The EPO's decision G 2/06 on the patentability of human embryonic stem cells: Sounding the bell for the next round?

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It was not unexpected - the outcome of the recent decision G 2/06 of the EPO's Enlarged Board of Appeal (EBA) on the patentability of the WARF application filed by James Thomson and the Wisconsin Alumni Research Foundation in 1995: No EP-patent on inventions the exploitation of which involves destruction of a human embryo.

However, this decision is nevertheless subject to discussion as to whether it should be considered as the EPO's final "No" on the patentability of human embryonic stem (hES) cells in Europe. While the WARF application describes a method for obtaining hES cell cultures which necessarily involves the use and destruction of human embryos, the technical development in the embryonic stem cell research field after the filing date of the WARF application allows the generation of hES cells without the need to use and/or destroy human embryos. In view of this, applicants may have expected more clarity from decision G 2/06 with respect to the patentability of hES cells in general.

INTRODUCTION

The Appeal underlying the present proceedings was against the decision of the Examining Division refusing EP patent application No. EP 96 903 521.1. This decision related to an application with a set of claims 1 to 10, of which claim 1 reads:

1. A cell culture comprising ***primate*** **embryonic stem cells** which
   (i) are capable of proliferation *in vitro [sic]* 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 culture, and
   (iv) are prevented from differentiating when cultured on a fibroblast feeder layer. (emphasis added)

The Examining Division recognized that the application also covered the generation of hES cell cultures which fell under the claims, notwithstanding the absence of specific examples: hES cell lines according to the application had been deposited with the NIH Human Embryonic Stem Cell Registry.

While claim 1 of the WARF application is directed to hES cell cultures, the method for obtaining the claimed hES cells is not part of the claims. As regards the generation of hES cell cultures, the use of spare pre-implantation embryos as starting material was described in the original application as being indispensable.

The Examining Division refused the application for the reason that claims 1 to 7, 9 and 10 did not comply with the requirements of Rule 28(c) EPC (Rule 23d(c) under the former EPC1973) in

conjunction with Article 53(a) EPC[1]. Rule 28 ("Exceptions to patentability") reads:

> Under Article 53(a), European patents shall not be granted in respect of biotechnological inventions which, in particular, concern the following:
> (a) processes for cloning human beings;
> (b) processes for modifying the germ line genetic identity of human beings;
> (c) ***uses of human embryos for industrial or commercial purposes***;
> (d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes. (emphasis added)

Article 53(a) states:

> European patents shall not be granted in respect of inventions the commercial exploitation of which would be contrary to "ordre public" or morality; such exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States.

The Examining Division saw the use of a human embryo as starting material for the generation of a product of industrial application (*i.e.* the claimed embryonic stem cell cultures) as falling within the exclusion of Rule 28(c) and therefore rejected the claims under this provision in conjunction with Article 53(a). The Applicant lodged an Appeal against the decision of the Examining Division.

[1] In the following, any citation of Articles and Rules relates to the EPC as in force since 13 December 2007 ("EPC2000").

THE QUESTIONS REFERRED TO THE ENLARGED BOARD OF APPEAL

The EPO's Technical Board of Appeal (TBA) dealing with the patentability of the claimed invention of the WARF application considered the question of the patentability of hES cells as well as of the conditions by which such patentability should be assessed as an exceedingly important point of law, and referred the following questions to the Enlarged Board of Appeal (EBA):

1. Does Rule 28(c) EPC (23d(c) EPC1973) apply to an application filed before the entry into force of the rule?

2. If the answer to question 1 is yes, does Rule 28(c) EPC (23d(c) EPC1973) forbid the patenting of claims directed to products (here: human embryonic stem cell 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 of 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: e.g. derivation from available human embryonic cell lines)?

THE ANSWER TO QUESTION 1: RULE 28(c) APPLIES TO APPLICATIONS FILED BEFORE ITS ENTRY INTO FORCE

By its decision of 16 June 1999, the Administrative Council of the EPO inserted a new chapter entitled "Biotechnological Inventions" into the EPC Implementing Regulations (the current Rules 26 to 29), thereby implementing the Directive

98/44/EC of the European Parliament on the legal protection of biotechnological inventions in the European Patent Convention. The provisions of Rule 28 were specifically intended to clarify the interpretation of Article 53(a), to which this rule expressly refers as explained above.

The new provisions entered into force on 1 September 1999, *i.e.* after the filing of the WARF application in 1995. The EBA explained that the introduction of the new rules without any transitional provisions can only be taken as meaning that it was to be applied to all then pending applications. Accordingly, the EBA answered the first question to the effect that Rule 28(c) applies to all pending applications including those filed before the entry into force of the rule. Prior to the EBA's decision and upon the EBA's invitation, some parties made submissions expressing the opinion that Rule 28(c) should only be applicable to applications filed after its coming into force. Despite this, the vast majority of the briefs, as well as the applicant itself, agreed on this answer of the EBA.

THE ANSWER TO QUESTION 2: NO PATENT ON INVENTIONS THE EXPLOITATION OF WHICH INVOLVES HUMAN EMBRYO DESTRUCTION

Rule 28(c) prohibits biotechnological inventions which concern uses of human embryos for industrial or commercial purposes. The Appellant and interested parties argued that since the key point is that Rule 28(c) relates to the direct use of human embryos, it does not prohibit patents in respect of products which are derived from human embryos.

The EBA explained, however, that in general a claimed new and inventive product must first be made before it can be used, and that such making is the ordinary way to commercially exploit the claimed invention. According to the EBA, such making falls within the monopoly granted, as someone having a patent application with a claim directed to this product has, upon grant, the right to exclude others from making (or using) such product.

Accordingly, the EBA pointed out that the provisions of Rule 28(c) are not directed exclusively to the claimed subject matter, but rather concern the "invention" in the context of its industrial or commercial exploitation, thus including all aspects that make the claimed subject matter available to the public. In other words, looking solely at the explicit wording of the claims is not enough when assessing Rule 28(c). Rather, the technical teaching of the application as a whole as to how the invention is to be performed (exploited) must also be considered.

In the case referred to the EBA, the only teaching of how to perform the invention, *i.e.* how to make hES cells cultures, involves the use and inevitable destruction of human embryos. The description of the WARF application provides no source of starting cells other than a pre-implantation embryo. The EBA regarded this necessary use involving destruction of the human embryo for obtaining the hES cells as an integral and essential part of the industrial or commercial exploitation of the claimed invention – an exploitation which violates Rule 28(c) in conjunction with Article 53(a).

While the claims relate only to the claimed product, namely hES cell cultures, the method of how to obtain the product is not part of the claims. The EBA, however, clarified that the provisions of Rule 28(c) cannot be circumvented by the mere fact that the claims do not include making the claimed product from human embryos. It was therefore irrelevant that the claimed subject matter related to cell cultures and not to a method of production of said cultures. As further stated, restricting the application of Rule 28(c) to the explicit wording of the claims would undesirably result in applicants seeking clever and skilful drafting of the claims in order to avoid the patenting exclusion governed by that rule.

This second question and the EBA's answer to it addressed the heart of the matter. Rule 28(c) forbids the patenting of claims directed to products (here: hES cell cultures) which – as described in the application – could only be prepared on the filing date by a method necessitating the destruction of the human embryos en route to the claimed products. This holds even if the method is not part of the claims. Thus, the Board made it perfectly clear that any claimed invention, the exploitation of which involves the destruction of human embryos, will not be patentable.

NO ANSWER TO QUESTION 3: ARTICLE 53(a) DID NOT COME INTO PLAY

Since questions 1 and 2 had been answered with yes, the EBA said that question 3 required no answer. No further comments were given.

THE ANSWER TO QUESTION 4: TECHNICAL DEVELOPMENTS AFTER THE FILING DATE OF THE WARF APPLICATION CANNOT BE TAKEN INTO CONSIDERATION

The EBA ruled that when assessing whether a claim contravenes Rule 28(c), technical developments which became publicly available only after the filing date cannot be taken into consideration, and that it cannot be relevant whether later either the applicant himself or others made something further available that would then have allowed the product to be made in an innocuous manner. The EBA compared the situation with an invention which is insufficiently described in the application as filed and noted that, similarly, lack of any disclosure in the application as filed allowing the skilled person to carry out the invention in a manner not falling under Rule 28(c), cannot be cured by the occurrence of subsequent technical developments. Any other conclusion would lead to legal uncertainty, to the detriment of any third party who later provided an innocuous way to carry out the invention.

Accordingly, question 4 was answered to the effect that it is irrelevant that after the filing date the same products could be obtained without having to resort to a method necessarily involving the destruction of human embryos.

The following discussion points address potential issues that we foresee in the future.

THE *USE INVOLVING DESTRUCTION* OF HUMAN EMBRYOS IS ONLY ONE EMBODIMENT FALLING UNDER RULE 28(c)

The hES cell cultures claimed in the WARF application could only be prepared by a method necessarily involving the destruction of the source human embryos. The description of the WARF application provided no other source and/or way for obtaining the claimed hES cells. Accordingly, question 2 referred to the EBA was formulated in that it specifically addressed a method which necessarily involves the destruction of the human embryos used for isolating hES cells. However, Rule 28(c) relates to "uses of human embryos for commercial or industrial purposes" in general, of which the *use involving destruction* of human embryos is only one possibility.

Given this narrow basis for the decision, the EBA's answer to question 2 did not appear to be surprising to most of the professionals in Europe. However, it would nevertheless have been desirable to receive some clarity and guidance on the patentability of hES cells produced by other routes that have opened up after the filing date of the WARF application, and which avoid the inevitable use and/or destruction of human embryos.

THE SCOPE OF EXEMPTIONS UN-DER RULE 28(c) REMAINS OPEN FOR SEVERAL REASONS

Meanwhile, it is possible to produce hES cells from a human embryo by methods *without* destroying the embryo they come from. In particular, it has been shown that it is possible to remove a single cell from a living embryo without interfering with the embryo's full developmental potential. While the extracted cell is biochemically coaxed to divide and form a new stem cell line, the embryo continues to develop normally. The extraction procedure is similar to that commonly used during *in vitro* fertilization, in which a single cell is removed from a young embryo for pre-implantation genetic diagnosis.

Accordingly, in light of G 2/06, the term "use" as recited in Rule 28(c) may be narrowly construed, *i.e.* merely excluding the *use involving destruction* of human embryos. Therefore, hES cell cultures obtained from human embryos which are *not* destroyed during their use for generating the embryonic stem cells may be considered patentable. This issue, however, was not specifically addressed in decision G 2/06, and may await future clarification in one or more future decisions, where one might expect that the EPO would follow along the line of G 2/06, *i.e.* construing even the use *without* destruction of a human embryo as a use thereof for the industrial or commercial exploitation of the claimed invention prohibited under Rule 28(c) in conjunction with Article 53(a).

THE INTERPRETATION OF RULE 28(c) REQUIRES AN INTERPRE-TATION OF THE TERM "HUMAN EMBRYO"

In the WARF application, the starting material for generating the hES cell culture was a pre-implantation embryo resulting from *in vitro* fertilization of an oocyte by sperm. Thus, in light of decision G 2/06, the "uses of human embryos for industrial or commercial purposes" as given in Rule 28(c) may be narrowly construed, *i.e.* merely excluding uses of human embryos which result from fertilization. Accordingly, one may consider as patentable hES cell cultures obtained by methods which do not start from embryos resulting from *in vitro* fertilization, but involve the use of an embryo that is generated by another route, e.g. in the course of "therapeutic cloning".

The process known as "therapeutic cloning" describes nuclear transfer to produce embryonic stem cells, and involves removing the nucleus from a human egg cell (unfertilized oocyte), and replacing it with the nucleus from an adult somatic cell of a patient in order to produce hES cells genetically identical to that patient for 'autologous' transplantation[2]. This nuclear-transplanted cell ("reconstructed oocyte") is stimulated to develop into an embryo, which is then allowed to develop until the blastocyst stage. The cells from the inner mass of the blastocyst are then harvested and will continue to develop into pluripotent embryonic stem cells, which are used for establishing and maintaining hES cell lines. These embryonic stem cells are considered to exhibit the same properties as "conventional" embryonic stem cells derived from embryos produced by fertilization. Furthermore, the embryonic stem cells resulting from nuclear transfer are expected to be genetically identical to the nucleus donor except for the mitochondrial genome, which is derived from the oocyte.

Thus, in contrast to the embryos used in the WARF application, the embryo produced during the process of therapeutic cloning is not a pre-implantation embryo resulting from *in vitro* fertilization of an oocyte by sperm.

In decision G 2/06, the Board explained that neither of the EU nor EPC legislators have chosen to define the term "embryo"

[2] As such, the term "therapeutic cloning" is somehow misleading since it has been proposed that the term "cloning" be reserved for reproductive cloning.

as used in the Directive 98/44/EC or now in Rule 28(c). The Board went on to say that this contrasts with the German law where "embryo" is defined as including a *fertilized* egg[3], or the UK law where "embryo" includes the two cell *zygote* and an egg in the process of *fertilization*[4]. Further, the EU and the EPC legislators must presumably have been aware of the definitions used in national laws on regulating embryos, and yet chose to leave the term undefined. Given the purpose to protect human dignity and prevent the commercialization of embryos, the Board presumed that "embryo" was not to be given any restrictive meaning in Rule 28(c), as to do so would undermine the intention of the legislator.

Accordingly, the decision G 2/06 may at first glance exempt inventions relying on hES cells isolated from embryos, which are generated in the above-described method of therapeutic cloning. However, it also specifically mentions that the question of embryo identity is one of fact in the context of any particular patent application. Hence, in view of the fact that the debate on the patentability of the WARF application was based on the use of pre-implantation embryos produced by *in vitro* fertilization, there exists the need for some clarity and guidance on what else the term "human embryo" in Rule 28(c) embraces.

In connection with the above, uncertainty arises from the fact that the Directive itself does not contain a legal definition of the term "embryo". As mentioned above certain definitions do exist on the national law level. At the same time, these definitions vary considerably. Some of the definitions, like the ones in Germany, include moral evaluative criteria whereby the human embryo is defined in terms of its potential to develop into a human being:

> Embryo means any human totipotent cell which has the potential to divide and to develop into a human being if the necessary conditions prevail.[5]
>
> or
>
> An embryo already means the human egg cell, fertilized and capable of developing, from the time of fusion of the nuclei, and further, each totipotent cell removed from an embryo that is assumed to be able to divide and to develop into an individual under the appropriate conditions for that.[6]

As mentioned above, need arises to further define the meaning of the term "human embryo" as given in Rule 28(c). This would certainly bring further clarity as to the scope of exemptions falling under Rule 28(c).

THE TWO-STEP EXAMINATION UN-DER RULE 28(c) AND ARTICLE 53(a)

A purpose of Rule 28 is to provide guidance for the interpretation of the more general moral exclusion in Article 53(a), which stipulates that European patents shall not be granted in respect of inventions the commercial exploitation of which would be contrary to "ordre public" or morality, as described herein above. Clearly, the exemptions under Article 53(a) are not limited to the examples of Rule 28. Therefore, even where Rule 28, in particular Rule 28(c), may not apply in light of G 2/06, the claimed subject matter must be considered for compliance with the more general provision under Article 53(a). In other words, one must still address the question as to whether or not the application should be refused on the grounds that it is generally contrary to

[3] Section 8 of the Embryo Protection Act of (1991).
[4] Section 1(1) of the Human Fertilization and Embryology Act (1990).
[5] Section 3 of the Stem Cell Act (2002).
[6] Section 8(1) of the Embryo Protection Act (1991).

"ordre public" or morality. This requires a two-step examination for inventions relating to, for example, hES cells which are obtained by reprogramming adult somatic cells ("induced pluripotent stem cells") or hES cell lines which are derived from publicly available stem cell line deposits. The same applies to inventions relating to hES cells produced by "therapeutic cloning" when construing the term "human embryo" in Rule 28(c) as being restricted to the product of fertilization, so that Rule 28(c) might not be a bar to patenting.

Prior to any assessment on the patentability of any claimed subject matter under Article 53(a), the meaning of the concepts of "ordre public" and morality must be defined by way of interpretation. As for Rule 28(c), the provision of Article 53(a) is centred on the criterion of "exploitation" of an invention. However, while overcoming Article 53(a) requires passing of a *general* morality test, the provisions of Rule 28 are much narrower and were specifically intended to clarify the interpretation of Article 53(a).

Thus, if Rule 28(c) in light of decision G 2/06 would not forbid the use of embryos other than those produced by *in vitro* fertilization for the industrial or commercial exploitation of an hES cell-related invention, the question nonetheless arises whether the more general moral exclusion clause in Article 53(a) would prohibit patents on such inventions. Consequently, there exists significant room for further decisions in the field of hES cell inventions.

FURTHER MORALITY HURDLES ON THE WAY TO A PATENT ON HUMAN EMBRYONIC STEM CELLS: RULE 28(a)

The above being said, one may consider whether Rule 28(a) may additionally exempt hES cell-related inventions from patent protection. Rule 28(a) states that European patents shall not be granted in respect of biotechnological inventions which concern "processes for cloning human beings". In addition to Rule 28(c), this rule may be relevant as well since *e.g.* the method of therapeutic cloning described above results in the creation of embryos with the same genetic information as another embryo. However, while the plain reading of Rule 28(a) leaves no doubt that the provision prohibits the patenting of processes for the cloning of human beings, discussions may arise in the future as to whether this Rule really extends to the so called "therapeutic cloning" as addressed herein above.

The ambiguity lies, *inter alia*, in the meaning and scope of the term "human being". Rule 28(a) was adopted in the context of publication of the successful cloning of Dolly the sheep, and the considerations that the cloning of human beings may become a technical possibility. Extending the expression "human being" in Rule 28(a) to include "human embryo" may lead to a bar to the patenting of "therapeutic cloning".

AND FURTHER POTENTIAL BARS: RULE 29

Rule 29 ("The human body and its elements") states:

(1) The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.

(2) 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.

(3) The industrial application of a sequence or a partial sequence

of a gene must be disclosed in the patent application.

From the plain language of Rule 29(1) one may assume that patenting of *human embryos* is exempted since a human embryo constitutes one of the *stages in the formation and development* of the human *body*. In contrast to Rule 28(a) as discussed above, Rule 29(1) does not use the term "human *being*". While it is not clear from the wording of Rule 29(1) whether the exemption was intended to apply to both the human embryo in its natural state and the human embryo *in vitro*, to the best of our knowledge there has never been any question of patenting a human embryo itself. Again, also for this Rule, case law may one day have to define what is meant by the "human body at the various stages of its formation".

The above being said, another question arising in the discussion of Rule 29 is whether *totipotent hES cells* may be excluded from patentability under this Rule. Totipotent hES cells have the potential to divide and develop into an entire human body under appropriate conditions. In view of this potential, such cells may not be patentable because they may be regarded as the human body at the various stages of its formation and development and, hence, excluded from patentability. The basis of such an exclusion would thus reside in the cell's "potential" to develop into a human body.

The above considerations may not extend to *pluripotent hES cells*, which lack the potential to develop into a human body and, once isolated from the human body by means of a technical process, should fulfil the patentability requirements under Rule 29(2). It follows that pluripotent hES cells and the processes for isolating the cells are *prima facie* patentable, provided that the claimed invention otherwise fulfils the criteria of novelty, inventive step and industrial application. Still, pluripotent hES cells and processes to derive them could be excluded from patentability if patenting of inventions based on the use of pluripotent embryonic stem cells would be contrary to "ordre public" and morality under Article 53(a).

ARE THERE PRATICAL IMPLICA-TIONS FOR THE PRACTITIONER?

Given the narrow fact pattern underlying G 2/06, the EBA has decided that no claims will be allowed defining hES cell cultures which could be prepared exclusively by a method which necessarily involves the destruction of the source human embryos. Still, the decision may not be construed as a green light for patent applications which describe methods that do not necessarily involve the destruction of human embryos. Any such applications are likely to be challenged under Rule 28(c) in future decisions, or alternatively may face problems under Rule 28(a), Rule 29 or the general provision under Article 53(a).

The above being said, applicants may consider introducing a disclaimer into their claims specifying that the claimed hES cell cultures are not obtained by a method involving the use (and inevitable destruction) of human embryos[7]. However, this may be applicable only to patent applications which themselves describe alternative methods for obtaining the claimed hES cell cultures, or at the filing date of which such alternative methods were already known in the art. Otherwise, problems under Article 83 ("enablement")[8] may arise since, except for the disclaimed method(s), there exists no alternative way of generating the claimed hES cell cultures which would enable the skilled person to perform the claimed invention.

[7] The EBA's decisions G 1/03 and G 2/03 provide as basis for excluding from claims non-patentable subject matter by virtue of an undisclosed disclaimer.

[8] Article 83 EPC stipulates that European patent applications shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

SUMMARY

The EPO has said “no” to inventions the exploitation of which involves the use and inevitable destruction of human embryos. However, it would have been preferable to have clarity on the patentability of claims involving the use of embryos, the use of which does not lead to the destruction of the human embryo. This would at least allow applicants to proceed with some degree of certainty.

Further debates on the patentability of hES cells produced by alternative methods without having to resort to a method necessarily involving the destruction of human embryos may be expected. In addition, the further exemptions under Rule 28(a), Rule 29 and Article 53(a) are expected to someday be the subject of decisions in the field of hES cells.

Thus, the ruling in the WARF application may have sounded the bell for the next round in the debate on the patentability of hES cells in Europe. And perhaps, a similar scenario as in the diagnostic field may arise, *i.e.* that after the issuance of G 2/06 another referral reaches the EBA.