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Datasheet for the decision of 17 April 2015

Case Number: T 0427/10 - 3.3.08

Application Number: 99921681.5

Publication Number: 1078095

IPC: C12N15/86

Language of the proceedings: EN

Title of invention:
Viral production process

Patent Proprietor:
CANJI, Inc.

Opponent:
GlaxoSmithKline Biologicals SA

Headword:
Microcarrier culture/CANJI

Relevant legal provisions:
EPC Art. 56, 83, 84, 123(2), 123(3)
RPBA Art. 12(4)

Keyword:
"Auxiliary request II - sufficiency of disclosure - (yes)
Inventive step - (yes)"

Decisions cited:
G 0009/92, G 0004/93, G 0003/14, T 0402/01, T 0908/07

Catchword:

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Chambres de recours

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Case Number: T 0427/10 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 17 April 2015

Appellant: (Opponent)	GlaxoSmithKline Biologicals SA Rue de l'Institut 89 1330 Rixensart (BE)
Representative:	Johnston, Caroline GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Respondent: (Patent Proprietor)	CANJI, Inc. 3525 John Hopkins Court San Diego, CA 92121 (US)
Representative:	von Menges, Albrecht Uexküll & Stolberg Patentanwälte Beselerstrasse 4 22607 Hamburg (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 21 December 2009 concerning maintenance of the European Patent No. 1078095 in amended form.**

Composition of the Board:

Chairman	M. Wieser
Members:	M. R. Vega Laso
	J. Geschwind

Summary of Facts and Submissions

I. European patent No. 1 078 095 with the title "Viral production process" was granted on European patent application No. 99921681.5, which had been filed as international application under the PCT and published as WO 99/57297 (in the following "the application as filed").

II. The patent, which had been granted with 16 claims, was opposed on the grounds for opposition under Article 100(a), (b) and (c) EPC, in particular that the subject-matter of the patent lacked novelty (Article 54 EPC) and inventive step (Article 56 EPC), and extended beyond the content of the application as filed, and that the invention was not disclosed in the patent in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

III. In an interlocutory decision under Article 101(3)(a) and 106(2) EPC posted on 21 December 2009, an opposition division of the European Patent Office found that, taking into account the amendments introduced by the patent proprietor into the set of claims according to auxiliary request II and pages 2, 3, 5, 6, 10 and 12 of the patent specification, all filed during the oral proceedings, the patent and the invention to which it related met the requirements of the EPC.

IV. Claim 1 of auxiliary request II reads as follows:

"1. A method of achieving a cell density greater than $5x10^6$ producer cells/ml in a cross-linked dextran microcarrier based bioreactor process for the production of a virus in a producer cell, said method comprising the steps of:

a) preparing a culture of producer cells attached to cross-linked dextran microcarriers wherein the ratio of producer cells to microcarriers is 10 cells/ microcarrier,
b) seeding the bioreactor with a quantity of the producer cell-coated microcarriers prepared in step (a) to a density greater than approximately 6 grams (based on the dry weight of the microcarrier) of producer cell-coated microcarriers per liter of bioreactor media volume; and
c) culturing the producer cells in the bioreactor under perfusion conditions in serum containing media to a density of greater than 100 cells/microcarrier, wherein

the virus produced by the method is selected from baculoviridiae, parvoviridiae, picornaviridiae, herpesviridiae, poxviridae, or adenoviridiae."

Dependent claims 2 to 8 are directed to variants of the method according to claim 1, and claims 9 to 16 to a method of producing a population of producer cells containing a high titer of viral particles.

V. In the interlocutory decision, the opposition division found that the amendments introduced into the claims of auxiliary request II did not offend against Article 123(2)(3) EPC. As regards Article 83 EPC, the opposition division held that, since in document (32) a ratio of 3.3 cells/microcarrier was used, the method described therein did not fall under the scope of the claims of the patent as amended. Thus, the content of document (32) could not support the objection that the claimed invention cannot be put into practice. Moreover, the opposition division took the view that the fact that the application lacked an example showing

the "workability" of the claimed method did not necessarily mean that the invention as claimed was insufficiently disclosed (see section 2.3.2 of the decision under appeal).

For the assessment of inventive step (Article 56 EPC), the opposition division considered document (32) to be the closest state of the art. The objective technical problem to be solved was formulated as the provision of an improved cell culture method for virus production. In the view of the opposition division, it was credible (and not proven to the contrary) "*... that viruses can be produced by the method of the invention and further that the required cell density can be reached ...*". Confronted with the problem of providing an improved cell culture method for virus production, a person skilled in the art was not prompted by any of the prior art documents to which the opponent referred, in particular by documents (11) and (17), or by the common general knowledge at the relevant date, to modify the method of document (32) as proposed by the invention as claimed in the patent. Thus, the subject-matter of the amended claims involved an inventive step within the meaning of Article 56 EPC (see section 2.3.3 of the decision under appeal).

VI. Both the patent proprietor and the opponent lodged an appeal against the interlocutory decision of the opposition division. Together with its statement of grounds of appeal, the appellant (opponent) submitted document (35) (see paragraph IX below) as new evidence.

VII. The board summoned the parties to oral proceedings requested by both parties as a subsidiary request. In a communication under Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) attached to

the summons, the board expressed a provisional opinion on some procedural and substantive issues to be discussed at the oral proceedings.

VIII. During the oral proceedings held on 17 April 2015, the patent proprietor (respondent) withdrew its appeal.

IX. The following documents are referred to in the present decision:

(8): M. Reiter et al., 1990, Cytotechnology, Vol. 3, pages 39 to 42;

(11): Microcarrier cell culture, principles & methods, Pharmacia Biotech, December 1981;

(16): S. Goetghebeur and W.-S. Hu, 1991, Appl. Microbiol. Biotechnol., Vol. 34, pages 735 to 741;

(17): R. Z. Mendoça and C. A. Pereira, 1995, Bioprocess Engineering, Vol. 12, pages 279 to 282;

(32): B. H. Junker et al., 1992, Cytotechnology, Vol. 9, pages 173 to 187;

(35): L. Fabry et al., 1989, Advances in Animal Cell Biology and Technology for Bioprocesses, ed. by R. E. Spier et al, pages 361 to 365.

X. The submissions made by the appellant concerning issues relevant to this decision, were essentially as follows:

Admission of new evidence into the proceedings

Document (35) had been filed together with the statement of grounds of appeal in response to

amendments to the claims. The document had not been identified in either the initial search for relevant art, or a subsequent search carried out in preparation for oral proceedings before the opposition division, because the breadth of the claims as granted had made a meaningful search difficult. It was only when the claims were amended that search terms including examples of the named viruses and the defined seed density had been used. Since the respondent had had almost five years to comment on document (35), the board should exercise its discretion by admitting the document, as it had been done in decisions such as T 402/01 of 21 February 2005 and T 908/07 of 16 May 2008.

Article 83 EPC

The opposition division's finding that the invention as claimed was sufficiently disclosed in the application as filed was incorrect. The sole difference between the method described in document (32) and the method according to claim 1 was that in the latter an initial ratio of 10 cells/microcarrier - instead of 3.3 cells/microcarrier as in document (32) - was used. In the examples of the patent, however, an initial ratio of 3 cells/microcarrier was used and yet final densities of 8-10x10^6 cells/ml were still achieved. It was thus clear that there were technical features missing from claim 1 which enabled this result to be achieved.

A possible explanation for the difference between the final cell density reported in document (32) and that in the examples of the patent was that a different type of producer cell was used. It was shown in document (16) that the 293 cells used in the examples of the patent in suit could reach a maximum cell

density of $1.3x10^7$ cells/ml, while CHO and Vero cells under the same culture conditions reached a maximum cell density of only 2.7 and $2.0x10^6$ cells/ml, respectively.

Article 56 EPC

Document (8) was regarded as the closest state of the art. This document described a method with all the features of claim 1, except that the seeding density was 20 cells/microcarrier. Starting from document (8), the problem to be solved was to provide an alternative method of achieving a cell density greater than $5x10^6$ producer cells/ml. There was no technical effect or advantage associated with a seeding density of 10 cells/microcarrier. Any seeding density between 3 and 20 cells/microcarrier would work. In view of document (11), a person skilled in the art would have been motivated to reduce the seeding density, and 10 cells/microcarrier would be one of the densities mentioned in that document. Thus, an inventive step should be denied.

XI. The respondent's submissions on the relevant issues were essentially as follows:

Admission of new evidence into the proceedings

Document (35) should not be admitted into the appeal proceedings because the evidence provided by the document was not *prima facie* highly relevant, and in any case not more relevant that evidence already on file.

Article 83 EPC

Document (32) had been relied upon by the appellant in opposition proceedings to support its objections of lack of novelty and lack of sufficient disclosure. The arguments of the appellant were contradictory. The results in document (32) could not be extrapolated to the present invention.

Article 56 EPC

The solution proposed in the claims involved an inventive step. The skilled person would not have considered reducing the seeding density described in document (8), but if he/she had, there was no expectation of achieving the same final cell densities as obtained by the method of document (8).

XII. The appellant (opponent) requested that the decision under appeal be set aside and the patent be revoked.

XIII. The respondent (patent proprietor) requested that the appeal be dismissed.

Reasons for the Decision

Admission of new evidence into the proceedings (Article 12(4) EPC)

1. Document (35) was submitted together with the appellant's statement of grounds of appeal to support a new line of argument on inventive step. In a later submission, this document was cited by the appellant also in the context of the assessment of novelty.

2. The arguments put forward by the appellant fail to persuade the board that document (35) could not have been filed in opposition proceedings (see Article 12(4) RPBA). As regards the appellant's argument that a meaningful search for relevant prior art was only possible when the claims were amended to specify particular types of viruses and a defined seed density, the board observes that the feature "*... the virus produced by the method is selected from baculoviridiae, parvoviridiae, picornaviridiae, herpesviridiae, poxviridae, or adenoviridiae*" was already included in claim 1 of the auxiliary request filed by the proprietor on 27 August 2007 in reply to the notice of opposition. Moreover, while it is true that the amendment to replace "*approximately 10 cells/ microcarrier*" (as in claim 1 of the patent as granted) by "*10 cells/microcarrier*" (as in auxiliary request II) was introduced for the first time during the oral proceedings before the opposition division, such an amendment was foreseeable, especially in view of the interpretation of this feature on which the opponent relied in its notice of opposition to support the objection of lack of novelty.

3. Contrary to the appellant's view, the board is not persuaded that the content of document (35) is more relevant than that of other documents already on file, for instance, document (8), which also describes a method that differs from the claimed method in the seeding density used (20 cells/microcarrier).

4. At the oral proceedings before the board, the appellant argued that document (35) is highly relevant because in the method described therein a seeding density of 10 cells/microcarrier is used. This argument is in contradiction with the appellant's own statements in

section 7.3.4 of its statement of grounds of appeal where the seeding density used in the method of document (35) was said to be 21 cells/microcarrier (in the experiment of Figure I) and 19 cells/microcarrier (in Figure II). Moreover, it was stated by the appellant that the "*... only feature missing* [in the method of document (35)] *is that the microcarriers were not seeded at exactly 10 cells/microcarrier*" (see last paragraph on page 12 of appellant's statement of grounds of appeal).

5. For these reasons, the board exercises its discretion by not admitting document (35) into the appeal proceedings.

Principle of reformatio in peius

6. Since the sole appellant against the interlocutory decision of the opposition division is now the opponent, the respondent (patent proprietor) is restricted to defending the patent as amended according to auxiliary request II (see decisions G 9/92 and G 4/93 of the Enlarged Board of Appeal published in OJ EPO 1994, 875).

Articles 123(2)(3) and 84 EPC

7. At the oral proceedings, the appellant, upon request, stated that it had no objections under Articles 123(2) and 84 EPC. The board is satisfied that the subject-matter of the amended claims according to the auxiliary request II does not extend beyond the content of either the application as filed or the patent as granted (see Article 123(2) (3) EPC), and that the amendments to the claims do not introduce non-compliance with Article 84 EPC (see decision of the Enlarged Board of

Appeal G 3/14 of 24 March 2015, to be published in the Official Journal).

Article 83 EPC

8. In its written submissions in appeal proceedings, the appellant did not actually dispute that the claimed invention can be carried out, but rather contended that technical features required for achieving the final cell density specified in claim 1 were missing from the claim. The board cannot accept this argument.

9. Article 83 EPC requires that the claimed invention is described **in the patent application** in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. A requirement that the claims must include all technical details required for carrying out an invention cannot be derived from Article 83 EPC. In the board's view, it is not the purpose of the claims to provide a complete technical guidance how to put the invention into practice, but to define the matter for which protection is sought (see Article 84 EPC).

10. In a further line of argument, the appellant relied on document (16) to support its allegation that the final cell density specified in claim 1 could be achieved for the 293 cell line used in the examples of the patent, but not for other cell lines. However, document (16) cannot serve as conclusive evidence that the method disclosed in the application as filed cannot be reproduced using cell lines other the 293 cell line, specifically CHO or Vero cells, because the experimental conditions described in document (16) are not the same as those required in claim 1. For instance, in the experiments described in document (16)

the cells were cultured in spinner flasks (see page 736, first sentence of the third paragraph from the bottom), rather than in a bioreactor under perfusion conditions, as required in claim 1. Alone for this reason, results obtained applying the method described in document (16) cannot be extrapolated to the method according to the invention.

11. At the oral proceedings before the board, the appellant argued that in the experiments described in document (32) different seeding densities were used, but nevertheless a plateau in the growth curve at a cell density lower than $5x10^6$ cells/ml was always observed. In the appellant's view, the results in document (32) strongly suggested that if a seeding density of 10 cells/microcarrier were used, the same plateau would be reached.

12. In the board's view, this argument is not based on a solid factual basis. It should be noted that Figure 2 in document (32) relates to a cell culture in a batch-refed bioreactor, and that only Figure 5 illustrates the results of **two** experiments under perfusion conditions as required in claim 1. The observation that in these two experiments the growth curve reaches a plateau at a similar cell density - even though different seeding densities were used - does not allow to conclude that the same plateau would be reached using whatever seeding density, and in particular a seeding density of 10 cells/microcarrier as specified in claim 1.

13. Summarizing the above, the board concludes that the arguments and evidence brought forward by the appellant cannot support its objection of lack of sufficient disclosure in the application as filed.

Article 54 EPC

14. In appeal proceedings the appellant did not raise an objection of lack of novelty with respect to the subject-matter of the claims according to auxiliary request II. In view of the content of the documents on file, the board regards the requirement of Article 54 EPC as fulfilled.

Article 56 EPC

15. At the oral proceedings before the board, the appellant did not contest the adverse findings in the decision under appeal in respect of its objection of lack of inventive step based on document (32) as the closest state of the art (see section V above), but brought forward a line of argument on Article 56 EPC starting from document (8) as the most relevant state of the art (see section X above).

16. Document (8) describes a device useful for aeration and cell retention in continuous perfused microcarrier cultures, and a method using this device for culturing producer cells. In the experiments illustrated in Figure 4 of document (8), Vero cells were cultivated on cross-linked dextran microcarriers (Cytodex® 3) under perfusion conditions in serum containing media. It is undisputed that Vero cells are producer cells suitable for the production of viruses (see document (17)). When the bioreactor was seeded with microcarriers at a density of 10 or 15 g/l, a final density of greater than $5x10^6$ producer cells/ml and 100 cells/microcarrier was achieved.

17. It is common ground between the parties that the sole difference between the method of the invention and the method described in document (8) is that in the latter the microcarriers are seeded with cells at a density of 20 cells/microcarrier, instead of 10 cells/microcarrier as proposed by the invention as claimed. Hence, compared to the method described in document (8), the method of the invention requires a substantially lower amount of cells for seeding the same amount of microcarriers, but still achieves equivalent final cell densities of producer cells. In the board's view, this must be regarded as a technical effect and a clear advantage of the claimed method.

18. Thus, starting from document (8), the problem to be solved is to provide an improved method of cultivating producer cells for the production of a virus. In the absence of any evidence on file to the contrary, the board has no reason to doubt that this problem is in fact solved by the method according to the present claims.

19. The final question is whether or not it was obvious to a person skilled in the art to lower the seeding density from 20 to 10 cells/microcarrier. In this respect, the appellant pointed to document (11), in which principles and methods for microcarrier cell culture are described. However, the board is unable to see in this document any clear hint which may lead the skilled person towards the solution provided by the claimed method. The passage on page 49 of document (11) under the heading "3.4.4. Inoculation density" on which the appellant relied, contains general statements about the importance of using a suitable inoculation density for the survival and growth of the cells in microcarrier cultures, in particular Cytodex®

microcarriers. In the passage bridging pages 49 and 50, reference is made to Figure 28 and various seeding densities for particular cell types are mentioned, *inter alia*, a cell density of 10 human fibroblasts/ microcarrier. A further passage on page 53 pertaining to Table 8, to which the appellant pointed, contains general statements on the relationship between plating efficiency of a cell and parameters critical during the initial phase of a microcarrier culture, *inter alia*, the number of cells per microcarrier at inoculation.

20. However, there is no mention of Vero cells in any of these passages, let alone a clear statement suggesting to the skilled person that the final cell densities of Vero cells as described in document (8) could also be achieved using a much lower seeding density of 10 cells/microcarrier. Even if the skilled person could have considered seeding at a density of 10 cells/ microcarrier, in view of the statements in the passage of document (11) ("*Inoculation density effects both the proportion of microcarriers bearing cells at the plateau stage of culture (fig. 28) and the yield from the culture (fig. 26)*"), he/she would not have expected that a final cell density as described in document (8) can be achieved.

21. For these reasons, the board holds that it was not obvious to a person skilled in the art seeking to improve the method described in document (8) to reduce the seeding density to 10 cells/microcarrier. Hence, the invention as claimed involves an inventive step.

Conclusion

22. In view of the findings above, the appellant's request to set aside the decision under appeal and revoke the patent must fail.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated