Appeal Ref. CH/2012/0488

Neutral Citation Number: [2013] EWHC 807 (Ch)

IN THE HIGH COURT OF JUSTICE

CHANCERY DIVISION

PATENTS COURT

Rolls Building, Royal Courts of Justice
7, Rolls Building, Fetter Lane,
London, EC4A 1NL

Date: 17/04/13

Before :

Henry Carr QC
(sitting as a Deputy Judge of the High Court)

- -

ON APPEAL FROM THE COMPTROLLER GENERAL OF PATENTS
DECISION No. BL O/316/12

INTERNATIONAL STEM CELL CORPORATION

Appellant

-and-

COMPTROLLER GENERAL OF PATENTS

Respondent

Mr Piers Acland QC (instructed by **DLA Piper UK LLP**) for the **Appellant**
Mr Tom Mitcheson (instructed by **the Treasury Solicitor**) for the **Respondent**

Hearing date:

- -

JUDGMENT

Introduction

1. This is an appeal concerning two patent applications in the name of International Stem Cell Corporation ("ISCC"), both relating to human stem cells. In a decision dated 16 August 2012, the Hearing Officer, Dr Cullen, held that the inventions disclosed in the patent applications were excluded from patentability under paragraph 3(d) of Schedule A2 to the Patents Act 1977. This provides as follows:

> "BIOTECHNOLOGICAL INVENTIONS
>
> 3. The following are not patentable inventions –
> …
> (d) uses of human embryos for industrial or commercial purposes;"

2. Paragraph 3(d) of Schedule A2 implements Article 6(2)(c) of Directive 98/44/EC on the Legal Protection of Biotechnological Inventions ("the Biotech Directive"). Guidance was given by the Court of Justice of the European Union ("the CJEU") as to the correct interpretation of Article 6(2)(c) in Case C-34/10 *Oliver Brüstle v Greenpeace eV* [2012] 1 CMLR 41. The Comptroller agrees with ISCC that this appeal turns on the reasoning of the CJEU in *Brüstle.*

3. This appeal raises a question of considerable importance. What is meant by the term "human embryos" in Article 6(2)(c) of the Biotech Directive? In particular, what was meant by the CJEU in *Brüstle* by the expression "capable of commencing the process of development of a human being"? Does that contemplate the commencement of a process which must be capable of leading to a human being? Or does it contemplate the commencement of a process of development, even though the process cannot be completed, so that it is incapable of leading to a human being?

4. The Hearing Officer decided that he was bound by *Brüstle* to reject the patent applications. At the time of his Decision, Dr Cullen had only been shown the UK Observations in *Brüstle.* The Comptroller maintains that the decision of the Hearing Officer, on the material before him and at that level of tribunal, was the correct one. Since then, ISCC has obtained the Observations of Prof. Brüstle, Greenpeace, Portugal, Sweden and the Commission. In the light of that further material, the Comptroller accepts that the issue of whether parthenotes (the meaning of which is explained below) are properly to be regarded as human embryos within Article 6(2)(c) of the Biotech Directive is not *acte clair* in the light of the current state of the art. Therefore, the Comptroller supports ISCC's request for a further reference to the CJEU on the central point in this appeal.

5. However, ISCC goes further. Its primary case is that the issue is *acte clair* in its favour and that the appeal should be allowed without a further reference to the CJEU. By the conclusion of the hearing, I had formed the clear view that a reference was required, and I informed the parties of this. This Judgment

sets out my reasons.

The legal framework

6. The Biotech Directive came into force on 30 July 1998 and seeks to harmonise national patent laws concerning biotechnological inventions. The legal context of the Biotech Directive and the relevant Recitals and Articles are set out by the CJEU in the *Brüstle* decision at paragraphs 3-7. I reproduce below the parts of the Biotech Directive which are of most relevance to this Appeal.

7. The preamble to the Directive states as follows:

> '…
> (2) Whereas, in particular in the field of genetic engineering, research and development require a considerable amount of high-risk investment and therefore only adequate legal protection can make them profitable;
> …
> (16) Whereas patent law must be applied so as to respect the fundamental principles safeguarding the dignity and integrity of the person; whereas it is important to assert the principle that the human body, at any stage in its formation or development, including germ cells, and the simple discovery of one of its elements or one of its products, including the sequence or partial sequence of a human gene, cannot be patented; whereas these principles are in line with the criteria of patentability proper to patent law, whereby a mere discovery cannot be patented;
> (17) Whereas significant progress in the treatment of diseases has already been made thanks to the existence of medicinal products derived from elements isolated from the human body and/or otherwise produced, such medicinal products resulting from technical processes aimed at obtaining elements similar in structure to those existing naturally in the human body and whereas, consequently, research aimed at obtaining and isolating such elements valuable to medicinal production should be encouraged by means of the patent system;
> …
> (20) Whereas, therefore, it should be made clear that an invention based on an element isolated from the human body or otherwise produced by means of a technical process, which is susceptible of industrial application, is not excluded from patentability, even where the structure of that element is identical to that of a natural element, given that the rights conferred by the patent do not extend to the human body and its elements in their natural environment;
> (21) Whereas such an element isolated from the human body or otherwise produced is not excluded from patentability since it is, for example, the result of technical processes used to identify, purify and classify it and to reproduce it outside the human body, techniques which human beings alone are capable of putting into practice and which nature is incapable of accomplishing by itself;
> …

(37) Whereas the principle whereby inventions must be excluded from patentability where their commercial exploitation offends against *ordre public* or morality must also be stressed in this Directive;

(38) Whereas the operative part of this Directive should also include an illustrative list of inventions excluded from patentability so as to provide referring courts and patent offices with a general guide to interpreting the reference to *ordre public* and morality; whereas this list obviously cannot presume to be exhaustive; whereas processes, the use of which offend against human dignity, such as processes to produce chimeras from germ cells or totipotent cells of humans and animals, are obviously also excluded from patentability;

(39) Whereas *ordre public* and morality correspond in particular to ethical or moral principles recognised in a Member State, respect for which is particularly important in the field of biotechnology in view of the potential scope of inventions in this field and their inherent relationship to living matter; whereas such ethical or moral principles supplement the standard legal examinations under patent law regardless of the technical field of the invention;

…

(42) Whereas, moreover, uses of human embryos for industrial or commercial purposes must also be excluded from patentability; whereas in any case such exclusion does not affect inventions for therapeutic or diagnostic purposes which are applied to the human embryo and are useful to it;

(43) Whereas pursuant to Article F(2) of the Treaty on European Union, the Union is to respect fundamental rights, as guaranteed by the European Convention for the Protection of Human Rights and Fundamental Freedoms signed in Rome on 4 November 1950 and as they result from the constitutional traditions common to the Member States, as general principles of Community law;

...'

8. It will be seen that these recitals express two competing policy considerations. On the one hand, that research in the field of biotechnology is to be encouraged by means of the patent system, and on the other hand, that patent law must be applied so as to respect the fundamental principles safeguarding the dignity and integrity of the person; so that the human body, at any stage in its formation or development, cannot be patented. The Biotech Directive is to be interpreted in a way that balances these competing policy considerations.

9. The Biotech Directive then provides:

Article 5

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.

…

Article 6

> 1. Inventions shall be considered unpatentable where their commercial exploitation would be contrary to *ordre public* or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation.
>
> 2. On the basis of paragraph 1, the following, in particular, shall be considered unpatentable:
> (a) …
> (b) …
> (c) uses of human embryos for industrial or commercial purposes;
> (d) …

Technical Background

10. The following technical background is contained in the expert reports and exhibits of Dr De Sousa and Professor Ansell (referred to in paragraph [36] of the decision of Dr Cullen) and the Judgment of the Bundesgerichtshof in *Brüstle*. It is common ground between the parties.

Human embryogenesis

11. Development of a human being begins with fertilisation of the ovum. Strictly speaking, the unfertilised ovum is referred to as an oocyte. Penetration of a sperm cell induces the oocyte to mature into a fertilised ovum. The oocyte itself is haploid (it contains half the usual complement of genetic material) and acquires a full genetic complement upon fertilisation. The fertilised ovum is diploid – it contains two copies of each chromosome, one from the mother and the other from the father.

12. The initial stages of embryogenesis are characterised by cell division leading to the formation of a hollow sphere containing 100-200 cells called a blastocyst. The latter comprises a central group of cells from which all embryonic tissues are derived (referred to as the inner cell mass) surrounded by a layer of cells (the trophectoderm) from which the extra-embryonic tissues such as the placenta are derived.

13. The development of a human being requires the presence of both maternal and paternal DNA because of a phenomenon known as genomic imprinting. This is a mechanism by which the maternal or paternal copies of certain genes are not expressed in the developing embryo. Specifically, a number of genes involved in the development of extra-embryonic tissues are only expressed from the paternal DNA, the equivalent maternal genes being repressed. Accordingly in the absence of any paternal DNA, development cannot proceed to term because of the absence of any proper extra-embryonic tissues.

14. Human embryogenesis can also be initiated without fertilisation by a process known as somatic-cell nuclear transfer (SCNT) or therapeutic cloning. In this

process, the nucleus of an unfertilised ovum is removed and replaced with a donor nucleus from a mature adult cell. The ovum is thereafter diploid (both maternal and paternal DNA being derived from the nucleus of the mature adult cell) and is therefore capable of undergoing all the normal stages of embryonic development into a human being.

15. Cells produced in the very first few divisions after fertilisation are totipotent – they are capable of differentiating into embryonic and extra-embryonic tissues. At the blastocyst stage, cells of the inner cell mass are pluripotent – they are capable of differentiating into embryonic but not extra-embryonic tissues. It remains to be established whether such pluripotent stem cells can in fact be reprogrammed to the totipotent state – to date this has not been demonstrated.

Parthenogenesis

16. Parthenogenesis refers to the initiation of embryogenesis without fertilisation by activation of an oocyte in the absence of sperm. Such activation can be induced with a variety of chemical and electrical techniques. The activated oocyte (referred to as a parthenote) contains a single or double set of maternally derived chromosomes but does not contain any paternal DNA.

17. A parthenote is capable of developing into a blastocyst-like structure comprising trophectoderm and an inner cell mass. However it cannot develop to term because of the absence of any paternal DNA. As explained above, paternal DNA is required for the proper development of extra-embryonic tissues.

18. In contrast to a fertilised ovum and its early stage descendants the cells of a parthenogenetically-activated oocyte are pluripotent, not totipotent, even in the first few cell divisions after activation. The same is true of the cells in a parthenogenetic blastocyst-like structure.

19. Mr Mitcheson, who appeared for the Comptroller, referred to the expert report of Dr Paul De Souza, in particular at paragraphs 15-16. Dr De Souza explains, amongst other things, that "Parthenogenesis refers to the initiation of embryogenesis without fertilisation, but rather by activation of the oocyte in the absence of sperm…Brevini *et al (Cell Prolif 41:20-30,2008*...provides that "[m]ammalian parthenotes can develop to different stages after oocyte activation, depending on the species, but **never to term**" (Brevini at page 21)".

20. Table 1 on page 21 of the Brevini paper summarises the day of pregnancy when different non-human mammalian species arrest development following parthenogenetic activation (maximum development) and the related length of pregnancy (pregnancy length). So for example, for a mouse the maximum development was 10 days and the pregnancy length was 21 days. For a rabbit, the maximum development was 10-11 days and the pregnancy length was 31 days. Human parthenotes have thus far been shown to develop only to the blastocyst stage, over about five days.

Findings of Fact made by the Hearing Officer

21. In the light of the evidence before him, the Hearing Officer made the following findings of fact, which are not challenged on this Appeal:

> The parthenotes produced by the methods of the invention are incapable of continued normal development i.e. they cannot develop into a viable human being. (paragraph [46])
>
> Because of the unmet need for paternal imprinting in parthenotes produced by the activation of oocytes, development into a viable human being is not possible without further intervention or manipulation. (paragraph [57])
>
> A fertilised ovum has the capability to develop into a human being whereas a parthenogenetically-activated oocyte does not. (paragraph [62])
>
> In the present case, the use of parthenogenesis to activate the unfertilised oocyte, starts a process that although similar to that which a fertilised ovum undergoes, will not lead to the development of a human being. The parthenogenetically-activated oocyte is only pluripotent and lacks some of the elements essential for development of a human being. (paragraph [68]).

22. Furthermore, the Hearing Officer found that the stimulated human oocyte divided in a manner analogous to that of a fertilised human embryo, to produce a parthenogenetically derived structure analogous to that blastocyst stage of normal embryonic development. He stated as follows at [7]:

> "The applications in suit concern methods to produce human stem cells, and corneal tissues derived from such stem cells, using parthogenesis to activate a human oocyte; i.e. stimulation of a human oocyte, without fertilisation by a sperm cell, to produce a parthenogenetically-activated oocyte. The stimulated human oocyte divides in a manner **analogous** to that of a fertilised human embryo, to produce a parthenogenetically-derived structure **analogous** to the blastocyst stage of normal embryonic development, from which stem cells can be obtained." (emphasis added).

ISCC's patent applications

23. There are two applications in issue. GB0621068.6 is entitled *"Parthenogenetic activation of oocytes for the production of human embryonic stem cells"*. Claims 1-29 as proposed to be amended are for methods of producing pluripotent human stem cell lines from parthenogenetically-activated oocytes. Claim 30 and 31 are for stem cell lines

produced according to the claimed methods and claim 32 is an omnibus claim relating to a stem cell line.

24. The second application GB0621069.4 is entitled *"Synthetic cornea from retinal stem cells"*. As with GB0621068.6, there are method claims (all of which involve the isolation of pluripotent stem cells from parthenogenetically-activated oocytes), product-by-process claims and an omnibus claim.

25. For the purposes of this appeal, it is not necessary to distinguish between the two applications.

The decision in Brüstle

26. *Brüstle* was a reference for a preliminary ruling under Article 267 TFEU in which the CJEU was asked to consider the concept of 'uses of human embryos for industrial or commercial purposes' within the meaning of Article 6(2)(c) of the Biotech Directive.

27. The patent in issue concerned isolated and purified neural precursor cells, processes for their production from embryonic stem cells and the use of neural precursor cells for the treatment of neural defects. On application by Greenpeace, the Bundespatentgericht (Federal Patents Court) declared that the patent was invalid insofar as it related to precursor cells obtained from human embryonic stem cells. Prof. Brüstle appealed to the Bundesgerichtshof (Federal Court of Justice) which referred three questions to the CJEU for a preliminary ruling. Of particular relevance to this appeal is the first question.

28. The first question comprises a number of related questions, all concerned with the meaning of "human embryos" in Article 6(2)(c) of the Directive. Specifically:

> (a) Does it include all stages of the development of human life, beginning with the fertilisation of the ovum, or must further requirements, such as the attainment of a certain stage of development, be satisfied?
>
> (b) Are the following organisms also included:
>
> (i) unfertilised human ova into which a cell nucleus from a mature human cell has been transplanted;
>
> (ii) unfertilised human ova whose division and further development have been stimulated by parthenogenesis?
>
> (c) Are stem cells obtained from human embryos at the blastocyst stage also included?

29. The key reasoning of the CJEU is at paragraphs 32-38. I have emphasised

certain passages of particular importance:

> "32 In that regard, the preamble to the Directive states that although it seeks to promote investment in the field of biotechnology, use of biological material originating from humans must be consistent with regard for fundamental rights and, in particular, the dignity of the person. Recital 16 in the preamble to the Directive, in particular, emphasises that 'patent law must be applied so as to respect the fundamental principles safeguarding the dignity and integrity of the person'.
>
> 33 To that effect, as the Court has already held, Article 5(1) of the Directive provides that the human body at the various stages of its formation and development cannot constitute a patentable invention. Additional security is offered by Article 6 of the Directive, which lists as contrary to *ordre public* or morality, and therefore excluded from patentability, processes for cloning human beings, processes for modifying the germ line genetic identity of human beings and uses of human embryos for industrial or commercial purposes. Recital 38 in the preamble to the Directive states that this list is not exhaustive and that all processes the use of which offends against human dignity are also excluded from patentability (see *Netherlands* v *Parliament and Council*, paragraphs 71 and 76).
>
> 34 The context and aim of the Directive thus show that **the European Union legislature intended to exclude any possibility of patentability where respect for human dignity could thereby be affected. It follows that the concept of 'human embryo' within the meaning of Article 6(2)(c) of the Directive must be understood in a wide sense**.
>
> 35 Accordingly, **any human ovum must, as soon as fertilised, be regarded as a 'human embryo' within the meaning and for the purposes of the application of Article 6(2)(c) of the Directive, since that fertilisation is such as to commence the process of development of a human being.**
>
> 36 **That classification must also apply to** a non-fertilised human ovum into which the cell nucleus from a mature human cell has been transplanted and **a non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis. Although those organisms have not, strictly speaking, been the object of fertilisation, due to the effect of the technique used to obtain them they are, as is apparent from the written observations presented to the Court, capable of commencing the process of development of a human being just as an embryo created by fertilisation o**f **an ovum can do so.**
>
> 37 As regards stem cells obtained from a human embryo at the blastocyst stage, it is for the referring court to ascertain, in the light of scientific developments, whether they are capable of commencing the process of development of a human being and, therefore, are included

within the concept of 'human embryo' within the meaning and for the purposes of the application of Article 6(2)(c) of the Directive.

38 In the light of the foregoing considerations, the answer to the first question is that:

– any human ovum after fertilisation, any non-fertilised human ovum into which the cell nucleus from a mature human cell has been transplanted and **any non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis constitute a 'human embryo' within the meaning of Article 6(2)(c) of the Directive;**

– it is for the referring court to ascertain, in the light of scientific developments, whether a stem cell obtained from a human embryo at the blastocyst stage constitutes a 'human embryo' within the meaning of Article 6(2)(c) of the Directive."

30. At [53] the Court ruled inter alia that Article 6(2)(c) must be interpreted as meaning that "any non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis constitute a 'human embryo'.

Submissions of ISCC

31. On its face, the decision in *Brüstle* would appear to preclude the current applications, on the basis that they relate to non-fertilised human ova whose division and further development have been stimulated by parthenogenesis. However, Mr Acland QC, who appeared for ISCC submitted that, as a starting point, it is necessary to establish what the CJEU meant by *"capable of commencing the process of development of a human being"* since the Court adopted this test not only in relation to parthenotes but also in relation to fertilised ova, non-fertilised ova subjected to somatic-cell nuclear transfer and stem cells obtained from human blastocysts (see [34]-[36]).

32. According to ISCC, the key question is whether, for an organism to be *"capable of commencing the process of development of a human being"* it must be:

i. capable of commencing the process of development which leads to a human being; or

ii. capable of commencing a process of development even if that process is incapable of leading to a human being.

33. ISCC submits that the test adopted by the CJEU is clearly directed at the first alternative, for the following reasons:

34. First, the subject matter of the CJEU's test is the process of development of a human being. The natural meaning of the language is inconsistent with a process which is incapable of leading to development of a human being.

35. Second, in relation to fertilised ova and non-fertilised ova subjected to somatic-cell nuclear transfer, the act of fertilisation or nuclear transfer initiates the process of development which leads to a human being. It is most unlikely that the Court intended the same language to mean one thing in relation to fertilised ova and non-fertilised ova subjected to somatic-cell nuclear transfer and something completely different in relation to parthenotes. Accordingly, ISCC submits that the CJEU's reasoning for ruling as it did in relation to parthenotes must have been that it considered such organisms to be capable of completing the process of development leading to a human being.

36. Third, ISCC points to the reasoning of the Bundesgerichtshof following the ruling of the CJEU in *Brüstle.* In paragraph 34 of its judgment of 27 November 2012, the Federal Court of Justice characterised the CJEU's definition of a human embryo as "an organism [which has] the capacity of setting in motion the process of development of a human" and on this basis held the removal of cells from non-viable embryos could not be regarded as use of an embryo. So the Bundesgerichtshof interpreted the CJEU judgment as permitting the use of embryonic stem cells extracted from an organism or structure which was not capable of commencing the process of the development of a human being, even though it may have been so capable immediately after fertilisation and had undergone a process of development resembling that of a fertilised ovum. Thus, whilst the German Court did not have to consider the question of parthenotes, its interpretation of the CJEU's decision is consistent with that of ISCC.

37. Fourth, it submits that a correct understanding of the decision of the CJEU is that parthenotes are only excluded insofar as they are capable of giving rise to totipotent cells. In this regard, ISSC points to the Opinion of the Advocate General in *Brüstle* at [84]-[85]:

> 84 "Science teaches us – and it is now universally accepted, at least in the Member States – that development from conception begins with a few cells, which exist in their original state for only a few days. These are totipotent cells whose main characteristic is that each of them has the capacity to develop into a complete human being. They hold within them the full capacity for subsequent division, then for specialisation, which will ultimately lead to the birth of a human being. The full capacity for subsequent development is therefore concentrated into one cell.
>
> 85 Consequently, in my view totipotent cells represent the first stage of the human body which they will become. They must therefore be legally categorised as embryos."

38. The Advocate General specifically considered parthenotes at [91] and his reasoning reflects that the written observations had suggested (contrary to the findings in the present case) that parthenotes could be totipotent:

> "On the basis of this definition, I consider, moreover, that every totipotent cell, whatever the means by which it has been obtained, is an embryo and that any patentability must be excluded. This definition therefore covers unfertilised ova into which a cell nucleus from a mature cell has been transplanted **and unfertilised ova whose division has been stimulated by parthenogenesis in so far as, according to the written observations submitted to the Court, totipotent cells would be obtained in that way.**" (emphasis added).

39. Assuming that its interpretation of the Court's decision is correct, ISCC submits that the CJEU wrongly assumed it to be common ground from the observations that parthenotes were capable of commencing the process which leads to development of a human being and proceeded on a basis which was inconsistent with the facts as found by the referring Court in *Brüstle*. It points out that the when ruling on the interpretation or validity of Community provisions, the CJEU is empowered to do so only on the basis of the facts put before it by the referring court (Case C-418/01 *IMS Health GmbH & Co. OHG v NDC Health GmbH & Co. KG* [2004] 4 CMLR 28 at [18]).

40. ISCC states that there was no consensus in the written observations submitted to the CJEU on the subject of the developmental potential of parthenotes. Prof. Brüstle equated parthenotes with fertilised ova but only up to day 14 and before implantation. Greenpeace sought to equate parthenogenesis with the development of human life but without providing any technical basis for its position. The Portuguese Government said that it was "reasonable to accept" that parthenogenetic embryos have the potential to create a human being, although it acknowledged that the viability of embryos to birth had not been unequivocally proven. The Swedish Government said that is was too early to decide whether parthenotes should be regarded as embryos given the early stage of scientific research in this area. The Commission said that it was not clear whether a parthenote could develop into a complete human being. The UK's observations were at best equivocal as to the capacity for parthenotes to develop into human beings.

41. ISCC then states that the referring court made the following finding of fact in relation to the development of parthenotes (paragraph [44] of the Bundesgerichtshof's judgment dated 17 December 2009, emphasis added):

> As a further method for obtaining human embryonic stem cells, the defendant has also mentioned the so-called parthenogenesis, i.e. the division and further development of an unfertilised egg without fertilisation and without transplantation of an external nucleus. **Whether this method is truly viable and whether such a cell could effectively develop into a complete individual is not conclusively clarified by science**.

42. Thus, ISCC submits that the facts as found by the Bundesgerichtshof

contradict the proposition in paragraph [36] of the CJEU's Judgment. Accordingly insofar as the CJEU decided that parthenotes are to be regarded as embryos within the meaning of the Directive because they are capable of commencing the process of development which leads to a human being, the Court exceeded its jurisdiction.

Submissions of the Comptroller

43. The Comptroller agrees with ISCC that the key issue in the present case requires an understanding of [36] of the CJEU judgment and in particular, what was meant by "capable of commencing the process of development of a human being just as an embryo created by fertilisation of an ovum can do so". However the Comptroller submits that it may be that this test focuses only on the start of the process, and does not require completion of the process of development leading to the birth of a viable human being. It points out that there is support for this interpretation in the Judgment of the CJEU.

44. In particular, as shown in the passages emphasised above, the Court considered that the Biotech Directive intended to exclude any possibility of patentability where respect for human dignity could thereby be affected. Therefore, it concluded that the concept of 'human embryo' within the meaning of Article 6(2)(c) of the Directive must be understood in a wide sense.

45. Parts of the Judgment can be read as concerned specifically with the commencement of the process of fertilisation, rather than its completion. For example, paragraph 35 states that:

> "any human ovum must, **as soon as fertilised**, be regarded as a 'human embryo' within the meaning and for the purposes of the application of Article 6(2)(c) of the Directive, since that fertilisation is such as to commence the process of development of a human being." (emphasis added).

46. The Comptroller submits that this is an issue of great delicacy, on which different member states may have different views and that, given that the CJEU has clearly ruled that parthenotes are excluded from patentability as human embryos, it is not for this Court to attempt to rewrite the ruling to find in ISCC's favour at this stage.

47. The Comptroller agrees that there was no consensus in the Observations before the CJEU as to the developmental potential of parthenotes. However, it is submitted, correctly in my view, that several of the observations highlighted the similarity between the initial development of parthenotes and fertilised embryos (for example the observations from the UK, Sweden and Portugal), and contained broad statements of policy which appear to support the conclusion reached by the Court. Therefore, there was material before the Court which entitled it to reach the conclusion that it did, **if** it was concerned with the commencement of the process of fertilisation rather than its completion.

48. As to the referring Judgment, the Comptroller points out that the citation from [44] relied on by ISCC is incomplete. Once one takes into account the remainder of this paragraph, it is much more difficult to suggest that the conclusion of the CJEU expressly contradicted the findings of the Bundesgerichtshof. In particular, the German Court went on to say:

> "Independent of this one point in favour of qualification as an embryo as defined in Art. 6 para 2c) of the Directive could be the fact that such cells in any event in the first division stages go through the same development as a fertilized egg cell and therefore appear equally worthy of protection."

My understanding of this passage is that the Bundesgerichtshof was pointing to the similarity between initial stages of development of parthenotes and fertilised egg cells and hypothesising that it could be said that parthenotes were equally worthy of protection from patentability.

49. The Comptroller further submits, correctly in my view, that whilst the Advocate General was clear that the dividing line was whether the cells were totipotent or pluripotent, it does not appear that the CJEU followed this distinction. Unlike the Advocate General, the Court did not frame its decision in relation to parthenotes on a conditional basis, even though it clearly had in mind the distinction between pluripotent and totipotent cells (see paragraph [22] of the CJEU Judgment).

50. Therefore, the Comptroller submits that it is unclear whether the test that the CJEU had in mind turned on merely commencing the process of development of a human being (whether or not the potential exists for the completion of the process), or commencing a process which is capable of leading to the birth of a viable human being. For the reasons given by Mr Mitcheson on behalf of the Comptroller, I agree.

The need for a further reference

51. I also agree with the opinion of the Comptroller that there is insufficient clarity as to what the CJEU did mean in *Brüstle*, combined with a new factual matrix which may lead to a different outcome, to justify a further reference to the CJEU.

52. The factual background found by the Hearing Officer may be summarised as follows:

    (i) Like cells from a blastocyst, and in contrast to cells from a fertilised ovum, cells from a parthenote are at all times pluripotent only;
    (ii) A parthenote contains only maternal DNA and can never develop into a viable human being;
    (iii) As a result of genomic imprinting, certain genes which are essential for development to term are repressed in parthenotes,

while other genes which would normally be repressed may be abnormally expressed. (The proposed amended claims in the present case exclude the prospect of additional genetic manipulation to overcome this.)

53. This factual matrix is different to that before the CJEU in *Brüstle*. In particular, genomic imprinting means that in contrast to a fertilised ovum, there are no totipotent cells present in a parthenote, even in the first few cell divisions after activation. On the current state of knowledge in the art, despite the superficial similarities in initial development highlighted in the UK government's observations and the reference from the Bundesgerichtshof, parthenotes and fertilised ova are **not** identical at any stage.

54. On this basis there is sufficient doubt as to the precise meaning of the ruling in *Brüstle* and as to whether the CJEU would have come to the same conclusion it did on parthenotes with the current facts, to justify making a further reference.

My preliminary view

55. Since I have reached a view on the issue to be referred, it may be helpful if I express it. I agree with ISCC that if the process of development is incapable of leading to a human being, as the Hearing Officer has found to be the case in relation to parthenotes, then it should not be excluded from patentability as a 'human embryo'.

56. Like the Advocate General in *Brüstle,* I consider that totipotent cells should be excluded from patentability, whereas pluripotent cells should not. I note that totipotent cells are expressly referred to in recital 38 as an example of cells which are obviously excluded from patentability. This would seem surprising, if the intention of the legislation is to exclude pluripotent cells as well.

57. Stem cells have the potential to revolutionise the treatment of human disease. Because of their capacity to differentiate into almost any type of adult cell, human stem cells open the door to a wide variety of new therapies and other medical applications. For instance, cardiac muscle cells could be used to alleviate ischaemic heart disease, pancreatic islet cells for treatment of diabetes, liver cells for hepatitis and neural cells for degenerative brain diseases such as Parkinson's. Other potential applications include the treatment of burns, strokes, eye disease, spinal cord injuries and certain forms of cancer.

58. The recitals to the Biotech Directive show that a part of its purpose is encourage research in the field of biotechnology by means of the patent system. The balance between this objective and the need to respect the fundamental principles safeguarding the dignity and integrity of the person may properly be struck by excluding from patentability processes of development which are capable of leading to a human being. However, to exclude processes of development which are incapable of leading to a human being does not, in my view, strike a balance at all. This is particularly so in

the case of parthenotes, which are not the same as fertilised ova at any stage. It is more akin to a total exclusion from patent protection of the fruits of stem cell research, to the detriment of European industry and public health.

The question to be referred

59. The parties have suggested that the following question should be referred. In my judgment this succinctly identifies the issue. Subject to any further submissions, this is the question that I intend to refer:

> Are unfertilised human ova whose division and further development have been stimulated by parthenogenesis, and which, in contrast to fertilised ova, contain only pluripotent cells and are incapable of developing into human beings, included in the term "human embryos" in Article 6(2)(c) of Directive 98/44/EC on the legal protection of biotechnological inventions?

60. The parties should attempt to agree the terms of the Order for reference within the next 21 days. If there is any issue that cannot be agreed, it should be referred back to me.