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D E C I S I O N
of 11 November 2002

Case Number: T 0646/99 - 3.3.4

Application Number: 89201779.9

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Language of the proceedings: EN

Title of invention:

IBDV production in continuous cell lines

Patentee:

Akzo Nobel N.V.

Opponent:

MERIAL

Headword:

IBDV vaccine/AKZO NOBEL N.V.

Relevant legal provisions:

EPC Art. 56

Keyword:

"Inventive step - (no)"

Decisions cited:

-

Catchword:

-



Case Number: T 0646/99 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 11 November 2002

Appellant:
(Opponent)

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Decision under appeal:

**Decision of the Opposition Division of the
European Patent Office posted 27 April 1999
rejecting the opposition filed against European
patent No. 0 352 835 pursuant to Article 102(2)
EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: A. L. L. Marie
S. U. Hoffmann

Summary of Facts and Submissions

I. The appeal lies from the decision of the opposition division of 27 April 1999 to reject the opposition and maintain the patent as granted despite the objections of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) raised by the opponent against claims 3 to 6 and 8 to 11 for all contracting states except ES and GR and claims 3 to 9 for ES and GR. Claims 3 and 5 read:

"3. An Infectious Bursal Disease Virus vaccine comprising inactivated Infectious Bursal Disease Viruses, characterized in that the viruses are derived from a mammalian cell line infected with Infectious Bursal Disease Viruses."

"5. An Infectious Bursal Disease Virus vaccine according to claim 4, characterized in that the ape cell line is a Vero cell line.",

and on a set of 10 claims for the designated states ES and GR, claims 3 and 6 of which read:

"3. A method for the preparation of inactivated Infectious Bursal Disease Virus immunogenic material comprising:
(a) culturing Infectious Bursal Disease Viruses on a mammalian cell line,
(b) harvesting Infectious Bursal Disease Virus antigen mass obtained under step (a), and
(c) inactivating the harvested antigen mass obtained under step (b)."

"6. A method according to claim 5, characterized in

that the ape cell line is a Vero cell line.".

II. The following documents are cited in the present decision:

- (1) US-4,530,831
- (2) D.H. Jackwood et al., *Avian Diseases*, 1987, Vol. 31, No. 2, pages 370 to 375
- (3) F.S.B. Kibenge et al., *Avian Diseases*, 1988, Vol. 32, pages 298 to 303
- (4) P.D. Lukert et al., *Am. J. Vet. Res.*, 1975, Vol. 36, No. 4, pages 539 to 540
- (14) V. Kardi et al., *Acta Veterinaria Hungarica*, 1988, Vol. 36 (1-2), pages 123 to 134
- (16) A. Zanella and R. Marchi, *Develop. Biol. Standard.*, 1981, Vol. 51, pages 19 to 32
- (20) G.C. Schild et al., *Nature*, 1983, Vol. 303, pages 706 to 709
- (22) US-4,525,349
- (23) US-4,664,912
- (24) T.W.F. Pay et al., *Developments in Biological Standardization*, 1983, Vol. 60, pages 171 to 174
- (25) US-3,228,840
- (26) FR-2.133.504

- (33) Compendium of Veterinary Products, Poultry Edition, 1993
- (34) Diseases of Poultry, 1984, 8th edition, M.S. Hofstad et al., editors, Iowa State University Press, Ames, Iowa, USA
- (35) Diseases of Poultry, 1991, 9th edition, B.W. Calnek et al, editors, Wolfe Publishing Ltd.

III. The appellant, who did not contest the decision of the opposition division on Article 54 EPC (statement of grounds of appeal of 6 September 1999), first criticized the conclusion of the opposition division, according to which documents (1), (2), (3), (4), (14) and (16) defined a technical prejudice against the use of mammalian cell lines for growing Infectious Bursal Disease Virus (IBDV) to prepare inactivated IBDV vaccines. Further, considering document (1) as the closest prior art, the appellant defined the problem to be solved as the provision of an alternative production system of IBD viruses for the preparation of inactivated IBDV vaccines deprived of the drawbacks related to the use of animal cells/organs or embryonated eggs. The solution described in the patent in suit, ie the use of a mammalian cell line, being obvious in view of the teaching of documents (1), (3), (4), (14) and the common general knowledge of the skilled person (grounds of appeal of 6 September 1999, page 26) or even in view of document (14) alone (*ibidem*, page 27). These documents taught that Vero cells were used for growing IBD viruses without loss of antigenic properties and that a live vaccine was produced which was efficient when parenterally administered. The appellant also cited documents (22)

to (26), disclosing the propagation of polio-, rabies, Newcastle Disease and fowl plague viruses on mammalian cell lines to demonstrate that the use of such cell lines was already well-known by the skilled person in the field of vaccine preparation.

- IV. The respondent argued that document (1), the closest prior art, actually taught away from the subject-matter of the patent in suit, ie the use of mammalian cell lines, since it particularly favoured the use of IBDV culture systems of avian origin, so that the skilled person would not see, as the appellant did, the technical problem to be solved in relation to the drawbacks of avian systems. The respondent defined said problem slightly differently as being the provision of an alternative propagation system to produce IBDV antigen material to be further processed into an efficacious inactivated IBDV vaccine. The respondent further stressed the difference between the concepts of "antigenic mass" and "infectious titer", the former governing the immuno-protective potency of an inactivated preparation and being relevant for the ability of a preparation to induce an immune response, whereas the latter was nothing else than a measure of the amount of infectious particles as shown in documents (2) and (3), which, further, were not related to the production of vaccines. Document (4) described an avirulent IBD virus obtained after cultivation on Vero cells, which was, however, not effective when administered via the drinking water. Furthermore, documents (2) to (4) indicated that the replicative cycle of IBDV in mammalian cell lines was much longer than in culture systems of avian origin. As a consequence, the skilled person would not have combined document (1) with documents (2) to (4). The problem to

be solved in document (14), ie the development of a time and labour-saving diagnostic method for monitoring IBD virus growth during the process of vaccine production, was unrelated to that of the patent in suit, so that the skilled person would not have combined said document with document (1). Further, document (14) did not define which type of vaccine production was to be monitored nor was the type of culture system specifically disclosed and, although the test sample was derived from a culture on Vero cells, the method of document (14) was to be applied to cell cultures of chicken origin. In particular, document (14) did not disclose an efficacious inactivated IBDV vaccine derived from a Vero cell line and confirmed that IBDV vaccines were usually grown in cell cultures of avian origin. As far as documents (22) to (24) were concerned, the respondent argued that they concerned non-avian (polio and rabies) viruses and a transposition of this knowledge to IBDV, ie an avian virus, was not possible. The same conclusion applied to documents (25) and (26), which disclosed the cultivation of Newcastle Disease (NDV) and fowl plague viruses on mammalian BHK 21 and/or IB-RS-2 cell lines, since said viruses, although from avian origin, were unrelated to the IBD virus. Furthermore, documents (4), (25) and (26) were respectively published 13, 22 and 16 years before the priority date of the patent in suit, so that it could be concluded that they had not motivated the skilled person to use mammalian cell lines. On the contrary, documents (33) to (35) demonstrated that until the priority date of the patent in suit, NDV and IBDV were propagated on culture systems of avian origin for the production of vaccines, so that the skilled person could be assumed not to have experienced the alleged inappropriateness of culture

systems of avian origin evoked by the appellant for the definition of the technical problem underlying the patent in suit. The respondent thus summarizing his view concluded that there was no incentive in the prior art for the skilled person pointing to the solution described in the patent in suit.

- V. The appellant requested that the decision under appeal be set aside and the patent revoked. Oral proceedings were requested in case the Board would not be prepared to allow the request for revocation.
- VI. The respondent requested that the appeal be dismissed. No request for oral proceedings was submitted.

Reasons for the Decision

Article 54 EPC

1. The opposition division acknowledged novelty for the subject-matter of the claims as granted and the appellant does not contest the decision of the first instance on novelty (grounds of appeals of 6 September 1999, page 1).

Article 56 EPC

2. The patent in suit concerns both live and inactivated IBDV vaccines. The opposition was only directed to claims 3 to 6, related to an **inactivated** IBDV vaccine, and to claims 8 to 11, concerned with a method for the preparation of the inactivated vaccine, for all the designated states, except ES and GR, and to method claims 3 to 9 for ES and GR.

Claims 8 to 11

3. The Board shares the opinion of the appellant, the respondent and the opposition division and also considers document (1) as the closest prior art. This document describes the preparation of **live** and **inactivated** IBDV vaccines on the basis of IBDV strain D78, also used in the patent in suit. Example III of document (1), concerned with a **live** IBDV vaccine indicates, as a preferred method for the propagation of the virus, the cultivation on confluent monolayers of chicken embryo fibroblast (column 7, lines 10 to 16). In column 2, lines 63 to 64, the virus is also said to be cultivated on SPF chicken eggs or in a cell culture preferably from avian tissue. Among the alternative cultivation methods cited in column 7, lines 17 to 23 the propagation of IBDV viruses on permanent cell lines (eg Vero-cells) is mentioned. Claim 8, directed to an improved method for the preparation of an inactivated IBDV vaccine envisages the cultivation of IBDV on newborn mice. Example IV, concerned with inactivated IBDV vaccines, states on column 7, lines 42 to 46 that the propagation method of the viruses for the preparation of **inactivated** IBDV vaccines is the same as described for the live IBDV vaccines. Thus the cultivation on permanent mammalian cell lines, such as the Vero cell line, is also in the context of inactivated IBDV vaccines contemplated as an alternative propagation method. However, Example IV does not specifically indicate which propagation method has actually been used and there is no technical data showing that said propagation has been carried out on mammalian cell lines such as the Vero cells. In column 3, lines 20 to 23 IBDV strain D78 is said to be suitable to prepare an **inactivated** vaccine and to

retain its immunogenicity after inactivation by formaline, propiolactone or ethylene-imine. Polyvalent vaccines, in which D78 is associated with other avian pathogens, such as NDV virus, Infectious Bronchitis virus, Reo- and/or Adeno-virus are also contemplated (column 3, lines 35 to 40 and claim 3). However, as far as an efficacious inactivated IBDV vaccine with a propagation of IBD viruses on mammalian cell lines such as the Vero cells is concerned, the teaching of document (1), in view of the disclosure of Example IV, must be considered as hypothetical.

4. Since document (1) is silent about possible drawbacks of the propagation of IBD viruses in avian systems, the objective technical problem to be solved in view of document (1) cannot make reference to said drawbacks and must be defined as the performance of the hypothetical teaching.
5. The patent in suit shows in Examples 3, 4, 8 and 9 that this hypothetical teaching has been successfully performed by the subject-matter of the claims mentioned above.
6. The two questions to be answered in view of Article 56 EPC are whether the skilled person would have been prompted to use the particular route involving a propagation of the IBD virus on a mammalian cell line, such as the Vero cell line, in order to prepare an efficacious inactivated IBDV vaccine and whether he/she would have considered said route as promising. In other words, would have the skilled person been motivated and confident?
7. In the Board's judgement, the teaching of document (1)

would have prompted the skilled person to use a mammalian cell line to propagate the IBD virus in order to further prepare an efficacious inactivated IBDV vaccine. Several reasons contribute to this opinion. First of all, by indicating that the growth of IBD viruses on confluent monolayers of chicken embryo fibroblasts is the preferable method, whereas the use of mammalian cell lines is mentioned as an alternative method, document (1) does not teach away from methods using mammalian cell lines. Rather, the mention of said propagation method as an alternative to the preferable one shows that said method must have some kind of value, since it has been considered by the authors of document (1) worth to be cited as a method susceptible to be used instead of the preferable method. Furthermore, an incentive in favour of the propagation of IBD viruses in mammalian cell lines can also be found in documents (2) and (3). Document (3), for instance, indicates that the proliferation systems of avian origin produce low yield of virus (page 298, right column, last sentence) and, if the proliferative cycle of the IBD virus is approximately twice as long as in systems of avian origin, the yield obtained with the Vero cell line may be 180 times higher (page 301 and Table 1). In view of these advantages, document (3) concludes that *"...the use of such cells offers a valuable culture system for propagating IBDV."* (page 302). Document (2) mentions as advantages of the mammalian cell lines their infinite lifespan, their ease of use and the absence of extraneous avian viruses (page 375, left column). These advantages prevail, in the Board's judgement, over the slightly longer proliferative cycle. Although documents (2) and (3) are not primarily concerned with the preparation of IBDV vaccines, they nevertheless belong to the art which has

to be taken into consideration by the skilled person engaged in vaccine preparation, because they concern the propagation of IBD virus, ie the increase of the virus titer, which, in fact, constitutes (one of) the first step(s) in the preparation of a vaccine, as illustrated by document (16) on page 23.

8. Therefore, in the Board's judgement, the skilled person would have been motivated by the disclosure of document (1), considered alone or in combination with the teaching of any of the documents (2) or (3), to propagate the IBD virus on a mammalian cell line, such as the Vero cell line.

9. The question whether the skilled person would have been confident in preparing an **efficacious inactivated** IBDV vaccine after propagation of the IBD virus in a mammalian cell line remains to be answered. Document (1) states in column 3, lines 20 to 23, that D78, the IBD virus strain used in document (1), retains its immunogenicity after inactivation. Confirmation thereof can be found in column 2, lines 55 to 60, where chickens and turkeys after vaccination with **inactivated** antigen of D78 strain are said to produce precipitating and neutralizing antibodies against IBDV and are immune against a subsequent IBDV infection. If D78 is still immunogenic after inactivation, this means that the step(s) before the inactivation has/have not introduced any antigenic drift or loss in immunogenicity. Furthermore, since several propagation routes of IBD virus are mentioned in document (1) and this statement is made independently of a reference to a particular route, this implies that a loss of immunogenicity has not to be expected with any of these propagation routes. Therefore, the skilled person would have been

confident in propagating IBD viruses in any of the cultivation systems mentioned in column 7, lines 10 to 23, *inter alia* in mammalian cell lines, such as the Vero cells, to prepare an efficacious inactivated IBDV vaccines.

10. This teaching is contrary to the assumption of the respondent, according to which the skilled person would have reached a negative conclusion on the use of mammalian cell lines in view of document (4), which states on page 539, right column, that the avirulent Vero-cell-adapted IBD virus is not efficacious when given in drinking water, but has to be administered subcutaneously. This only shows that drinking water is not a suitable administration route for eliciting an efficient immunological response and does not necessarily imply that an antigenic drift has occurred after propagation of the IBD virus on mammalian cell lines such as the Vero cell line. This teaching goes further against the technical prejudice seen by the first instance in view of the teaching of document (3), which on page 302 indicates that studies are in progress to examine the structural characteristics of Vero-propagated IBDV and of document (16), which states on page 23, that the virus, after propagation still has to be immunogenic. In the Board's judgement, neither document (3) nor document (16) may constitute a technical prejudice, since they are, contrary to the requirements of the established case law of the boards of appeal (cf Case Law of the Boards of Appeal of the European patent Office, 4th edition, 2001, pages 134 to 135), isolated publications only reflecting the opinion of isolated persons and not a common opinion widely spread in the scientific community involved in the field of vaccine preparation or virus propagation.

Furthermore, they do not point in a concrete manner at a difference between IBDV propagated on Vero cells and those cultured in a system of avian origin.

Furthermore, if as suggested by document (1) (cf supra paragraph 9) inactivated D78 strain can still induce an immune response, then inactivated D78 strain must still be, as far as the immunogenicity and the structure of the virus particles are concerned, similar to D78 strain itself. In this context, the Board is reluctant to transpose the teaching of document (20) on the antigenic drift of the influenza virus to the IBD virus, since both viruses are unrelated to each other.

11. It is true that documents (4), (25) and (26), which are all concerned with the propagation of viruses (IBDV in document (4), NDV in document (26) and foot-and-mouth disease, herpes simplex, NDV, fowl plague, influenza A viruses in document (25)) in mammalian cell lines have been published 13, 22 and 16 years before the priority date of the patent in suit, but have not resulted in a trend for cultivating viruses on mammalian cell lines, as shown by documents (33) to (35). However, this argument is besides the point, since they do not constitute the relevant prior art used for reaching the present decision. On the contrary, document (1), the closest prior art, has been published two years before the priority date of the patent in suit and the other documents, the teaching of which may be combined with that of document (1), ie documents (2) or (3), have also been published one and two years respectively before the priority date.
12. The Board is thus convinced that the skilled person would have been prompted and confident in applying the teaching of document (1) in case combined with those of

any of documents (2) or (3) in order to prepare an efficacious inactivated IBDV vaccine according to a process involving a propagation of said IBDV on a mammalian cell line, such as the Vero cell line, and would have thus straightforwardly come to the subject-matter of claims 8 to 11 of the patent in suit which are directed to a method for the preparation of inactivated IBDV vaccines comprising, besides said, in view of document (1), straightforward step of cultivation of IBDV on a mammalian cell line (cf supra, point 12), the steps of harvesting and inactivating IBDV, which were at the priority date of the patent in suit part of the basic common knowledge of the skilled person in the field of vaccine preparation. Claims 8 to 11 hence lack an inventive step and do not fulfil the requirements of Article 56 EPC.

13. The conclusions mentioned above also apply to claims 3 to 9 for ES and GR.

Articles 113 and 116 EPC

14. The appellant had requested oral proceedings only in the case the Board would take an adverse position on his request to revoke the patent in suit, whereas the respondent had not made such a request. The present decision is thus given without oral proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar:

The Chairwoman:

P. Cremona

U. Kinkeldey