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D E C I S I O N
of 24 November 1999

Case Number: T 0372/97 - 3.3.4

Application Number: 88304557.7

Publication Number: 0292293

IPC: A61K 39/17

Language of the proceedings: EN

Title of invention:
Newcastle disease virus vaccine and method for the application thereof

Patentee:
YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM

Opponent:
Akzo Nobel N.V.

Headword:
Newcastle disease virus vaccine/YISSUM RESEARCH

Relevant legal provisions:
EPC Art. 56, 104(1)

Keyword:
"Inventive step - main request (yes)"
"Different apportionment of costs (no)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0372/97 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 24 November 1999

Appellant: (Opponent)
Akzo Nobel N.V.
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Nl-6824 BM Arnhem (NL)

Representative:
-

Respondent: (Proprietor of the patent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 29 January 1997 concerning maintenance of European patent No. 0 292 293 in amended form.

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: R. E. Gramaglia
W. Moser

Summary of Facts and Submissions

I. European patent No. 0 292 293 (application No. 88 304 557.7) was granted on the basis of 5 claims. The patent relates to a Newcastle Disease (ND) virus vaccine and a method for the application thereof. Independent claim 1 as granted read as follows:

"1. A vaccine composition for respiratory tract application against Newcastle Disease and containing a live Newcastle Disease Virus characterised in that the composition comprises a live immunogenic, lentogenic or mesogenic strain of Newcastle Disease virus in combination with a liquid containing a mineral or vegetable oil adjuvant carrier."

Claims 2 to 5 were directed to specific embodiments of the vaccine of claim 1.

II. Notice of opposition was filed by the appellant (opponent). Revocation of the patent in its entirety was requested on the grounds of Article 100(a) EPC, ie lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC).

III. By its decision given orally and issued in writing on 29 January 1997, the opposition division maintained the patent on the basis of claims 1 to 5 of the main request submitted on 11 October 1996, of which claim 1 had the format of a second/further veterinary use:

"1. Use of a composition comprising a live immunogenic, lentogenic or mesogenic strain of Newcastle Disease virus in combination with a liquid containing a mineral or vegetable oil adjuvant carrier for the manufacture

of a vaccine composition for respiratory tract application against Newcastle Disease.",

and claims 2 to 5 were directed to specific embodiments of the veterinary use according to claim 1.

IV. Of the documents cited during the opposition proceedings, the following are referred to in the present decision:

(1) GB-A-2 170 708;

(2) JP-A-52087221 and English translation thereof;

(3) Allan W.H. et al., in "Newcastle Disease Vaccines, their Production and Use", FAO Animal Production and Health Series No. 10, Food and Agriculture Organization of the United Nations, Rome, pages 74-92 (1978);

(4) Bennejean G. et al., Avian Pathology, vol. 7, pages 15-27 (1978).

V. The appellant filed a notice of appeal against this decision and a Statement of Grounds of Appeal. The respondent (proprietor of the patent in suit) filed counterarguments. On 22 October 1999, the appellant submitted further documents, inter alia:

(10) GB-A-1,408,437;

(11) Spanoghe L. et al., Avian Pathology, vol. 6, pages 101-109 (1977).

VI. Oral proceedings were held on 24 November 1999.

VII. The appellant submitted in writing and at the oral proceedings essentially the following arguments:

Inventive step

- The closest prior art was represented by document (3) which described the general practice of vaccinating young chickens against ND virus by application of live ND viruses via the respiratory tract. It was stated in this document that this vaccination technique gave the most reliable host's immune response.

- Assuming that the problem to be solved by the patent in suit in the light of this prior art document were to provide a live ND vaccine for application via the respiratory tract with improved immunogenic properties (long-term immunity), the solution proposed in claim 1 of the patent in suit (ie, adjuvating live ND virus vaccines for respiratory tract application with a mineral or vegetable oil) failed to solve this problem because Table 1 thereof was not concerned with (and thus did not show) any improvement of the oil-adjuvated vaccine over the one without oil. Further, it was known that a single spray of a **non-oil-adjuvated** live ND virus vaccine was sufficient to confer a relatively long-term immunity on all young chickens vaccinated between the age of one and 10 days (see document (11)). Document (3) also showed that spraying of a non-oil-adjuvated live ND virus vaccine induced both humoral cellular antibody response, in particular local antibody response. Thus, it was doubtful that the addition of an oil adjuvant could further

improve the host's immune response.

- Even by assuming that the claimed oil-adjuvated vaccine achieved some improvement of the immune response over the one without oil, the skilled person would have arrived at the solution proposed in claim 1 of the patent in suit without the exercise of an inventive step in the light of the following facts:

- The skilled person was aware that a way for improving vaccine immunity was the addition of adjuvants. A series of documents already disclosed addition of adjuvants, in particular an oil, in order to improve the immune response to said vaccines.

  Document (1) disclosed the use of a w/o emulsion as adjuvant in a live ND vaccine for application via injection and taught the skilled person that the addition of oil adjuvants in the context of live vaccines had no adverse effect such as inhibition of the virus' replication. It was stated that the latter exerted their adjuvating effect via a depot function (slow release effect) when administered parenterally. However, they could also be used in a different pharmacological context such as the application via the respiratory tract without loss of the adjuvating capacity.

  Document (2) disclosed the use of a mineral oil, in the application of live and inactivated vaccines via the respiratory tract to improve immunity of poultry (page 3, third paragraph).

Document (4) disclosed the combined use of a live ND vaccine applied via the respiratory tract and oil-adjuvated inactivated ND vaccine.

Document (10) disclosed oil/water vaccines for immunizing vertebrates including livestock by inter alia a nasal spray technique.

VIII. The respondent submitted in writing and at the oral proceedings essentially the following arguments:

Late filed documents

- The documents filed by the appellant on 22 October 1999 (see paragraph V supra) had to be disregarded.

Inventive step

- Application of live ND vaccine via the respiratory tract resulted mainly in humoral antibody response which was of short duration. Therefore the problem arose of providing a live ND virus vaccine for application via the respiratory tract with improved (long-term) immune response.

- Comparative Examples A and B of the patent in suit showed an improvement of the effect of the oil-adjuvated vaccine over the one's without oil.

- The application of a live ND virus vaccine with an oil adjuvant to the respiratory tract of young chickens was not suggested by any prior art document. The skilled person would not have used oil adjuvants, which were known for injection, for

application via the respiratory tract of a live replicating virus in its natural site: there was no need of a slow release of the virus. There was rather the possibility that the oil adjuvant might have interfered with the virus absorption and multiplication.

- Document (2) was mainly concerned with adding surface active agents to vaccines. Page 3 thereof listed surface active agents and mineral and vegetable oil were also included in this list although they did not exhibit any surface active property. In order that the skilled person reading document (2) arrived at the claimed vaccine, (s)he had to make a narrow selection among a huge number of combinations.

Reimbursement by the appellant of all the costs incurred during the appeal proceedings

- The appellant was a large company with considerable resources. Forcing the respondent, a small research company associated with a university, to go through more rounds of written and oral proceedings before the EPO represented a significant drain on his limited resources. For reasons of equity, the appellant had thus to bear all the costs incurred by the respondent, in accordance to Article 104(1) EPC.

IX. The appellant requested that the decision under appeal be set aside and that the European patent No. 0 292 293 be revoked.

The respondent requested as main request that the

appeal be dismissed, or that the decision under appeal be set aside and that the patent be maintained on the basis of the following documents filed on 22 October 1999:

(a) claims 1 to 5 as auxiliary request 1, or

(b) claims 1 to 4 as auxiliary request 2.

The respondent further requested that all of its costs incurred during the appeal be borne by the appellant for reasons of equity, in accordance with Article 104(1) EPC.

Reasons for the Decision

1. The appeal is admissible

Late filed documents

2. The respondent requests that the documents filed by the appellant on 22 October 1999 (see paragraph V supra) be disregarded. However, the board observes that the respondent took up these documents and had the opportunity to comment on their relevance during both the written phase and the oral proceedings. The board is thus not prepared to exclude these documents from the present appeal proceedings, having also regard to the introduction by the respondent himself of four new references in response to the Statement of Grounds of Appeal (see point 1.31 of the respondent's submission of 12 November 1997).

Main request

Inventive step (Article 56 EPC)

3. The board agrees with the parties that document (3) represents the closest prior art. This document discloses the general practice of vaccinating young chickens against ND virus by application of live ND viruses via the respiratory tract (see page 86, lines 9 to 11).

4. The problem the patent in suit purports to solve is to improve the live ND virus vaccine known from document (3) so as to obtain a long term host's immune response thereto upon administration to young chickens via the respiratory route. This is achieved according to the claim 1 of the patent in suit by addition to the known ND virus live vaccine of a mineral or vegetable oil as adjuvant.

5. The appellant maintains that Table 1 of the patent in suit does not show an improvement of the immunogenic properties of the claimed vaccine adjuvated by means of a vegetable or mineral oil over the ones of the vaccine devoid of said oil, inter alia because the experiments of Table 1 do not compare the effects of the oil-adjuvated vaccine with those of the vaccine devoid of said oil. However, in the board's view, Comparative Example A (see patent in suit, page 5) shows that the local immune response of chickens immunized with the oil-adjuvated vaccine is twice as high than that of the vaccine without oil (HI antibody titres in the lungs: 1:56 versus 1:22 respectively). It is also stated in Comparative Example B (page 5, lines 30 to 33) that "One day old chicks were immunized with aqueous solutions of lentogenic LaSota strain alone and with lentogenic strain mixed with mineral oil. Ninety

percent of the chicks immunized intraocularly or by spray with the LaSota strain alone died after challenge". This experimental evidence thus convincingly shows that chickens treated with the oil-adjuvated vaccine according to claim 1 of the patent in suit develop **more** local antibodies than the ones treated with the vaccine without oil. Therefore, while agreeing with the appellant that the non-oil-adjuvated live ND virus vaccine known form document (3) also induces some local antibody response, the board notes that the latter is clearly insufficient and/or of short duration since 90% of the chickens treated with said vaccine without oil adjuvant die upon virus challenge. Thus, in view of the experimental results reported in the patent in suit, it is reasonable to assume that there is a correlation between, on the one hand, the very high mortality upon virus challenge in the case of both the administration of the vaccine without oil (90% mortality; see supra) and of non vaccinated control chickens (100% mortality; see Table 1: 0% survival and page 6, line 18: "All controls died"), and on the other hand, the lack of a sufficient and/or long-lasting local secretory antibody response (see Comparative Example A and Tables 2 and 3).

The appellant also maintains that a **single** spray of non-oil-adjuvated live ND virus vaccine of the prior art is sufficient to confer a relatively long-term immunity and hence argues that the addition of an oil adjuvant does not further improve the host's immune response. However, this submission by the appellant is contradicted by eg document (1) (see page 1, lines 22 to 23: "The immunity which results from vaccination of animals with live vaccines is often very short lived") and document (3) (see page 91, first full paragraph),

according to which two doses of the live vaccine have to be administered in order to obtain long-term immunity. All these facts are in line with the statement made on page 104, second full paragraph of document (11), according to which "local HI-titres waned and were not detectable 3-4 weeks after the spray vaccination".

In view of the above findings, the board is satisfied that the use of claim 1 of the patent in suit solves the problem as set out supra.

6. The appellant also argues that oils were widely used as adjuvants and that documents (2) and (4) teach that this type of adjuvant can be used to further improve the immunogenicity of live and inactivated vaccines for spraying chickens to protect them from poultry diseases. However, the board is unable to unambiguously derive this teaching from document (2). It is stated in document (2) (see English translation, paragraph bridging pages 2 and 3) that about 15 pathogens responsible for fowl coryza, ND, Marek disease, fowl pox disease, fowl cerebrospinal inflammation, infectious bronchitis, infectious laryngitis, fowl diphtheria, chronic respiratory disease, synovitis, Rinderpest, brucella disease of cattle, sheep, goat and swine, paratyphoid fever, influenza of horse, infectious enterogastritis and bordetella infectious disease of swine can be combatted by administration of a "preventive agent" orally, nasally or by injection (3 ways of administration: see last paragraph of page 3) in combination with an emulsifier and optionally an adjuvant selected from 7 adjuvants (including an oil) listed in the third paragraph of page 3. Thus, document (2) theoretically embraces 15x3x7=315 possibilities. In

the board's view, the selection among these 315 possibilities of the claimed combination (live ND/oil adjuvant/applied via the respiratory tract) in the hope of solving the problem of significantly improving the immunogenicity of a ND live virus vaccine is not obvious, more so as the document might not relate to live vaccines in view of the statement made on the top of page 4: "The inventor is the first one who has tried to administer the vaccines as a preventive agent, except in the case of live virus vaccines". This statement is in keeping with all the Examples of document (2) relating to killed pathogens. As for document (10), it is even less relevant than document (2) because it relates to multiple oil-water emulsion vaccines intended for injection to domestic animals such as cats, dogs, guinea pigs, pigs, sheep and cattle. Not only is the immune system of fowl different from that of mammalians, but more importantly, document (10) relates to "antigenic material" rather than to live viruses, let alone ND viruses. In conclusion, documents (2) and (4) do not motivate the skilled person to use an oil-adjuvant for further improving the immunogenic properties of a live ND virus vaccine to be administered to chickens via the respiratory tract.

7. The appellant argued that the skilled person has no prejudice in using an oil adjuvant in combination of a live virus vaccine administered via the respiratory tract, in the light of eg document (1). Although the latter document is concerned with parenteral injection, it teaches that the addition of oil adjuvants in the context of live vaccines improves the host's immune response and has no adverse effect such as inhibition of the virus' replication. The board has thus to decide whether or not the skilled person would expect an

improvement in terms of immunity by adjuvating with an oil the live ND virus vaccine **applied via the respiratory tract**, ie to use the oil known to improve the live virus vaccine administered parenterally, in a different pharmacological context.

8. The pharmacological context of an oil adjuvated live virus vaccine administered parenterally can be depicted as follows: (1) the live virus is normally not in its environment of replication, (2) the oil's adjuvating effect occurs inter alia through a depot function, namely a slow release of the immunogen into the bloodstream (see document (1), bottom of page 1 and document (4), page 16, line 4: "disperses antigen slowly") and (3) the parenteral route of immunization achieves mainly a humoral rather than local immunity (see document (1), page 2, line 45: "The immunity was very high, as expressed by the circulating antibody levels"; document (2), page bottom of page 5: "the increasing ratio of the HI titre in blood" and document (4), page 17: "Serological results").

If an oil is used as adjuvant with a live ND virus vaccine applied via the respiratory tract, the skilled person reasonably expects that: (1) the live virus is in its environment of replication; (2) the virus is entrapped by the oil on the respiratory mucosae, and no slow release of the immunogen into the bloodstream occurs; (3) the host's local immune response increases to the expense of the humoral immune response. In conclusion, the effects of an oil addition in the respiratory mode of application are expected by the skilled person to be **diametrally opposite** to those achieved in the context of the parenteral mode of administration. It is thus unlikely that the skilled

person, faced with the problem of improving the host's immune response of a live ND virus vaccine administered to respiratory tract, would use an oil as adjuvant.

9. Since the prior art does not comprise any pointer to the solution proposed in the veterinary use of claim 1, it is the board's conclusion that the subject-matter of claim 1 and dependent claims 2 to 5 of the main request satisfy the requirements of Article 56 EPC. In view of this, no need arises for the board to consider auxiliary requests 1 or 2.

Request for a different apportionment of costs incurred (Article 104 EPC)

10. Pursuant to Article 99(1) EPC, any person, ie also a legal person constituting a big firm, may give notice to the EPO of opposition to a European patent granted; and this person may subsequently lodge an appeal if it is adversely affected by the ensuing decision of the opposition division (Article 107 EPC). Filing a notice of opposition and the subsequent lodging of a notice of appeal can thus not be regarded as a procedural abuse justifying a different apportionment of costs incurred within the meaning of Article 104(1) EPC. Consequently, the respondent's request relating to a different apportionment of costs incurred has to be refused.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

2. The request relating to a different apportionment of costs incurred is refused.

The Registrar: The Chairwoman:

M. Beer U. Kinkeldey