Gene patenting and stem-cell related inventions

Gene patent applicants are considering the implications of an apparent relaxation of the "same invention" requirement for entitlement to priority; while patentability is exercising those involved in stem-cell research

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This two-part article looks at topical issues in Europe in relation to gene patenting and stem-cell related inventions.

Gene patenting

A recent development in relation to gene patenting concerns the perceived relaxation of the "same invention" requirement for entitlement to priority for European patent applications on method claims where DNA or amino acid sequences are used.

In order to enjoy the benefit of priority from a patent application filed less than 12 months earlier, European patent applications must claim the same invention as disclosed in the earlier filed application. In 2001 the European Patent Office's (EPO) Enlarged Board of Appeal Decision G2/98 held that the requirement for claiming priority of "the same invention" means that priority of a previously filed application can be acknowledged only if a skilled person can derive the subject matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole. Decision G2/98 thereby rejected a looser interpretation whereby the presence of non-essential features that were not disclosed in the priority filing would not necessarily affect entitlement to priority.

For claims relating to protein and DNA sequences, the strict application of the "same invention" requirement could mean that a single amino acid and/or nucleotide difference between the sequence in the European application and the corresponding sequence in the earlier priority filing would result in a loss of entitlement to priority.

Consider the following hypothetical scenario, which is not uncommon. An inventor rushes to file his patent application on a new gene on the basis of a DNA sequence which is not yet completely accurate. Soon after filing the patent application, the inventor publishes the gene sequence in a scientific journal. During the course of the priority year, the inventor discovers that the gene sequence contains several inaccuracies. Next, a European patent application is filed with the correct sequence and claiming priority from the earlier filing containing the inaccurate sequence. Because the European application is filed subsequent to publication of the scientific paper, entitlement to priority is essential in order to ensure that the scientific paper does not affect the requirements of novelty and/or inventive step. The crucial question is thus whether the European application can enjoy priority despite the differences in the sequence: is the inaccurate sequence in the priority filing the same invention as the correct sequence in the European application?

Until recently, the EPO Boards of Appeal have consistently answered this question with a clear "no", irrespective of whether the sequence deviations had any effect on the function of the claimed DNA or amino acid sequences. In one of the earliest decisions on the subject, T923/92, the Board of Appeal stated that "the primary amino acid sequence of a protein (or nucleotide sequence of a DNA) constitutes a true

technical feature and relying on a given sequence rather than on another one for the definition of the subject matter in a claim makes a critical difference". The Board denied entitlement to priority on the basis of three nucleotide differences (resulting in three amino acid differences) between the priority sequence of the human t-PA gene and the later corrected sequence in the European patent. The approach taken in this early decision has since been confirmed in many later decisions such as T351/01, T70/05, T30/02 and even T1213/05, issued in September 2007, which is the first of three Board of Appeal decisions on three related European patents by Myriad Genetics and the University of Utah on the BRCA1 gene sequences and their use in the diagnosis of breast and/or ovarian cancer.

The factual matrix underlying the three European BRCA1 patents is very similar to the hypothetical scenario described above. The BRCA1 sequence of the first priority filings contained several sequencing errors, as well as nucleotides whose presence, but not identity, was disclosed. This incorrect and incomplete BRCA1 sequence was subsequently published in a scientific paper. Some 10 months later, three European patent applications were filed, each with a corrected BRCA1 sequence (15 corrections in the 5,592-nucleotide sequence).

In T1213/05 the Board of Appeal dealt with the opposition against the first of the three BRCA1 patents: EP 0 705 902, with product claims directed to DNA sequences comprising the BRCA1 coding sequence. The claims in question conferred absolute product protection on the claimed DNA molecules. The Board of Appeal therefore considered that it would be inappropriate to take into account whether the sequence deviations had an effect on the function of the claimed DNA sequence (in this case, as a diagnostic target or tool) in deciding whether the corrected sequence in the granted claims could enjoy priority from the deviating sequence in the priority document. As a result, the patent was finally maintained with severely limited claims directed at only a few small probes from the BRCA1 gene which were correctly disclosed in the relevant priority document.

In the second of the three BRCA1 cases decided by the Board of Appeal, T666/05, the patentee had limited the claims of EP 0 705 903 to methods for diagnosing predisposition for breast and ovarian cancer by determining the presence of one particular mutation in the BRCA1 gene, which is a more frequently occurring mutation, particularly in the Ashkenazi Jewish population. None of the 15 sequence deviations in the priority document could have any effect on the claimed method of diagnosing this mutation, and probably for this reason the Board of Appeal upheld the limited claims.

Finally, the third BRCA1 patent (EP 0 699 754) in T80/05 related to broad claims on methods for diagnosing predisposition for breast and ovarian cancer by determining mutations in the BRCA1 gene. In this case the Board of Appeal decided to maintain the patent in an amended form with still fairly broad claims directed at diagnostic methods for the detection of a predisposition for cancer caused by a specific group of mutations of the gene - so-called "frame shift mutations". The priority document correctly identified the BRCA1 reading frame and allowed the identification of frame shift mutations despite the 15 sequence deviations. The Board of Appeal therefore probably again reasoned that because the sequence deviations had no effect on the subject matter as claimed, the priority document disclosed the same invention as claimed.

At the time of writing, the Board of Appeal's written decisions in T666/05 and T80/05 have not yet been issued. Its exact considerations and how its reasoning might affect future situations are thus still unknown. However, it does appear that where, for product claims on DNA or amino acid sequences, entitlement to priority is lost on the basis of sequence deviations in the priority document, this is not necessarily the case for method claims wherein DNA or amino acid sequences are used, as long as the sequence deviations do not affect the claimed method.

Impact of *WARF* decision on protection of stem cell-related inventions

Stem-cells are found in almost all multi-cellular organisms. Stem cells are totipotent or multipotent: that is, they have the ability to renew themselves and to differentiate into a diverse range of specialised cell types. There are two types of mammalian stem cell: embryonic stem cells, found in embryos, and adult stem cells, found in adult tissue. Embryonic stem cells differentiate into all embryonic tissue during the development of the embryo. Adult stem cells form a repair system and maintain the turnover of regenerative organs such as blood, skin and intestinal tissue.

Stem-cell research has evolved significantly in the last 40 years. Researchers can now grow stem cells and

allow them to differentiate into various tissues. Adult stem cells are already used in medical therapies. While adult stem cells can be obtained from various sources, such as umbilical cord blood and bone marrow, embryonic stem cells can be obtained only from embryos, which potentially precludes their use in medical therapies for ethical reasons.

Article 53(a) of the European Patent Convention (EPC) excludes "inventions the commercial exploitation of which would be contrary to 'ordre public' or morality". Rule 23d(c) (now Rule 28(c)) of the EPC further stipulates that under Article 53(a), European patents shall not be granted in respect of biotechnological inventions which, in particular, concern the use of human embryos for industrial or commercial purposes. Rule 26 reminds us that the EU Biotech Directive (98/44/EC) shall be used as a supplementary means of interpretation.

Several patent applications have been filed in Europe in a bid to protect the results of stem-cell research that could potentially lead to new and innovative medical therapies. One of the most famous cases concerns European Patent Application No 96903521 in the name of Wisconsin Alumni Research Foundation (WARF). This patent application claimed an *in vitro* cell culture comprising primate embryonic stem cells. Claim 1 of the application read as follows:

A cell culture comprising primate embryonic stem cells which

(i) Are capable of proliferation in vitro culture for over one year,

(ii) Maintain a karyotype in which all chromosomes normally characteristic of the primate species are present and are not noticeably altered through culture for over one year,

(iii) Maintain the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the cultures, and

(iv) Are presented from differentiating when cultured on a fibroblast feeder layer.

The Examining Division refused the application on the grounds that it did not meet the requirements of Article 53(a) in combination with Rule 23d(c) (now Rule 28(c)) of the EPC. The application disclosed that the use of human embryos as a starting material for obtaining primate embryonic stem cells was indispensable. The Examining Division concluded that such use of human embryos constituted use for an industrial or commercial purpose and therefore contravened Rule 23d(c) (now Rule 28(c)) of the EPC, even if such use was not claimed as such.

WARF appealed the decision. The Board of Appeal (T1374/04) decided to refer the following questions to the Enlarged Board of Appeal (G02/06):

1. *Does Rule 23d(c) [now 28(c)] EPC apply to an application filed before the entry into force of the rule?*
2. *If the answer to question 1 is yes, does Rule 23d(c) [now 28(c)] EPC forbid the patenting of claims directed to products (here: human embryonic stem cultures) which — as described in the application — at the filing date could be prepared exclusively by a method which necessarily involved the destruction of the human embryos from which the said products are derived, if the said method is not part of the claims?*
3. *If the answer to question 1 or 2 is no, does Article 53(a) EPC forbid patenting such claims?*
4. *In the context of questions 2 and 3, is it of relevance that after the filing date the same products could be obtained without having to recur to a method necessarily involving the destruction of human embryos (here: eg derivation from available human embryonic cell lines)?*

Third parties were invited to submit written submissions. On 24th June 2008 oral proceedings were held and a written decision was subsequently published, identified as G02/06.

The Enlarged Board of Appeal answered the first question in the affirmative. No transitional provisions were included when introducing Chapter VI, entitled "Biotechnological inventions", comprising Rule 23d(c) (now Rule 28(c)), into Part II of the EPC Implementing Regulations. Therefore, this rule applies to all pending applications, even those filed before the entry into force of this rule.

The answer to the second question was also affirmative. The Enlarged Board of Appeal confirmed that European applications comprising claims directed to products derived from human embryos wherein embryonic stem cells used to obtain the product claimed can be prepared exclusively by a method which necessarily involves the destruction of the human embryos are excluded from patentability, even if this method is not part of the claims.

The Enlarged Board of Appeal clarified three points underlying its decision:

- First, since the term "embryo" is not further defined either in the directive or in the EPC, the exclusion clearly applies to any embryo and therefore cannot be restricted to an embryo of a certain age (eg, 14 days or more), as WARF suggested.

"The EPO makes no distinction between the commercialisation of human embryos as such and any invention comprising a product derived from human embryonic stem cells"

- Second, the fact that no claims were directed to such embryo was irrelevant. Rule 23d(c) (now Rule 28(c)) clearly stipulates that European patents shall not be granted in respect of biotechnological inventions which, in particular, concern the use of human embryos for industrial or commercial purposes. One must thus assess whether the application of the invention will inevitably lead to the use of the embryo.
- Third, it could not be argued that in this case the embryos were not used for an industrial or commercial purpose. Any patentable product first must be made. This process represents the exploitation or commercialisation of the invention, and in this case involved the destruction of the embryos. As such, it was to be considered as an industrial or commercial use of the embryos, even if one of the applications of the product related to research.

The third question required no response, since the second question was answered in the affirmative.

The answer to the fourth question was negative. Technical developments which become available after the filing date of the application cannot be taken into consideration. A parallel was drawn with insufficient disclosure of an application: an application which is considered insufficiently disclosed upon filing cannot later be considered sufficiently disclosed by referring to data that becomes available after the filing date.

This decision of the Enlarged Board of Appeal seems rather formal and rigid. It seems that the EPO makes no distinction between the commercialisation of human embryos as such and any invention comprising a product derived from human embryonic stem cells. This decision is more restrictive than the legislation of several EPC member states - for example, neither the extraction of embryonic stem cells from human embryos that are less than 14 days old nor the culture of such cells is prohibited in the United Kingdom, while the destruction of supernumerary embryos that are not used for research is mandatory under the Dutch Embryo Act. The decision is expected to have a negative impact on the development of human embryonic stem-cell research.

The decision deals exclusively with human embryonic stem cells. Therefore, it should not affect inventions involving human adult stem cells or non-human embryonic stem cells.

The decision clearly indicates that any invention for therapeutic or diagnostic purposes applied to the human embryo itself is not excluded from patentability. However, the development of such therapeutic or diagnostic methods may become possible only after preliminary research on human embryonic stem cells. Such preliminary research would be encouraged were it possible to protect the results. *iam*

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