INTELLECTUAL PROPERTY OFFICE

BL O/050/11

16 February 2011

**PATENTS ACT 1977**

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| APPLICANT | Cellartis AB |
| ISSUE | Whether patent application GB 0807891.7 complies with section 2, section 14(3) and paragraph 3(d) of Schedule A2 |
| HEARING OFFICER | C L Davies |

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**Introduction**

1. International patent application PCT/EP2006/009697 entitled "A method for obtaining a xeno-free HBS cell line" was filed on 6 October 2006 in the name of Cellartis AB and claimed priority from two earlier applications; PA 2005 01413 filed on 7 October 2005 and US 60/724,815 filed on 11 October 2005. The international application was published by WIPO as WO 2007/042225 on 19 April 2007, entered the UK national phase as GB 0807891.7 and was re-published as GB 2445338 on 02 July 2008.

2. During the course of substantive examination, the applicant has been unable to convince the examiner that the application is not directed to an unpatentable invention as defined in paragraph 3(d) of Schedule A2 of the Patents Act 1977, with the examiner maintaining throughout that the invention relates to a method involving the use of human embryos for industrial or commercial purposes. In the last examination report dated 10 September 2010 the examiner also raised objections of insufficiency, novelty and of inventive step.

3. In a letter dated 24 November 2010 the applicant requested a formal decision be made on all outstanding matters based on the papers on the file.

**The application**

4. The application relates to methods for obtaining a xeno-free human blastocyst-derived stem cell line (hBS). A stem cell is a cell type that can renew itself and give rise to specialized or differentiated cells. Most research has focussed on two types of stem cells, embryonic and somatic stem cells: embryonic stem cells being derived from the pre-implanted fertilized oocyte, *i.e.* the blastocyst, whilst somatic stem cells are present within the adult organism, *e.g.* in the bone marrow. The term "xeno-free" means never exposed to, directly or indirectly, material of non-human animal origin,

such as cells, tissues and/or body fluids during culture.

5. It is stated in the application that it has so far not been possible to derive and continuously culture hBS cell lines in a completely xeno-free system and in order to do so three hurdles have to be overcome. First a protocol for the derivation of new hBS cell lines under xeno-free conditions must be developed, whilst second and third, a xeno-free feeder culture system in combination with the use of a xeno-free medium is necessary.

**The claims**

6. The latest set of claims (53 in total), which were filed with the applicant's letter dated 06 July 2010, comprises three independent claims 1, 35 and 39.

7. Claim 1 relates to a method for propagating and maintaining isolated xeno-free hBS cells and reads:

> *"1. A method for propagating and maintaining isolated xeno-free human blastocyst-derived stem cells, (hBS cells) the method comprising the steps of:*
>
> *i) placing inner cell mass cells obtained by a xeno-free method in which the zona pellucida was removed and the trophectoderm was at least partly removed from a blastocyst on a layer of human feeder cells in a xeno-free medium,*
>
> *ii) co-culturing of the inner cell mass cells with human feeder cells for a time period of from about 5 days to about 50 days in a xeno-free medium,*
>
> *iii) releasing the inner cell mass cells or cells derived therefrom from trophectoderm overgrowth, if any, by a xeno-free procedure selected from*
>
> *a) using a mechanical procedure*
>
> *b) using glass capillaries as a cutting tool, or*
>
> *c) using one or more recombinant enzymes selected from the group consisting of recombinant trrypsin and TrypLE™ Select,*
>
> *iv) selectively transferring the inner cell mass cells or cells derived therefrom to a fresh layer of human feeder cells in a xeno-free medium to obtain xeno-free hBS cells,*
>
> *v) propagating the xeno-free hBS cells by co-culturing with human feeder cells in a xeno-free medium to obtain a xeno-free hBS cell line, wherein one or more passages are performed during the propagation of the xeno-free hBS cells and wherein the passage is performed by:*
>
> *a) using a mechanical procedure, or*
>
> *b) using one or more recombinant enzymes selected from the group*

*consisting of recombinant trypsin, TrypLE™Select, and recombinant collagenase."*

8. Claim 35 reads:

*"35. A method for propagating and maintaining xeno-free human blastocyst–derived inner cell mass cells wherein the cells are free from zona pellucida and at least partly free from trophectoderm, the method comprising the steps of:*

*1) placing the inner cell mass cells obtained by a xeno-free method in which the zona pellucida was removed and the trophectoderm was at least partly removed from a blastocyst on a layer of human foreskin fibroblast feeder cells in a xeno-free medium comprising DMEM, human serum, recombinant bFGF, L-glutamine or glutamax, non-essential amino acids, 0-mercaptoethanol, penicillin and streptomycin,*

*2) co-culturing of the inner cell mass cells with human foreskin fibroblast feeder cells in a xeno-free medium for a time period of from about 5 days to about 15 days changing at least 50% of the xeno-free medium every 3-5 days,*

*3) releasing the inner cell mass cells or cells derived thereof from trophectoderm overgrowth, if any, by using TrypLE™ Select (Invitrogen) as enzymatic treatment,*

*4) selectively, transferrring the inner cell mass cells or cells derived thereof to fresh layers of human foreskin fibroblast feeder cells in a xeno-free medium to obtain xeno-free hBS cells,*

*5) propagating the xeno-free hBS cells by co-culturing with human foreskin fibroblast feeder cells in a xeno-free medium to obtain a xeno-free hBS cell line."*

9. Claim 39 relates to an isolated hBS cell line:

*"39. A xeno-free hBS cell line SA611"*

10. There is also a product by process claim 38:

*"38. A xeno-free hBS cell line obtained by a method as defined in any of the preceding claims".*

**The Law**

11. Relevant major sections of the law which relate to this application are summarised below. Other sections are referenced as they arise.

12. Paragraph 3(d) of Schedule A2 to the Patents Act:

*3. The following are not patentable inventions-*

*(a)…;*
*(b)…;*
*(c)…;*
*(d) uses of human embryos for industrial or commercial purposes*
*(e)…;*
*(f)…*

13. Section 14 of the Act deals with sufficiency and the relevant part of section 14 reads as follows:

> *14(3) The specification of an application shall disclose the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art.*

14. The examiner has also raised an objection to the novelty and inventiveness and these are governed by sections 2 and 3 of the Patents Act 1977.

**Issues to be decided**

15. From what I have before me on the papers, I consider the issues to be decided are whether claims 1-53 relate to the use of human embryos for industrial or commercial purposes and therefore not patentable inventions by virtue of paragraph 3(d) of Schedule A2 to the Patents Act. In addition, if the claims are considered to relate to patentable inventions, I then need to decide whether they are sufficient and are novel and involve an inventive step.

16. **Claims 1-37**

**Patentability**

17. Claim 1, as it currently stands, relates to a method of propagating and maintaining human blastocyst derived stem cells (hBS). Following amendment of the claims published with the WIPO specification, this claim now no longer contains the following steps:

> *i) removing the zona pellucida from a blastocyst to obtain trophectoderm-enclosed inner cell mass by a xeno-free procedure,*
>
> *ii) at least partly removing the trophectoderm to obtain isolated inner cell mass cells by a xeno-free procedure,*

18. The applicant argued in his letter dated 08 April 2010 that amendment of the claims to remove the above two steps now means that the claims relate to a method of propagating and maintaining isolated xeno-free hBS inner cell mass (ICM) cells and that such a method does not involve the destruction of a blastocyst since ICM cells are not an embryo. Although it is true that the method of current claim 1 now begins with the step of "…placing the inner cell mass cells…on a layer of human feeder

cells…", there are no means detailed in the present application by which such ICM cells may be obtained other than by destruction of an embryo. The relevant ICM cells are not stated to be available from a deposit institution, neither are they decribed as being available commercially.

19. The applicant in his letter dated 06 July 2010 argues that at the filing date of the present application, xeno-free stem cell lines were already established and available to the public and he provides some marketing material used by Cellartis which states that cell line SA611 was established and offered to the public before the filing date, yet after the priority date, of the present invention. This I believe is intended to provide evidence that ICM cells, suitable for working the invention of present claim 1, were available. However, the description indicates that the SA611 cell line is the final result of the method of claim 1, *i.e.* hBS cells, and not ICM cells. For example, at page 8 of the description, the explanation of step iv) from the original claims, now step ii), refers to co-culturing of the ICM cells on a feeder layer and at lines 27-28 states that "During the propagation of the inner cell mass cells performed in step iv), some of these cells might begin their transformation into blastocyst-derived stem (BS) cells". And at page 9, in the description of step vi), now step iv): "After having released the inner cell mass cells or cells derived thereof from trophectoderm, if any, the inner cell mass cells or cells derived thereof are selected upon visual inspection in a microscope and transferred to a fresh layer of human feeder cells in a xeno-free medium to obtain xeno-free hBS cells.". Furthermore, example 1 describes "…placing the inner cell mass cells onto mitomycin-C inactivated xeno-free human foreskin fibroblast feeders…The blastocyst was then incubated…and after 10 days the cells were mechanically passaged to fresh hFF feeder cells. From passage 2 the hBS cells (cell line SA6111) have been passaged mechanically…".

20. I cannot see how the availability of SA611 cells at the filing date can make it possible to carry out the method of claim 1. The fact that xeno-free stem cells were established and available to the public does not help with the working of the method of claim 1. The resulting hBS cells may very well have been available but the means to make them, by the method of claim 1, was not. I am of the opinion that it was not possible to carry out the method of claim 1 without the need to resort to a new blastocyst as the source of cells, since no source of ICM cells is provided. The availability of xeno-free stem cells prior to the filing does not surmount the problem that there is no starting material, other than a blastocyst, available. The applicants assertion that it was possible to carry out the method of claim 1 without the need to resort to a new blastocyst is therefore not accepted. The SA611 cell-line does not represent ICM cells and therefore, with the lack of such a starting material, it would be necessary to follow the steps of the originally filed claims and destroy an embryo each time the invention is to be worked.

21. The applicant also asserts that claim 1 does not offend the decision G2/06 which specifies as a conclusion that "Rule 28(c) EPC…forbids the patenting of claims directed to products which – as described in the application – at the filing date could be prepared exclusively by a method whch necessarily involved the destruction of the human embryos from which the said products are derived…". This is also not accepted: since a source of ICM cells, such as a deposited cell-line, was not available to the public at either the priority date or the filing date, the method could not be worked without destruction of human embryos.

22. The patentability of claims 1-37 hinges on whether there is a means to carry out the methods without destruction of an embryo, that is, is there a starting ICM material available with which to commence working the method of claims 1 and 35. The applicants seem to be implying that the SA611 cell-line is such a material and that this cell-line represents an ICM material which may be placed on a layer of human feeder cells in a xeno-free medium in order that part (i) of claims 1 and 35 may be carried out. I do not think that this is the case. The SA611 cell-line is, from reading the present description, the result of the method of claims 1 and 35, *i.e.* it represents the hBS cells that are propagated and maintained, following culture of ICM cells in a particular manner, it is not itself an ICM cell-line.

23. It is my opinion therefore that it is not possible to work the invention of claims 1-37 without the destruction of a human embryo each time, since a source of ICM cells is not available. Claims 1 and 35 are considered to be unpatentable by virtue of paragraph 3(d) to Schedule A2 to the Patents Act as relating to uses of human embryos for industrial or commercial purposes. All claims dependent on these two claims are also unpatentable.

24. **Claims 39 and 40-45 (in part).**

25. Claim 39 relates to the xeno-free hBS cell line SA611. Both priority documents referred to in paragraph 1 teach how to make SA611 cells from the one embryo that was obtained from an IVF clinic. It should be noted that the SA611 designation relates only to the cell line that was derived from the embryo used in the examples of the present application. Although the description as filed teaches how to create a cell line from an embryo, no other cell line produced from any other starting embryo will be the SA611 cell line as claimed. So, in order to work the invention of claim 39 there would need to be either starting material available, *i.e.* the embryonic material from which SA611 was derived, or a deposit of SA611 cells.

**Patentability**

26. The examiner objected that claim 39 was not patentable under paragraph 3(d) of schedule A2 to the Patents Act. The reasons for the examiner's objection are based on his contention that at the priority date the invention defined by claim 39 could not be worked without the necessary destruction of a human embryo because the SA611 cell-line was neither available to the public nor deposited in a cell bank. However, it is my view that the only way to make SA611 cells is from the starting material obtained from the embryo used in the examples of the application; SA611 cannot be made from the destruction of another, different embryo because the cells would then not be SA611. If a suitable starting material was available then claim 39 could be worked but, since there are no other options available for making these cells, *i.e.* the destruction of another, different embryo, they cannot be considered non-patentable by virtue of paragraph 3(d) of schedule A2. In my view therefore, such a cell-line would be patentable if a starting, embryonic, material was available or the correct procedures had been followed to deposit these cells.

27. Since I have concluded that the SA611 cell-line is indeed patentable it remains to be decided whether the fact that the cells had not been deposited at the priority dates

has any bearing on the sufficiency of the priority documents and/or on the novelty or inventiveness of the SA611 cells themselves.

**Sufficiency**

28. Rule 13(1) of The Patents Rules 2007 is concerned with the deposit of biological material:

> *"13.-(1) The provisions of Schedule 1 prescribe the circumstances in which the specification of an application for a patent, or of a patent, for an invention which involves the use of or concerns biological material is to be treated as disclosing the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art."*

29. Schedule 1, which is to be read along with this rule, indicates at paragraphs 2 and 3 that:

> "*2.-(1) This paragraph applies where the specification of an application for a patent, or of a patent, for an invention which involves that use of or concerns biological material does not disclose the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art.*
>
> *(2) Where this paragraph applies, the specification is to be treated as disclosing the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art, if-*
>
> *(a) the first requirement and the second requirement are satisfied; and,*
> *(b) the specification of the application as filed contains such relevant information as is available to the applicant on the characteristics of the biological material.*

***The first and second requirements***

> *3.-(1) The first requirement is that-*
> *(a) on or before the date of filing of the application, the biological material has been deposited in a depositary institution; and*
> *(b) that institution will be able to furnish subsequently a sample of the biological material.*
>
> *(2) The second requirement is that before the end of the relevant period –*
> *(a) the name of the depositary institution and the accession number of the deposit are included in the specification;…"*

30. Section 5 of the Patents Act is concerned with priority dates and section 5(2) states that

> *"If in or in connection with an application for a patent (the application in suit) a declaration is made, whether by the applicant or any predecessor in title of his, complying with the relevant requirements of rules and specifying one or*

*more earlier relevant applications for the purposes of this section made by the applicant or a predecessor in title of his and the application in suit has a date of filing during the period allowed under subsection (2A)(a) or (b) below, then-*

*(a) if an invention to which the application in suit relates is supported by the matter disclosed in the earlier relevant application or applications, the priority date of that invention shall instead of being the date of filing the application in suit be the date of filing the relevant application in which that matter was disclosed or, if it was disclosed in more than one relevant application, the earliest of them;*

*(b) the priority date of any matter contained in the application in suit which was also disclosed in the earlier relevant application or applications shall be the date of filing the relevant application in which that matter was disclosed or, if it was disclosed in more than one relevant application, the earliest of them."*

31. The test for deciding whether an invention is supported and sufficiently described by matter disclosed in an earlier application is basically the same as that for deciding whether a claim of a specification is supported and sufficiently described by the description, as detailed in Section 14(3) of the Act. Neither the first nor the second requirements of Rule 13, as set out in Schedule 1, were fulfilled at the date of the priority filings and it is my view therefore that the invention of current claim 39 is not sufficiently described by matter disclosed in either of the priority documents, since a deposit of SA611 had not taken place. Anyone wishing to work the invention at the priority date could not have done so since the description was insufficient inasmuch as the lack of deposit of SA611 would have made it unachievable. That being the case, I find that that the present application, with respect to the invention of claim 39, is not entitled to a priority date of either 07 October 2005 or 11 October 2005.

**Novelty and Inventive step**

32. Now that I have decided that claim 39 is not entitled to either of the earlier priority dates I can consider the novelty and inventiveness of this claim having regard to the filing date of 06 October 2006 only. The document "Stem Cells, Vol.24, 2006, Ellerström, C. *et al*., "Derivation of a xeno-free human embryonic stem cell line", pp.2170-2176 ("Ellerström"), cited on the International Search Report, was published on 01 June 2006 and describes the production of the SA611 cell-line *via* the xeno-free method described in the present application. Hence I find that claim 39 is anticipated by this document. I also find claims 40-45 are anticipated by this document when appendant to claim 39.

33. The applicant has argued in his letter of 08 April 2010 that cells of the SA611 cell-line "…were cultured for more than 11 passages at the priority date", as is described in Example 1 of the present description, and that for this reason "…this cell line was publicly available at the priority date". I do not agree with this conclusion. Merely stating that a cell-line has been passaged 11 times at the priority date does not, in my view, make the cell-line available.

34. In his letter of 06 July 2010 the applicant also stressed that the cell-line SA611 was

available prior to the ***filing*** (emphasis mine) date of the present application and that the intervening acts carried out in Ellerström between the priority date and the filing date do not invalidate the present application as specified in section 6.

35. Section 6 of the Act reads:

> "*Section 6(1)*
>
> *It is hereby declared that for the avoidance of doubt that where an application (the application in suit) is made for a patent and a declaration is made in accordance with section 5(2) above in or in connection with that application specifying an earlier relevant application, the application in suit and any patent granted in pursuance of it shall not be invalidated by reason only of relevant intervening acts.*
>
> *Section 6(2)*
>
> *In this section –*
>
> *"relevant application" has the same meaning as in section 5 above; and*
>
> *"relevant intervening acts" means acts done in relation to matter disclosed in an earlier relevant application between the dates of the earlier relevant application and the application in suit, as for example, filing another application for the invention for which the earlier relevant application was made, making information available to the public about that invention or that matter or working that invention, but disregarding any application, or the disclosure to the public of matter contained in any application, which is itself to be disregarded for the purposes of section 5(3) above.*"

36. This section confirms that if an invention in an application in suit is entitled for priority to the filing date of an earlier application then any disclosure or use of matter contained in that earlier application on or after the filing date of the earlier application cannot invalidate a claim. An invention which is not entitled to the priority date of an earlier application can be invalidated by the disclosure or use, between the filing dates of the earlier application and the application in suit, of matter contained in the earlier application.

37. As I have found that the invention of claim 39 is not entitled to the priority dates of 07 October 2005 or 11 October 2005, the points raised by the applicant in regard to "intervening acts" are not considered relevant since there is no intervening period in which to consider such acts. The invention of claim 39 is not entitled to either priority date so it is invalidated by the disclosure in Ellerström. I would agree that if the claim to priority were upheld then any intervening act relating to disclosure of SA611 may not prevent grant of the present claim, but since the invention of claim 39 is not entitled to either of the priority dates it is anticipated by Ellerström.

38. In summary, claim 39, although found to be patentable, is insufficiently supported in the priority documents and is therefore not entitled to either of the priority dates of 07 October 2005 or 11 October 2005. This claim, and also claims 40-45 (when

appended to claim 39) is thereby anticipated by Stem Cells, Vol.24, 2006, Ellerström, C. et al., "Derivation of a xeno-free human embryonic stem cell line", pp.2170-2176.

39. **Claims 38, 40-45 (in part) and 46-53**

40. Claim 38 is a product-by-process claim and is interpreted as a claim to the product *per se* and is therefore considered to relate to any xeno-free hBS cell-line made by any process. A product-by-process claim is not allowed if another means of defining the product is available. As can be determined from the present description, the cells obtained by the process provided by the Examples result in an hBS cell with the following characteristics: positive reactions for alkaline phosphatase (ALP), Oct-4, Tra1-60, Tra1-81, SSEA-3 and SSEA-4 and a diploid nomal karyotype. The application at pages 22-23 indicates that xeno-free hBS cells derived in accordance with the present invention may be tested for sialic acid Neu5Gc (a membrane bound sugar molecule), a negative test indicating that no direct or indirect exposure to non-human animal material has occurred. However, there is no indication that this test was indeed carried out on the cells obtained by the method of the present application, although it may be considered unlikely that such a test would be positive given the conditions under which the cells were derived and cultured.

41. For ease in dealing with the issues arising in relation to claims 38, 40-45 (in part) and 46-53 I shall consider sufficiency/support and novelty aspects first and the patentability aspects afterwards.

**Sufficiency/Support**

42. The examiner objected to claim 38 as insufficient under section 14(3), arguing that since such product-by-process claims are construed as relating to any xeno-free hBS cell, irrespective of how they are made, the full breadth of claim 38 is not enabled. I do not agree with this reasoning. Although it is true that such product-by-process claims are considered to relate to any xeno-free hBS cell, an example of such a cell is provided in the application as filed, as is a means to make it, and hence the application is sufficient in this regard. However, there is only support for the one specific cell line having certain characteristics (given in example 6) and since these characteristics can be used to describe the hBS cells it is not necessary to characterise them by their method of production. I therefore do not agree with the examiner that claim 38 is insufficient; a xeno-free cell-line produced by the methods of the invention is provided, however there is only support for cells made by the exemplified method and with the particular characteristics as detailed above.

**Novelty**

43. The examiner has further attacked the novelty of this claim based on his objection that it is insufficient and is not entitled to the priority date. I do not agree with this conclusion and am of the opinion that since there is support for an hBS cell-line in the priority document, then the present application is entitled to its priority date with respect to the invention of claim 38. However, I do agree with the examiner that this claim is anticipated by document WO2006/029198 ('198), cited on the International Search Report and by the examiner in his last report. This document is section 2(3) art with a publication date of 16 March 2006 and priority dates of 08 September 2004

and 29 June 2005 and has entered the regional phase as EP1797172. '198 describes the xeno-free derivation and culture of human ES cells from blastocysts that "…express a series of markers characteristic of human ES cells" and "…are entirely free of Neu5Gc". Although the cells disclosed in this document are not made by the same method of the present invention, they may be considered a "…xeno free hBS cell-line" and hence anticipate claim 38.

44. Present claims 46-53 relate to general uses of stem cells and are also considered to be anticipated by '198 given paragraph [0003] at page 1 which states that *"The existence in culture of human embryonic stem cells offers the potential of unlimited amounts of human cells and tissues for use in a variety of therapeutic protocols and research programs to assist in human health. It is envisioned in the future human embryonic stem cells will be proliferated and directed to differentiate into specific lineages so as to develop differentiated cells or tissues which can be transplanted into human bodies for therapeutic purposes"*. Such generalised description of well known uses of embryonic stem cells is considered enough to anticipate claims 46-53.

45. The applicant states in the letter dated 08 April 2010 that the test for sialic acid Neu5Gc may be used to distinguish the cells of the present invention from the cells of '198. If the characterising feature of the cells of the present application is determined to be lack of sialic acid Neu5Gc then the cells of '198 anticipate the cells of claim 38. Although the other stem cell markers described in the present application are not specifically mentioned in '198 these are common markers of embryonic stem cells and their omission from the description of '198 does not mean that they are not present. The given characteristics of the cells of '198 indicate that they are embryonic stem cells, having common stem cell markers, without sialic acid Neu5Gc and grown in xeno-free conditions: the same features as the hBS cell-line of claim 38.

46. A further issue that needs to be considered is whether the embryonic stem cells disclosed in '198 are truly xeno-free. In the letter of 08 April 2010, the applicant has asserted that none of the cited art discloses a truly xeno-free hBS cell-line. '198 does state that the cells produced are sialic acid free and this would indicate that they have not seen non-human animal products at any point in their production. In addition, various passages of '198 indicate that the embryonic stem cells produced by the method therein are fully xeno-free and have been xeno-free from the point of derivation. For example at page 7, paragraph [00026]:

> *"Also described below is the derivation of new lines of human embryonic stem cells using this medium. These lines of human ES cells have thus never been exposed to feeder cells, conditioned medium, animal products or animal proteins. It has previously been reported that prior human ES cell lines exhibit a sialic acid form (Neu5Gc) that is not natively found in human cells whether in cultue or in the body. Since the prior human ES lines acquired the Neu5Gc from culture conditions including murine components, the new human ES cell lines described here will be and are entirely free of Neu5Gc."*

47. At page 9,paragraph [0039]:

*"…embryos were thawed and cultured to the blastocyst stage using a commercially available sequential embryo culture system (Vitrolife-GIII series). After removal of the zona pellucida, the inner cell mass (ICM) of the human blastocysts were isolated either by immunosurgery (Solter and Knowles, 1975, Proc. Natl. Acad. Sci. USA, 72, 5099-5102) or as cultured whole mounts (Evans and Kaufman, 1981, Nature, 292154-292156) and plated in 4-well culture plates onto the defined medium TeSR1 with the defined humanized matrix as defined above".*

48. Note that "Vitro-life GIII" is a media for use in human assisted reproduction and that example 1 of the present application decribes culture of blastocysts in "…media traditionally used in IVF treatment." Furthermore, at page 10, paragraph [00040] it is stated that:

> *"Using TeSR1 medium on the four human matrix components identified above, we have derived two new human ES cell lines from 5 cultured blastocysts. As of this writing, both human ES cell lines have now been continuously in culture for 6 months through successsive passaging. The lines are stable and morphologically similar to previous stem cell lines. FACS analysis and RT-PCR, and Western blotting demonstrated that these cells express a series of markers characteristic of human ES cells".*

49. These paragraphs are sufficient to convince me that the embryonic stem cells disclosed in '198 are truly xeno-free and have been derived under conditions that did not involve any non-human animal products at any point in their production. It seems to me that it would be a pointless exercise to produce cells under only partial xeno-free conditions; if xeno-free cells are required then such conditions would necessarily need to be followed at all stages of their production.

**Patentability**

50. It may be argued that the cells of the present application are necessarily different to those in '198 since their method of production is different. This has also been asserted by the applicant in the letter of 08 April 2010: "…none of the cited prior art discloses a cell line obtained by a method of propagating and maintaining isolated xeno-free human blastocyst-derived inner cell mass cells in accordance with the present invention". I cannot reject a product-by-process claim entirely if the cells are indeed novel and inventive over those disclosed in '198: such claims may be allowable in the absence of any other way to distinguish the cells from similar cells in the prior art. However, allowing characterization of the hBS cells by a process of their production brings us back to a claim that would require an unallowable method to be used each time it is carried out and which would necessitate the destruction of an embryo each time such a product-by-process claim is worked. This cannot be allowable by virtue of paragraph 3(d) of Schedule A2 and so we end up with a combination of the issues discussed above in relation to independent claims 1 and 39: no embryonic or ICM starting material is available and no xeno-free hBS cells have been deposited, so claim 38 cannot be worked other than by an unpatentable method involving destruction of an embryo.

51. In summary, I do not consider claim 38 to be fully supported: only a cell-line defined

by the markers provided, or made by the method of claim 1, has full support. This claim, together with claims 40-45 (when appended to claim 38) and 46-53 is therefore anticipated by WO 2006/029198 which provides a sialic acid Neu5Gc negative embryonic stem cell-line having markers characteristic of human embryonic stem cells. If the hBS cells of claim 38 were allowed to be characterized by the method of their production this claim would fall as unpatentable in a similar way to claim 1.

**Inventive Step**

52. Since I have found that the claims are not patentable under section 2 and paragraph 3(d) of Schedule A2, there is no need for me to consider inventive step.

**Conclusion**

53. Taking into full consideration the applicant and examiner's arguments, the specification and the priority documents, I conclude that (a) claims 1-37 are not patentable by virtue of paragraph 3(d) of Schedule A2; (b) Claim 39 is insufficient and, together with claims 40-45 (when appended to claim 39), is not novel; (c) Claim 38 is not fully supported and, together with claims 40-45 (when appended to claim 38), and 46-53 is not novel. I therefore refuse the application under 18(3) for failing to comply with paragraph 3(d) of Schedule A2, section 14(3) and section 2 of the Patents Act 1977.

**Appeal**

54. Under the Practice Direction to Part 52 of the Civil Procedure Rules, any appeal must be lodged within 28 days.

**C L Davies**
Deputy Director acting for the Comptroller