10 After *Myriad*: The Comparative Study on Biotechnology Patent Practice (*)

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The substance of the patent system is to protect innovation and facilitate the development of industries. Since the start of the Human Genome Project, Patent Offices in the U.S., Japan, and Europe have held many discussions concerning the patentability of DNA sequences. Most Patent Offices have adopted similar standards for judging the examination of practices related to DNA. In 2013, the U.S Supreme Court rendered a decision in the Myriad Case that DNA isolated from nature is a product of nature and thus unpatentable subject matter. This caused a significant change in patent practices. The USPTO revised examination standards twice in March and December 2014 and the amendment drafts caused a great deal of discussion throughout the world. This report discusses the impact of the Myriad Case in the U.S. on examination practices for claims for substances, analyzes the criteria for patent eligibility in Europe, Japan, and Taiwan, and proposes a substitute structure that can be established in order to balance the patent system and public health.

The *Myriad* Case revolves around the patentability of two genes, BRCA1 and BRCA2, and their application for examination. BRCA1/2 genes are tumor-suppressor genes and Myriad obtained patents related to them in 1997 and 1998. Today, breast cancer is the second highest cause of death after lung cancer among cancers in women in the U.S. and the attention to and understanding of breast cancer have increased. The need for early diagnosis in the healthcare business market is expanding and research and development as well as patents related to BRCA1 and BRCA2 are of particular importance.

Myriad held many patents, including patents for the BRCA1/2 genes, the methods for using and isolating these genes, and the method of examination for mutation. Myriad imposed strict licensing conditions on research institutions and others by requiring them to use the results of analysis only for research experiments and prohibiting them from providing the results to patients. Therefore, medical institutions, patients, researchers, and genetic counselors of the Breast Cancer Prevention Center became considerably dissatisfied with Myriad, which seemed to monopolize the research and examination market of BRCA1/2 genes. In 2009, the Association of Molecular Pathology (AMP) and many researchers and women adopted the American Civil Liberties Union (ACLU) as their representative and filed with the U.S. District Court for the Southern District of New York for a declaratory judgment to invalidate 15 claims[1] in 7 patents held by Myriad. The District Court gave a summary judgment that claims on all genes, including BRCA1/2, or a combination of part of genes did not conform to the provisions of 35 U.S.C. § 101 and were not patentable. As the reason, the District Court stated that isolated BRCA genes listed in the patent specifications were not markedly different than genes found in nature, and that when comparing isolated DNA to DNA in human body, the fundamental features were completely the same and their genetic codes were identical as well. With regard to claims related to cDNA, the District Court also found that cDNA was a product of nature since naturally occurring products, which means genotype DNA, produce mRNA by pre-mRNA splicing.

Myriad eventually filed an appeal with the United States Court of Appeals for the Federal Circuit (CAFC). The CAFC rendered a judgment[2] where the court upheld part of the judgment of the lower court and reversed another part of said judgement. The CAFC upheld the part where the District Court judged that claims related to the method of comparing or analyzing DNA sequences of BRCA1/2 were invalid but ruled that product claims related to the isolation of DNA sequences and method claims for the screening of

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therapeutic substances for potential cancer risks were patentable. The majority opinion of the CAFC was that isolated DNA sequences are patentable subject matter because isolated DNA is produced by chemical method, does not bind to other genes after the isolation, and therefore is different than DNA naturally found in the human body. However, the U.S. Supreme Court rendered the final decision on June 13, 2013 and gave a different decision from the CAFC on the Claims of isolated genotype DNA. This decision was also different from the patent examination practices of the USPTO related to DNA over the many years. The Supreme Court judged that products of nature should be patent ineligible and that said DNA was unpatentable even if it was isolated artificially. However, while cDNA has the exon of naturally occurring DNA, it is distinguished from genotype DNA found in nature, and therefore cDNA is a patentable subject matter.

The *Myriad* Case raised disputes over the patentability of BRCA genes in the countries other than the U.S., for examples Europe and Australia. The judgment of the Technical Boards of Appeal of the European Patent Office in T 1213/05[3] was as follows: the claims at issue were obtained by technical means from parts of gene sequences, including human BRCA1; according to the provisions of Rule 23e (2) of the Rules of the European Patent Convention,[4] since these probes are elements isolated from the human body, although their structure and the elements found in nature are the same, if the gene sequence or element containing part of the sequence is produced by technical means, it is a patentable subject matter. In the lawsuit against Myriad in Australia, revocation of the patent was sought by a cancer survivor, Yvonne D'Arcy, on the grounds that the isolated BRCA nucleic acid molecule is actually the same nucleic acid molecule found in nature and has the same gene information; and therefore, it is not patentable under Australian Patent Law. The first instance Federal Court and the Full Federal Court, at the second trial, judged that the patent in question was valid. Australian Patent Law considers products of nature as patentable subject matter. If the court judged that the scope of invention that Myriad claimed was not the coding, information, or sequence of characters, but the chemical substance, the nucleic acid molecule is created artificially; and the most important point is that there is a further significant difference between its functions and those of the nucleic acid molecule found in nature. In this judgment of the Federal Court of Australia, it is noted that the U.S. Supreme Court found in *Association for Molecular Pathology v. Myriad Genetics, Inc.* that the isolated nucleic acid molecule is patent ineligible; however, this is the exception for patentability of a product of nature under the doctrine of binding precedents of the U.S. Patent Act and it is different from Australian Patent Law; therefore it is impossible to argue the issue by comparing these judgments. D'Arcy was dissatisfied with the judgment and appealed to the Australian High Court. The High Court will hold a hearing for this Case for one to two days in April 2015. We will have to keep an eye on it in the future.

After the Examination Guidelines were published in March 2014, the USPTO reviewed various opinions and then published the 2014 Interim Guidance on Patent Subject Matter Eligibility[5] on December 16, 2014. It stated that this Interim Guidance was a substitute for the Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena, & Natural Products published in March 2014. This Interim Guidance continues to review patent eligibility not only of DNA subjects, but also of all products of nature; however, the standard for judging patent eligibility was relaxed from those in the Memorandum published in March. This Interim Guidance defines the meaning of "directed to[6] a judicial exception" and the definition of "markedly different" is relaxed. The change is made at this point where if the subject matter recited in the claim is markedly different in its structure, function, and/or other characteristics, the subject matter is markedly different than products found in nature. An important and simple analysis method was added to this Interim Guidance, called streamlined eligibility analysis. As long as the claim passes the analysis, it is not necessary to implement the markedly different characteristics analysis and the claim can be directly approved as patentable subject matter. Examples are focused on claims related to nature-based products. Claims related to biotechnology are judged using the second analysis step (step 2B or part 2 Mayo test)[7] on whether the claim recites the additional elements or whether the element is sufficient to present that the difference of the claimed invention is "significantly more" than judicial exception; however, this report analyzed that the number of the claims in question here is very small and applications for most of these processes are made

for method of analysis. In cases of biotechnology claims, the patentability of most of them are judged in the first analysis step in practice.

Since 1995, the strictness of examination guidelines for the patentability of genes has changed many times in the U.S. After 1995, many biotechnology companies alleged that the utility requirements were too strict and it was therefore difficult for new biotechnology companies to raise the funds necessary for research and development. Therefore, the utility requirements were relaxed. However, examination requirements based on the 1995 Utility Examination Guidelines were too relaxed despite fast progress in biotechnology. Therefore, the Utility Examination Guidelines were published in 2001 based on external opinions on gene patents. The Guidelines defined new standards for utility and presented a Three-pronged test: specific,[8] substantial,[9] and credible.[10] Later, the judgment of the CAFC in *In Re Fisher*[11] confirmed the USPTO's policy for the revision of guidelines. However, the U.S. Supreme Court rendered its decision in the *Myriad* Case on June 13, 2013 that DNA isolated from nature is unpatentable subject matter. Therefore, the guidance published in 2014 applied the interpretation of said Supreme Court judgment on patent eligibility not only to DNA, but also to all products of nature. This changed the conventional examination standards for biotechnology drastically. If patentability is denied only on the grounds that the claim is not markedly different than the substance found in nature, the scope may include chemicals, microorganisms, cells, antibiotics, antibodies, and other elements. This examination standard of the U.S. is very distinctive internationally. Under the patent examination standards in Europe, Japan, and Taiwan, if the claim relates to biological materials found in nature, the patentability of the claim will not be refused on the grounds that it is obtained or isolated by man-made technical means. On the other hand, judgments after the U.S. Supreme Court in the Myraid Case, such as the judgment of the CAFC in *In re Roslin Inst.*[12] or *In Re BRCA1- And BRCA2-Based Hereditary Cancer Test Patent Litigation*[13] (*Myriad II*), embody the spirit of the U.S. Supreme Court judgment and both cloned sheep and DNA segments that are created by somatic cell nuclear transfer (SCNT) technology were found to be unpatentable subject matters since they were not markedly different than equivalent substances found in nature. Therefore, we must continue to watch the future development of practices in the U.S.

The impact of the judgment of the U.S. Supreme Court in the *Myriad* Case can be found in the changes between 2013 when the judgment in the *Myriad* Case was rendered and 2014 when BRCA1/2 diagnosis and examination products were available at only two companies, Myriad and the UCLA Diagnostic Molecular Pathology Laboratory. Now, however, 16 biotechnology companies at least can provide relevant diagnoses. From the perspective of general citizens, there is no doubt that the range of selection in the market increased and it reduced the costs for diagnosis. With regard to the right infringement lawsuits between Myriad and other biotechnology companies, Myriad reached a reconciliation with the last defendant company, GeneDX, by February 16, 2015; however, the impact of the Supreme Court's decision in the *Myriad* Case has just begun. For example, this year (2015), a U.S. scientist discovered a new antibiotic, teixobactin, in unclean soil. This antibiotic was discovered in nature and therefore it seems to be unpatentable under the new examination guidelines of the U.S. RNAi technology is used for the research and development of medical treatments to suppress the formation of oncogene by using molecules and has significant effects, unlike conventional medical treatment. RNAi itself is a nucleic acid molecule segment and it was judged by the CARC in *In re BRCA1- and BRCA2-based Hereditary Cancer Test Patent Litigation (Myriad II)* (Fed. Cir. 2014) that any DNA has a complementary property and all of applications of any DNA were developed based on the complementary property. Primers or probes used for diagnosis are included in them and the judgment considers that RNAi, nucleic acid molecule segments, and other elements are also applications of the complementary property. Therefore, it may become very difficult to find that nucleic acid molecule segments are patentable subject matters.

In order to reduce the negative impact on public health by limiting DNA patents in the biotechnology industry, relevant examination guidelines were revised after the judgment of the U.S. Supreme Court in the *Myriad* Case in 2013 and the U.S. government adopted a different policy than other countries. In other words, DNA and patent subject matters that are not markedly different than products of nature are excluded from patentable subject matters. I wonder if this policy can be adopted by other countries under Civil Law. Based on the current situation, other countries have not adopted the policy. The patent

practices in the U.S. are fundamentally different than in other countries in regards to the following points: the scope of "exceptions to testing and research" of the patent is particularly small and the scope of DNA patents approved by the U.S. is considerably large. Moreover, the U.S. is a country under Common Law and changes in practical method by judgments is much faster than the amendment of acts in countries under Civil Law. Countries under Civil Law, including Taiwan, should continue to watch the progress of patent practices in the U.S. and their impact and should examine them for their future patent policies.

[1] (1) U.S. Patent 5,747,282 (282 patent): Claims 1, 2, 5, 6, and 7; (2) U.S. Patent 5,837,492 (492 patent): Claims 1, 6, and 7; (3) U.S. Patent 5,693,473 (473 patent): Claim 1; (4) U.S. Patent 5,709,999 (999 patent): Claim 1; (5) U.S. Patent 5,710,001 (001 patent): Claim 1; (6) U.S. Patent 5,753,441 (447 patent): Claim 1; and (7) U.S. Patent 6,033,857 (857 patent): Claims 1 and 2.

[2] 653 F. 3d 1329 (Fed. Cir. 2011).

[3] Refer to the following website for the judgment of the Technical Boards of Appeal of the European Patent Office in T 1213/05 on September 27, 2007, see the following website: http://www.epo.org/law-practice/case-law-appeals/recent/t051213eu1.html

[4] Provisions of Rule 23e(2) of the Rules of the European Patent Convention 1973: An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.

[5] https://www.federalregister.gov/articles/2014/12/16/2014-29414/2014-interim-guidance-on-patent-subject-matter-eligibility

[6] 2014 Interim Guidance on Patent Subject Matter Eligibility, page 11.

[7] 2014 Interim Guidance on Patent Subject Matter Eligibility, page 21-25.

[8] The Guidelines required that the description for utility must be specific. For example, if the utility of the invention is described for a medical diagnosis, the description does not fulfill the requirements of a specific utility. The specific utility of specifying a disease by medical diagnosis must be defined or it cannot fulfill the requirements of specific utility.

[9] The Guidelines indicated that the invention is substantial only if it is used in the real world. For example, a new protein can be isolated in general academic research; however, if it is not clear how it is used in the "real world," the description in the specifications cannot fulfill the requirements of substantial utility.

[10] The cases where an assertion does not conform to the utility standards of credibility are those cases where the logic underlying the assertion is seriously flawed or where a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use.

[11] 421 F.3d 1365 (Fed. Cir. 2005).

[12] Appeal No. 2013-1407 (Fed. Cir. May 8, 2014).

[13] No. 2014-1361, -1366 (Fed. Cir. Dec. 17, 2014).