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Datasheet for the decision of 19 May 2006

Case Number: T 1023/02 - 3.3.04

Application Number: 91918320.2

Publication Number: 0500917

IPC: A61K 39/12

Language of the proceedings: EN

Title of invention:
Recombinant herpes simplex viruses vaccines and methods

Patentee:
Arch Development Corporation

Opponents:
University College London
The University Court of the University of Glasgow

Headword:
HSV vaccines/ARCH DEVELOPMENT

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2), (3)
RPBA Art. 10b

Keyword:
"Added matter (no) - novelty, inventive step, sufficiency of disclosure (yes)"

Decisions cited:
G 09/91

Catchword:
-

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Case Number: T 1023/02 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 19 May 2006

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 31 July 2002 revoking European Patent No. 0500917 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: R. Moufang
Members: B. Claes
R. Gramaglia

Summary of Facts and Submissions

I. European patent No. 0 500 917 with the title "Recombinant herpes simplex viruses vaccines and methods" was granted based on European application No. 91918320.2 with claims 1 to 13 for all designated Contracting States except ES and GR, claims 1 to 8 for the Contracting State ES and claims 1 to 13 for the Contracting State GR.

II. Claim 37 to 39, 43 and 44 of the application as originally filed read:

"37. A method for preparing a herpes simplex virus vaccine comprising the steps of: preventing transcription of an active product from an ICP34.5 gene in an otherwise substantially intact herpes simplex virus; and combining said vaccine virus with a pharmaceutically acceptable carrier."

"38. The method as recited in claim 37 wherein said preventing step comprises the step of deleting a portion of said ICP34.5 gene."

"39. The method as recited in claim 38 wherein said herpes simplex virus genome is an HSV-1 genome."

"43. The method as recited in claim 37 wherein said preventing step comprises the step of inserting a stop codon in reading frame between a first and a last codon of a coding sequence of said ICP34.5 gene."

"44. The method for preparing a herpes simplex virus vaccine as recited in claim 43 wherein said inserting

step comprises the step of introducing a stop codon at a BstEII restriction endonuclease site in the ICP34.5 gene of HSV-1(F)."

III. Claims 9 to 11 and 13 of the patent as granted for all designated Contracting States except ES and GR read:

"9. A method for preparing a herpes simplex virus vaccine comprising the steps of: preventing transcription of an active product from $_{\gamma 1}$ 34.5 gene in a herpes simplex virus; and combining said virus with a pharmaceutically acceptable diluent, adjuvant or carrier."

"10. The method as recited in claim 9 wherein said herpes simplex virus genome is an HSV-1 genome or an HSV-2 genome."

"11. The method as recited in claim 9 or 10 wherein said preventing step comprises the step of deleting a portion of said $_{\gamma 1}$ 34.5 gene, particularly the step of deleting a coding sequence between BstEII and StuI restriction endonuclease sites in HSV-1(F).

"13. The method as recited in claim 9 or 10 wherein said preventing step comprises the step of inserting a stop codon in reading frame between a first and a last codon of a coding sequence of said $_{\gamma 1}$ 34.5 gene, particularly the step of introducing a stop codon at a BstEII restriction endonuclease site in the $_{\gamma 1}$ 34.5 gene of HSV-1 (F)."

The set of claims for the Contracting State GR of the patent as granted contained identical claims 9 to 11

and 13, with the exception of the addition of the indefinite article "a" before "γ_1 34.5 gene" in claim 9.

Claim 1 and 8 of the patent as granted for the Contracting State ES read:

"1. A method for producing a non virulent herpes simplex virus genome for use in the preparation of a vaccine destined for the immunization against HSV virus, wherein the herpes simplex virus genome is treated so as to lack γ_1 34.5 genes encoding an active ICP34.5 gene product."

"8. A method for preparing a herpes simplex virus vaccine comprising the steps of: preventing transcription of an active product from a γ_1 34.5 gene in a herpes simplex virus according to one of claims 1 to 7; and combining said virus with a pharmaceutically acceptable diluent, adjuvant or carrier."

IV. Notices of opposition had been filed by opponents 01 and 02 which requested the revocation of the patent as a whole on the grounds of Article 100(a), novelty and inventive step, Article 100(b) and 100(c) EPC. The opposition division decided to revoke the patent. It was held that the subject-matter of claims 1 and 9 as granted and claim 1 of a first auxiliary request then on file (being identical to claim 9 as granted) extended beyond the content of the application as filed (Article 100(c) EPC), whereas the subject-matter of claim 1 of a second auxiliary request then on file lacked novelty.

V. The patent proprietor (appellant) lodged an appeal against the decision of the opposition division, submitted a statement of grounds of appeal and paid the appeal fee. With the statement of grounds, the appellant filed a new main request consisting of claims 1 to 12 and requested the reimbursement of the appeal fee in accordance with Rule 67 EPC.

VI. The board, with a communication dated 19 December 2002, invited the appellant to supplement its submissions on the issue of inventive step.

VII. The appellant submitted arguments in support of inventive step of the subject-matter of the main request filed with the statement of the grounds of appeal.

VIII. Opponents 01 and 02, who are respondents I and II in the present appeal proceedings, responded to the grounds of appeal.

IX. The board sent a communication pursuant to Article 11(1) RPBA dated 1 March 2006 indicating its preliminary, non-binding opinion.

X. The appellant responded to this communication by letter dated 18 April 2006 and submitted a new main request as well as seven auxiliary requests.

XI. Oral proceedings were held before the board on 18 and 19 May 2006 during which the parties were heard on a number of issues arising from the requests on file. The final and new main request of the appellant consisted of two sets of claims, i.e. claims 1 to 3 for all

designated Contracting States except ES and claims 1 to 3 for the Contracting State ES. All other requests, including the request for the reimbursement of the appeal fee, were withdrawn.

Claim 1 of the new main request for all designated Contracting States except ES read as follows:

"1. A method for preparing a herpes simplex virus-1 vaccine comprising the steps of: preventing only transcription of an active product from the ICP34.5 genes in an intact herpes simplex virus-1; and combining said virus with a pharmaceutically acceptable carrier."

Claim 1 of the new main request for ES read as follows:

"1. A method for preparing a herpes simplex virus-1 vaccine **destined for the immunization against HSV virus** comprising the steps of: preventing only transcription of an active product from the ICP34.5 genes in an intact herpes simplex virus-1; and combining said virus with a pharmaceutically acceptable carrier." (emphasis added).

The wording of claims 2 and 3 was identical for all designated Contracting States and read:

"2. The method of claim 1, wherein said preventing of transcription includes the step of deleting a portion of said ICP34.5 genes."

"3. The method of claim 1, wherein said preventing of transcription includes the step of inserting a stop

codon in reading frame between a first and a last codon of a coding sequence of said ICP34.5 genes, particularly the step of introducing a stop codon at a BstEII restriction endonuclease site in the ICP34.5 genes of HSV-1 (F)."

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

(2) US 4,859,587

(3) Taha *et al.* (1989), J. gen. Virol., 70, 705-716.

(4) Taha *et al*. (1989), J. gen. Virol., 70, 3073-3078.

(7) Thompson *et al.* (1989), Virology, 172, 435-450.

(9) Chou & Roizman (1990), J. Virol., 64(3), 1014-1020.

(15) Bernstein & Stanberry (1999), Vaccine, 17, 1681-1689.

(17) Lagunoff & Roizman (1994), J. Virol., 68(9), 6021-6028.

(27) Taha (1990), Thesis titled: "Analysis of neurovirulence in the mouse model system using deletion variants of herpes simplex virus type 2 (HSV-2)", presented for the Degree of Doctor of Philosophy in the Faculty of Sciences at the University of Glasgow, UK.

XIII. The submissions of the appellant, insofar as they are relevant to the present decision, can be summarised as follows:

Admission into the proceedings of the new main request

– The new main request addressed all the issues raised by the respondents and the board and did not raise new issues requiring further hearing of the parties.

Articles 123(2),(3) and 84 EPC

– The claims complied with the requirements of Article 123(2),(3) and 84 EPC.

Novelty and inventive step

– None of the cited documents relevant under Article 54(2) EPC disclosed the claimed subject matter. Accordingly the claimed subject-matter was new.

– The closest prior art was represented by the disclosure in document (2) as it was the only document disclosing HSV-1 vaccine viruses that were not virulent. The problem to be solved by the invention as defined by claim 1 of both sets of claims of the main request was the provision of a vaccine against HSV-1 based on a HSV-1 virus which is as complete as possible.

– Neither document (2) taken alone nor combined with the teaching in any of the remaining cited documents relevant under Article 54(2) EPC suggested to the

skilled person that the mere deletion of the ICP34.5 genes in an intact HSV-1 and the formulation of this virus in a vaccine composition would be sufficient and necessary for solving that problem.

Sufficiency of disclosure

– The respondents had not submitted any proof that the invention as disclosed and claimed was not enabled or non-workable. Furthermore, the respondents had not discharged their burden of proof that expression of the ORF-P reading frame was necessary for providing a functional HSV-1 vaccine. The post-published fact that the ORF-P gene was positioned anti-sense to the ICP34.5 gene could therefore not render the invention insufficiently disclosed.

– The fact that document (15) reported that in 1999 no proven effective vaccine against HSV was available did not prove the non-workability of the present invention since there may have been other reasons, e.g. regulatory reasons, for not producing vaccines according to the invention. Furthermore, for compliance with the requirements of Article 83 EPC, it was not required to undertake and disclose clinical trials.

XIV. The submissions of the respondents, insofar as they are relevant to the present decision, can be summarised as follows:

Admission into the proceedings of the new main request

– The claims of both sets of claims of the new main request did not clearly address all the issues raised by the respondents and the board. The new main request should therefore not be allowed into the proceedings.

Article 123(2) EPC

– Claim 37 and the passage in the first paragraph at page 5 of the description of the application as originally filed did not form a basis for compliance of claim 1 of both sets of the main request with the requirements of Article 123(2) EPC.

– The omission of the words "otherwise substantially" from the term "otherwise substantially intact herpes simplex-1 virus" did not comply with the requirements of Article 123(2) EPC.

– There was no disclosure in the application as originally filed for a method step concerning “preventing only transcription”.

Article 84

– The identity of the final product of the method of claim 1 of both sets of claims of the main request was unclear since the wording "comprising the steps of" left open which other steps were possibly also covered by the claim. The introduction of the word "only" into claim 1 did not remedy this deficiency.

Furthermore, the wording "preventing only transcription of an active product from ... gene" was unclear in general and particularly in relation to the word "only".

– Claim 1 lacked support in the description as it did not specify the condition which the vaccine was effective for.

– Later technical knowledge revealed that the examples as contained in the application not only prevented the transcription of an active product from the ICP34.5 genes but equally from the ORF-P gene present and transcribed at the anti-sense position of the ICP34.5 genes in the HSV-1 genome. The insertion of the wording "only" was therefore inaccurate and unclear.

– The qualification of the herpes simplex virus-1 to be "intact" was unclear as "intact HSV-1" went beyond what was taught in the application.

Novelty and inventive step

– The closest prior art was represented by either of the documents (2), (7) or (9).

– Starting from document (2), the technical problem to be solved was the provision of an alternative vaccine virus to that disclosed in document (2). The subject-matter claimed was an obvious solution to this problem since document (9) rendered it obvious that the ICP34.5 gene was required for neurovirulence of HSV-1.

– Starting from document (7), the technical problem to be solved was the determination of the HSV-1 factor responsible for restoring the neurovirulence of the intertypic recombinant RE6. The subject-matter claimed was an obvious solution to this problem in view of the fact that document (9) rendered it obvious that the ICP34.5 gene was required for neurovirulence of HSV-1.

– Similarly, starting from document (9), the technical problem to be solved was the determination of the HSV-1 factor responsible for neurovirulence in HSV-1. Document (9) taken either alone or in combination with the disclosure in document (4) rendered it obvious that the ICP34.5 gene was this factor and that thus prevention of transcription of this factor would provide a virus suitable for the formulation of a vaccine.

Sufficiency of disclosure

– It was clear from post-published document (17) that any genetic modification of ICP34.5 genes in HSV-1 simultaneously resulted in genetic modifications in the gene ORF-P located anti-sense to the ICP34.5. The patent did therefore not disclose a method as now claimed.

– The subject-matter of claim 1 was not restricted to a method for preparing a vaccine against HSV-1 as the claim did not explicitly indicate this feature. Accordingly, the burden of proving the functionality of the invention for vaccines against other viruses

including other herpes viruses lay with the appellant.

– Even if the vaccine as prepared by the subject-matter of claim 1 was merely required to be functional against HSV-1, the application lacked sufficiency of disclosure in this respect since the description was devoid of any data on such vaccines.

– Furthermore, it could be taken from document (15) that even as late as 1999 no effective vaccines to HSV had become available. Accordingly, further inventive work was still necessary. The application therefore lacked an enabling disclosure.

XV. The appellant requested that the decision under appeal be set aside and the patent be maintained in amended form on the basis of the new main request filed at the oral proceedings and consisting of claims 1 to 3 for all designated Contracting States except ES and claims 1 to 3 for ES. Both respondents requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible as it complies with the requirements of Articles 106 to 108 and Rule 64 EPC.

Admission into the proceedings of the new main request

2. The board has used its discretion to admit the new main request filed by the appellant in the course of the oral proceedings. This request addresses the various

issues raised by the requests on which the parties were previously heard. Furthermore, the amendments made are such that the other parties could reasonably be expected to deal with it without adjournment of the oral proceedings (Article 10b RPBA).

The invention in the patent

3. According to the description of the patent as granted, herpes simplex virus (HSV) is a relatively common human pathogen which can cause fatal disease in the young or immunosuppressed. There are two distinct serotypes, herpes simplex virus type 1 (HSV-l) and herpes simplex virus type 2 (HSV—2), respectively associated with fever blisters and genital lesions. HSV is characterized by the ability to establish latent infections in the central nervous system of its host, specifically of the neural ganglia. This may result in encephalitis (see page 2, lines 15 to 23).

4. Furthermore, the patent states that it is useful to obtain a stable, non-transforming live viral vaccine which either does not establish latent infections or which cannot be reactivated from a latent state, and which is effective against a HSV. This can be achieved by a virus which contains only a small alteration in the genomic structure, thereby preserving the ability to replicate well outside the host while maintaining normal expression of immunity-inducing viral components (see page 2, lines 34 to 38).

5. The invention disclosed in the patent as granted is based on the recognition that the genes for ICP34.5, a specific viral protein expressed in infected cells,

determine the ability of HSV to multiply and to destroy central nervous system tissue (see page 7, lines 15 to 16). The invention is described as relating to recombinant HSV strains, live viral vaccines incorporating such strains, methods for making such strains and vaccines wherein a vaccinal viral DNA does not encode an active ICP34.5 gene product, and mentions as an example a HSV virus having a deletion or a stop codon in reading frame within a coding region in all copies of the ICP34.5 gene (see page 2, lines 5 to 10). It is stated that the genome of the HSV according to the invention consists essentially of an otherwise virulent HSV (HSV-l or HSV-2) which is avirulent only for lacking an ICP34.5 gene encoding an active gene product (see patent at page 2 lines 56 to 59).

The invention as claimed in the new main request

6. In order to be able to address the various objections put forward by the respondents, the board considers it appropriate to first give its view on the proper technical interpretation of the subject-matter as claimed.

7. In accordance with established principles the skilled person, when considering a claim, should rule out interpretations which are illogical or which do not make technical sense. He should try, with synthetical propensity, i.e. building up rather than tearing down, to arrive at an interpretation of the claim which is technically sensible and takes into account the whole disclosure of the patent. The patent must be construed by a mind willing to understand, not a mind desirous of misunderstanding (see Case Law of the Boards of Appeal

of the European Patent Office, 5th edition, 2006, page 205).

8. The sole independent claim 1 for all designated Contracting States except ES is directed to a method for preparing a HSV-1 vaccine comprising the steps of preventing only transcription of an active product from the ICP34.5 genes in an intact herpes simplex virus-1 and combining said virus with a pharmaceutically acceptable carrier. This claim, in contrast to the wording of claim 1 for the Contracting State ES, does not explicitly specify that the vaccine to be prepared is "*destined for the immunization against HSV virus*". The respondents have therefore argued that the subject-matter of claim 1 was not restricted to a method for preparing a vaccine against HSV, let alone to a method for preparing a vaccine against HSV-1, since the claim did not explicitly indicate this functionality.

The board considers, however, that the skilled person commonly understands a term such as "disease X vaccine" or "virus Y vaccine" as referring to a vaccine for immunoprotection against the disease X or the virus Y, respectively. Even if one takes into account the possibility that it may be envisaged to develop vaccines which are based on a HSV and would provide immunoprotection against another virus or disease, the specification of the patent does not mention such a possibility at all and is only concerned with vaccines against HSV, be it HSV-1 or HSV-2 (see page 2, lines 37 to 38, page 3, lines 6 to 9). In the context of the teaching of the patent, the skilled person would therefore not interpret the term "herpes simplex virus-1 vaccine" in claim 1 for all designated Contracting

States except ES as to refer to a vaccine which provides immunoprotection against viruses different from HSV-1.

9. According to claim 1 of both sets of claims of the new main request, the HSV-1 vaccine is prepared by preventing (only) "**transcription**" of an active product from the ICP34.5 genes. The respondents have argued that, following recognised scientific terminology in the technical field, the claim thus requires that the transcription from the DNA of an active product, i.e. mRNA, is prevented rather than the (proper) translation from the mRNA into an active protein. This would mean that only such genetic modification steps which e.g. inactivate the promoters of the ICP34.5 genes are encompassed by the wording of claim 1 and not such genetic modification steps which merely impair the translation. The board acknowledges that the language of the claims may be regarded as rather unfortunate. Nevertheless, the understanding put forward by the respondents is in contradiction with the description of the invention. In particular the board draws the attention to the following passage at page 3 of the patent:

"*A method for preparing a herpes simplex virus (HSV–1 or HSV–2) vaccine according to the present invention includes the steps of preventing transcription of an active product from an ICP34.5 gene an* [sic] *otherwise substantially intact herpes simplex vaccine virus, and combining said vaccine virus with a pharmaceutically acceptable carrier.*

In the method for preparing a herpes simplex virus

(HSV—l or HSV-2) vaccine, the preventing step may include a step of deleting a portion of said ICP34.5 gene, and the deleting step may include the step of removing a coding sequence which may be 1000 base pairs in length between BstEII and StuI sites in HSV-1(F). Alternatively, the preventing step may include a step of inserting a stop codon in reading frame between a first and a last codon of a coding sequence of said ICP34.5 gene, and more particularly may include a step of introducing a stop codon at a BstEII site in the ICP34.5 gene of HSV-l(F)."

It follows from these passages that the step of "preventing transcription" as used in the description is envisaged to relate to steps which disturb the open reading frame encoding the active ICP34.5 proteins without interfering with the transcription of the genes. This interpretation is furthermore confirmed by the examples in the patent which concern specific embodiments as generally described in these passages.

The board therefore concludes that, in the light of the description, the skilled person would **not** interpret claim 1 in the manner as advocated by the respondents, but would consider that what the claim requires is that the translation into an active protein is prevented.

10. The first step according to the method of claim 1 consists of "preventing **only** transcription of an active product from the ICP34.5 genes in an intact herpes simplex virus-1", whereas in the second step "said virus" is combined with a pharmaceutically acceptable carrier. The board interprets the term "said virus" as recited in the second method step of claim 1 therefore

to refer to the result of the first method step, i.e. an (otherwise) intact HSV-1 in which only the transcription of an active product from the ICP34.5 genes is prevented. In view of the above considerations the subject-matter of claim 1 is to be construed as a method for preparing a HSV-1 vaccine which comprises at least two distinct steps, i.e. a step of preventing **only** transcription of an active product from the ICP34.5 genes in an intact HSV-1 virus and the formulation of the virus resulting from the previous step (i.e. "said virus") with a pharmaceutically acceptable carrier.

11. The respondents have argued that post-published document (17) revealed the existence of a ORF-P gene coincident with but anti-sense to the ICP34.5 gene in the HSV genome. Therefore, and in view of the term "only" which had been introduced in the claims during the appeal procedure, the claim had to be interpreted as requiring that the first method step did not interfere with the expression of this ORF-P gene.

However, the board notes that the patentee, when filing the application, could not retrieve any information from the prior art as to such an anti-sense gene and, as is apparent from the description, had not envisaged its existence either. The contrary has not been argued by the respondents. Furthermore, it is apparent from the description that none of the embodiments exemplified in the patent advocate caution as to not disturb the antisense sequences and may, as known today, result in an interference with the activity of the ORF-P gene. The skilled reader would therefore, in the light of the description, not interpret the subject-

matter of claim 1, notwithstanding the use of the term "only", as requiring that the step of preventing the transcription of an active product from the ICP34.5 genes does not interfere with the expression of this ORF-P gene. Accordingly, post-published knowledge of further technical details and/or complications as to the impact of the method of preparing the vaccine as disclosed in the patent cannot justify the above advocated interpretation of claim 1.

12. Since claim 1 defines the method for preparing the vaccine as "comprising" two specified method steps, its subject-matter is not restricted to methods consisting only of these two steps, but may comprise further method steps. It may therefore be argued that claim 1 encompasses subject-matter which in addition to the very specific modification in the first step could include further genetic alteration steps. It is, however, the opinion of the board that a claim using "comprising" language should generally not be construed as covering subject-matter which includes further steps of a nature that would manifestly counteract the specified technical purpose of the step(s) recited in the claim. When applying this principle to the claim at issue, it follows that the skilled person would neither consider that the method may include any further step of undoing the combination of the prepared virus with the pharmaceutically acceptable carrier as specified in the second method step, nor, in view of the wording "only" in the first method step, consider that the method may include further genetic modifications.

Added subject-matter - Article 123(2) EPC

13. The respondents have argued that claim 1 of both sets of claims of the new main request, which constitutes an amended version of claim 37 as originally filed, infringes the requirements of Article 123(2) EPC since its subject-matter goes beyond the disclosure of the application as originally filed. Accordingly, the following amendments which have been made vis-à-vis the original application need consideration under Article 123(2) EPC.

14. Whereas claim 37 as originally filed is concerned with HSV in general, claim 1 of both sets of claims of the new main request is restricted to HSV-1. This amendment finds a basis at page 4, lines 16 to 24, and in the first paragraph at page 5 of the description as originally filed which recites both **HSV-1** and HSV-2 in a method for preparing a herpes simplex virus vaccine in accordance with claim 37 as filed.

15. Claim 37 as originally filed has furthermore been amended in that the definition of the first method step "**preventing transcription** ... in an **otherwise substantially intact** herpes simplex virus ..." has been replaced by "**preventing only transcription** ... in an **intact** herpes simplex virus..." (emphasis added). The board considers that two aspects of this amendment need to be addressed for the examination of its compliance with the requirements of Article 123(2) EPC.

Insofar as the amendment consists of the insertion of the word "**only**" and the deletion of the word "**otherwise**", it does not change the technical meaning

of the first method step, but rather defines it in a more accurate way by clarifying that the starting material in which the genetic modification is made is an intact HSV. The amendment thus avoids any intrinsic ambiguity in the wording of claim 37 as originally filed, where the term "otherwise substantially intact virus", in the interpretation of the board, was meant to refer to the end product of the first method step whereas from a grammatical point of view the argument could have been made that it referred to the starting product for the first method step.

Insofar as the amendment concerns the omission of the word "**substantially**" which qualified the "intact herpes virus" in claim 37 as originally filed, the board considers that it equally complies with the requirements of Article 123(2) EPC. The description as originally filed contains embodiments where the first method step is performed on an intact herpes simplex virus. In particular, examples 5 and 8 disclose the complete method of production of strain R4009 comprising stop codons in all three reading frames of both ICP34.5 genes starting from the wild type HSV-1 strain F. The board thus considers that a method for preparing a HSV-1 which, apart from the genetic modifications of the ICP34.5 genes, is intact was clearly and unambiguously disclosed in the application as originally filed. Furthermore, since claim 1 of the main request is not to be construed as requiring that its first method step does not interfere with the expression of the anti-sense ORF-P gene (see point 11 above), the amendment does not introduce subject-matter in this respect.

16. The further amendment of the wording "from an ICP34.5 gene" in claim 37 as originally filed to "from the ICP34.5 gene**s**" in claim 1 of both sets of claims of the main request, finds support in the description of the application as originally filed at page 1, lines 13 to 17. Throughout the application it is taught that in order to work the invention and to prevent transcription of an active product from the ICP34.5 gene, both copies of the gene have to be modified (see e.g. example 6, passage at page 28, lines 29 to 33). Accordingly, also this amendment complies with the requirements of Article 123(2) EPC.

17. Claim 1 of the main request for the Contracting State ES contains, as compared to claim 1 for the other designated Contracting States, the additional feature that the herpes simplex-1 virus vaccine is "*destined for the immunization against HSV virus*". At page 4, lines 16 to 18, the description of the application as filed explicitly refers to the use of the vaccines of the invention for immunization against HSV and hence supports this amendment.

18. Dependent claims 2 and 3, which are identical in both sets of claims of the new main request, find a basis in claim 38 and claim 43, combined with claim 44, respectively, of the application as originally filed.

19. In view of the above considerations claims 1 to 3 of the main request comply with the requirements of Article 123(2) EPC.

Article 123(3) EPC

20. Claim 1 of both sets of claims of the main request for all designated Contracting States except ES differs from claim 9 as granted for the same Contracting States in respect of the following features:

(i) the restriction of the herpes simplex virus to be a herpes simplex virus-1;

(ii) the insertion of the wording "only" between the words "preventing" and "transcription";

(iii) the substitution of "γ_1 34.5 gene" to "ICP34.5 genes";

(iv) the qualification of the herpes simplex virus to be "intact"; and

(v) the deletion of "diluent" and "adjuvant" from the second method step.

21. Apart from amendment (iii) which basically amounts to a mere change of equivalent nomenclature (see patent, page 3, lines 53 to 54), all the above amendments constitute the deletion of alternatives from or other limitations of the claimed subject-matter, which merely exclude subject-matter from the scope of protection provided by claim 9 as granted. The board is therefore satisfied that the scope of protection provided by claim 9 as granted for all designated Contracting States except ES has not been extended by the claims of the main request for the same Contracting States.

22. For the same reasons, the scope of protection of claim 8 as granted for the Contracting State ES has not been extended by the claims of the main request for this State.

23. In view of the above considerations the claims of the main request comply with the requirements of Article 123(3) EPC.

Article 84 EPC

24. In accordance with decision G 9/91 of the Enlarged Board of Appeal (OJ EPO 1993, 408, point 19), amendments made to a patent during opposition proceedings are to be examined as to their conformity with the requirements of the EPC. Whereas Article 102(3) EPC does not provide for objections to be based upon Article 84 EPC if they do not arise out of the amendments made to the patent during opposition proceedings, Article 102(3) EPC requires such amendments to be examined to ascertain whether the EPC, including Article 84 EPC, is contravened as a result. In accordance with these principles, the amendments in the claims of the main request, which need examination under the requirements of Article 84 EPC are those listed in point 20 above.

25. The board does not see any clarity problems with regard to amendments (i), (iii) and (v). None of these amendments, i.e. the restriction of the herpes simplex virus to be herpes simplex virus-1, the substitution of "γ_1 34.5 gene" to "ICP34.5 genes" and the deletion of "diluent" and "adjuvant" from the second method step generate terminology in the claim which is unclear for

a skilled person. The board is furthermore satisfied that these amendments are supported by the description in accordance with Article 84 EPC. It is noted in particular that the limitation to a method for preparing HSV-1 vaccines is supported by the paragraph at page 3, lines 16 to 18 of the patent, which explicitly refers to "a method for preparing a herpes simplex virus (HSV-1 or HSV-2) vaccine according to the present invention".

26. With respect to amendment (iv), the respondents have argued that the meaning of **"intact"** herpes simplex virus-1 is unclear and is not supported by the application as originally filed. The board cannot concur with this argument as the disclosure of the complete method of production of strain R4009, consisting of a wild type, i.e. "intact", HSV-1 strain F solely being modified for comprising stop codons in all three reading frames of both ICP34.5 genes as described in examples 5 and 8, not only provides support for the claim in the description, but also confirms the routine understanding of the term "intact herpes simplex virus-1" by the skilled person, i.e. an unmodified herpes simplex virus-1.

27. The respondents have objected to amendment (ii) under Article 84 EPC, with the argument that post-published document (17) revealed the existence of an ORF-P gene coincident with but anti-sense to the ICP34.5 gene in the HSV genome. The insertion of the word "only" rendered the claim language ambiguous since the claim might now be interpreted as requiring that the first method step did not interfere with the expression of

this ORF-P gene.

As already set out in point 11 above, the board considers that, in the light of the description which did not envisage the existence of the ORF-P gene, the skilled reader would not interpret the claim in this way. Furthermore, at the filing date of the patent in suit when the relevant knowledge contained in post-published document (17) was not yet available, a skilled reader would not have understood a claim, if drafted in identical terms to claim 1 of the main request, as requiring non-interference with the ORF-P gene. Under these circumstances, it would not be appropriate to deny, on the basis of Article 84 EPC, the proprietor the opportunity to amend the claim in opposition proceedings in the manner as requested (which, as already set out in point 15, last paragraph, above, complies with the requirements of Article 123(2) EPC), for the sole reason that post-published knowledge, taken as such and without having regard to the description, might animate to a possibly different interpretation.

28. The respondents further objected that claim 1 of both sets of claims of the new main request for all designated Contracting States except ES lacked clarity since it did not explicitly indicate the condition for which the vaccine prepared was intended to be used and since it contained the misleading term "transcription" in the definition of the first method step, the latter objection equally applying to claim 1 of the new main request for the Contracting State ES.

However, the board notes that the relevant wording of claim 1 for all designated Contracting States except ES was already part of the wording of claim 9 of the patent as granted for the same Contracting States and is therefore in this respect not open for objection under Article 84 EPC (see above point 24). This equally applies with respect to the use of the term "transcription" in claim 1 for the Contracting State ES which was already part of the wording of claim 8 of the patent as granted for the same State.

29. In view of the above considerations the board concludes that all of the amendments made in the new main request comply with the requirements of Article 84 EPC.

Novelty

30. None of the prior art documents relied upon by the parties disclose a method for preparing a HSV-1 vaccine in accordance with claim 1 of both sets of claims of the main request, characterised by preventing only transcription (i.e. translation, see above point 9) of an active product from the ICP34.5 genes in an intact herpes simplex virus-1.

31. Documents (3), (4) and (27) concern variants of HSV-2 strains and do not therefore prejudice the novelty of the claimed subject-matter.

32. Although documents (7) and (9) relate to HSV-1 strains and variants, the documents do not concern nor disclose vaccines based on such strains or variants. Therefore they are not detrimental to novelty either.

33. Although document (2) discloses vaccines for immunoprotection against HSV-1 and HSV-2, the HSV-1 variants on which these vaccines are based contain deletions which cover all of the sequences located between the terminus of the α27 gene and the promoter region of the α4 gene. It can be taken from the description of document (2), column 6, line 65 to column 7, line 13, that this deletion spans a multitude of genes (including the ICP34.5 gene) rather than only the ICP34.5 gene(s). Accordingly, document (2) does not prejudice the novelty of the claimed subject-matter.

34. For the above reasons, the board considers the subject-matter of claims 1 to 3 of both sets of claims of the new main request to meet the requirements of Article 54 EPC.

Inventive step

35. In order to assess whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal consistently apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art. In accordance with established case law of the boards of appeal, the closest prior art is a teaching in a document conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications to arrive at the claimed invention.

The closest prior art

36. The general aim of the invention as disclosed in the patent (page 2, lines 30 to 32) is the provision of a vaccine against HSV based on a HSV strain which is avirulent, stable (i.e. does not revert to the virulent state) and provides immunity to wild-type HSV strains. It should have low pathogenicity and be incapable of transforming host cells.

37. The respondents have considered either of the teachings of documents (2), (7) or (9) to represent the closest prior art. However, documents (7) and (9), as can be taken from point 32 above, do not disclose vaccines based on a HSV-1. On the other hand, document (2), a US patent having the same inventor as the patent in suit, explicitly sets out, in column 2, lines 26 to 31, the object to provide live, recombinant virus strains and vaccines incorporating such strains, effective against virulent, disease-producing (wild-type) HSV-1 and HSV-2, methods of making the vaccines and methods of immunising a host using the vaccines.

Similar to the patent in suit, document (2) states that a virus strain useful in a vaccine against HSV should be avirulent, stable, provide immunity to wild-type HSV strains, have low pathogenicity and be incapable of transforming host cells (column 2, lines 10 to 15). It discloses, in particular, recombinant HSV-1 with attenuated neurovirulence in which a genome portion responsible for neurovirulence yet non-essential for growth and located at or near the internal inverted repeated sequences of the HSV-1 genome is deleted (column 5, lines 61 to 65). The deleted genome portion

includes (see column 6, lines 65 to 69, and column 7, lines 1 to 13)

"*(a) unidentified genes located between the α27 gene and the α0 gene; (b) one copy of the α0 gene located in the internal inverted repeats; (c) one copy of the $\gamma_1$34.5 gene located between the α0 gene and one or more a sequences forming the natural junction between the L and S components; (d) all a sequences and one copy of the sequences designated as C' and located between the a sequence and the 3' terminus of the α4 gene; and (e) all of the coding sequences of the α4 gene and the copy of the 5' transcribed non-coding sequences and of the α4 gene located in the internal inverted repeats up to the BamHI cleavage site between BamHI Y and BamHI N fragments."*

As can be taken from the patent in suit at page 4, lines 29 to 35, the above deleted region has a size of 14,5 kb spanning the internal repeats of HSV-1. In addition to the deletion, a portion of the HSV-2 genome is inserted between the end points of this deletion (see document (2), column 5, lines 61 to 65 and claim 1).

38. Thus, document (2) and the invention share the same purpose, i.e. providing HSV vaccines based on herpes virus strains, and have furthermore in common that in the virus on which the vaccine is based the genome has been altered in the portion responsible for neurovirulence. Accordingly, the board agrees with the appellant and considers document (2) to represent the closest prior art for the assessment whether or not the

subject-matter of claim 1 of the two sets of claims of the main request involves an inventive step.

39. The claimed subject-matter differs from the teaching of document (2) in that, apart from the absence of any insertion of HSV-2 genome sequences, the herpes simplex virus-1 on which the vaccine is based has a genomic structure which is only minimally altered which results in the effect that normal expression of immunity-inducing viral components, as far as possible, is maintained.

The problem to be solved

40. The problem to be solved by the claimed invention may therefore be formulated as the provision of a vaccine against herpes simplex virus-1 which is based on a herpes simplex virus-1 and which maintains maximal normal expression of immunity-inducing viral components.

41. The board is satisfied that the subject-matter of claim 1 of both sets of claims of the main request solves this problem. It can be deduced from the disclosure of the present invention, in particular from its experimental part, that brain cells do not express genes whose products can substitute for the HSV ICP34.5 gene product and complement the deletion mutant lacking a functional ICP34.5 gene product. This leads to the conclusion that the ICP34.5 protein is necessary for the dissemination of the virus from cell to cell and the destruction of brain tissue characteristic of human encephalitis (see page 12, lines 58 and 59 and page 13, lines 1 and 2). It is thus made plausible that the absence of a functional ICP34.5 gene product from a

herpes simplex virus-1 is **necessary and sufficient** for a non-neurovirulent phenotype which preserves the immunological properties of the virus in a maximal manner. In particular the neurovirulence studies on page 12, example 10, especially in Table 1, and in the latency studies on page 13, example 11, document the suitability of the disclosed HSV-1 deletion mutants to be formulated as vaccines.

42. In view of the above problem, the relevant question is whether the prior art rendered it obvious to the skilled person that the mere prevention of the transcription of both copies of the ICP34.5 gene from an intact HSV-1 would have led to the loss or substantial attenuation of HSV-1 neurovirulence thereby rendering it useful for the formulation of a vaccine which maintained the immunogenic properties of the virus as complete as possible.

43. Document (2) itself states, in the paragraph bridging columns 5 and 6, that "*[s]pecifically, it has been found that deletion from the HSV-1 genome of all sequences between the 3' terminus of the α27 gene and the promoter region of the α4 gene is sufficient to attenuate the genome without inhibiting its ability to grow, while providing sufficient space for the insertion of genetic material without affecting the packaging of the genome.*". Document (2) therefore does not suggest that the sole alteration of the ICP34.5 genes, as opposed to the deletion of the whole 14,5 kb region spanning various HSV-1 genes, is necessary and sufficient for avirulence whilst maximally preserving the immunogenic properties of the virus. In particular, document (2) is silent on any particular role of the

ICP34.5 genes and their products. Document (2) taken alone can therefore not be considered to render the subject-matter of claim 1 of both sets of claims of the main request obvious.

44. Document (9) reports on the sequences of the ICP34.5 genes of various pathogenic HSV-1 strains (see Fig. 2) and states that the function of the ICP34.5 gene was not known but had become of interest because several loci related to virulence mapped in its vicinity. The authors therefore re-examined the sequence of the gene (see e.g. page 1014, right hand column, lines 17 to 20). The results demonstrate that, with minor variations, the open reading frame is conserved in three analysed HSV-1 genomes but not in the genome of HSV-1(17)syn+ (see abstract lines 13 to 15), in which the ICP34.5 open reading frame *"is thoroughly disrupted"* (see e.g. page 1014, right hand column, lines 13 to 17). HSV-1(17)syn+, which is considered to be a multipassage HSV-1 laboratory strain (see p. 1014, right hand column lines 27 to 29), is known to be pathogenic and neurovirulent (see document (7), abstract, lines 3 and 4, and page 437, right hand column line 2).

The board considers that, since in one of four HSV-1 strains sequenced the ICP34.5 open reading frame was "thoroughly disrupted" while that strain remained pathogenic, the skilled person would not derive from the teaching of document (9) that alteration of the ICP34.5 gene in HSV-1 leads to the absence of neurovirulence. Therefore, the teachings of documents (2) and (9), even if combined, do not render the claimed subject-matter obvious.

45. Document (7) reports on the restoration of the neurovirulent phenotype in the intertypic recombinant RE6 (which contains sequences from both HSV-1 (67%) and HSV-2 (33%), the latter contributing the internal and terminal repeats of the long unique region; see patent, page 4, lines 37 to 38) by a 1,6 kb fragment contained in pathogenic and neurovirulent HSV-1(17)syn+ strain and which fragment contains the ICP34.5 gene (see page 436, left hand column, lines 29 to 35, page 437, lines 1 to 4, page 448, left hand column, lines 37 to 43 and Fig. 1). From the described studies it is concluded in document (7) that recombinants which incorporate this fragment are substantially more neurovirulent than RE6 (see abstract, page 443, left hand column, lines 17 to 20, and Fig. 1). The results demonstrate that HSV-1 sequences residing in the fragment were able to produce highly neurovirulent viruses when incorporated into the RE6 genome (see page 439, right hand column, lines 12 to 16). It is noted in the document that further analysis will be required to determine if a gene product is encoded in this region (see page 448, left hand column, lines 45 to 47).

In view of the above the board notes that the experiments carried out according to document (7) relate to an artificial HSV-1/-2 intertypic recombinant, of which about one third of the genome consists of HSV-2 sequences. Thus the skilled person would have doubts whether a fragment causing neurovirulence in this intertypic recombinant represents the decisive neurovirulence factor in wild type HSV-1. Indeed, at page 448, right hand column, penultimate paragraph, the authors of document (7) themselves acknowledge that

they have not ruled out the possibility that the phenotype displayed by RE6 is solely a result of its intertypic genomic structure.

Furthermore, the 1,6 kb fragment referred to in document (7) was taken from strain HSV-1(17)syn+. It was, however, known at the priority date (see e.g. document (9) and point 44 above) that in this strain the ICP34.5 gene, which had been localised within the limits of the fragment, is "thoroughly disrupted". Therefore the skilled person would not conclude that the ICP34.5 gene is implied in the restoration of the neurovirulence in RE6, let alone assume the ICP34.5 gene to constitute neurovirulence factor in wild type HSV.

46. Documents (3), (4) and (27) disclose variant JH2604 of HSV-2 strain HG52 which does not display neurovirulence in mice whereas it grows like the wild type strain in a single-cycle growth experiment. JH2604 is a deletion mutant of strain HG52 having a 1488 bp deletion within the 3 kb long *Bam*HI v fragment located within the long repeat of the HSV-2 genome. It follows from the documents that the results imply that sequences within the 3 kb terminal portion of R_L are required for virulence of HSV-2 strain HG52 (see e.g. document (3), abstract, last sentence) and that sequences within the described 1488 bp fragment confer neurovirulence in BALB/c mice (see e.g. document (4), page 3077, lines 42 to 44). Document (27) reports on the identification of the ICP34.5 gene in HSV-1 which is located in the same genomic region as the deletion in the HSV-2 deletion mutant strain JH2604. The document states further that it was still under analysis whether the deleted

sequences in the HSV-2 variant contained an ORF (see page 132, lines 10 to 11 and page 133, lines 7 to 10).

In summary, documents (3), (4) and (27) do not teach the skilled person that it was solely the deletion of a HSV-2 gene corresponding to the ICP34.5 gene of HSV-1 which was responsible for the non-neurovirulent phenotype in the disclosed HSV-2 variant, let alone that the sole alteration of the ICP34.5 genes in HSV-1 would provide a suitable HSV-1 vaccine virus.

47. For the above reasons the board concludes that a combination of the disclosure of document (2) with either of documents (3), (4), (7), (9) or (27) does not render the claimed subject-matter of the new main request obvious. Therefore the cited prior art is not detrimental to inventive step of this subject-matter.

Sufficiency of disclosure

48. The respondents have argued that it followed from post-published document (17) that any genetic modification of ICP34.5 genes in HSV-1 simultaneously resulted in genetic modifications of the gene ORF-P located anti-sense to the ICP34.5. Since the patent did not disclose a method which did not interfere with the expression of the ORF-P gene there was a lack of enabling disclosure. However, according to the claim interpretation adopted by the board (see above point 11), the claimed method does not require that, when preventing only the "transcription" of an active product from the ICP34.5 genes, interference with the expression of the ORF-P gene has to be avoided. Therefore this argument of the respondents fails.

49. The respondents have furthermore argued that the subject-matter of claim 1 of the new main request for all designated Contracting States except ES was not restricted to a method for preparing a vaccine against HSV-1 as the claim did not explicitly indicate this functionality. The scope of this claim 1 was therefore broader and accordingly the burden of proving the functionality of the invention for vaccines against other viruses or herpes viruses lay with the appellant.

However, as already set out above in point 8, the board does not follow this claim interpretation of the respondents but interprets the term "herpes simplex virus-1 vaccine" in claim 1 of the new main request for all designated Contracting States except ES as requiring that the vaccine provides immunoprotection against HSV-1.

50. The respondents have additionally argued that there was no enabling disclosure of a HSV-1 vaccine since the description was devoid of any experimental data in this respect. It could be taken from post-published document (15) that, even as late as 1999, no effective vaccines to HSV had become available. Accordingly, further inventive work was still necessary departing from the disclosure of the patent.

The board is nevertheless satisfied that the claimed subject-matter solves the technical problem underlying the present invention of providing a vaccine against HSV-1 (see already point 41). The respondents have failed to substantiate their objections by verifiable facts. Furthermore, even if, as maintained by the

respondents and stated in document (15), no save and effective HSV vaccine was yet available in 1999, this does not prove the non-workability of the present invention in view of various possible reasons, e.g. of economic or regulatory nature, for hampering the market introduction of such vaccines. Indeed, the same document (15), in the paragraph bridging pages 1685 and 1686, explicitly reports on plans for human trials with HSV vaccines based on ICP34.5 deleted herpes simplex viruses.

51. In view of the above considerations, the board has come to the conclusion that the claimed subject-matter has to be regarded as sufficiently disclosed.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent in amended form on the basis of the main request filed at the oral proceedings and consisting of claims 1 to 3 for all designated Contracting States except ES and claims 1 to 3 for ES, and a description to be adapted.

The Registrar The Chairman

P. Cremona R. Moufang