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Datasheet for the decision of 20 September 2011

Case Number: T 1205/07 - 3.3.08

Application Number: 96917735.1

Publication Number: 0833934

IPC: C12N 15/861

Language of the proceedings: EN

Title of invention:
Packaging systems for human recombinant adenovirus to be used in gene therapy

Patentee:
Crucell Holland B.V.

Opponents:
Laboratoires Serono S.A.
CEVEC Pharmaceuticals GmbH

Headword:
Adenoviral packaging system/CRUCELL

Relevant legal provisions:
EPC Art. 56, 83, 123(2)

Keyword:
"Main request - added matter (yes)"
"Auxiliary request 1 - sufficiency of disclosure (yes)"
"Inventive step (no)"

Decisions cited:
G 0009/92, G 0004/93, T 0838/97, T 1262/04

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1205/07 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 20 September 2011

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 11 May 2007 concerning maintenance of European patent No. 0833934 in amended form.**

Composition of the Board:

Chairman: M. Wieser
Members: M. R. Vega Laso
R. Moufang

Summary of Facts and Submissions

I. European patent No. 0 833 934 with the title "Packaging systems for human recombinant adenovirus to be used in gene therapy" was granted on European patent application No. 96 917 735. The application had been filed as International application PCT/NL96/00244 under the Patent Cooperation Treaty, and was published as WO 97/00326 (hereinafter "the application as filed"). The patent was granted with 38 claims.

II. Two oppositions were filed against the grant of the patent. The oppositions were based on the grounds for opposition mentioned in Article 100(a), (b) and (c) EPC 1973, in particular that the claimed subject-matter lacked either novelty (Article 54 EPC 1973) or an inventive step (Article 56 EPC 1973), and also extended beyond the content of the application as filed, and that the invention as claimed 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 Articles 102(3) and 106(3) EPC 1973 posted on 11 May 2007, the opposition division found that the amendments introduced into claims 1 and 24 of the main request then on file offended against Article 123(2) EPC. Moreover, the invention claimed according to the first auxiliary request was regarded as not being sufficiently disclosed in the application as filed, contrary to Article 83 EPC. However, the second auxiliary request filed during the oral proceedings was found to meet the requirements of the EPC. Accordingly,

the opposition division decided that the patent could be maintained on the basis of claims 1 to 19 of the second auxiliary request and a description adapted thereto which was filed also at the oral proceedings.

IV. The patent proprietor and opponent 01 each lodged an appeal against the interlocutory decision of the opposition division.

V. In its statement of grounds of appeal, the patent proprietor (the present appellant) submitted arguments against the adverse findings in the decision under appeal. While it pursued the sets of claims underlying the decision under appeal further, additional amendments in different combinations were proposed. The appellant also requested that oral proceedings be held prior to any adverse decision.

VI. Opponent 01 (the present respondent I) submitted together with its statement of grounds of appeal arguments and fresh evidence in respect of the set of claims on the basis of which the opposition division intended to maintain the patent. Oral proceedings were requested if the board was not inclined to revoke the patent.

VII. In a communication sent to the parties on 5 December 2007, the board commented on the appeal of opponent 01 and requested the present appellant to submit "in paper form" any sets of amended claims it wished to have considered by the board.

VIII. In reply to the board's communication, the present appellant filed by letter dated 14 February 2008 a

fresh set of claims (claims 1 to 22) replacing the claims of the main request previously on file, and re-filed the sets of claims according to the auxiliary requests 1 and 2 underlying the decision under appeal.

IX. Claims 1 and 22 of the set of claims according to the new **main request** read as follows:

"1. A combination consisting of:

a recombinant nucleic acid molecule based on or derived from an adenovirus, said nucleic acid molecule having a functional encapsidating signal and at least one functional Inverted Terminal Repeat or a functional fragment or derivative thereof, and

a packaging cell, said recombinant nucleic acid and said packaging cell together comprising all elements which are necessary to generate a recombinant adenoviral particle comprising said recombinant nucleic acid molecule,

wherein said recombinant nucleic acid molecule has no overlapping sequences which allow for homologous recombination leading to replication competent virus in said packaging cell, and wherein the genome of said packaging cell comprises nucleic acid that encodes the adenoviral E1A and E1B proteins but lacks pIX sequences.

22. A packaging cell, characterized in that it comprises in its genome nucleic acid that encodes the adenoviral E1A and E1B proteins but lacks pIX sequences."

Claims 2 to 9, 11 to 15, 17, 18 and 21 are directed to specific embodiments of the combination of claim 1, and claim 16 relates to the use of the combination for

producing recombinant adenovirus particles. Claims 10, 19, 20 and 22 are directed to packaging cells.

X. The set of claims of **auxiliary request 1** consists of 22 claims. Claim 1 differs from claim 1 of the main request in that the wording "*the genome of said packaging cell comprises nucleic acid that encodes the adenoviral E1A and E1B proteins but lacks pIX sequences"* has been replaced by the wording "*the genome of said packaging cell comprises an adenoviral sequence consisting of Ad5 nucleotides 459-3510*". A similar amendment has been introduced into claim 22. The remaining claims are identical to those of the main request.

XI. Each party was given the opportunity to submit comments in reply to the statements of grounds of appeal.

XII. Opponent 02 (respondent II) replied to the grounds of appeal and raised objections under Article 123(2) EPC to particular amendments introduced into the claims of the main request, and objections under Article 83 EPC in respect of both the main request and auxiliary request 1.

XIII. By letter dated 14 October 2008 under the letterhead of opponent 01, the board was informed on behalf of Laboratories Serono SA, Coinsins, Switzerland that "*we hereby withdraw from the Appeal proceedings*".

XIV. The parties were summoned to oral proceedings. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) annexed to the summons, the board requested opponent 01 to clarify the

statements in its letter of 14 October 2008, and provided observations on some of the issues to be discussed at the oral proceedings, in particular issues concerning Articles 123(2) and 83 EPC. The board also remarked that, if opponent 01's appeal was withdrawn, the patent proprietor would be the sole appellant. Consequently, in accordance with decisions G 9/92 and G 4/93 of the Enlarged Board of Appeal (OJ EPO 1994, 875) neither the board nor the non-appealing opponents could challenge the maintenance of the patent on the basis of the claims according to the second auxiliary request and the amended description filed during the oral proceedings before the opposition division.

XV. In reply to the communication, the board was informed that Laboratories Serono SA was the universal successor of opponent 01. Withdrawal of the appeal was confirmed.

XVI. Oral proceedings were held on 20 September 2011. Although duly summoned, opponent 01 (respondent I) was not represented.

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

(3): GenBank Accession No. X02996 (1992);

(8): F. J. Fallaux et al., 1996, Human Gene Ther., Vol. 7, pages 215 to 222;

(21): WO 94/28152, published on 8 December 1994;

(21a): US 6,040,174, published on 21 March 2000;

(27): G. Acsadi et al., 1995, J. Mol. Med., Vol. 73, pages 165 to 180;

(32): EP 1 230 354, published on 25 May 2000;

(33): WO 98/39411, published on 11 September 1998;

(34): DE 19 754 103, published on 10 June 1999;

(35): J.-S. Kim et al., 2001, Experim. Mol. Med., Vol. 33, pages 145 to 149;

(43): G. Schiedner et al., 2000, Human Gene Ther., Vol. 11, pages 2105 to 2116;

(48): B.A. Zavizion et al., 1990, Bull. Exp. Med., Vol. 109, pages 519 to 522.

XVIII. The submissions made by the appellant may be summarized as follows:

Admission of the fresh main request into the proceedings

The set of claims filed on 14 February 2008 should be admitted into the proceedings. The amendments to the claims were occasioned by grounds of opposition and had been already made in requests submitted during the proceedings before the opposition division. Even though the fresh main request had not been filed at the outset of the appeal proceedings, the introduced amendments had been suggested in the statement of grounds of appeal. Moreover, since the claims had been filed well

in advance of the oral proceedings, the respondents had ample time to file comments.

Main request - Article 123(2) EPC

Although there was no *verbatim* basis in the application as filed for the feature "... *the genome of said packaging cell comprises nucleic acid that encodes the adenoviral E1A and E1B proteins but lacks pIX sequences*", a person skilled in the art would understand that this feature was implicitly disclosed. One of the ideas underlying the invention was that there should be no overlap between the adenoviral sequences in the genome of the packaging cell and the adenoviral sequences in the vector. The skilled reader would regard this fundamental idea - the so-called "mirror image" idea - as an umbrella that covered the rest of the disclosure in the application. Thus, later passages of the application, like the passage on page 9, lines 28 to 31 referring to combinations of packaging cells and vectors, and points 4 to 6 on pages 10 and 11, had to be interpreted so that they still fell under the umbrella.

Point 4 on page 10 of the application taught that cells expressed E1A and E1B after immortalization, and point 5 on page 11 exemplified this by transfection of the E1A and E1B expressing plasmid pIG.E1A.E1B in HER cells, resulting in specific (exemplary) cell lines. In point 6 on page 11 of the application as filed, adenoviral vectors lacking sequences homologous to E1 sequences in the packaging cell lines disclosed in the preceding point 5, but containing pIX promoter sequences and the pIX gene were disclosed. Having in

mind the "mirror image" idea underlying the invention, the skilled person would directly and unambiguously understand that packaging cells used in combination with these adenoviral vectors must lack pIX sequences. The construct pIG.E1A.E1B including E1A and E1B but lacking pIX, which was described in the example on page 25 of the application as filed, supported this general implicit disclosure. This construct was inserted into the genome of cells to prepare packaging cells.

Auxiliary request 1
Articles 123(2)(3) and 84 EPC

The wording "said cell lines" in point 6 on page 11 would be interpreted by the skilled person as relating to any cell line that was prepared with the same plasmid containing nt. 459-3510. Thus, when reading the claims the skilled person would not be confronted with subject-matter that was not directly and unambiguously derivable from the application as filed.

The skilled person, in view of the complete technical teaching in the application, would realize that the use of the pIG.E1A.E1B plasmid was not limited to making the specific cell lines of point 5 on page 11. The use of this plasmid for other cells (HER, HEK, HEL) was discussed on page 17, lines 25 to 36. Moreover, on page 19, lines 3 to 19 the use of the same plasmid for further cell types (established cell lines) was described, all completely in line with the umbrella teaching.

Article 83 EPC - Sufficiency of disclosure

The aim of the invention was to improve the safety of adenovirus-based therapies, and the solution proposed was to combine packaging cells and adenoviral constructs without any sequence overlap to avoid generation of replication-competent adenoviruses. This solution was the same regardless of the type of packaging cell being used. The selection of a suitable cell line was of no relevance to the proposed solution.

The adverse findings in the decision under appeal were based solely on a single failure reported in the application and alleged difficulties in transforming primary human cells. The opposition division relied on the statement in documents (8) and (43) that transformation of primary human cells was straightforward only when using HEK, HEL or HER cells.

The opposition division was wrong to focus on the transformation of primary human cells, because the invention did not require the use of such cells. In any case, prior art document (48) reported that HCEC primary human cells had been immortalized and transformed by expression of adenoviral E1 proteins, and documents (32) to (43) published after the filing date showed that the invention had successfully been performed using primary human amniocytes. Post-published evidence of success transfecting established cell lines with a construct including E1A and E1B was provided by documents (33), (34) and (35). Contrary to the opposition division's view, these documents confirmed that the cells were able to package

replication-deficient adenovirus. Hence, the relevant E1 proteins must have been expressed.

The fact that few publications described successful transformation of primary human cells was due to the difficulties in obtaining the starting material. Primary cells from humans were not easily available. This was confirmed by document (32) (paragraph 31) and document (43) (page 2107, left column, last four lines). Apart from this, obtaining a stable cell line was time-consuming and costly but by no means did it involve an undue burden.

According to decision T 838/97 of 14 November 2000, the fact that the skilled person may not know with absolute certainty whether the teaching could be successfully applied to all possible cell types, was not necessarily indicative of undue burden, if the results could be easily tested and no further concepts had to be developed in order to achieve the desired result; this was the case for the present invention, which could be applied to further cell types without requiring any conceptual leap.

Article 56 EPC - Inventive step

Starting from the document (21) as the closest prior art, it would not be obvious to a skilled person to arrive at the claimed solution. Document (21) pointed in a different direction as its teaching was to have pIX in the packaging cell. It was stated in document (21) that the sequence of pIX overlapped the E1B region and was included in the construct. Since the presence of pIX in the packaging cell rather than in

the adenoviral vector resulted in an increased capacity for the vector, there was no reason for the skilled person to consider having pIX in the vector instead. Thus, the solution provided by the patent was a non-obvious alternative to the solution provided in document (21).

XIX. The submissions made by the respondents either orally or in writing, as far as they are relevant to the present decision, may be summarized as follows:

Admission of the fresh main request into the proceedings

The claims should not be admitted into the proceedings because they had not been filed together with the statement of grounds of appeal. Contrary to Article 12(2) RPBA, the statement of grounds did not contain a complete and clear request corresponding to the fresh main request.

Main request - Article 123(2) EPC

The feature "*lacks pIX sequences*" had been disclosed in the application only in the context of specific vectors and cells. Thus, the introduction of this feature into claims 1 and 22 led to an unallowable generalisation of the disclosure in the application as filed.

Auxiliary request 1
Article 123(2) EPC

There was no basis in the application as filed for the combination of any packaging cell with the specific

Adenovirus 5 (Ad5) fragment between nucleotides 459-3510.

Article 83 EPC - Sufficiency of disclosure

Neither the specification nor the common general knowledge provided the skilled person with the necessary information to perform the invention with any cell, in particular any primary human cell other than HER, HEK or HEL cells. The appellant himself admitted that not all primary cells could be transformed by standard methods. However, transformation of primary human cells was one of the main aspects of the patent, because only primary human cells would be approved for clinical trials.

The patent showed success only for one type of primary human cells, namely HER cells, while the experiments using an established cell line, the human A459 bronchial carcinoma cell line, had not been successful. The general concept of the invention, namely the combination of packaging cells and adenoviral constructs without any sequence overlap, could be considered enabled only for HER, HEK and HEL cells, which were the only cells that have been successfully transformed before the filing date, while several different primary human cells have been shown to be refractory to transformation with adenovirus. Since it was not predictable which primary cells could be successfully transformed, trial and error was required and the chances to fail were very high. Reference to post-published data (documents (32) to (35)) could not remedy deficiencies in the disclosure of the claimed invention.

Article 56 EPC - Inventive step

Document (21) was the closest prior art. Starting from this document, the contribution of the claimed invention to the art was merely the presence in the packaging cell of the specific fragment of Ad5 between nucleotides 459 and 3510. Document (21) belonged to the same field as the patent, as it addressed the problem of providing complementation cell lines for adenoviral vectors, and it also described the same concept of complementation *in trans* using a functional language. Primary human cells, e.g. retinal cells taken from a human embryo were used. The complementation lines comprised a portion of the genome of an adenovirus, and adenovirus 5 was regarded as advantageous.

Additionally, document (21) described an adenoviral vector which had a deletion in the E1A and E1B regions. The deletion did not include pIX sequences. It was explicitly stated in document (21) that an overlap between the sequences of the adenoviral vector and the adenoviral genome fragment integrated into the complementation line should be avoided. In view of Example 2 of document (21) and document (3), which disclosed the adenovirus 5 genome, it was apparent to a person skilled in the art that document (21) disclosed a construct with nucleotides 468-3509 of Ad5. Such a construct differed only by one nucleotide from the Ad5 fragment specified in claim 1. There was no technical effect associated with this difference, which most likely had to do with practical reasons such as the use of appropriate restriction sites. Thus, the patent merely provided an obvious alternative to the solution

of document (21) and this alternative solution was actually less advantageous than the one provided by the prior art document because the adenoviral vector had less cloning capacity.

XX. The appellant (patent proprietor) requested that the decision under appeal be set aside and the patent maintained on the basis of the main request or, in the alternative, the auxiliary request 1, both requests having been filed by letter dated 14 February 2008.

XXI. Respondent I (opponent 01) requested - prior to withdrawing its appeal - that the decision under appeal be set aside and the patent be revoked.

XXII. Respondent II (opponent 02) requested that the appeal be dismissed.

Reasons for the Decision

Procedural status of opponent 01

1. Since opponent 01 withdrew its appeal during the appeal proceedings, its present procedural status is that of a respondent. The patent proprietor is, thus, the sole appellant against the interlocutory decision of the opposition division.

Admission of the fresh main request into the proceedings

2. The set of claims filed by the appellant on 14 February 2008 as its fresh main request differs from the claims of the main request on which the opposition

division decided in that claims 7 and 11 have been omitted, and claims 8 to 10 and 12 to 24 renumbered accordingly. Moreover, independent claim 1 as well as the claims that either depend thereon or refer thereto now read "*A combination consisting of ...*", instead of "*A packaging system comprising ...*" as in the corresponding claim of the previous main request. Claim 22, which corresponds to claim 24 of the previous set of claims, has been limited to "*A* ***packaging*** *cell ...*" (emphasis added by the board).

3. The specific amendments introduced into claims 1 and 22 had been proposed by the appellant in its statement of grounds of appeal (see paragraphs 4.9, 4.11, 4.14 and 4.15 of the statement of grounds), in the event that the board – like the opposition division - should find that the subject-matter of the claims of the previous main request did not have a basis in the application as filed. Moreover, the same amendments were included in the corresponding claims of the second auxiliary request underlying the decision under appeal, which had been found by the opposition division to conform to Article 123(2) EPC and fulfil the further requirements of the EPC.

4. Even if it is true that a set of claims including these particular amendments could, in principle, have been filed together with the statement of grounds of appeal, the claims were filed at a rather early stage of the appeal proceedings upon the board's request (see paragraphs VII and VIII above). Moreover, it is observed that, even though the respondents had ample time and opportunity to submit observations, either in

writing or during the oral proceedings, no specific objections to the amendments as such were raised.

5. Since the amendments did not take the respondents by surprise, nor gave rise to new issues, but rather seemed to overcome at least some objections raised by the opponents under Article 123(2) EPC, the board, exercising its discretion under Article 114(2) EPC and Article 13(1) RPBA, decided to admit the set of claims of the fresh main request into the appeal proceedings.

Main request - Article 123(2) EPC

6. In the decision under appeal, the opposition division held that the feature "*lacking pIX*" introduced into claims 1 and 24 of the main request then on file to characterize the packaging cell, had been disclosed in the application as filed only in the context of specific vectors and cells. Thus, the subject-matter of the amended claims was regarded as an unallowable generalisation of the specific disclosure in the application. Consequently, claims 1 and 24 were found to offend against Article 123(2) EPC.

7. Claim 1 as presently on file, while including amendments which were not present in claim 1 of the main request on which the opposition division decided (see paragraph 2 above), still specifies that "... *the genome of said packaging cell comprises nucleic acid that encodes the adenoviral E1A and E1B proteins but lacks pIX sequences*". A similar wording is included also in claim 22. Thus, the question arises whether or not the findings of the opposition division on

Article 123(2) in respect of the main request then on file apply also to the present request.

8. On appeal, the appellant admitted that there is no *verbatim* basis in the application as filed for the subject-matter of claims 1 and 22, in particular with regard to the feature "*lacks pIX sequences*". However, the appellant argued that, contrary to the opposition division's view, the feature in question could be derived, directly and unambiguously, from the application as filed in a general context, i.e. not limited to specific vectors and cells.

9. The board does not share this view. The passages of the application as filed indicated by the appellant as basis for a packaging cell as specified in claim 1 are either rather general and do not refer to any particular adenoviral genes (e.g. page 5, line 34 to page 6, line 1), or relate to specific cells (diploid human cells) transfected with particular constructs such as pIG.E1A.E1B (see page 17, lines 25 to 36 in combination with page 25, lines 19 to 33, and page 30, lines 6 to 35). None of these passages can be regarded as a basis for a combination according to claim 1.

10. As regards page 10, line 26 to page 11, line 23 (points 4 to 6) of the application as filed, the appellant argued that this passage was to be read in connection to the statements on page 9, lines 28 to 31 relating to the construction of combinations of packaging cell lines and recombinant adenoviral vectors. However, the board observes that the paragraphs following that passage, which are numbered as points 1 to 10, relate to **either** packaging cell lines **or**

adenoviral vectors, rather than to any combinations of both.

11. In the paragraph bridging pages 10 and 11 (point 4), packaging cells immortalized by expression of E1A and requiring also the expression of E1B are disclosed, but there is no indication whatsoever as regards the absence of pIX sequences. The following paragraph (point 5) on page 11, lines 3 to 14 of the application describes seven specific cell lines (PER.C1, PER.C3, etc.) that were established by transfection of HER cells with the "*construct pIG.E1B*" (the board assumes that construct pIG.E1a.E1b is meant, because Figure 4 of the application, to which this passage refers, illustrates the construction of pIG.E1a.E1b). pIX sequences are not mentioned in this paragraph either.

12. It is only in point 6 (see page 11, lines 15 to 21), which concerns **adenoviral vectors**, where it is stated:

> "*6. New adenovirus vectors with extended E1 deletions (deletion nt. 459 - 3510). Those viral vectors lack sequences homologous to E1 sequences in said packaging cell lines. These adenoviral vectors contain pIX promoter sequences and the pIX gene, as pIX (from its natural promoter sequences) can only b* [sic] *expressed from the vector and not by packaging cells ...*"

13. This passage describes adenoviral vectors with a **specific** deletion in the E1 region (nucleotides 459 to 3510), which vectors are said to contain sequences from which pIX can be expressed. However, from this

particular disclosure a person skilled in the art cannot derive, clearly an unambiguously, a **general** disclosure of an adenoviral vector that lacks the sequences encoding the adenoviral E1A and E1B proteins but contains pIX sequences.

14. Since the passage in question does not make available to the skilled person such an adenoviral vector, it cannot make available - implicitly - its "mirror image", i.e. a packaging cell encoding the adenoviral E1A and E1B proteins but lacking pIX sequences. Hence, the board cannot acknowledge in the passage in question an appropriate basis for a packaging cell as specified in claims 1 and 22.

15. Consequently, the amendment of claim 1 and 22 to introduce the feature "*lacks pIX sequences*" does not conform to Article 123(2) EPC.

16. It follows from the above that the patent cannot be maintained on the basis of the claims according to the main request.

Auxiliary request 1

Articles 123(2)(3) and 84 EPC

17. The claims according to the present auxiliary request 1 are identical to those of the first auxiliary request underlying the decision under appeal. The amendments introduced into the claims were found by the opposition division to conform to Article 123(2)(3) EPC (see items 5.2.1 and 5.2.2 of the decision under appeal). Moreover,

the requirements of Article 84 EPC were considered to be met (see item 5.3 of the decision under appeal).

18. The board sees no reason to diverge from these findings. A basis for a packaging cell comprising an adenoviral sequence consisting of Ad5 nucleotides 459-3510 is found in claim 21 of the application as filed, which is not limited to any specific type of packaging cell.

19. No objections under Article 123(3) EPC or 84 EPC were raised by the respondents in appeal proceedings, and the board does not see any reason to raise any of its own motion.

Article 83 EPC - Sufficiency of disclosure

20. In the decision under appeal the opposition division held that the invention claimed in claims 1 and 22 of the first auxiliary request did not fulfil the requirements of Article 83 EPC, because neither the application nor the common general knowledge in the relevant technical field provided the guidance required for carrying out the claimed invention over the whole scope of the claims, in particular as regarded the preparation of packaging cells starting from primary cells other than HEL, HEK or HER cells. As evidence in support of these findings, the opposition division pointed to the patent itself and to documents (8) and (43) which were cited as expert opinion.

21. The opposition division correctly found that neither claim 1 nor claim 22 imposes any limitation to the type of cell suitable for use as packaging cell, except for the presence in its genome of an adenoviral sequence

consisting of Ad5 nucleotides 459 to 3510. Thus, claim 22 encompasses any possible type of cell of any possible origin, be it a primary human cell or a cell from an established cell line. Similarly, claim 1 encompasses any combination of a recombinant nucleic acid molecule as defined in the claim with any type of packaging cell harbouring in its genome the Ad5 sequences specified in the claim.

22. The opposition division also held that the examples of the patent described successful generation of packaging cell lines only by transfection of human embryonic retina (HER) cells with E1A and E1B sequences of Ad5, while the transformation of the established human bronchial carcinoma cell line A549 was not successful because a significant expression of E1A could not be achieved. The opposition division thus concluded that the patent provided only one example of how to obtain packaging cells as defined in claim 22.

23. These findings, although based on the disclosure content of the patent - instead of the application as filed which is the relevant disclosure for the assessment whether or not the requirements of Article 83 EPC are fulfilled – are, in principle, correct, since in the present case the disclosure content of the application as filed and the patent as granted are, at least in the relevant passages, identical.

24. The opposition division went on to observe that the patent did not provide the skilled person with a general teaching how to obtain a human cell line expressing adenoviral E1A and E1B proteins, and that,

therefore, the question to be addressed was whether or not the skilled person would have been able to carry out the invention over the whole scope of claims 1 and 22 based on the common general knowledge at the relevant date.

25. In this respect the board does not agree with the opposition division. A general teaching how to obtain a human cell line expressing adenoviral E1A and E1B proteins is found in the passage from page 17, line 25 to page 19, line 19 of the application as filed. A plasmid including adenoviral sequences encoding E1A and E1B proteins (plasmid pIG.E1A.E1B) is described on page 25, lines 19 to 33 and Figure 4, and a standard protocol for transfection of cells with suitable plasmids on page 28, lines 10 to 16. Thus, the application as filed discloses indeed technical details and measures which enable a person skilled in the art to prepare, possibly with some amount of trial and error, a packaging cell as defined in claims 1 and 22.

26. Apart from the failure to transform the established cell line A549 reported in the application as filed, there are no other verifiable facts on file that support the allegation that, at the filing date of the patent in suit, there were insurmountable difficulties in transforming **primary** human cells by transfecting them with adenoviral E1A and E1B sequences. There is, however, documentary evidence, in particular documents (43) and (32) showing that primary human cells can be transformed applying the teachings of the application.

27. While the documents in question were published after the filing date, the board believes that the evidence they provide is not aimed at "curing" any alleged insufficiency of disclosure, but rather at confirming that the teachings of the application are, in fact, applicable to cell lines other than HEL, HEK or HER cells. Thus, contrary to the opposition division's view, the board holds that, under the circumstances of the present case, post-published evidence may be considered (see decision T 1262/04 of 7 March 2007, not published in the OJ).

28. Documents (43) and (32) describe the efficient transformation of primary human amniocytes by transfection with adenoviral E1 sequences. It is stated in document (43) that the E1-transformed cell lines produced the E1A proteins and the 21-kDa E1B proteins in comparable amounts, whereas in preliminary experiments expression of the 55-kDa E1B protein was found to be more variable (see page 2111, left column, paragraphs under the heading "Synthesis of Ad5 E1 proteins in E1-transformed amniocyte cell lines", and Figure 4). Whether or not the primary human amniocytes used in the experiments described in document (32) are mentioned in the specification of the patent in suit is, contrary to the opposition division's view, immaterial. The decisive fact is that primary human amniocytes, i.e. primary human cells other than HEK, HEL or HER cells, can transformed by transfection with adenoviral E1 sequences, as shown in documents (32) and (43).

29. As regards post-published document (33), an International application filed in 1998 claiming the priority of a previous application filed in 1997, the

opposition division remarked that only the expression of E1B p55 but not of any other E1B proteins was reported. This is correct. However, in Example 3 of this document it is stated that E1-deleted Ad5-CA-GFP adenovirus was propagated through 20 passages on A549E1-68 cells, a cell line obtained by transfection of A549 human lung carcinoma cells with E1A and E1B sequences of Ad5. This implies that all E1 functions missing in the Ad5-CA-GFP adenoviral vector, including those of other E1B proteins were necessarily supplied by the packaging cell. The same applies in respect of the Hela-E1 packaging cell line described in document (35), which the opposition division regarded as disclosing solely the expression of E1A.

30. The board observes that the A549 cell line used in the experiments described in document (33) appears to be the same cell line which, in the examples of the application, failed to produce detectable levels of E1A and E1B. Since document (33) does not appear to describe any particular technical measures which may have been necessary to obtain a different result - nor did the respondents indicate any such measures -, it seems that the failure reported in the application, on which the opposition division based its doubts concerning the sufficiency of the disclosure, may have been either fortuitous or due to factors unrelated to the ability of the A549 cell line to be transformed upon transfection with adenoviral E1 sequences.

31. In view of the above the board is persuaded that, in spite of the alleged difficulties in transforming primary human cells, the evidence on file shows that with the guidance given in the application as filed

supplemented with the common general knowledge at the filing date, and with a reasonable amount of experimentation, a person skilled in the art could obtain packaging cells for replication-defective adenoviruses starting from either primary cells or established cell lines.

32. It is therefore concluded that, as regards the packaging cell according to claim 22 and the combination of claim 1, the requirements of Article 83 EPC are met.

Article 54(2) EPC - Novelty

33. In appeal proceedings, the sole objection of lack of novelty was directed against claim 17 of auxiliary request 2. This objection was, however, not pursued either by respondent I or respondent II in respect of auxiliary request 1. Since the board considers that the objection in question is not within the scope of the appeal proceedings, it decides to disregard it.

Article 56 EPC - Inventive step

34. In the decision under appeal, the issue of inventive step was not decided in respect of the first auxiliary request, as this request was rejected on the grounds of insufficiency of disclosure. Inventive step was however discussed in connection with claim 19 of the second auxiliary request which differs from claim 22 of the present request in that it was limited to HEK, HER or HEL cells.

35. The opposition division regarded document (21), an International application under the PCT published in French on 8 December 1994, as the closest prior art. However, in the written decision the opposition division referred to passages of document (21a), a member of the same patent family which was published in English. Even though document (21a) cannot be considered to belong to the state of the art because it was published after the priority date of the present patent, for the sake of a better understanding also the corresponding passages of document (21a) will be indicated in the following.

36. It is undisputed that document (21) belongs to the same technical field as the present patent and addresses the same problem, namely to avoid the generation of recombination competent adenoviruses when using adenoviral vectors and to thereby improve the safety of adenovirus-based gene therapy (see document (21), page 4, lines 20 to 35, and document (21a), column 3, lines 11 to 34). The complementation cell lines described therein also share the most relevant features with the claimed packaging cells. Hence, document (21) is considered to be an appropriate starting point for the assessment of an inventive step in respect of the subject-matter of claim 22.

37. Document (21) describes defective adenoviruses for the transfer and expression of exogenous nucleotide sequences in a host cell or organism in the context of gene therapy, as well as complementation cell lines (i.e. packaging cell lines) for preparing the defective adenoviruses (see Abstract). The complementation cell lines comprise a portion of the genome of an adenovirus,

preferably human adenovirus type 5 (see page 16, lines 7 to 10 of document (21), and the corresponding passage on column 10, lines 53 to 57 of document (21a)). Document (21) suggests the "mirror image" idea, i.e. that the complementation cell line must provide those adenoviral functions which are deleted in the vector (see page 13, lines 26 to 29 of document (21) and the paragraph bridging columns 8 and 9 of document (21a)), and that a sequence overlap between the adenoviral vector and the complementation cell line should be avoided (see page 4, lines 24 to 31 and page 6, lines 28 to 30 of document 821); column 3, lines 17 to 27 and column 4, lines 47 to 51 of document (21a)).

38. It is stated in document (21) that, according to an advantageous embodiment, the complementation cell line comprises all or part of the E1A region and the whole of the sequences **coding for** the early proteins of the E1B region ("*tout ou partie de la région E1A et l'intégralité des sequence codant pour les protéines précoces de la région E1B*"; see page 15, lines 6 to 8 of document (21), and column 10, lines 4 to 7 of document (21a)).

39. During the oral proceedings before the board, it was discussed whether or not the wording "the sequences coding for the **early** proteins of the E1B region" could be interpreted as including or excluding pIX sequences. Respondent II pointed to document (27) as expert opinion. In the passage on page 168, right column, lines 3 to 5 under the heading "Biology and structure of human adenoviruses", it is stated:

"*There is an additional **late** gene product, the polypeptide IX (p IX), which is transcribed from an internal promoter located at the 3' end of the E1B region*" (emphasis added by the board)

40. This evidence, which was not contested by the appellant, is confirmed by statements in document (21) itself. On page 6, line 24 (see column 4, line 42 of document (21a)) concerning specific embodiments of the adenoviral vectors, it is referred to "... *les séquences codant pour la **protéine tardive IX***". Hence, pIX does not appear to belong to the early proteins of the E1B region.

41. In order to determine the exact boundaries of the adenoviral sequences in the complementation cell line proposed in document (21), a person skilled in the art requires the nucleotide sequence of the Ad5 genome. This information was readily available from sequence databases at the filing date of the patent in suit. Moreover, document (21) already indicates a source for the nucleotide sequence of Ad5, namely reference M73260 of the GeneBank database (see page 6, lines 27 and 28 of document (21)).

42. From document (3) it is apparent that the primary transcript of the E1A region starts at nucleotide 499 (see page 4, lines 3 to 5 of document (3)), a possible start of the promoter region being located - in analogy to Ad2 - at nucleotides 468 to 475 (see page 3, first row in the table). On the other end, the coding sequence of E1B 55k protein ends at nucleotide 3506 (see page 5, lines 26 and 27) and the coding sequence

of the IX protein starts at nucleotide 3609 (see page 5, lines 8 and 9 from the bottom).

43. Taking into account this information, document (21) discloses a complementation cell line which comprises in its genome an adenoviral sequence, in particular of Ad5 consisting of the E1A region starting at nucleotide 499 and the coding region for the early E1B proteins ending at nucleotide 3506. This adenoviral sequence does not contain pIX sequences.

44. The opposition division correctly formulated the technical problem to be solved in view of document (21) as the provision of an alternative packaging cell line for adenoviral vectors. As a solution to this problem the patent proposes a packaging cell line according to present claim 22 which comprises in its genome an adenoviral sequence consisting of Ad5 nucleotides 459-3510, i.e. the adenoviral sequence contains the E1A and E1B coding sequences of Ad5, but lacks pIX. The board considers the technical problem formulated above to be credibly solved.

45. The claimed packaging cell differs from the complementation cell line described in document (21) solely in few additional nucleotides at both ends of the adenoviral sequence. It is not apparent from the patent which technical effect is associated with those additional nucleotides nor has the appellant put forward any arguments in this respect. Thus, the choice of the particular fragment specified in claim 22 must be considered as an arbitrary choice without any inventive merits.

46. The appellant argued that document (21) actually taught away from the solution of the patent because in the defective adenovirus generated in Example 2 only the pIX sequences between nucleotides 4047 to 6241 were included. This implied that the complementation cell line must have the remaining pIX sequences. The skilled person would not have been motivated to depart from this teaching.

47. This argument fails to persuade the board. It is true that document (21) describes also complementation cell lines that include at least part of the pIX sequence, in particular sequences corresponding to the transcription termination signal which overlaps the sequences coding for the late protein IX (see paragraph 38 above). However, there is no contradiction between the two disclosures. A person skilled in the art reading document (21) would recognise that they correspond to different embodiments of the more general teaching of adenoviral vectors and complementation cell lines without common adenoviral sequences.

48. It is thus concluded that, starting from the closest prior art document (21), the subject-matter of claim 22 cannot be regarded as involving an inventive step. The same applies to the subject-matter of claim 1 which is directed to a combination of a complementation cell line with an adenoviral vector having no overlapping sequences.

49. Consequently, auxiliary request 1 does not meet the requirement of Article 56 EPC.

Auxiliary request 2 - Prohibition of "reformatio in peius"

50. According to decisions G 9/92 and G 4/93 of the Enlarged Board of Appeal (OJ EPO 1994, 875), if the patent proprietor is the sole appellant against an interlocutory decision maintaining a patent in amended form, neither the Board of Appeal nor the non-appealing opponent(s) may challenge the maintenance of the patent as amended in accordance with the interlocutory decision. The ruling of the Enlarged Board is based on the principle of prohibition of "*reformatio in peius*" which prevents a sole appellant being put in a worse situation than it was in before it appealed.

51. Since in the present case the patent proprietor is the sole appellant against the interlocutory decision of the opposition division (see paragraph 1 above), the principle of prohibition of "*reformatio in peius*" applies. Consequently, the set of claims according to auxiliary request 2, which is identical to the set of claims regarded by the opposition division as a basis on which the patent could be maintained, cannot be challenged in appeal proceedings.

Conclusion

52. For the reasons given above, neither the main request nor the auxiliary request 1 can be allowed. Thus, the appeal must be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski M. Wieser