BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

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Datasheet for the decision of 19 February 2009

Case Number: T 1475/07 - 3.3.08

Application Number: 97308133.4

Publication Number: 0841392

IPC: C12N 1/10

Language of the proceedings: EN

Title of invention:
Attenuated live neospora vaccine

Patentees:
PFIZER INC., et al

Opponents:
Wyeth
Akzo Nobel N.V.

Headword:
Attenuated Neospora vaccine/PFIZER

Relevant legal provisions:
EPC Art. 101(2) first sentence, 100(a), 56
RPBA Art. 15(3),(6)

Keyword:
"Granted claims - inventive step (no)"

Decisions cited:
-

Catchword:
-

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Case Number: T 1475/07 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 19 February 2009

Appellant: (Opponent 02)
Akzo Nobel N.V.
Velperweg 76
NL-6824 BM Arnhem (NL)

Representative:
Keus, Jacobus Albertus Ronald
INTERVET INTERNATIONAL B.V.
P.O. Box 31
NL-5830 AA Boxmeer (NL)

Respondents: (Patent Proprietors)
PFIZER INC.
235 East 42nd Street
New York
N.Y. 10017-5755 (US)

Auburn University
309 Samford Hall
Auburn, AL 36849-5112 (US)

Representative:
Courgeon, Antonie
Pfizer
European Pharma Patent Department
23-25, avenue du Docteur Lannelongue
F-75668 Paris Cedex 14 (FR)

Party as of right: (Opponent 01)
Wyeth
Five Giralda Farms
Madison
New Jersey 07940-0874 (US)

Representative:
Mannion, Sally Kim
c/o Wyeth Laboratories
Huntercombe Lane South
Taplow
Maidenhead
Berkshire SL6 0PH (GB)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 21 June 2007 rejecting the opposition filed against European patent No. 0841392 pursuant to Article 102(2) EPC 1973.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julià
T. Karamanli

Summary of Facts and Submissions

I. Two oppositions were filed against European patent No. 0 841 392 (filing date: 14 October 1997, priority date: 12 November 1996) on the grounds as set forth in Articles 100(a) and (b) EPC 1973 for lack of novelty and of inventive step (Articles 54(1) and 56 EP 1973) and for insufficiency of disclosure (Article 83 EPC 1973). The opposition division considered that the patent granted with 14 claims fulfilled the requirements of the EPC and the opposition were therefore rejected (Article 102(2) EPC 1973).

II. On 31 August 2007, opponent 02 (appellant) filed a notice of appeal, paid the appeal fee on the same day and, on 2 November 2007, filed the statement setting out the grounds of appeal.

III. In a letter dated 21 March 2008, the patentees (respondents) replied to the appellant's statement of grounds of appeal.

IV. With a summons to oral proceedings dated 18 September 2008, the board sent a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), indicating its preliminary, non-binding opinion. The board noted that, since no arguments were raised against the findings of the opposition division on Article 100(a) EPC 1973 for lack of novelty (Article 54(1) EPC 1973), the subject-matter of the appeal was restricted to Articles 100(a) and (b) EPC 1973 for lack of inventive step and for insufficiency of disclosure.

V. In a letter dated 16 January 2009, the appellant replied to the board's communication and filed an expert declaration of Prof. Dr. J. M. Wastling.

VI. No reply to the board's communication was received from the respondents or opponent 01 (party as of right).

VII. In a fax dated 12 February 2009, the respondents announced that they would not be attending the oral proceedings scheduled to take place on 19 February 2009. In faxes dated 17 and 18 of February 2009, respectively, the appellant and opponent 01 announced that they would not be attending the oral proceedings.

VIII. Oral proceedings took place on 19 February 2009 in the absence of all parties.

IX. Claim 1 of the patent as granted reads as follows:

"1. A culture of cells of a strain derived from a pathogenic parent strain of a species of *Neospora*, which cells exhibit attenuated pathogenicity compared to those of the parent strain but which are capable of triggering an immune response that protects a mammal against neosporosis when administered as a live vaccine."

Claims 2 to 5 concerned particular embodiments of claim 1. Claims 6 to 9 were directed to a vaccine to protect a mammal against neosporosis comprising an immunologically effective amount of live cells of a strain defined as in claim 1 and a veterinary acceptable carrier. Claims 10 and 11 related to a method for preparing a culture of attenuated cells of a

species of *Neospora* for use in a vaccine, and claims 12 and 13 to a method for preparing a vaccine to protect a mammal against neosporosis. Claim 14 concerned a combination vaccine comprising an immunologically effective amount of live cells of a strain defined as in claim 1 and one or more other antigens that triggered an immune response that protected the mammal against a disease or a pathological condition and a veterinary acceptable carrier.

X. The following documents are cited in this decision:

D1: EP 0 100 710 (publication date: 15 February 1984);

D2: D.S. Lindsay et al., Am. J. Vet. Res., January 1996, Vol. 57, pages 68 to 72;

D3: WO 95/25541 (publication date: 28 September 1995).

XI. The appellant's arguments submitted in writing, insofar as relevant to the present decision, may be summarized as follows:

Article 56 EPC 1973

Document D1, the closest prior art, had the same purpose (obtaining an attenuated mutant for use as a live attenuated vaccine) as the patent in suit and disclosed all features of claim 1 except for the type of parasite cells used, namely *Toxoplasma* instead of *Neospora*. However, both parasites were closely related as shown by the fact that *Neospora* had initially been termed a "*Toxoplasma*-like" organism. Thus, a skilled person, knowing the teachings of document D1 as regards

Toxoplasma, would have had no hesitation to apply them also to *Neospora* without any difficulty and using standard techniques well-known in the art. If doubts remained on the applicability of those teachings to *Neospora*, then document D2 showed that no technical problems were to be expected and no modifications required. As a matter of fact, even the patent in suit relied on the results obtained with *Toxoplasma* for supporting the use of standard recombinant DNA techniques in *Neospora* attenuation. Although the skilled person had many alternatives at hand for attenuating *Neospora*, the steps described in the patent in suit (chemical mutation and mutagen, conditions, selection techniques and cell-culturing used, aim for a temperature sensitive (ts) mutation and for a live attenuated mutant vaccine) were all identical to those of document D1. Thus, it was obvious for the skilled person to apply the teachings of D1 to *Neospora* with a reasonable expectation of success, since no technical problems were to be expected as shown by document D2. The combination of these two documents taught the claimed subject-matter.

The technical problem had not, however, been solved in the patent in suit since there was no proof that the described *Neospora* cells were indeed attenuated or that immune protection was provided beyond that of the wild-type vaccination already known in the art. The patent in suit provided only proof for the *Neospora* cells to be attenuated in inbred laboratory mice. Nevertheless, such attenuation was apparently not repeatable using outbred mice (even when immune-suppressed) or a more realistic animal model, such as goats. In the light of the limited facts

provided by the patent in suit, the speculations made therein on the attenuated character of the described *Neospora* cells were not plausible and therefore, they did not fulfil the criteria established by the case law of the boards of appeal.

XII. The arguments submitted in writing by the respondents, insofar as relevant to the present decision, may be summarized as follows:

Article 56 EPC 1973

The selection of document D1 as the closest prior art implied hindsight, since it related to a technical field different from that of the patent in suit, namely vaccines containing a low virulence *Toxoplasma gondii* strain for protection of human, cattle and other mammals against toxoplasmosis. The specific low virulence strain was the ts-4 mutant which was isolated by selection of temperature dependent mutants and then tested for attenuated virulence in mice. Document D1 did not even mention the technical field of the patent in suit, namely attenuated protective *Neospora* strains for use as live vaccines. Whereas the ts-4 mutant had been known from 1976, *Neospora* was identified only in 1988 and yet the present invention was not made until 1996. Also toxoplasmosis was a distinct set of pathologies from that of neosporosis. The extent of relatedness between *Toxoplasma* and *Neospora* was not settled in the prior art and did not allow any prediction from one species to the other. There was prior art on file showing that before the priority date of the patent in suit there was insufficient information to assess similarity between *Toxoplasma* and

Neospora. Although a number of their genes shared a certain degree of homology, the general consensus was that they were distinct species, their pathologies were not the same and the results from one organism could not always apply to the other. Document D1 did not prove that the disclosed vaccine protected against *Toxoplasma* foetal infection (since the strain was never tested in uterus infection) and did not even mention a potential protection against abortion. Document D1 did not suggest that the method taught could be applied to other organisms, in particular to *Neospora*, which was never mentioned in that document. From document D1 alone, it was not possible to imply that the disclosed approach would have been successful with other parasites since, although chemical mutagenesis was shown to produce ts mutants for multiple species, it did not guarantee attenuation or useful vaccines.

There was also no reason to combine documents D1 and D2, certainly not because both documents used NMNG chemical mutagenesis. There was no evidence that the skilled person would have considered documents D1 or D2 in any way helpful in the *Neospora* vaccine art. Document D2 did not provide any motivation to use the disclosed chemical mutagenesis for selecting a live attenuated protective *Neospora* strain. Therefore, since document D1 was not the closest prior art and the problem to be solved was not that proposed by the appellant and since there was no reason to combine documents D1 and D2 and, even if they were combined, document D2 did not bridge the gap between the two documents, the combination of these two documents was not detrimental to inventive step.

Document D3, the closest prior art, related to biologically pure *Neospora* cultures for use as vaccines or as a source of antigenic *Neospora* polypeptides for use in vaccines. The technical problem to be solved was the provision of an alternative *Neospora* vaccine - safer than a cultured parent strain and protective against neosporosis in mammals - by methods other than use of a subunit antigen or a transformed viral vector. The solution provided by the patent in suit was, in the first place, the conception that a live pathogenically attenuated *Neospora* strain could be created and would be useful and, in the second place, the proof of principle that protective pathogenically-attenuated live strains of *Neospora* could be created. None of the prior art suggested the use of an attenuated *Neospora* strain for protective use nor did the prior art provide any attenuated *Neospora* strain to the skilled person. There was no suggestion in document D3 that protective pathogenically-attenuated *Neospora* strains were desirable or possible and therefore, there was no motivation for the skilled person to achieve the claimed subject-matter. Although in the vaccine art it was known that attenuation of pathogens sometimes resulted in successful protection, in the absence of any protective attenuated *Neospora* strain available, the skilled person had no basis on which to judge the prospect of success. It was only with the first proof of principle, i.e. the disclosure of the patent in suit, that the concept of reasonable expectation of success in creating a protective attenuated *Neospora* strain had a real meaning.

Example 2 of the patent in suit demonstrated that without immune-suppression HSD:ICR mice were resistant

to *Neospora* infection and that, despite such resistance, those mice produced an immune response to both wild-type and mutant *Neospora* strains. Examples 1, 3 to 5 and 7 showed that the NCTS-8 strain was attenuated relative to the parent NC-1 strain and was substantially protective in pigmy goats, which were mammals suffering neosporosis and, in the art, considered to be a predictive model for cattle. In Example 1, mutants NCTS-4, NCTS-8 and NCTS-12 were attenuated in their ability to bring about death to the mouse when compared to NC-1 strain (Table 2). Attenuation of the mutants was then confirmed in Example 3 where NC-1 killed all five mice, whereas the mutants did not kill as many (NCTS-4 did not kill any) (Table 7). The claimed subject-matter was not limited to protective attenuated *Neospora* strains in pregnant cows alone but in mammals in general. The use of inbred laboratory mice as a test mammal for neosporosis was of utility and predictive value. The use of standard laboratory animals (mice, rabbit, hamster and squirrel monkeys) was admitted as a credible predictive model of toxoplasmosis for mammal species of interest (cattle, sheep, goats, etc.) in document D1. There was no evidence on file showing that pygmy goat was not a predictive model of the target animals. Indeed, it was generally accepted that clinical diseases observed in that animal as a result of infection (abortion and stillbirth), along with the pathologic lesions found in foetal brains, as well as the gestational ages of the aborted kids, fairly showed the outcome of these infections to resemble those seen in target animals, particularly in cattle.

XIII. The appellant (opponent 02) requested in writing that the decision under appeal be set aside and that the patent be revoked.

XIV. The respondents (patentees) requested in writing that the appeal be dismissed.

Reasons for the Decision

1. The present decision was taken after the revised European Patent Convention ("EPC 2000") entered into force on 13 December 2007. Since the European patent in suit was already granted at that time, the Board applies the transitional provisions in accordance with Article 7(1), second sentence, of the Act revising the EPC of 29 November 2000 and the Decisions of the Administrative Council of 28 June 2001 (Special edition No. 1, OJ EPO 2007, 197) and 7 December 2006 (Special edition No. 1, OJ EPO 2007, 89). Articles and Rules of the revised EPC and of the EPC valid until that time are cited in accordance with the Citation Practice (cf. the 13th edition of the European Patent Convention, page 4).

2. Since, all duly summoned parties did not attend the oral proceedings (cf. Sections IV and VII *supra*) the board relied for its decision only on the parties' written submissions (Article 15(3) RPBA). The board was in a position to decide at the conclusion of the oral proceedings, since the case was ready for decision (Article 15(6) RPBA) and the voluntary absence of the parties was not a reason for delaying the decision (Article 15(3) RPBA).

The claims as granted

Inventive step (Article 100(a) EPC 1973, Article 56 EPC 1973)

3. To assess inventive step, the boards apply the "problem-solution approach" which requires as a first step the selection of the closest prior art. This is normally a prior art document disclosing subject-matter conceived for the same purpose as the claimed invention and having the most relevant technical features in common with the patent in suit (cf. "Case Law of the Boards of Appeal of the EPO", 5th edition 2006, I.D.3.1, page 121). In line with the decision under appeal, the board considers document D3 to represent the closest prior art.

4. Document D3 discloses the isolation and *in vitro* cultivation of *Neospora* from bovine foetuses (isolates BAP1 to BAP6) (cf. Example 1, page 24). These isolates (and purified proteins thereof) are used for raising antibodies specifically reactive with *Neurospora* antigens as well as for preparing pharmaceutical compositions to be used as vaccines. Although it is stated that "*preferred vaccines comprise partially or completely purified Neospora protein preparations*" and that "*preferred vaccines are subunit vaccines that elicit antibody and cell-mediated immunity (CMI) to antigens of bovine Neospora*" (cf. page 23, lines 23 to 25 and page 21, lines 26 to 29), document D3 also contemplates the use of "*a crude extract of Neospora tachyzoites, bradyzoites or other stages*" as "*vaccines of the invention*" (cf. page 23, lines 20 to 22). Notwithstanding the possible experimental deficiencies of Example 5 in document D3, the fact is that this document explicitly states that "*cows infected using*

culture-derived tachyzoites mount a protective immune response and prevent transplacental infection of the fetus" (cf. page 21, lines 33 to 37 and page 52, Example 5). In this context reference is also made to an "*attenuated Neospora vaccine*" which, according to document D3, "*can only be used in the absence of a risk of human infection should the milk or tissues of immunized animals be consumed*" (cf. page 21, lines 24 to 26).

5. In view of this disclosure, the conception of an "*attenuated Neospora vaccine*" does not provide any contribution over the prior art, let alone an inventive one. The indication of preferred embodiments in a prior art document does not automatically exclude and render doubtful or meaningless other non-preferred embodiments. The less so in those cases where these non-preferred embodiments might well be advantageous under certain particular conditions. At least in cases where "*the absence of a risk of human infection*" is given, the production of subunit vaccines or isolated immunogenic proteins might be more difficult (selection of a suitable antigen) and less advantageous (immunity against a single antigen) than the production of attenuated vaccines (stimulation of both humoral and cell-mediated immunity by multiple antigens). The more so in view of the results shown in document D3 for cows infected using culture-derived *Neospora* tachyzoites, even though disputed by the respondents. Therefore, the technical contribution of the patent in suit over the closest prior art document D3 is - using the words of the respondents - the provision of "*the proof of principle that protective, pathogenically attenuated, live strains of Neospora can be created*".

6. Starting from document D3, the technical problem to be solved is thus the provision of alternative means for generating a protective immune response against *Neospora*. The solution proposed in the patent, namely the use of an attenuated *Neospora* vaccine, is essentially based on the suggestion put forward in document D3. For the reasons given below, the board concludes that the underlying technical problem is indeed solved by the proposed solution (cf. points 10 and 11 *infra*).

7. Although document D3 identifies 11 proteins that are specifically recognized by antibodies from *Neospora* infected cattle (cf. page 9, lines 13 to 25), none of these antigens has been purified and tested for production of a vaccine. In fact, the examples of document D3 concern only *Neospora* isolates. Example 1 describes the isolation, *in vitro* cultivation and characterization of *Neospora* from aborted bovine foetuses (cf. pages 24 to 38). Isolates BPA1 and BPA2 were maintained in cultures of bovine 87-3 trophoblast cells, bovine cardiopulmonary aortic endothelial cells (CPAE), or M617 bovine macrophages. Contrary to *N. caninum* and *Hammondia heydorni* which grow better in bovine monocyte cells, the best growth for *Neospora* was observed in the 87-3 and CPAE cultures (cf. page 33, lines 7 to 9 and page 36, lines 24 to 28). Control cultures of *T. gondii* (RH strain) were also maintained in CPAE and M617 monolayer cultures (cf. page 27, lines 14 to 17). Example 2 describes an indirect fluorescent antibody test for detection of *Neospora*-specific antibody responses in cattle that were naturally infected with *Neospora* or experimentally

infected with culture-derived tachyzoites of BPA1 *Neospora* isolates (cf. page 38 to 46). Tachyzoites of both BPA1 and *T. gondii* (RH) isolates were obtained from CPAE monolayer cultures (cf. page 38, lines 27 to 31, page 39, lines 17 to 21). Examples 3 and 4 are concerned with the isolation of DNA encoding nss-rRNA and the preparation of primers and probes for the detection of *Neospora* (cf. pages 46 to 52). Example 5 describes experimental infections of pregnant cows using culture-derived tachyzoites of the BPA1 *Neospora* isolate (cf. pages 52 and 53).

8. In view of the fact that the advantages of attenuated live vaccines were known in the art (cf. point 5 *supra*), even more - and specially - when compared to culture-derived tachyzoites, the production of attenuated *Neospora* strains are the logical and obvious next step after the disclosure of the results shown in Example 5 of document D3. The more so in absence of an identification of any appropriate antigen or subunit vaccine (cf. point 7 *supra*).

9. There has been much discussion amongst the parties about the relationship between *Toxoplasma* and *Neospora* and a large body of evidence has been submitted for demonstrating a close relationship or for emphasizing their differences. The fact is that document D3, even though disclosing their antigenic differences (cf. *inter alia* page 8, lines 16 to 19, page 32, Table 1, page 34, Table 2), explicitly acknowledges that "*the most closely related and morphologically similar genera of protozoa ...* (are) *... Toxoplasma, Hammondia and Sarcocystis*" (cf. page 8, lines 19 to 23). Even more important in the board's view is the fact

that *Toxoplasma gondii* is used as a significant (coccidial parasite) control in all the examples of document D3 (cf. point 7 *supra*). Hence, no hindsight is required to consider prior art concerned with *T. gondii* when faced with the above technical problem. The combination of documents D3 and D1, the latter using the very same *T. gondii* strain (RH) as in the former (cf. page 6, line 18 in document D1 and page 27, lines 14 and 15 of document D3) for producing an attenuated *T. gondii* strain ("ts-4" mutant) for use as a vaccine in mammals, is fully justified. And so does the appellant's argumentation on the relevance of document D2 as well (cf. Section XI *supra*).

10. Although for a different purpose, namely the isolation of pyrimethamine resistant strains, the use of chemical mutagenesis disclosed in document D2 for *Neospora caninum* (which document D3 identifies as closely related to *Neospora*; cf. page 30, line 36 to page 37, line 3 and page 33, lines 23 to 30), demonstrates that no difficulties were to be expected when carrying out the teachings of document D1 in the cultured-derived *Neospora* tachyzoites of document D3. Nor were technical difficulties to be expected in the methods used for selecting *Neospora* mutants having the desired properties, i.e. attenuated and immunoprotective. It is also established case law, that high expectations are normally associated with less ambitious goals. In the present case, the patent in suit defines both "*attenuated*" and "*protective immune response*" in broad terms (cf. paragraphs [0015] and [0018]) and hence, a reasonable expectation of success is also given in the present case.

11. It is also in the light of this prior art and taking into account the broad definition of the terms "*attenuated*" and "*protective immune response*" that the appellant's argumentation that the technical problem has not been solved has to be considered. The results shown in the examples of the patent in suit using vaccinated mice and pygmy goats are relevant and sufficient for demonstrating that the technical problem has been solved. However, as stated above, the proposed solution is obvious in view of the combined teachings of documents D3 and D1.

12. Thus, the claims as granted do not fulfil the requirements of Article 56 EPC 1973 and therefore, the ground of opposition under Article 100(a) EPC 1973 prejudices the maintenance of the patent as granted. Accordingly, the patent must be revoked (Article 101(2) first sentence EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

A. Wolinski L. Galligani