How Can We Specify the Second Use Drugs from Patent Information?: R&D on the Second Use Drugs May Lead to Further Development of Pharmaceutical Industries

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***Abstract*--Needless to say, it is not easy to develop new drugs because of huge amount of investment on R&D. For the pharmaceutical companies, which have difficulty to enter into new drugs development, it will be one of the opportunities to make R&D to find the second use of commercialized drugs. The second use drugs are known as the drugs which its new effects have been found out after the original drugs and the new effect shall be different from the original effects. The result of R&D of the second use drugs can be patented as use claims depending on its inventive step. However, it is not easy to specify which patent claim is the second use drug, and there are no well-established methods to identify them. So, in this research we will propose the way to identify them with patent information by using the variation of IPCs, the description of patent claims, and the joint applicants. Then, for the collected second use drugs' patent information based on the proposed method, we made analysis of the situation of R&D strategy targeting the second use drugs, as an example, Takeda Pharmaceutical Company Limited. We believe the proposed method and the results of empirical study will contribute to further growth of pharmaceutical companies by defining R&D strategy which is well balanced developments between new drugs and the second use drugs.**

I. INTRODUCTION

As showed in fig. 1, it is said that the worldwide volume of market of the drugs have increased, and it became about $ 953 billion in 2011. Japanese pharmaceutical market volume also has increased and reached about $ 112 billion in 2011, though the market share is only around 10 % [1].

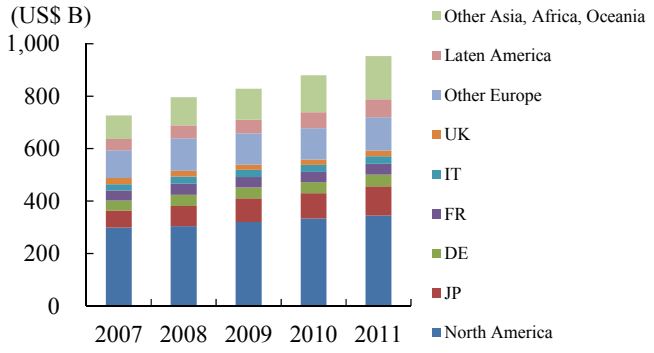

Fig. 1. The worldwide volume of market of drugs
Source: Ministry of Health, Labour and Welfare (2013)

There were big discussions that the protection period of patents of the original drugs owned by the big pharmaceutical companies had been expired around 2010. This was called as "2010 problems" in the pharmaceutical industry. It was a big problem because the generic companies might enter the market and it would be difficult for original companies to maintain their sales without patent protections. According to the article from Nikkei Asian Review, Takeda Pharmaceutical Company (abbreviate as Takeda); which has the biggest sales in Japan, found new effect and added another effect on *Takepuron* in 2004; which is the medicine used to treat ulcers and whose patents expired in 2009[2][3]. And, from this article, we understand that Takeda has been trying to find the second use of original drugs, and it is getting important for pharmaceutical companies which invented original drugs to find out the new effects from the original one.

The second use drugs are known as the drugs which its new effects have been found out after the original drugs and the new effect shall be different from the original effects. The result of R&D of the second use drugs can be patented as use claims depending on its inventive step. In Japan Patent Examination Guidelines, the second use drugs are defined as Medical Inventions, and it means "an invention of a product" which intends to provide a new medicinal use of a material, based on discovering an unknown attribute of the material[4]. In the previous research, the second use drugs are studied about its law, especially compared the Patent law of the U.S., Europe, and Japan. From Institute of Intellctual Property, they showed the case study of the second use drugs[5][6][7][8][9][10][11]. They showed examples of the second use drugs. However, there are no studies to specify the second use claims.

Also, we tried to interview the second use drugs to the search instructor of the Japan Industrial Property Digital Library, the patents examiner of the medical field, the member of the Intellectual Property of MITSUI & CO., LTD., and TEIJIN LIMITED. They gave us there were no classifications to show the second drugs, and also no duty to mention whether the second drugs or not in the patent specifications.

Needless to say, it is not easy to develop new drugs because of huge amount of investment on R&D. For the pharmaceutical companies, which have difficulty to enter into new drugs development, it will be one of the opportunities to make R&D to find the second use of commercialized drugs. However, it is difficult to specify which patent claim is the second use drug, and there are no well-established methods to identify them. So, in this research we will propose the way to determine them with patent information. Then, for collected second use drugs' patent information based on the proposed method, we made analysis of the situation of R&D strategy targeting the second use drugs, as an example Takeda

Pharmaceutical Company Limited. We believe the proposed method and the results of empirical study will contribute to further growth of pharmaceutical companies by defining R&D strategy which is well balanced developments between new drugs and the second use drugs.

II. RESEARCH METHODOLOGY

A. Methodology to find out the second use drugs

In order to find out the second use drugs, we propose 4 steps as showed in fig. 2. First, we made search patent data which related to the specific field. In this research we selected drugs related to cancer. Second, we extracted inventions of the product. Third, we selected the mother group for the second use drugs by using the variation of IPCs, the description of patent claims, and joint applicants. Finally, we specified the second use drugs from the data in the mother group.

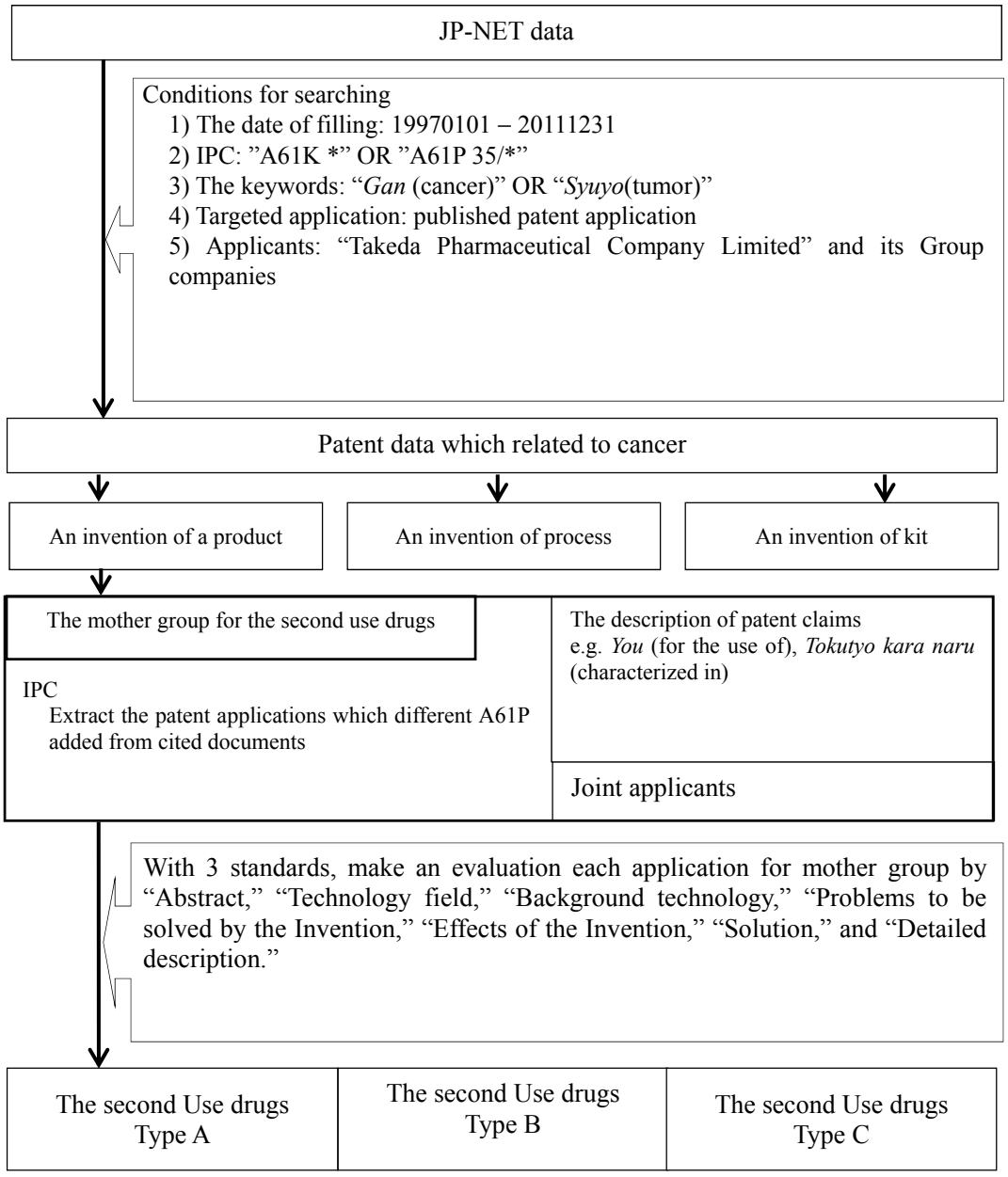

Fig. 2. The proposed method to specify the second use drugs

In the first step, with JP-NET from Japan Patent Data Service Co., Ltd, we collected published patent application related to cancer. We used 4 conditions for searching; the day of filling, the symbols of IPCs, the keywords being included in the claims, and the name of applicant. The date of filling is from January 1st 1997 to December 31st 2011. Applications numbers in 2012 and 2013 were not exact because of the date of the publication needs 1.5 years, so we excluded them. For the symbol of IPCs, we used A61K for preparations for medical, dental, or toilet purpose, or A61P 35 for antineoplastic agents[12]. For the keywords we used various word we called cancer in Japanese; e.g. *Gan*(cancer), *Syuyo*(tumor)[13][14]. We chose Takeda as an applicant for this research[15][16]. We collected all Takeda and Takeda's group companies.

After collected the applications about cancer in the first step, we classified them as an invention of a product, process, or kit, then pick up inventions of a product. It is because in Japan Patent Examination Guidelines, the second use drugs is "an invention of a product" which intends to provide a new medicinal use of a material, based on discovering an unknown attribute of the material[4].

In the third step, from the inventions of a product, we extracted the mother group for the second use drugs by using the variation of IPCs, the description of patent claims, and joint applicants. For the variation of IPCs, we utilize A61P which shows specific therapeutic activity of chemical compounds or medicinal preparations. Each main group in A61P shows each distinctive region. So we compared A61P between each patent application and their cited documents, and then extracted the patent applications which different A61P added from cited documents. For the description of patent claims, there are some typical descriptions for the second use drugs, e.g. *You*(for the use of), *Tokutyo kara naru*(characterized in), and so on. It is not always written in all application of the second use drugs, however, it can be the tips to find them. For joint applicants, we especially paid attention to the companies who have strength in the different technological field from cancer. This was because it is most likely to work with those cooperative applicants who have high possibility to find out the second use of the existed drugs.

In the final step, we specified the second use drugs from the data in the mother group which collected in the third step. We made an evaluation of each application for mother group by "Abstract," "Technology field," "Background technology," "Problems to be solved by the Invention," "Effects of the Invention," and "Solution." If we could not find the second use from them, we also got information from "Detailed description." Then, claims of the second use drugs, which are written the point to evaluate as the second use drugs, were chosen.

B. Standards for the second use drugs

In order to make an evaluation, we needed standards for the second use drugs. We systematized as by three classifying as showed in fig. 3. Type A is the case that the product X known as a medicine for disease P is found another use for disease Q. Though it is in the field of cosmetic, JP3919250 is example of Type A that is Thujopsis whose whitening ability was known was newly discovered its effect on preventing wrinkles. Type B is the case that the product X known as a medicine for disease P is found another use for disease Q by changing administration time, method, dose and dosage part. It is one of the examples that JP3480939 which is the invention that changed the conponent ratio so that it was found for children's use. Type C is the case that the product X known as a medicine for disease P is found another use for disease Q by a combination of the known product Y. This combination is available more than two product. JP3361102 is example of Type C that paclitaxel which is known as an anticancer drug combined with cycloporin and 2'-methylpyridium, so that it became the medicine for internal use.

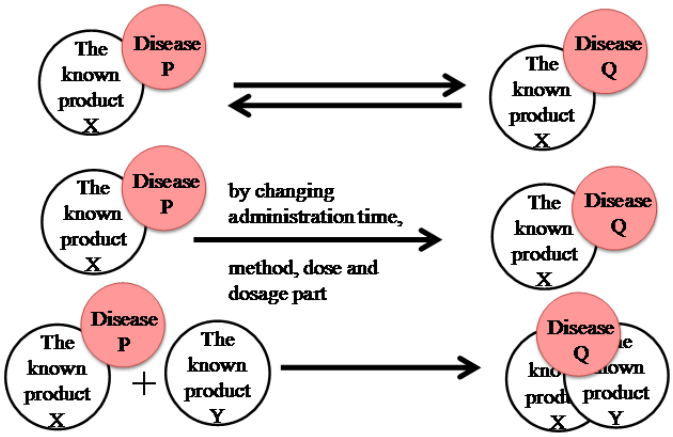

Fig. 3. Standards for the second use drugs

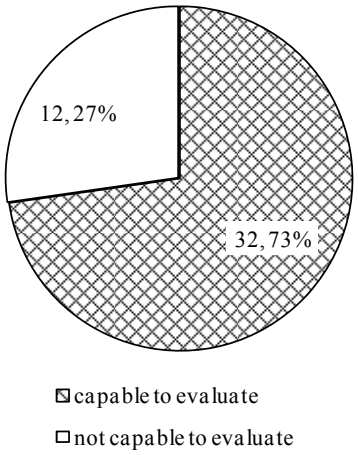

Fig. 4. Capable to evaluate the second use claim in "Abstract" or not.

C. "Abstract" as for evaluation

It was found that it was difficult to make an evaluation for the second use drugs with "Abstract." In "Abstract," they are written about problems to be solved by the invention ant its

solution, so that we can understand the known product X and disease Q which is the newly effect of product X, but not disease P of which the product X known as medicine. For Takeda case, 73 % of the second use claim could not make clearly evaluations as showed in fig. 4. From this, we suggest not to evaluate the second use claim in "Abstract."

D. Other part as for evaluation

Because we found that "Abstract" was not suitable to make an evaluation for the second use claim, we consider to look at the other part. In order to evaluate about the second use claim, at least we need the information about the known product X, disease P which medicine is the product X, disease Q which is the newly effect of product X, and additionally the information about administration time, method, dose and dosage part which needed to find out the disease Q which is the newly effect of product X.

The other parts, i.e. "Technology field," "Background technology," "Problems to be solved by the Invention," "Effects of the Invention," "Solution," and "Detailed description," especially "Background technology," "Problems to be solved by the Invention," "Effects of the Invention," and "Solution," include useful information. In "Background technology," past inventions or studies are written. There were some patent applications which mention in "Background" about disease P which is the past use, however not all patent applications did. In "Solution," elements which lead the second use are written. From "Problems to be solved by the Invention" and "Solution," we could found the points of novelty and progressiveness to make an evaluation. In "Effects of the Invention," mostly we found the disease Q which is the newly effect of product X. If we could not make a clear evaluation, we also got information from "Detailed description."

E. Situation of R&D strategy targeting the second use drugs

With the proposed method, we specify Takeda's the second use drugs of cancer. And we search about the situation of R&D strategy targeting the second use drugs. From the patent information which collected by the proposed method, we search the classification, number of patent applications, number of granted patent applications, registration rate, the term from an application to registration, number of pages of published patent application, number of claims, number of cited and quoted documents, applicants, number of inventors, technology field of the second use drugs.

F. Selection of the targeted company

The applicant we chose was Takeda, which owns the biggest sales in Japanese pharmaceutical companies. With the first step of the method showed before, we got the application ranking as showed in Table 1. The largest number of patent applications was Glaxo Smith Kline, and then Takeda, Phizer, Daiichi-Sankyo. The number of claims per an application is more than 25 with Takeda and Daiichi-Sankyo; Japanese companies, and less than 20 with Glaxo Smith Kline and Phizer. At first, we chose Takeda, which is Japanese Company. Takeda has the second largest number of patent application and the largest number of claims per an application. Also, one of their main product, *Takepuron*, which was known as the second use drugs, expired its patent in 2008. And we believed that Takeda develop not only new drugs but also the second use drugs. There for we chose Takeda as the targeted company and collected all Takeda's and Takeda's group companies' patent data.

TABLE 1. THE APPLICATION RANKING

Rank.	The name of the company	No. of application	No. of claims per No. of application
1	Glaxo Smith Kline	593	19
2	Takeda	390	27
3	Phizer	171	19
4	Daiichi-sankyo	130	25

III. RESULT

Let us show the process of finding the patents of the second use, by using the methods we proposed in Chapter II; 4 steps. Also we will show the situation of Takeda for the second use.

A. Patent application of cancer of Takeda

With the first step of the proposed method, we got 390 patent applications. An annual change of patent application is showed in fig. 5. In 2002, there were xxx applications for the patent, which was the largest numbers in 15 years. After 2004, numbers of patent application were decreasing. We think that Takeda tried hard to invent drugs related to the main products but also drugs for cancer, because the patents of the main products expired around 2010 and generic medicine companies might come into the market.

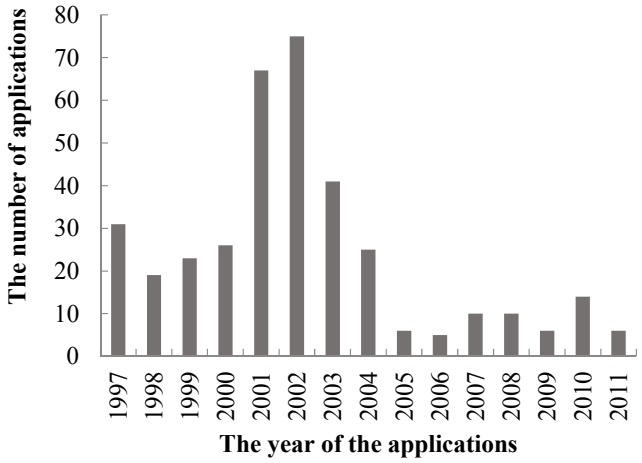

Fig. 5. An annual change of patent application

We collected the first given IPC, i.e. International Patent Classification, of each application. As showed in fig. 6, the

number of C12N, which shows Micro-organisms or enzymes; compositions thereof; propagating, preserving, or maintaining micro-organism; mutation or genetic engineering, culture media, is the biggest. This stems from the fact that cancer relates the genetic change of the cells.

373 per 390 patent applications were single application, and the other was joint applications as showed in fig. 7. As joint applicants, there were Takeda's group companies, the other companies, research institutions, and independent inventors.

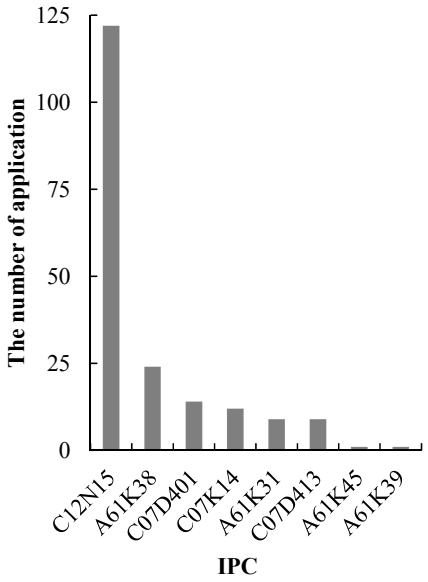

Fig. 6. The first given IPC

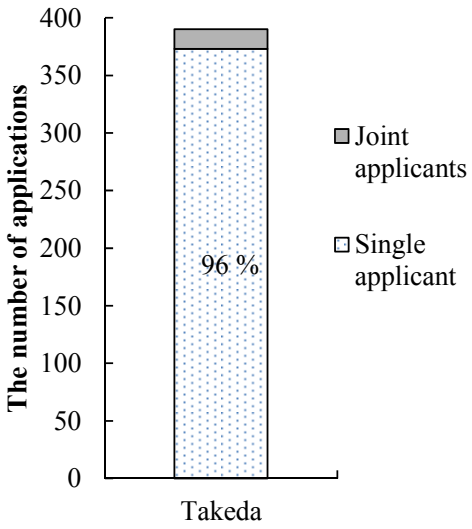

Fig. 7. Single or joint applicants

B. Inventions of product

As showed in fig. 8, we classified 10921 inventions which included Takeda's patent application of cancer into 3 inventions, i.e. product, process, and kit. We got 71 % of invention of product, 26 % of invention of process, and 3 % of invention of kit. From this result, Takeda made much account of invention of product.

C. Mother group for the second use drugs

We got 100 patent applications which appear to be the second use drugs. By comparing the variation of IPCs with cited documents, we got 100 patent applications. On the other hand, by the description of patent claims and joint applicants, we got only 5 or 0 applications. It is not always needed to

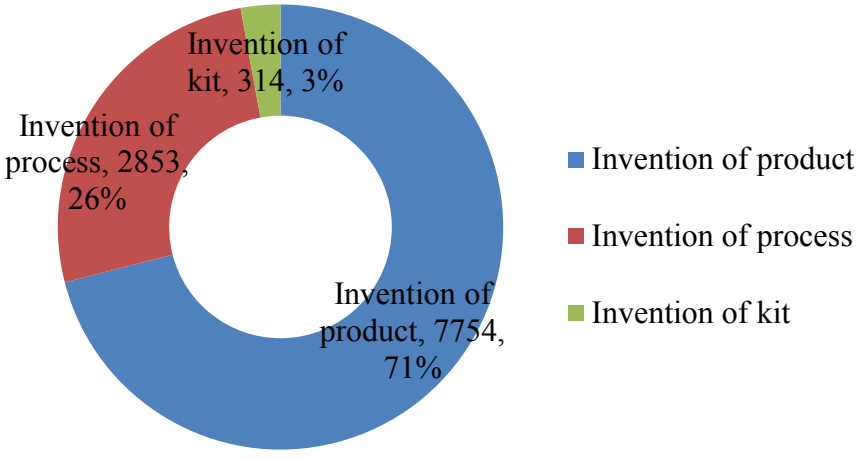

Fig. 8. Rate of inventions of product, process, and kit

write typical descriptions of patent claims, and sometimes the second use product described by "purpose for" is interpreted just the product because the description only shows usefulness. And, Takeda had only 16 applications which were the joint application. Therefore, in Takeda case, we could not get much data by description of patent claims and joint applicants, so that the using variation of IPCs was a useful method to decide mother group for the second use drugs.

D. The second use drugs

With the proposed method of step 4, we specified 44 patent applications of the second use drugs. Each application classified with systematized classifications as showed in fig. 9. We got 18, 18, and 8 patent applications of Type A, B, and C. Talking about Type A and B, they got the additional use if they kept to study about the known product. However, in Type C, they needed to combine products and its combination was not easily arrived. Therefore, the numbers of Type C is smaller than that of Type A and B.

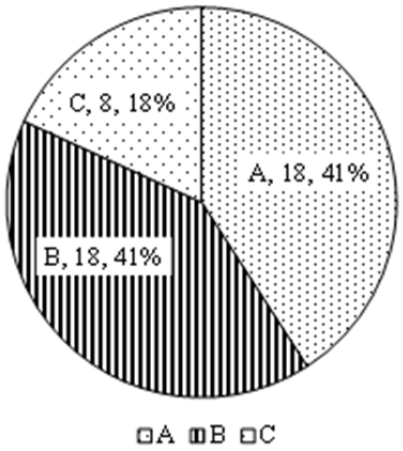

Fig. 9. Type A, B, and C of the second use drugs

E. Situation of Takeda's the second use drugs

We showed years of applications for the second use drugs in fig. 10 and years of registration in fig. 11. The numbers of patent application is the largest around 2002, and most applications patented around 2010. Also terms from patent application to registration of the second use drugs were 7.5 years in average, and that of cancer was 6.4 years. T-test level was $0.012 < 1.989$, and the term had no difference between the second use drugs and cancer. Because of the 2010 problems, we think that Takeda focused on R&D and patent application around 2002 in order to get registration around 2010. And, this is not only for the second use drugs but for drugs of all cancer.

24 of 44 patent applications for the second use drugs are patented as showed in fig. 12. Registration rate of the second use drugs was 55 %. It was a high rate comparing with the registration rate of all drugs for cancer which was 15 %. Therefore, the second use drugs tend to recognize novelty and inventive step.

Takeda got seeds of technology only from Takeda or its group companies, and they made little acount of collaborative research on the second use. Most of the second use drugs, their patent applicant was Takeda. There were not any applications which were joint applications. Even if group companies of Takeda applied patents, when they registrated their patentee were Takeda.

Takeda didn't change the number of researchers even if they invent the second use. As showed in fig. 13, the average number of researchers were about 3 both in the second use drugs and all drugs of cancer.

Various contents are included in the second use drugs. As showed in fig. 14, the average of it were 71 which was as same as the average pages of all applications of cancer. However, the number of pages was 343 at most. These patents might be said that their contents are written abundantly.

Takeda tended to get as wide scope of patent right as possible about the second use drugs. As showed in fig. 15, the numbers of claims The average number of claims was 33, however, there are at most 77claims per an applicants and there are several applications which have more than 40 claims.

The second use drugs tended to have more cited documents than all drugs for cancer, but they have few quoted documents. Cited documents showed when notices of reasons for refusals were sent or Examiner's decisions of refusals were decided. As showed in fig. 16, most of all applications had cited documents. 16 applications had more than 10 cited documents. It is not clearly compared because t-test lever is $0.801 < 1.973$, however, the average number of cited documents of the second use drugs 17were larger than that of all drugs of cancer. On the other hand, as showed in fig. 17, more than half of the second use drugs were not cited from other patent applications. There were a few applications which had 12 or 16 quoted documents, and they could be the seeds of another use. However, it can be said that most of the second use drugs cannot be a base of the future's drugs.

Talking about Takeda, they developed additional uses of not only a known drug but numerous drugs in various fields. In fig. 18, we showed the first IPC main group classified to the second use drugs in horizontal axis, and IPC classified to the cited documents in the vertical axis. Also, we showed the first IPC main group classified to the second use drugs in table 2, and IPC classified to the cited documents in table 3. As you can see in fig. 18 or table 2, A61K38 which is medical preparations containing peptides was the most classified to the second use drugs. A61K38, A61K47 which is medical preparations characterized by the non-active ingredients, and C12N15 which is mutation or genetic engineering; DNA or RNA concerning genetic engineering, vectors, or isolation, preparation or purification; Use of hosts therefor, are related to cell, DNA, or therapeutic activity of cancer. As you can see in fig. 18 or table 3, A61K which is preparations for medical, dental, or toilet purposes is the most classified to the cited documents. In A61K, preparations for

dental purposes are represented by bA61K6, and preparations for toilet purposes are represented by A61K8. Therefore most of A61K shows preparations of medical purposes. And this IPC suits for the second medical use drugs. A61P which is specific therapeutic activity of chemical compounds or medicinal preparations were classified to 19 cited documents. A61K and A61P were deployed in various IPC of the second use claims, so that the second use developed from varied fields and varied chemical compounds.

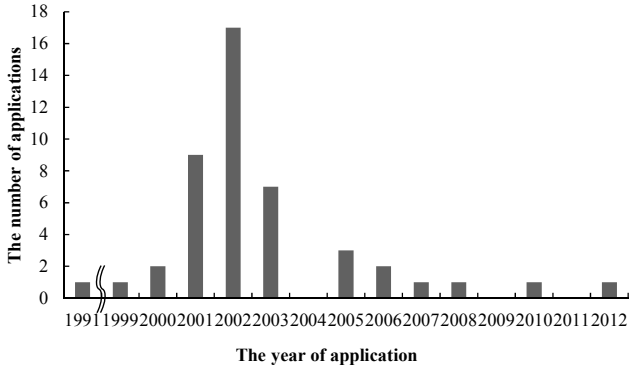

Fig. 10. The year of applications for the second use drugs

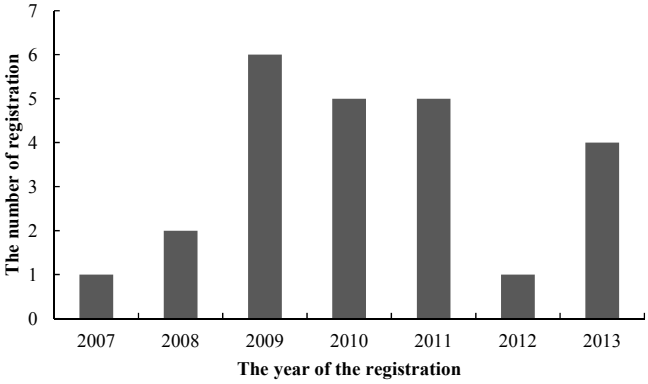

Fig. 11. The year of registration for the second use drugs

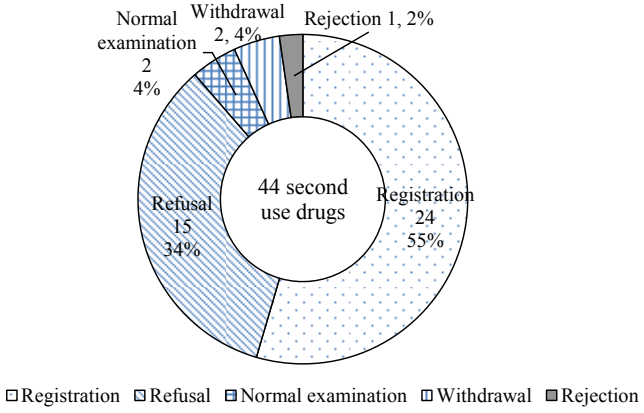

Fig. 12. Registration rate of the second use drugs

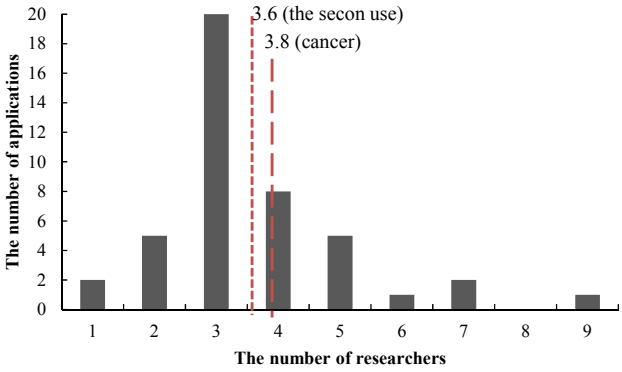

Fig. 13. The number of the researchers

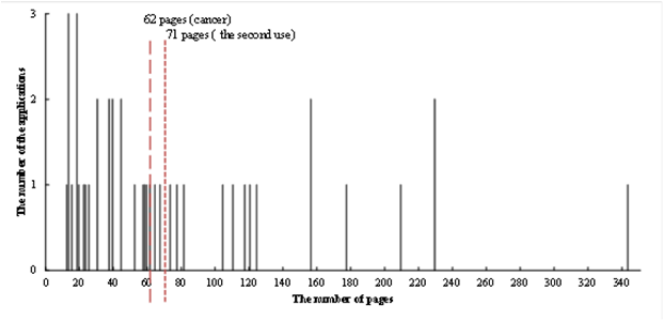

Fig. 14. The number of pages

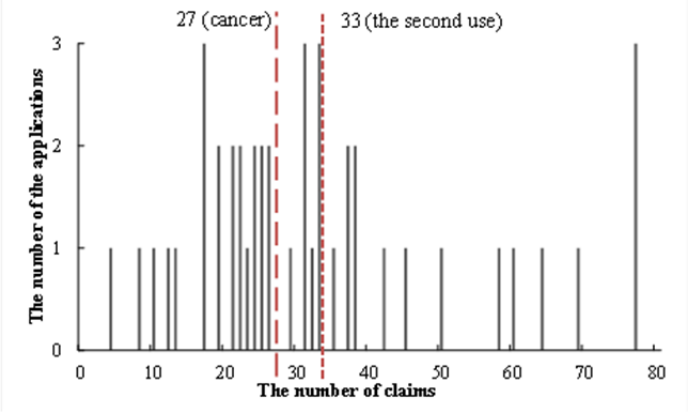

Fig. 15. The number of claims

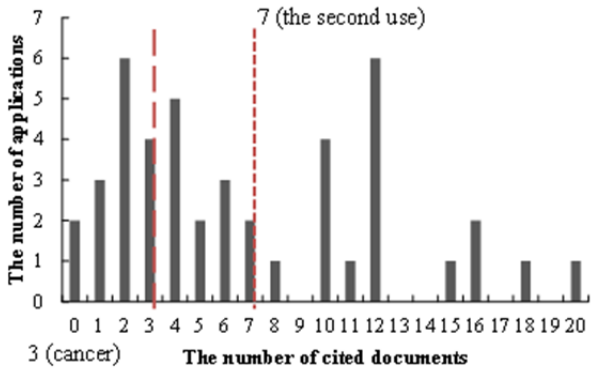

Fig. 16. The number of cited documents

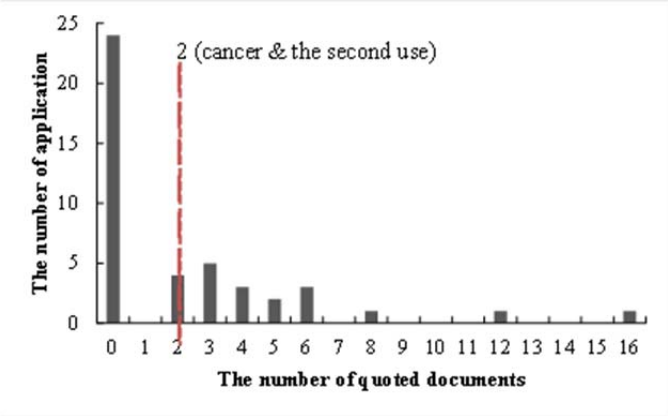

Fig. 17. The number of quoted documents

IV. DISCUSSION & CONCLUSION

A. Propose the method to find out the second use drugs

In this research, we proposed the method to find out the second use drugs. The method we proposed has 4 steps, 1) search patent data which related to the specific field, 2) extract inventions of the product, 3) select the mother group for the second use drugs by using the variation of IPCs, the description of patent claims, and joint applicants, 4) specify the second use drugs from the data in the mother group.

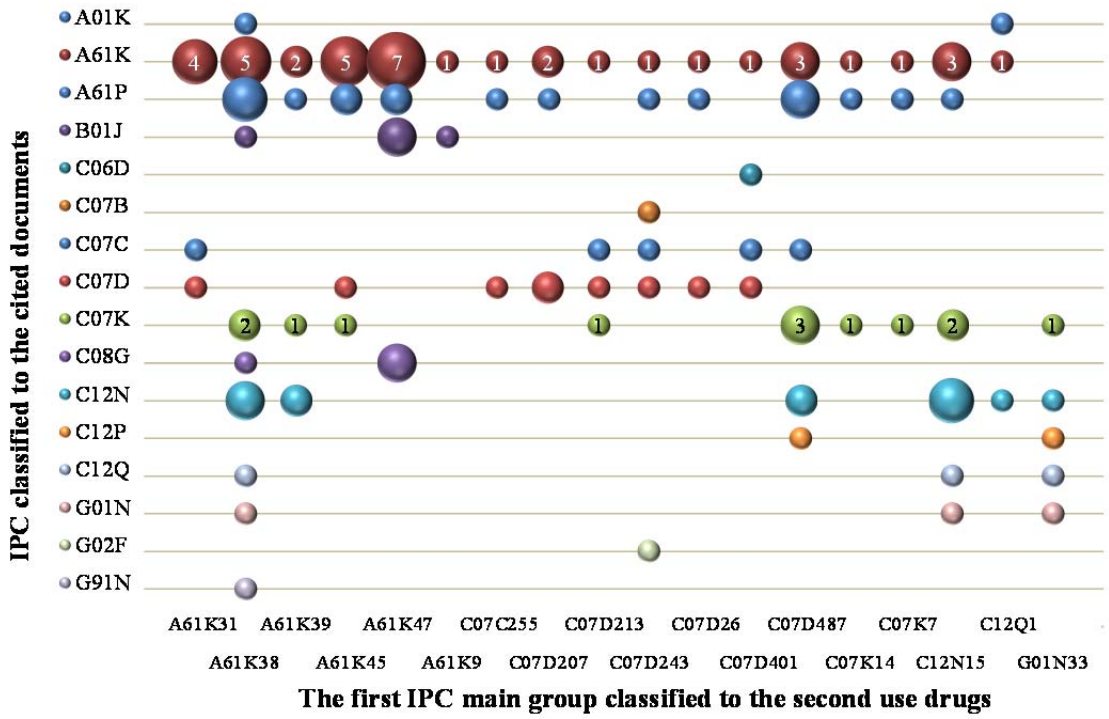

Fig. 18. IPC of the second use drugs and cited documents

TABLE 2. THE FIRST IPC MAIN GROUP CLASSIFIED TO THE SECOND USE DRUGS

A61K 31	A61K 38	A61K 39	A61K 45	A61K 47	A61K 9	C07C 255	C07D 207	C07D 213
6	20	6	9	15	2	3	5	4
C07D 243	C07D 267	C07D 401	C07D 487	C07K 14	C07K 7	C12N 15	C12Q 1	G01N 33
6	3	4	13	3	3	12	3	5

TABLE 3. IPC CLASSIFIED TO THE CITED DOCUMENTS

A01K	A61K	A61P	B01J	C06D	C07B	C07C	C07D
2	40	19	5	1	1	5	9
C07K	C08G	C12N	C12P	C12Q	G01N	G02F	G91N
13	4	13	2	3	3	1	1

In order to make an evaluation for the second use drugs, we needed standards for the second use drugs. We systematized as by three classifying, i.e. Type A, B, and C. Type A is the case that the product X known as a medicine for disease P is found another use for disease Q. Type B is the case that the product X known as a medicine for disease P is found another use for disease Q by changing administration time, method, dose and dosage part. Type C is the case that the product X known as a medicine for disease P is found another use for disease Q by a combination of the known product Y. This combination is available more than two product.

When we find for the second use drugs, "Background technology," "Problems to be solved by the Invention," "Effects of the Invention," and "Solution," include useful information. "Abstract" does not appropriate for evaluation.

In this research, we proposed the new method to specify the second use drugs, though there were no methods to specify them. Our proposed methods use 4 steps; 1) to search patent data which related to the cancer, 2) to extract invention of product, 3) to select the mother group for the second use drugs by using the variation of IPCs, the description of patent claims, and joint applicants, 4) specify the second use drugs by patent specification evaluating with systemized 3 standards. With this research, we believe that we could propose the effective method to specify the second use drugs.

B. The second use drugs for cancer of Takeda

We specified Takeda's second use drugs. At first, we collected published patent application related to cancer with JP-NET. We used 4 search expressions; 1) the day of filling was from January 1st 1997 to December 31st 2011, 2) the symbols of IPCs were A61K or A61P 35, 3) the keywords being included in the claims was cancer, and 4) the applicant was Takeda and its group companies. In second, classify them as an invention of a product, process, or kit, then pick up inventions of a product. In third, we extracted the mother group for the second use drugs by using the variation of IPCs, the description of patent claims, and joint applicants. Finally, we specified the second use drugs from the data in the mother group which collected in the third step with 3 standards.

With the proposed method, we specified 44 second use drugs for cancer of Takeda. We got 18, 18, and 8 patent applications of Type A, B, and C. For Type C, they needed to combine products and its combination was not easily arrived. Therefore, the numbers of Type C is smaller than that of Type A and B.

Registration rate of the second use drugs was a high rate comparing with the registration rate of all drugs for cancer. Therefore, the second use drugs tend to recognize novelty and inventive step.

About Takeda's situation of the second use drugs, we got several ideas. From years of applications and registration for the second use drugs, and terms from patent application to registration, because Takeda mentioned about the 2010 problems, they focused on R&D and patent application around 2002 in order to get registration around 2010.

Takeda contains various contents in the second use drugs. They also tends to get wide scope of patent right about the second drugs.

The numbers of cited documents are large in the second use drugs, however, that of quoted documents are not. The second use drugs got seeds of technology from other but it cannot be other's technology seed. Takeda got seeds of technology only from Takeda or its group companies, and they made little acount of collaborative research on the second use. Takeda didn't change the number of researchers even if they invent the second use. Also, they do not change the number of people constitution when they develop the second use.

Takeda developed additional uses of not only a known drug but numerous drugs in various fields. Some of IPC which classified to the cited documents were deployed in various IPC of the second use claims.

In this research, we made clear that Takeda, one of the big pharmaceutical companies, positively worked on the second use drugs. It was important for Takeda to develop not only new drugs but also the second use drugs. For the pharmaceutical companies, which have difficulty to invest for new drugs, it is needed to make a strong effort to invent the second use drugs. For generic drugs manufacturers which only copy the original drugs that the other companies developed and make generic drugs, it is also important to invent their original second use drugs. We believe that the second use drugs contribute to the further growth of pharmaceutical companies by defining R&D strategy which is well balanced developments between new drugs and the second use drugs.

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