reasons are three holds. First, they have been struggling with developing new drugs even though they have to do it. In order for a pharmaceutical company to keep growing up its pharmaceutical business, it must continue investing for next drugs.[110] Therefore, they are desperate to find a candidate for future new drugs.[111] Second, since there is a clear unmet medical needs[112] in the pharmaceutical industry, many pharmaceutical companies are conducting similar R&D accompanying severe competi-

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108 Takatori et al., *Seiyakukigyou to baiobentyâ to no araiansu: nichibeiou seiyakukigyou no hikaku bunseki (An alliance between a pharmaceutical company and bio venture company: Comparison and analysis of pharmaceutical companies in Japan, US and EU)* 31 (Nov., 2009), http://www.jpma.or.jp/opir/research/rs_048/paper-48.pdf.

109 *Id.* at 31.

110 Investment might bring a big profit to a pharmaceutical company ten years later. Without investment, sooner or later it will lose the source of profits in accordance of the expiration of patents.

111 Kenji Tomita, *Seiyakusangyou ni okeru raisensu-in/auto no muzukashisa (Difficulties in licensing-in/out in the pharmaceutical industry)* DousishaShogaku, Dai-66-kan, Dai-1-gou (Jul., 2014) 244, https://doors.doshisha.ac.jp/duar/repository/ir/16560/017066010015.pdf.

112 Unmet medical needs are medical needs for the patients for whom effective medical care has not been found yet. The concrete examples are serious diseases like a lifestyle-related disease, cancer, and dementia, and the diseases which is not fa-

tion. It is of great help for a pharmaceutical company to utilize useful knowledge of a venture business company for developing a new drug faster than other competitors. In the case of a new drug, once a pharmaceutical company obtains the patent for it, the third party can't follow the same drug. Accordingly, an originator pharmaceutical company is extremely advantageous and there is no room for the second.[113] Third, as is pointed out above, the successful rates of the development for a new drug is so exceedingly low that it will be more promising to rely on the development performed by venture business companies in addition to pharmaceutical companies. This is one of the business strategies to reduce the risk. It is efficient and less risky to license-in the golden egg, that is, promising candidate for a new drug, which was found by a venture business company as the result of researching and experimenting many candidates.[114] These are the reasons why larger pharmaceutical companies are willing to license-in the technology of a venture business company.

For the side of a venture business company, there are two reasons why it willing to license-out its technology to a larger pharmaceutical company.[115] First, since clinical trials will take long time and a lot of investment especially after phase II, it is almost impossible for a pharmaceutical company to conduct a whole R&D process without having enough corporate strength. In other words, a venture business company is unable to conduct clinical trials. Therefore, a venture business company takes charge of only pre-clinical trial research, leaving the following clinical trials to a larger pharmaceutical company. Second, since a venture business company usually does not have enough capital and has difficulty in financing, it wishes to sell or license the achievement at the stage of research (pre-clinical trial) as soon as possible to obtain the capital to start next research for a new drug.

The fields of diseases which a venture business company wishes to research are the one in which a new drug is likely to appear in near future, such as cancer, mental illness, and disease seen among old people.[116] On the contrary, a venture business company is reluctant to get involved in the

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tal but nevertheless the patients strongly demand the development of the effective medical care for better quality of life like insomnia and migraine.

113 Tomita, *supra* note 112, at 244.

114 Tomita, *supra* note 112, at 244.

115 Tomita, *supra* note 111, at 245.

116 Tomita, *supra* note 111, at 245.

field of disease such as lifestyle-related disease and rare diseases. As for the lifestyle-related disease, pharmaceutical companies have already acquired enough ability to research by their own such as lifestyle-related disease, and accordingly it is not an attractive to a venture business company. As for rare diseases, the market is not big enough for a venture business company to yield large profit. Thus a venture business company can't afford to pay expensive cost. But if there is the rare disease that pharmaceutical companies boggle at difficulty to launch the research, but nevertheless a venture business company is able to find promising candidate, a venture business company can license-out the technology.[117]

In addition to the above, there is one more factor that enhances the division of R&D. In the normal R&D process, there are two groups even in one pharmaceutical company: the group of experts conducting researches and experiments for pre-clinical trials, and the group of experts conducting development for clinical trials. They belong to the separated department and focused on their own specialized jobs, being mutually independent. The expert for the former will never conduct the job for the later and vice versa. In other words, there is the favourable circumstance for two different companies to take in charge of these two different jobs respectively, and to license-in/out each other.[118]

In this way, in the pharmaceutical industry, the interest for licensing-in/out is increasing for both sides of a larger pharmaceutical company and a venture business company.

3. The type of drugs a venture business company develops

Pharmaceutical drugs are divided into the low molecule pharmaceuticals and the biopharmaceuticals. With regard to the low molecular pharmaceuticals, researchers entirely synthesize them utilizing chemical synthesis technology, or utilize naturally occurring products. On the contrary, with regard to the biopharmaceuticals, researchers utilize the molecular found in the human body and its modifications. Examples are genetically modified pharmaceuticals (protein pharmaceuticals) and antibody pharmaceuti-

117 Tomita, *supra* note 111, at 245.
118 Tomita, *supra* note 111, at 245.

cals.[119] These biopharmaceuticals tend to be sold at very expensive price. And unlike the development of the low molecular pharmaceuticals, the development of the biopharmaceuticals requires special expertise.[120] Therefore, recently the number of the venture business company specialising the biopharmaceuticals (hereinafter referred as "bio-venture company") is rapidly increasing.

4. The reality of licensing-in/out

According to the survey which analysed origins of products for top ten pharmaceutical companies in US, EU and Japan, nearly 40-45% of the products found to be originated in the third party, among which 75-90% is from a venture business company.[121] There is no significant difference between three regions. This clearly shows larger pharmaceutical companies are actively licensing-in the third party's technology, especially from a venture business company.

The recent licensing-in/out often occurs in the region of cancer drugs. Most of the larger pharmaceutical companies place emphasis on the development of cancer drugs which is one of unmet medical needs, and aiming desperately at obtaining patents and commercialization as soon as possible, making that region highly competitive. As described above, in the process of developing a new drug, what matters most is the speed of the development. Therefore, a larger pharmaceutical company tends to active-

119 Antibody pharmaceutical is the antibody as a drug that links the specific antigen like cancer cell and pathogen, and works performing antigen and antibody response.

120 For example, since the method of cultivating the molecular found in the human body is not often established, and quality control is quite difficult accordingly, the high level of knowledge and experience of cultivation and quality control is required, which even a larger pharmaceutical company does not necessarily has.

121 Takatori et al., supra note 108, at 15 (Figure 2-1). They used Trend Analysis in the Pharmaprojects as of January 2009 as database (last visited September 7, 2016), https://citeline.com/products/pharmaprojects/. The pharmaceutical companies which were the subject of survey were, Takeda, Eisai, Daiichi Sankyo, Astellas, Otsuka, Mitsubishi Tanabe, Dainippon Sumitomo, Shionogi, Ono, and Kyowa Hakko Kirin (Japan), Pfizer, Johnson & Johnson, Merck & Co. Abbot, Lilly, Wyeth, Bristol-Myers Squibb, Schering-Plough, Baxtar, and Forest (US), GlaxoSmithKline, Novartis, Sanofi Aventis, AstraZeneca, Roche, Bayer, Boehringer Ingelheim, Novo Nordisk, Merk, and Servier (Europe).

ly license-in or buy the promising candidate. Because of these reasons, there are many bio-venture companies that specialize in cancer drugs.[122]

However, it is reported that the number of licensing-in/out in the pharmaceutical industry is not quite large regardless of the fact that there are many bio-venture companies who wish to license-out.[123] It is very difficult to know the accurate number of licensing-out cases because most of bio-venture companies' stocks are not listed and the information on their transaction including licensing-out is not published. There is the survey in which the reporter examined the number of license-in cases of top ten large pharmaceutical companies[124] in Japan based on their financial statements in which the important business contracts shall be reported.[125] The results are shown in Table 3.[126]

[Table 3]

	total	Bio-venture company		Pharmaceutical company	
		overseas	domestic	overseas	Domestic
2007	17	12	1	2	2
2008	12	11	0	0	1
2009	9	6	1	2	0
2010	17	11	4	0	2
2011	10	7	2	0	1
2012	4	4	0	0	0

Table 3 shows the situation of licensing-in/out in Japan for the period from 2007 to 2012. The numbers are the actual cases of licensing-in/out. The licensing-in/out by a pharmaceutical company could be carried out not only with a(n) (overseas/domestic) bio-venture company but also a(n) (overseas/domestic) pharmaceutical company. Table 3 classified these cases of licensing-in/out respectively.

122 Tomita, *supra* note 111, at 248-249.
123 Tomita, *supra* note 111, at 248-249.
124 These ten pharmaceuticals are, Takeda, Astellas, Daiichi Sankyo, Esai, Mitsubishi Tanabe, Otsuka, Chugai, Dainippon Sumitomo, Shionogi, and Ono.
125 The fact of licensing-in bio-venture patents is included here. But detailed licensing conditions such as price are not published.
126 Tomita, *supra* note 111, at 248 (Figure 2).

According to this survey, the number of license-in/out cases is found to be very small. Most of origin companies of license-in cases are bio-venture companies overseas. It should be noted that this number is only for license-in/out, and a pharmaceutical company has alternative options such as M&A, joint research and a capital tie-up to achieve the same result. But considering that licensing-in/out is common way for a bio-venture company, the actual number is estimated to be still small. Another report[127] published by one bio-venture researcher in Japan also refers to the difficulty of license-in/out between a pharmaceutical company and a bio-venture company. It reports that more than 1,800 venture companies that originated in the research in universities had been established since the Ministry of Economy, Trade and Industry, Japan encouraged universities to launch their businesses in 2001. There were more than 500 bio-venture companies included in those venture companies. However, only a handful of bio-ventures succeeded in licensing-out. Since a lot of investment and quite a long time are required to develop a candidate for a new drug, most of them suffer from financing and end up with going out of business or going dormant state. I would like to analyze this current situation and propose a possible solution.

5. Analysis of current situation

It is considered that there are several reasons why license-in/out between a pharmaceutical company and a bio-venture is not so successfully performed despite the fact that there are many pharmaceutical companies / bio-venture companies who wish to establish alliances each other. I will describe these reasons as follows.

a) Needs/Seeds mismatching

There is some possibilities that the needs of a pharmaceutical company and the seeds of a bio-venture company don't match properly in the phar-

127 Kenzo Takada, *Seiyakugaisya tono raisensu keiken kara mita koutaiiyakuhin kaihatsu (The development of antibody pharmaceuticals in the sense of licensing-out the technology to a larger pharmaceutical company)*, Yakugaku Zasshi, 133(1), 61-66.

maceutical market.[128] As described above, a pharmaceutical company is limiting the fields of diseases which they wish to develop in order to maximize profits and minimize risks. Therefore, a bio-venture company has to deliberately investigate what kind of new drugs are actually waited to appear in the pharmaceutical industry, and what exactly a pharmaceutical company expects a bio-venture company to develop. The latter is really important because the need of the market and that of a pharmaceutical company are not necessarily the same. Even if a bio-venture company develops a good candidate of a new drug for a certain field of disease, that might be the field which a pharmaceutical company wants to develop by its own, not by licensing-in. A bio-venture company can obtain this kind of information by reading relevant papers, attending international conferences, and analysis of relevant patents.

b) Unclear relationship of right

One of the fears that a pharmaceutical company confronts when it licenses-in the technology of a bio-venture company is that it might encounter some legal problems in the future arising from the negligence of a bio-venture company concerning clearing the relationship of rights. This relationship of rights includes issues concerning service invention. Even if the patent is filed by the bio-venture company as an applicant, it is still unclear whether or not the bio-venture company actually owns the right to be a patentee. As for job related invention, in some countries[129] the inventor initially owns the right to file the invention to patent office, whereas in other countries[130] the employer does. If the transfer of the inventors' rights has not been properly conducted, a pharmaceutical company might compensate for the inventors who would start claiming huge amount of remuneration after their invention are found to have brought huge profit to a pharmaceutical company. Or in a worst scenario, they might start insisting invalidity of the patent. Therefore, a pharmaceutical company has to make sure that all necessary rights belong to the bio-venture company. However,

128 *Id.* at 65.

129 The examples are US, Germany and Japan (Article 101 of US Patent Act, Article 6 of German Patent Act, Article 35 of Japan Patent Act.).

130 The examples are France and UK (Article 611-7(1) of French Intellectual Property Act, Article 39(1) of UK Patent Act).

with regard to the development for a new drug candidate by a bio-venture company, there are many people who get involved in the research and might be entitled to be one of inventors, including professor, project leader, staff, student and technical staff. It is almost impossible for a pharmaceutical company to completely make sure that all necessary rights are properly transferred to a bio-venture company. Accordingly, a pharmaceutical company has to take a risk of future claim for remuneration or invalidation when it licenses-in or buys a bio-venture company's technology.[131]

Another example is the relationship of right with regard to the informed consent from the donor. The development of biopharmaceuticals often requires donors to obtain human cells, organs such as blood. When a bio-venture company uses human blood for the development of an antibody drug for instance, it needs to acquire the informed consent from the donor which states that (i) the donor offers the blood for the purpose of antibody drug development, (ii) the donor shall not have any right and remuneration regarding the blood. If a bio-venture company uses the blood of patient, it might be required to obtain the approval of the medical institute.[132] This relationship of right will possibly lead to some problem in the future.

I think this unclear relationship of rights is one reason why a pharmaceutical company is afraid of license-in or buying a bio-venture company technology.

c) Geographical distance

Table 4 below shows nationality of a bio-venture company from which major pharmaceutical companies in US, EU and Japan license-in or buy. The number of US companies is overpowering that of other regions. Germany and Japan are less than a tenth of US.[133]

131 Of course, a pharmaceutical company can reduce this risk as much as possible by requesting documents from a bio-venture company, but basically, a pharmaceutical company does not know who are the real inventors in the development at a bio-venture company.

132 Takada, *supra* note 127, at 65.

133 Takatori et al., *supra* note 108, at 17 (Figure 2-2).

[Table 4]

ranking	The nationality of a bio-venture company	The number of drugs developed
1	US	334
2	UK	38
3	Canada	29
4	Switzerland	20
5	France	19
6	Germany	18
11	Japan	10

Table 5 shows the geographical relationship between a pharmaceutical company and a bio-venture company. As for US, EU and Japanese pharmaceutical companies, the nationality of the first ranked bio-venture company is US, followed by EU bio-venture company. On the other hand, if we look at this table from a bio-venture's point of view, it is found that the candidate of drugs developed by EU and Japan bio-venture companies are firstly introduced to EU and Japan pharmaceutical companies respectively, whereas that by US bio-venture companies are introduced all around to US, EU and Japan pharmaceutical companies.[134]

[Table 5]

The nationality of a bio-venture company	pharmaceutical companies		
	US	EU	Japanese
US	136	141	57
EU	59	85	21
Canada	14	9	6
Australia	4	7	5
Japan	1	2	7
Others	9	3	3

It should be also noted that EU and Japan pharmaceutical companies have the R&D canters in US, and this has a lot to do with the fact that EU and

134 Takatori et al., *supra* note 108, at 19 (Figure 2-4).

Japan pharmaceutical companies license-in or buy from US bio-venture companies. This shows that geographical proximity affects the alliance between them. There are some reasons why geographical proximity affects in favour of building an alliance. If a bio-venture company and R&D center of a pharmaceutical company are located nearby, it is easy for both sides to have face-to-face meetings frequently, and/or to visit the R&D center to know how the invention actually works. Additionally, it is likely that they can communicate in the same language without any stress. I think this geographical distance is one reason to cause both sides to stay away from building an alliance.

d) Risk of insufficient FTO performed by a bio-venture company

I think it is possible that the insufficient FTO performed by a bio-venture company is in the way of building smooth alliance. As described above, to achieve thorough FTO requires specific expertise and experience. However, it is considered that a bio-venture company usually lacks the ability to perform thorough FTO because the scale of the company is so small that it does not have enough money and time to spend on their "extra" job. A pharmaceutical company does not want to take the risk of insufficient FTO.

As a counter measure for that, a pharmaceutical company often requests a bio-venture company to guarantee that the sufficient FTO was performed and it is no legal obstacle for a pharmaceutical company to reduce in practice. But a bio-venture company will try to limit their responsibility in order to minimize their risk, for example, showing the range of the FTO and insisting that it won't carry responsibility even if the relevant patent is found from outside of that range[135]. In addition, if the relevant patent is found in the future and the patent holder demands injunction under the patent infringement by a pharmaceutical company, it has to stop the marketing. The pharmaceutical company is probably able to ask compensation against the bio-venture company insisting the breach of the contract. However, it is useless to obtain compensation from a bio-venture company be-

135 This range could be about region (ex. US, Germany and Japan), company (ex. top 10 ranked pharmaceutical companies), and use of a drug (ex. a drug used for the treatment of lung cancer).

cause the only purpose of the pharmaceutical company is to sell its drug to recoup its investment.

Of course it might be one option for a bio-venture company to ask an outside agency for its FTO, but as also described above, the FTO in the pharmaceutical industry needs very specific way to achieve FTO such as pharmaceutical technical considerations (Part III D), pharmaceutical patent information (Part III E), and patent term extension system (Part III G5(b)). However, there are two problems to utilize outside agency. First, I suppose there is no outside agency that specializes in the pharmaceutical industry and has enough ability to achieve sufficient FTO. If a bio-venture company asks general outside agency for its FTO, it is more likely that it fails to achieve thorough FTO, being unable to find some quite relevant patents. This likelihood is exactly what a pharmaceutical company detests. Second, as also described above, the FTO team should consist of wide range of staff including the team leader, the scientist who supervised the project, technology transfer personnel, and technicians/support staff in order to collect opinions from different point of view (Part III B). But it is impossible for the FTO team at outside agency to have such members because a bio-venture company is outsourcing the FTO.

Instead of the FTO performed by a bio-venture company, a pharmaceutical company might be able to conduct the FTO alone before it starts the negotiation for licensing-in. However, it is quite time consuming and almost impossible to conduct the sufficient FTO for all possible technologies before the negotiation. Furthermore, the FTO conducted by a pharmaceutical company has the same problem with that done by outside agency, that is, a pharmaceutical company, as a third party, can't build a proper FTO team.

In this way, a bio-venture company itself is considered to be the most appropriate one to conduct the FTO. Aside from the lack of skill of a bio-venture to conduct the FTO, there is another aspect that a bio-venture company is missing. That is the IP strategy. As described above (Part III H1(a)), in the whole process of developing a new drug, a pharmaceutical company should try to obtain "aggressive patent" in advance in order to make the future possible license negotiation easier to agree. However, a bio-venture company usually lacks this point of view because it normally license-out or sell its technology before the development proceeds to the clinical trial. A bio-venture company is never prepared for future possible negotiation for patent license, which a pharmaceutical company as a licensee or a buyer would encounter later on. One important thing I would

like to point out is the significance of "aggressive patent". In the pharmaceutical industry which has really cut-throat competition of R&D, the result of the FTO would almost always bring several adverse patents. A pharmaceutical company can't give up its development for the reason of the existence of several adverse patents. In this case, "aggressive patents" will work pretty well to continue the development by means of cross-license. Even if the technology itself is excellent, a pharmaceutical company might hesitate to license-in or buy it, being afraid of the tough negotiation in the future without "aggressive patents".

6. Some proposals

I would like to propose some solutions concerning this FTO issue.

a) More attention to the FTO analysis and licensing by a bio-venture company

I think that a bio-venture company should be more aware of the importance of the FTO analysis and licensing. Without the sufficient FTO, the technology transfer won't be easy even if that technology itself is quite sophisticated. I pointed out that the scale of a bio-venture company could be one reason, but no matter how small it is, a bio-venture company should try to organize its own FTO team to achieve thorough FTO to convince a future licensee or buyer. In addition to this, it would be of great help if a bio-venture company takes into account the whole process of the development of a new drug and have the IP strategy to obtain "aggressive patent" which could be effective for cross licensing in the future. Then when a bio-venture company offers license-out or sell the technology, it can show the thoroughness of its FTO and can also offer to give "aggressive patents" in case for the future license negotiation regarding a relevant adverse patent. I think this offer is really convincing to a pharmaceutical company that is afraid of legal trouble in the future.

b) The FTO by a pharmaceutical company at earlier stage of the development

On the other hand, there are things which a pharmaceutical company should prepare in advance to license-in the technology. As described above, a bio-venture company is basically the one that performs the FTO appropriately. But if a pharmaceutical company has the specific narrow area[136] in which it would like to license-in a bio-venture company's technology, it is a good chance to conduct the FTO by its own. Normally, the FTO analysis starts after the basic concept of the product/process is determined because it is too broad and time consuming to conduct the FTO without the product/process. However, in case that the area is quite limited, it is not impossible any more to check all patents/patent applications. If a pharmaceutical company conducts this type of FTO by its own, it would familiarize itself with existing patents/patent applications in that area so much that it becomes able to find the promising technology and determine to license-in the technology much faster than other competitor pharmaceutical companies. This speedy decision is very important because the promising technology is also the target of other competitors.

136 For example, a pharmaceutical company might be interested in license-in the technology with regard to the candidate for antibody drug on liver cancer, which is quite narrow and therefore the FTO analysis without any specific technology could be realistic.

V. Conclusion

The pharmaceutical industry is completely unique compared with other industries in terms of huge market, high R&D investment, high failure rates, and significance of patent as safeguard of innovator profits. First of all, in this pharmaceutical industry, the way to perform proper FTO (freedom-to-operate) was examined, taking into account the specific features in this industry.

One of the common strategies to achieve FTO is licensing-in the technology of the adverse patent. But it was found that licensing-in activity is not so easy in the pharmaceutical industry because the patent holder tends to monopolize the market to recoup its investment rather than making profit by licensing-out it to a competitor. Monopoly of the market is the best way to maximize the profit.

However, the IP strategy to prepare "aggressive patents" prior to license negotiation would greatly help to conclude a license-in agreement, in most cases, a cross licensing agreement. Therefore, it is significant for a pharmaceutical company to take this IP strategy long before it starts negotiating for a patent license. A pharmaceutical company should file patent applications not only for "defensive patents" to protect its core technology but also for "aggressive patents" to facilitate the licensing negotiation in the future.

Then, two issues of the FTO-licensing market in the pharmaceutical industry were examined. One issue is the FTO-licensing and EU competition law. In general, royalties on products produced without using licensed technology is considered to be anticompetitive under TTBER and the current Guidelines. However, in the pharmaceutical industry where the drug price would be determined by very complicated and unique factors, these general guidelines were found to be not appropriate anymore.

The other issue is the FTO-licensing between a pharmaceutical company and a bio-venture company. Despite the fact that both of them are willing to license-in/out, in reality, the number of licensing-in/out does not seem to be as large as it is expected. There are several reasons, but the inappropriate FTO that is conducted by a bio-venture company was deeply examined here and was found to be one of most decisive reasons. The concrete proposal to this issue was described. Normally, a bio-venture

company does not perform thorough FTO nor have careful IP strategy for future licensing negotiation. However, it is really important for a bio-venture company to grasp the whole map and prepare for "aggressive patents" on behalf of a pharmaceutical company, the future licensee or buyer.

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