

Internal distribution code:

- (A) Publication in OJ
(B) To Chairmen and Members
(C) To Chairmen
(D) No distribution

**Datasheet for the decision
of 19 December 2007**

Case Number: T 0603/05 - 3.3.04

Application Number: 96915746.0

Publication Number: 0830142

IPC: A61K 39/12

Language of the proceedings: EN

Title of invention:

PRRS (Porcine Reproductive and Respiratory Syndrome) virus
vaccine

Patentee:

BOEHRINGER INGELHEIM VETMEDICA, INC.

Opponent:

Wyeth

Headword:

PRRS/BOEHRINGER INGELHEIM

Relevant legal provisions:

EPC Art. 56

Keyword:

"Main request, auxiliary request 1, 2, 3, 4, 5, 6 - inventive
step (no)"

Decisions cited:

T 0197/86, T 1213/03

Catchword:

-



Case Number: T 0603/05 - 3.3.04

DECISION
of the Technical Board of Appeal 3.3.04
of 19 December 2007

Appellant I: BOEHRINGER INGELHEIM VETMEDICA, INC.
(Patent Proprietor) 2621 North Belt Highway
St. Joseph, MO 64506-2002 (US)

Representative: Kalhammer, Georg
Lederer & Keller
Patentanwälte
Prinzregentenstraße 16
D-80538 München (DE)

Appellant II: Wyeth
(Opponent) Five Giralda Farms
Madison, NJ 07940-0874 (US)

Representative: Mannion, Sally Kim
Wyeth Pharmaceuticals
Huntercombe Lane South
Taplow
Maidenhead,
Berkshire SL6 0PH (GB)

Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
22 March 2005 concerning maintenance of
European patent No. 0830142 in amended form.

Composition of the Board:

Chairman: M. Wieser
Members: B. Claes
R. Moufang

Summary of Facts and Submissions

I. The Patent Proprietor (Appellant I) and the Opponent (Appellant II) lodged appeals against the interlocutory decision of the Opposition Division, whereby the European patent No. 0 830 142 could be maintained in amended form pursuant to Article 102(3) EPC (1973).

II. The Opposition Division decided that the subject-matter of claims 1, 4 and 13 set out in Appellant I's main request (claims 1 to 16 as granted) lacked novelty contrary to the requirements of Article 54 EPC.

However, it was decided that claims 1 to 9 of the sole auxiliary request met all requirements of the EPC (1973).

III. The Board expressed its preliminary opinion in a communication dated 16 May 2007.

Oral proceedings were held on 19 December 2007.

IV. Appellant I requested that the decision under appeal be set aside and the patent be maintained as granted or, in the alternative, on the basis of auxiliary request 1, 2, 3, 4, 5, or 6, all filed with letter dated 19 October 2007.

Appellant II requested that the decision under appeal be set aside and the patent be revoked.

V. Claim 1 as granted read as follows:

"A vaccine composition comprising live porcine reproductive and respiratory syndrome (PRRS) virus in a

modified and substantially avirulent form and mixed with a pharmacologically compatible carrier agent, said modified and substantially avirulent virus being ATCC-VR2332 virus passaged at least 70 times in cell culture of the monkey kidney cell line MA-104 such that when the modified and substantially avirulent virus is administered to a swine or other mammal prone to PRRS, it fails to cause clinical signs of PRRS disease but is capable of inducing an immune response that immunizes the mammal against pathogenic forms of PRRS."

Claim 1 of auxiliary request 1 differed from claim 1 as granted in so far as, after the words "monkey kidney cell line MA-104", it contained the phrase "at a temperature ranging from 35° C to 37° C".

Claim 1 of auxiliary request 2 differed from claim 1 as granted as it contained the following words at its end:

"..., said modified and substantially avirulent virus being ATCC-VR2495."

Claim 1 of auxiliary request 4 was identical to claim 1 of auxiliary request 2.

VI. Claim 1 of auxiliary request 3, which was identical to claim 5 as granted and to claim 1 of the sole auxiliary request before the Opposition Division, read as follows:

"A method of producing a PRRS vaccine, comprising the steps of:

preparing a production culture of a substantially avirulent form of the ATCC-VR2332 virus, including the steps of passaging ATCC-VR2332 virus at least 70 times

in cell culture of the monkey kidney cell line MA-104 to modify and render the virus substantially avirulent such that when the modified and substantially avirulent virus is administered to a swine or other mammal prone to PRRS, it fails to cause clinical signs of PRRS disease but is capable of inducing an immune response that immunizes the mammal against pathogenic forms of PRRS, and generating a production culture from the modified and substantially avirulent ATCC-VR2332 virus;

harvesting the production virus culture;

adding a stabilizing agent to the production virus culture; and

lyophilizing the production virus culture."

Claim 1 of auxiliary request 5 differed from claim 1 of auxiliary request 3 in so far as, after the words "monkey kidney cell line MA-104", it contained the phrase "at a temperature ranging from 35° C to 37° C".

Claim 1 of auxiliary request 6 differed from claim 1 of auxiliary request 3 as it contained the following wording at its end:

"...; wherein the step of preparing includes infecting the simian cell line with said virus, and incubating the resultant culture at a temperature of from about 35° C to about 37° C."

VII. The following documents are referred to in this decision:

Declaration of Prof. Michael P. Murtaugh,

21 September 2004; accompanied by Annex, pages 1 to 76, submitted by Appellant I with letter dated 22 September 2004

- (1) EP-A-0 529 584

- (4) 4th International Symposium on Emerging and Re-emerging Pig Diseases; Rome, 29 June to 2 July 2003, pages 137 to 138

- (5) AJVR, Vol.58, No. 1, 1997, pages 40 to 45

- (8) Veterinary Microbiology, Vol.54, 1997, pages 101 to 112

- (9) The Veterinary Record, Vol.141, 1997, pages 497 to 499

- (11) Proceedings of the 15th IPVS Congress, Birmingham, England, 5 to 9 July 1998, page 128

- (13) American Association of Swine Practitioners, Nashville, US, 4 to 7 March 1996, pages 89 to 91

- (14) WO-94/18 311

- (15) WO-93/07 898

VIII. The submissions made by Appellant I, as far as they are relevant for the present decision, may be summarised as follows:

The closest state of the art was represented by document (1). The problem to be solved by the present

invention was the provision of a vaccine, respectively of a method for producing such vaccine, which, when compared to the vaccine of document (1), was safer and which in particular caused a lower rise in body temperature of vaccinated animals and did not shed.

The experimental data contained in the patent in suit and in the Annex to the declaration by Prof. Murtaugh, (hereinafter referred to as "the declaration"), showed that this problem has been solved by the claimed subject-matter.

IX. The submissions made by Appellant II, as far as they are relevant for the present decision, may be summarised as follows:

Document (1) represented the closest state of the art. The problem underlying the patent as formulated by Appellant I had not been solved. The experimental data submitted by Appellant I in the Annex to the declaration was not able to support an advantage of the claimed vaccine when compared to the vaccine disclosed in document (1).

Accordingly, the problem underlying the patent in suit had to be seen as the provision of an alternative vaccine, respectively of an alternative method for producing such vaccine. The solution to this problem according to the claims of all of Appellant I's requests was obvious, as it was well known in the art to produce a modified and substantially avirulent virus for use in a vaccine by passaging the virus in cell culture.

Reasons for the decision

1. During the proceedings Appellant II raised objections under Articles 54, 56, 84 and 123(3) EPC against the subject-matter of the claims of Appellant I's requests.

For the reasons outlined below, the Board does not consider it necessary to deal with all these issues in the present decision which is concerned exclusively with the issue of inventive step (Article 56 EPC).

2. In accordance with the problem and solution approach, the Boards of Appeal in their case law have developed certain criteria for identifying the closest prior art providing the best starting point for assessing inventive step. It has been repeatedly pointed out that this should be a prior art document disclosing subject-matter 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 (cf Case Law of the Boards of Appeal of the European Patent Office, 5th Edition 2006, chapter I.D.3.1).
3. It has been acknowledged by both parties, and is agreed by the Board, that the closest state of the art is represented by document (1) which discloses a vaccine composition comprising ATCC-VR2332 virus passaged in cell culture of the monkey kidney cell line MA-104 25 times at 34° C to 37° C and 12 times at 31° C.

Document (1) refers to the **efficacy** of the claimed vaccine by saying that swine vaccinated with the claimed composition did not develop symptoms of PRRS when exposed to pathogenic forms of PRRS virus (see on page 8, lines 1 to 2).

4. Appellant I emphasised at the oral proceedings that document (1) did not contain any information concerning the **safety** of the vaccine composition disclosed, which requires that swine to which the vaccine comprising a modified live virus has been administered do not show clinical signs of PRRS.

He accordingly defined the problem underlying the patent in suit as the provision of a vaccine, respectively of a method for producing such vaccine, which, when compared to the vaccine of document (1), was safer and which in particular caused a lower rise in body temperature of vaccinated animals.

It has to be examined whether or not this problem has been solved by the subject-matter of the claims of Appellant I's requests.

5. In examples 3 and 4 of the patent in suit the minimal protective dose of the PRRS virus (VR-2332 passage 75) and the duration of immunity are determined. In both examples, following intramuscular vaccination, the vaccinated pigs were monitored for any adverse reactions to the vaccine. The monitored parameters included body (rectal) temperature, white blood cell counts, weight gain, clinical symptoms, serology and viremia (see page 7, lines 35 to 36 and page 9, lines 18 to 20).

The board notes in this respect that the patent in suit does not consider the parameter "body (rectal) temperature" to fall within the term "clinical symptoms".

6. According to example 3 (page 7, lines 29 to 31), twenty-one PRRS seronegative piglets of a group 1 were vaccinated with **2.0 ml PRRS vaccine L-4 intramuscularly (4.0 logs/dose)**. Twenty-one piglets of a group 2 were vaccinated with 20 ml PRRS vaccine L-2 (2.0 logs/dose). Page 7, lines 39 to 41 reads:

"Body (rectal) temperatures were measured prior to and following vaccination. The group average temperature for group 1 increased on 2 DPV (*day past vaccination; added by the Board*) and 3 DPV while group 2 increased on 3 DPV. The duration of the temperature rise for either group was short, 2 days for group 1 and 1 day for group 2."

7. In example 4 (page 9, lines 7 to 9) twenty-one seronegative piglets of a group 1 were vaccinated with **2.0 ml PRRS-MLV passage 75 vaccine having 3.32 logs per dose**, and twenty-one piglets of a group 2 were vaccinated with **2.0 ml of this vaccine having 1.64 logs per dose**.

Page 9, lines 21 to 24 reads:

"Body (rectal) temperatures were monitored daily from -1 DPV through +4 DPV. The analysis of the group averages showed no significant increase in the treatment groups' temperatures as a result of the

vaccine. The vaccinated pigs of Group 1 experienced a maximum rise of 0.2° F as compared to the pre-vaccination average."

8. As the statistical analysis of all other post vaccination clinical scores (see point (5) above) indicated no difference between the vaccinated groups and the non-vaccinated control groups, it is concluded that the results of the post vaccination observations show that the treatment with the claimed vaccine do not have any severe undesirable effects on the treated animals (page 8, lines 6 to 7 and page 9, lines 45 to 46).
9. The patent in suit does not disclose that the claimed vaccine composition is safer, and in particular that it causes a lower rise in body temperature of vaccinated animals, when compared with known vaccine compositions, let alone with the vaccine of document (1).
10. It is for the Applicant/Patentee to furnish evidence of an improved effect of the subject-matter of a claim, which has been asserted, but was not mentioned in the application as filed, in the whole of the claimed area vis-à-vis the closest prior art (see decision T 1213/03 of 24 May 2005, points (2.2 to 2.3) of the reasons).

Appellant I, when arguing that it was the problem underlying the patent in suit to provide a vaccine composition with the above mentioned improved effects when compared with the vaccine disclosed in document (1), refers to the Annex to the declaration, which he considers to prove that in fact the claimed subject-

matter has the surprising advantages over the closest prior art and that therefore the posed problem has been solved.

11. The declaration consists of 5 pages signed by Prof. Murtaugh on 21 September 2004 and is accompanied by an Annex consisting of 76 pages which have been consecutively numbered by the Board. The Annex contains the following three studies:

- 623-850-92P-010 (hereinafter referred to as study no. 1, pages 1 to 44),
- 623-850-92P-041 (study no. 2, pages 45 to 61), and
- 623-850-93P-004 (study no. 3, pages 62 to 76)

Study no. 1 is concerned with the evaluation of virulence and shedding of the VR-2332 virus at passages 3, 27, and 43 at 35 to 36 °C and passage 12 grown at 31°C (25 passages at 35 to 36 °C plus 12 passages at 31°C) when given intranasally (see declaration, page 8). Thus, the last of the modified viruses mentioned above is the virus disclosed in document (1) (see point (3) above).

The objective of study no. 2 is to test three virus candidates for a MLV PRRS vaccine, namely VR-2332 passage 70, VR-2332 passage 50 at 31° C and VR-2332 passage 69-5 vero, by administering them intramuscularly and to test for shedding of the vaccine virus by incorporating susceptible animals as contact control to test for transmission of the virus from vaccinated animals (see pages 49 and 50).

Study no. 3 tests VR-2332 passage 70 by administering the virus intramuscularly, observing if any virus is transmitted to other pigs in contact with the vaccinated pigs and determining the safety of the virus in vaccinated pigs.

12. At the oral proceedings Appellant I, arguing that the problem as defined in point (4) above has been solved by the claimed subject-matter, referred to studies nos. 1 and 3.

Study no. 1 on page 3 discloses data referring to the body temperature of five groups of pigs (groups A to E) measured on the day of vaccination and on 3, 5, 7, 10, 12 and 14 DPV. The vaccine administered to the animals of group D is the vaccine composition disclosed in document (1). The animals were vaccinated **intranasally with 8 ml** of the composition having **a virus titer of $10^{4.8}$ TCID₅₀ per millilitre**. The results show, that on 3 DPV two of the three animals of group D, and from 5 DPV until the end of the test (14 DPV) all three animals of group D had a body temperature higher than 104° F, while in the same period all animal of the control group E showed no sign of fever.

The results on page 6 of the annex show that none of the test animals of group D developed any clinical signs of PRRS even on 14 DPV.

13. Study no. 3 discloses the results of the measurement of body temperature of a group of ten pigs vaccinated **intramuscularly with 2.0 ml of PRRS Modified Live Virus (MLV) passage 70, Lot 12793** (see pages 66, 67 ("Test Material") and 68 ("Experimental Design")). The average

body temperature, measured on the day of vaccination and daily on 1 to 14 DPV, lies above 104° F on days 5, 7, 9 and 13 DPV, but is below this value on all other days monitored (see figure 1 on page 70).

14. When comparing the experimental design of the tests of the Annex relied on by Appellant I, the Board notes that these tests, besides using different modified viruses, also are distinguished by a number of other parameters. The test described in study no. 1 (see point (12) above), which tests a vaccine containing the virus described in document (1), and the test described in study no. 3 (see point (13) above), which uses a vaccine containing a modified virus according to the patent in suit, differ in the amount of vaccine administered and in the way of administration of the vaccine. Moreover, it is not possible to compare the respective virus titers administered to the animals in these different tests and, in addition, the parameter in question, namely the body temperature of the vaccinated pigs, is determined on different DPV.

The Board notes that not only the different tests disclosed in the Annex are characterized by different experimental designs, but that the design of each of these tests also differs from the experimental design of each of examples 3 and 4 of the patent in suit (see points (6) and (7) above).

15. According to the established jurisprudence, a surprising effect demonstrated in a comparative test can only be taken as an indication of inventive step if the nature of the comparison with the closest state of the art is such that the said effect is convincingly

shown to have its origin in **the distinguishing feature of the invention** (see decision T 197/86, OJ 1989, 371, point (6.1.3) of the reasons).

16. In the present case, **the distinguishing feature of the invention** when compared with the closest state of the art, is the different nature of the modified virus contained in the respective vaccine composition, namely ATCC-VR2332 virus passaged in cell culture of the monkey kidney cell line MA-104 25 times at 34° C to 37° C and 12 times at 31° C according to document (1) and ATCC-VR2332 virus passaged at least 70 times in cell culture of the monkey kidney cell line MA-104, preferably at a temperature ranging from 35° C to 37° C.

Considering the large number of varying parameters comprised in the tests disclosed in the Annex, not only among one another and but also in comparison with the experiments of the patent in suit, the nature of comparison offered by the studies is not such that the alleged surprising effect, namely provision of a safer vaccine which in particular causes a lower rise in body temperature of vaccinated animals, is convincingly shown to originate from **the distinguishing feature of the invention.**

17. According to the established case law of the Boards of Appeal, alleged advantages to which the Patent Proprietor merely refers, without offering sufficient evidence to support the comparison with the closest prior art, cannot be taken into consideration in determining the problem underlying the invention and therefore in assessing inventive step.

Since the alleged advantages of the claimed subject-matter over the closest state of the art lack the required adequate support, the technical problem as defined by Appellant I at the oral proceedings (see point (4) above) needs reformulation (see Case Law of the Boards of Appeal, 5th Ed. 2006, chapter I.D.4.2).

18. During the written proceedings Appellant I had formulated the problem to be solved by the patent in suit as the provision of a safe vaccine that has no severe undesirable effects on the vaccinated animals and does not shed (see letter dated 1 August 2005, page 7, 5th paragraph).

The problem of shedding is mentioned only once in the patent in suit (paragraph [0110]), where it is stated that the VR-2332 virus, in parallel with the attenuation at 35° C to 37° C as described in example 1, was also cold adapted at a temperature of 31° C to 35° C to develop a vaccine strain that prevented shedding of the virus by infected animals.

19. On page 5, first paragraph of the letter dated 20 April 2006, Appellant I says:

"The declaration by Professor Dr Murtaugh and the experimental report filed therewith demonstrate that the virus passaged at least 70 times did not show shedding under the testing conditions that did result in shedding of passage 37 virus according to D1."

Page 4, 2nd full paragraph of Appellant I's letter dated 19 October 2007, reads:

"It is the proprietor's position that at least **under the specific testing conditions** indicated in experimental report annexed to Dr. Murtaugh's declaration, the lack of shedding is an inherent property which is automatically obtained in a repeatable and reproducible manner by passaging VR-2332 virus for at least 70 times in MA-104 cells (see section 7 of Dr. Murtaugh's declaration). Under these specific testing conditions, the virus passaged 70 times did not shed whereas the virus according to D1 did."

20. As shown in points (11) to (16) above, the experimental design of the tests disclosed in the Annex to the declaration and of the examples of the patent in suit differ in so many parameters that, on the basis of these tests and examples, it is not possible to attribute any alleged positive effect of the presently claimed vaccine to **the distinguishing feature of the invention** when compared to the closest state of the art, namely the different modified viruses.

In addition, the Board is aware of a number of post-published documents on file which each report shedding of the vaccine virus after vaccination of animals with a vaccine composition according to the patent in suit (see document (4), page 137; document (5), page 44; document (8), abstract; document (9), page 498; document (11), page 128 and document (13), page 90).

Accordingly, also the problem to be solved formulated by Appellant I in the written procedure (see point (18) above) needs reformulation.

21. Since the alleged advantages of the claimed subject-matter over the closest state of the art lack the required adequate support, the objective technical problem of the invention according to claim 1 of the main request and of auxiliary requests 1, 2 and 4 can only be seen as providing a further, alternative PRRS vaccine composition, respectively as providing an alternative method of producing such vaccine (claim 1 of auxiliary requests 3, 5 and 6).

22. The claimed subject-matter differs from the disclosure in document (1) in so far as the modified virus has been produced by different methods, namely by passaging ATCC-VR2332 virus in cell culture of the monkey kidney cell line MA-104 25 times at 34° C to 37° C and 12 times at 31° C according to document (1), and by passaging ATCC-VR2332 virus at least 70 times in cell culture of the monkey kidney cell line MA-104, preferably at a temperature ranging from 35° C to 37° C, according to the patent in suit.

23. The Board, taking the view that the problem formulated in point (20) above has indeed been solved by the claimed subject-matter, has to examine whether the solution claimed involves an inventive step as required by Article 56 EPC.

The skilled person in the here relevant technical field is aware that, for the preparation of any modified live or attenuated virus vaccine, it is necessary to alter the virus such that it can still infect the host in a limited manner but that it cannot cause clinical signs of disease in the host. Thus, the virus has to be at

least partly deprived of its pathogenic properties without losing its antigenic activity.

Document (1) itself does not contain a suggestion that would encourage a skilled person to amend the disclosed method for obtaining a modified PRRS vaccine virus.

However, the generally used routine method to obtain a modified virus for use in a live vaccine composition, is passaging the virus in cell culture. Documents representing this state of the art with regard to PRRS virus, wherein attenuation protocols comprising up to 200 passages are disclosed are document (14) (see pages 6 and 7) and document (15) (see page 7).

The Board is not aware of any disclosure in a prior art document, let alone any prejudice existing in the art, that would prevent a skilled person from passaging the PRRS virus VR-2332 in a way different from the one disclosed in document (1).

24. Therefore, a skilled person, trying to solve the problem underlying the patent in suit (see point (20) above) and starting from the disclosure in document (1), describing ATCC-VR2332 virus passaged in cell culture of the monkey kidney cell line MA-104 25 times at 34° C to 37° C and 12 times at 31° C, would consider to use an attenuation protocol different from the one disclosed in document (1).

A claim referring to a modified VR-2332 virus obtained by passaging it at least 70 times in MA-104 cells, wherein the virus has no unexpected and surprising advantages over the prior art which have been

adequately supported, as required by the case law of the Boards of Appeal, is therefore not considered to involve an inventive step.

Therefore, Appellant I's main request does not meet the requirements of Article 56 EPC.

25. The same applies to the subject-matter of claim 1 of auxiliary request 1, wherein the at least 70 passages are carried out at 35° C to 37° C, and to the subject-matter of claim 1 of auxiliary requests 2 and 4, wherein the passaged virus is defined by its accession number.

Accordingly, auxiliary requests 1, 2 and 4 also do not meet the requirements of Article 56 EPC.

26. Claim 1 of auxiliary request 3 refers to a method of producing a lyophilised PRRS vaccine, characterised in that the vaccine contains a stabiliser and VR-2332 virus passaged at least 70 times in MA-104 cells.

According to claim 1 of each of auxiliary requests 5 and 6, passaging (respectively preparation) of the virus takes place at 35° C to 37° C.

27. Stabilisation and lyophilisation are routinely employed in methods for producing vaccines. In the light of the Board's findings in points (11) to (16) above, the problem underlying the invention according to Appellant I's auxiliary requests 3, 5 and 6 is the provision of an alternative method for producing a PRRS vaccine (see point (20) above).

For the reasons already given in points (23) to (25) above, the subject-matter of claim 1 of each of auxiliary requests 3, 5 and 6 does not involve an inventive step.

These requests, accordingly, do not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided:

1. The decision under appeal is set aside.
2. The patent is revoked.

Registrar:

Chair:

P. Cremona

M. Wieser