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Datasheet for the decision of 17 May 2022

Case Number: T 1330/20 - 3.3.04

Application Number: 15794751.6

Publication Number: 3215188

IPC: A61K39/12, A61B17/20, A61B5/15

Language of the proceedings: EN

Title of invention:
Methods of using microneedle vaccine formulations to elicit in animals protective immunity against rabies virus

Applicants:
Boehringer Ingelheim Animal Health USA Inc.
Georgia Tech Research Corporation

Headword:
Microneedle DNA rabies virus vaccine/BOEHRINGER INGELHEIM

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 12(4), 12(6)

Keyword:

Inventive step - (no) - reasonable expectation of success (yes)
Late-filed request - should have been submitted in first-instance proceedings (yes)
Late-filed evidence - should have been submitted in first-instance proceedings (yes)

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Case Number: T 1330/20 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 17 May 2022

Appellant: (Applicant 1)	Boehringer Ingelheim Animal Health USA Inc. 3239 Satellite Boulevard, Bldg. 500 Duluth, GA 30096 (US)
Appellant: (Applicant 2)	Georgia Tech Research Corporation 505 Tenth Street N.W. Atlanta, GA 30332 (US)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 7 January 2020 refusing European patent application No. 15794751.6 pursuant to Article 97(2) EPC**

Composition of the Board:

Chair	B. Claes
Members:	A. Schmitt
	K. Kerber-Zubrzycka

Summary of Facts and Submissions

I. The appeal of the applicants (appellants) lies from the decision of the examining division refusing European patent application No. 15 794 751.6 (application), which had been filed under the PCT as an international patent application and was published as WO 2016/073410. The title of the application is "*Methods of using microneedle vaccine formulations to elicit in animals protective immunity against rabies virus*".

II. The examining division considered sets of claims of a main and an auxiliary request.

Claim 1 of the main request considered in the appealed decision reads as follows:

"1. A dissolving microneedle DNA rabies virus vaccine composition, which elicits in an animal a protective immune response against subsequent virulent rabies virus challenge, comprising a vector expressing a rabies antigen, wherein the vector is a plasmid DNA vector or an attenuated recombinant viral vector, wherein the composition is stable for at least three weeks at 4°C."

Claim 1 of the auxiliary request considered in the appealed decision reads as follows:

"1. A dissolving microneedle DNA rabies virus vaccine composition for use in a method for eliciting a protective immune response against rabies in an animal comprising placing the composition on a pinna of an ear of the animal, thereby piercing the animal's skin with the microneedles and releasing the vaccine, wherein the

composition comprises a vector expressing a rabies antigen, wherein the vector is a plasmid DNA vector or an attenuated recombinant viral vector, and wherein the composition is stable for at least three weeks at 4°C."

III. The examining division considered that the claimed subject-matter of the main request and the auxiliary request did not involve an inventive step (Article 56 EPC).

IV. With their statement of grounds of appeal, the appellants submitted sets of claims of a main request and auxiliary requests 1 to 6 and three documents (D13 to D15). The sets of claims of the main request and auxiliary requests 1 to 4 were new to the proceedings.

Claim 1 of the main request reads as follows:

"1. A dissolving microneedle DNA rabies virus vaccine composition, which elicits in an animal a protective immune response against subsequent virulent rabies virus challenge, comprising a vector expressing a rabies antigen, wherein the vector is a plasmid DNA vector or an attenuated recombinant viral vector."

Claim 1 of auxiliary request 1 is identical to claim 1 of the main request except for the further feature "wherein the dissolving microneedles are present in a dissolving microneedle patch".

Claim 1 of auxiliary request 2 reads as follows:

"1. A dissolving microneedle DNA rabies virus vaccine composition for use in a method of eliciting in an animal a protective immune response against subsequent virulent rabies virus challenge, wherein the

composition comprises a vector expressing a rabies antigen, wherein the vector is a plasmid DNA vector or an attenuated recombinant viral vector, further wherein the animal is a canidae."

Claim 1 of auxiliary request 3 is identical to claim 1 of auxiliary request 2 except that the feature "further wherein the animal is a canidae" has been replaced with the feature "further wherein the dose of the composition is administered in a range of 10 µg to 50 µg per dose".

Claim 1 of auxiliary request 4 reads as follows:

"1. A dissolving microneedle DNA rabies virus vaccine composition for use in a method of eliciting in an animal a protective immune response against subsequent virulent rabies virus challenge, wherein the composition comprises a vector expressing a rabies antigen, wherein the vector is a plasmid DNA vector or an attenuated recombinant viral vector, further wherein the vaccinated animals produce more than twice as many serum-neutralizing antibodies as animals vaccinated with an identical amount of the vector expressing the rabies G protein, but delivered as a single injection, instead of as a dissolving microneedle vaccine composition."

The sets of claims of auxiliary requests 5 and 6 are identical to the sets of claims of the main request and the auxiliary request considered in the decision under appeal, respectively (see section II.).

V. The board summoned the appellants to oral proceedings, as they had requested, and issued a communication pursuant to Article 15(1) RPBA, in which it provided

its preliminary opinion that, *inter alia*, it was inclined not to admit the main request, auxiliary requests 1 to 4 and documents D13 to D15 into the appeal proceedings and that the examining division had been right in finding that the subject-matter of claim 1 of each of auxiliary requests 5 and 6 did not involve an inventive step.

VI. Oral proceedings were held as scheduled. At the end of the oral proceedings, the Chair announced the board's decision.

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

D2 Ray et al., Vaccine, 15(8), 1997, 892-895

D5 DeMuth et al., Nat. Biotechnol., 2013, 31(12), 1082-1085

D6 Kommareddy et al., J Pharmaceutical Sci., 2012, 101(3), 1021-1027

D7 WO 2012/023044 A1

D8 Kim et al., Adv. Drug Deliv. Rev., 2012, 64(14), 1547-1568

D9 Laurent et al., Vaccine, 2010, 28(36), 5850-5856

D10 Suh et al., Clin Exp Vaccine Res, 2014, 3(1), 42-49

D14 Al-Zahrani et al., Expert Opin Drug Deliv., 2012, 9(5), 541-550.

VIII. The appellants' arguments, in so far as relevant to the decision, are summarised as follows.

Main request and auxiliary requests 1 to 4

Admittance (Article 12(4) and (6) RPBA 2020)

The set of claims of the main request had already been filed during the examination proceedings. It had never been withdrawn and had therefore been maintained.

Moreover, the examining division had decided that the additional feature in claim 1 of the main request considered in the decision under appeal was not linked to an unexpected effect and was therefore redundant. This decision had been unexpected and therefore provided a legitimate reason for submitting the new main request with the statement of grounds of appeal. In claim 1 of this new main request, the redundant feature had been deleted.

Auxiliary requests 1 to 4 had been submitted in response to the examining division's decision that the claimed subject-matter of the previous main request and auxiliary request lacked an inventive step. They should therefore also be admitted into the proceedings.

Auxiliary request 5

Admittance of document D14
(Article 12(4) and (6) RPBA 2020)

Document D14 was relevant for the decision because it disclosed that the skilled person had reservations about vaccine delivery by microneedles and therefore

addressed a key point of the claimed invention. It should therefore be admitted into the appeal proceedings.

Inventive step (Article 56 EPC) - Claim 1

Document D2, representing the closest prior art, disclosed a DNA rabies virus vaccine composition comprising a plasmid vector and its administration by intradermal and intramuscular injection. It did not disclose a dissolving microneedle vaccine composition. Administration of the claimed vaccine composition did not require a syringe and, therefore, was easier, less invasive and less painful and did not produce sharp waste. Moreover, as evident from Table 9 and Figures 4A and 4B of the application, the claimed DNA rabies virus vaccine composition had the additional technical effect that it provided an improved immune response.

Taking these technical effects into account, the objective technical problem was the provision of an improved DNA rabies virus vaccine composition.

Document D2 did not provide any motivation to investigate other means of administering the disclosed DNA rabies virus vaccine than by intradermal or intramuscular injection. Furthermore, for improving the disclosed vaccine composition for intradermal delivery, its teaching instead took a different approach, namely the use of adjuvants or immunostimulants (see page 894, right-hand column, last full sentence).

Having regard to the disclosure in documents D5 to D8 and D10, the skilled person had no reasonable expectation that a dissolving microneedle DNA rabies virus vaccine composition would elicit any protective

immunogenic response at all. Documents D5 to D8 concerned specific research studies for applying the microneedle technology to vaccines against single specific pathogens. Indeed, microneedle vaccine compositions were only known for a small number of other viruses such as HIV (document D5) and influenza virus (documents D6, D7, D8) and it was clear that the conclusions in these documents were limited to these specific vaccines. Document D10 merely speculated that microneedles could replace existing methods of vaccine administration and hence showed that the provision of microneedle vaccines was not routine (see page 47, left-hand column, paragraph, last six lines).

None of these documents contained a clear teaching towards dissolving microneedles for obtaining a comparable or even better immune response than obtained by conventional vaccine administration (see document D6, page 1025, right-hand column, first full paragraph, Table 3; document D7, page 18, lines 6 to 8, Figures 4 to 9). Document D5 did not relate to dissolving microneedle administration whereas document D8 disclosed that dissolving microneedles were mainly used for non-vaccine payloads, pointing instead towards solid or hollow microneedles for vaccine applications (see page 1556, left-hand column, first paragraph), and taught that the choice of microneedle design was "critical" for a given application (see page 1561, left-hand column, last paragraph).

The disclosure in document D9 taught away from using microneedles for a DNA rabies virus vaccine. It disclosed a skin abrasion method which was similar to dissolving microneedles since it used an array of microprojections to abrade the skin prior to topical administration of a rabies virus vaccine (see

page 5850, right-hand column, second paragraph; page 5852, left-hand column, paragraph, first paragraph). However, the fact that the topical delivery route was not sufficient to elicit an antibody response despite systemic adverse events (see paragraph bridging pages 3583 and 3584) suggested that epidermal Langerhans cells only played a limited role in inducing an antibody response to rabies vaccines (see page 5854, middle section of the right-hand column). Document D9 therefore provided a specific prejudice against using microneedles to administer rabies virus vaccines.

It was therefore highly surprising that the claimed vaccine composition worked at all, let alone that it worked even better than a conventional vaccination.

The claimed vaccine composition further differed from that of document D2 in that it was stable for at least three weeks at 4°C. None of the cited documents taught the skilled person that a DNA rabies virus vaccine could possess this level of stability when formulated in a dissolving microneedle. Documents D6 and D9 only concerned protein-based vaccines and document D5 did not concern dissolving microneedles. It was therefore not straightforward to stably formulate a viral vaccine in dissolving microneedles.

Auxiliary request 6

Inventive step (Article 56 EPC) - Claim 1

There was no teaching in the prior art towards dissolving microneedle administration of a DNA rabies virus vaccine to an animal, let alone into the pinna of the ear of the animal. The subject-matter of claim 1 of auxiliary request 6 thus involved an inventive step for

the same reasons as the subject-matter of claim 1 of auxiliary request 5.

IX. The appellants' requests, in so far as relevant to the decision, were that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims of the main request or one of the sets of claims of auxiliary requests 1 to 6, all submitted with their statement of grounds of appeal, and that document D14, newly filed with the statement of grounds of appeal, be admitted into the proceedings.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is admissible.

Main request and auxiliary requests 1 to 4

Admittance (Article 12(4) and (6) RPBA 2020)

2. With their statement of grounds of appeal, the appellants submitted a new main request and new auxiliary requests 1 to 4. In accordance with Article 12(4) RPBA 2020, these must be considered an amendment to the appellants' case and may therefore be admitted only at the discretion of the board. Under Article 12(6) RPBA 2020, the board must not admit, *inter alia*, requests which should have been submitted, or which were no longer maintained, in the proceedings leading to the decision under appeal, unless the circumstances of the appeal case justify their admittance.

3. A set of claims identical to the present main request had been submitted during the examination proceedings. However, it was replaced by a new main request prior to the oral proceedings in examination. By replacing the previous main request with a new *main* request, the appellants effectively withdrew their previous main request. Their argument that the previous main request was "maintained" simply because it had been submitted at one point during the examining proceedings therefore cannot be accepted.

4. The board is also not persuaded by the appellants' argument that the deletion from claim 1 of the feature that the composition is stable for at least three weeks at 4°C was a direct response to the examining division's decision that this feature was not linked to an unexpected technical effect and was "redundant". In fact, the feature had been introduced into claim 1 of a new main request submitted by the appellants in response to the summons to oral proceedings before the examining division. The appellants then chose not to attend the oral proceedings (see point 11 of the decision under appeal) and therefore gave up the opportunity to comment on any objections the examining division might possibly raise to this feature.

5. The appellants thus chose not to defend inventive step based on this feature in the oral proceedings before the examining division. Under these circumstances, the examining division's decision that this feature was not linked to an unexpected technical effect cannot give rise to exceptional circumstances which would allow the filing of new claim requests.

6. The appellants did not provide any reasons for submitting the new auxiliary claim requests 1 to 4 only

at the stage of the appeal proceedings and not earlier, during the examination proceedings. They only indicated that auxiliary requests 1 to 4 had been filed in response to the examining division's decision to reject the previous main and auxiliary requests and that they supposedly overcame the examining division's objections in respect of inventive step.

7. However, a negative decision by the examining division does not necessarily provide a justification for submitting new claim requests only at the appeal stage. Indeed, the examining division had already raised objections in respect of inventive step in the communication accompanying the summons to oral proceedings. In response, the appellants submitted the sets of claims of the main request and auxiliary request underlying the decision under appeal, which however, according to the examining division's decision, did not overcome the objections in respect of inventive step raised against the previous claim request.

8. The submission of the sets of claims of auxiliary requests 1 to 4 is therefore not a response to an unexpected decision of the examining division but rather a response to the examining division's objections in respect of inventive step already raised before the oral proceedings in examination. Consequently, auxiliary requests 1 to 4 could and should have been submitted during the examination proceedings.

9. In view of the above considerations, the board decided not to admit the main request and auxiliary requests 1 to 4 submitted with the statement of grounds of appeal into the appeal proceedings (Article 12(4) and (6) RPBA 2020).

Auxiliary request 5

Admittance of document D14
(Article 12(4) and (6) RPBA 2020)

10. The appellants did not submit any arguments as to why they could not have filed document D14 during the examination proceedings. They only argued that document D14 was relevant to their arguments in respect of inventive step and so for the board's decision and that it should therefore be admitted into the appeal proceedings.

11. However, under the provisions set out in Article 12(6) RPBA 2020, the board must not admit, *inter alia*, facts and evidence which should have been submitted in the proceedings leading to the decision under appeal. Since the examining division's objections in respect of inventive step had been raised prior to the oral proceedings in examination (see point 7. above), the appellants could and should have submitted document D14 and the arguments based on its disclosure during the examination proceedings.

12. Consequently, the board decided not to admit document D14 into the appeal proceedings (Article 12(4) and (6) RPBA 2020).

Inventive step (Article 56 EPC) - Claim 1

Closest prior art, technical effect and objective technical problem

13. The board agrees with the appellants and the examining division that the disclosure in document D2 represents the closest prior art.

14. The claimed subject-matter differs from the teaching in document D2 in that the vaccine composition is in the form of a dissolving microneedle and in that it is defined as being "stable for at least three weeks at 4°C". In the decision under appeal, it was considered that neither of these differences was associated with a technical effect.

15. The appellants did not submit any arguments relating to a technical effect of the second difference. Indeed, since no comparison of the stability of the claimed dissolving microneedle DNA vaccine composition with that of the vaccine composition of document D2 or any other DNA-based or dissolving microneedle vaccine compositions is available, it cannot be assessed whether the stability recited in the claim is different from that of known vaccine compositions. The examining division was therefore right in finding that no unexpected technical effect was associated with this difference.

16. However, the technical effects of the first difference are at least those known for dissolving microneedle vaccines, i.e. that the vaccine is administered without a syringe, which results in easier, less invasive, less painful administration that does not produce sharp waste.

17. The appellants argued that a further technical effect associated with the first difference was an increased antibody titre in the vaccinated animals, as shown in Table 9 and Figures 4A and 4B of the application.

18. However, Table 9 firstly shows that an increased antibody titre might only possibly be present at day 56 after vaccination but not at any other time point tested. Moreover, as is evident from Figure 4B, the increased antibody titre at day 56 appears to be caused by a single outlier animal, whereas the majority of the animals have antibody titres comparable to those in the conventional vaccination group. This casts doubt on the statistical relevance of this result. In line with this assessment, the mean antibody titres achieved by the two vaccination methods were considered in the application to be "comparable", i.e. no improvement was identified in the application (see lines 7 to 8 and 12 to 14 on page 26 of the application). Furthermore, Table 9 also shows that the antibody titre is dose-dependent and sufficient antibody titres can only be achieved at the higher dose, a feature not present in the claim.

19. Consequently, the board holds that the application does not support the contention that an improved immune response is achieved by the claimed vaccine composition over the whole range defined in the claim and this therefore cannot be taken into account when formulating the objective technical problem.

20. In view of the above considerations regarding the technical effects of the differences, the objective technical problem can be formulated as the provision of

a DNA rabies virus vaccine composition that can be more easily administered.

Obviousness

21. The examining division considered dissolving microneedles to be an obvious form of vaccine administration in view of the disclosure in documents D5 to D8 and D10. The board considers that this conclusion also holds true for the skilled person confronted with the reformulated problem of providing a DNA rabies virus vaccine composition which can be more easily administered (see point 20. above). The reason for this is that dissolving microneedles were known for having precisely this property in the state of the art, as is evident from, for example, document D6 (page 1022, left-hand column, first paragraph), document D7 (page 1, lines 11 to 16), document D8 (page 1548, right-hand column, first paragraph) and document D10 (page 43, right-hand column, second paragraph to left-hand column, first paragraph), and were therefore known to the skilled person as a solution to the problem to be solved.

22. In this respect, the skilled person does not require a motivation or pointer explicitly expressed in document D2 to contemplate an easier way of administering the disclosed vaccine because this was a known concern for all vaccines, as evident from documents D6 to D8 and D10 (*supra*). Furthermore, document D2 explicitly mentions "*alternate delivery systems*" as a means of optimising DNA vaccines (see page 895, left-hand column, first full paragraph) and therefore does not, as asserted by the appellants, only teach towards the use of adjuvants or immunostimulants for improving intradermal vaccination.

23. The board furthermore does not share the appellants' view that document D10 could not provide the skilled person with a reasonable expectation that the application of the DNA rabies virus vaccine by dissolving microneedles would elicit a protective immune response in an animal because it only speculated on future applications of microneedles for vaccination. Document D10 is a review article that concerns an overview of microneedle-based vaccination techniques, including for DNA-based vaccines (see page 46, right-hand column, first full paragraph to page 47, left-hand column, first paragraph), and reports the successful induction of immune responses by microneedle administration for a series of DNA-based vaccines, including by dissolvable microneedles. It concludes that "*it is plausible that microneedles, ... will be sure to establish a firm stand as one of the most effective and easily practiced drug delivery routes, if not replace some of the existing methods, in the near future*" (see document D10, page 47, left-hand column, last paragraph, last sentence).

24. Document D10 thus reports on a series of successful microneedle based vaccine compositions, does not express any reservations that the microneedle technique could not be applied to vaccines in general or DNA-based vaccines in particular and considers that microneedles will become an established vaccination route in general. Moreover, the disclosures in documents D6 (page 1026, right-hand column, last full paragraph), D7 (page 18, first paragraph) and document D8 (paragraph bridging pages 1556 and 1557) also support the fact that dissolvable microneedles can be used for successful vaccinations. Consequently, the skilled person would have expected from the teaching in

these documents that this technique could be applied to any vaccine known to be effective, in particular those known to be effective when applied intradermally (see document D10, page 43, left-hand column, first paragraph; Fig. 1).

25. The board is also unable to identify from the disclosure in document D9 an alleged prejudice in the art regarding a microneedle-based administration route for DNA rabies virus vaccines. The epidermal delivery method disclosed in document D9 consists of abrading the skin with a skin-microabrader and then topically applying a vaccine solution comprising inactivated rabies viruses to the skin (see section 2.3 on pages 5851 to 5852 of document D9). This technique is different from microneedle-based administration, where no skin abrasion takes place and the vaccine is directly injected into the (otherwise unharmed) skin. Furthermore, the skin also comprises dendritic cells different from Langerhans cells which are present in a layer targeted by microneedles (see e.g. Figure 1 of document D10). The suggestion in document D9 that epidermal Langerhans cells might only play a limited role in inducing an antibody response to a rabies virus vaccine based on inactivated viruses is therefore not sufficient to dissuade the skilled person from using dissolving microneedles for a DNA rabies virus vaccine.

26. On the contrary, document D2 in fact teaches that a DNA rabies virus vaccine can be efficiently administered via the intradermal route and document D9 discloses that rabies virus vaccination by the intradermal route "*is widely used and promoted by the WHO*" (see page 5850, left-hand column, last paragraph). The skilled person would thus have expected that DNA rabies

virus vaccines could also be effectively administered by a dissolving microneedle system targeting the skin.

27. On the second difference (see point 14. above), the appellants argued that it was unexpected for a DNA vector to be stable in a microneedle vaccine composition. However, the appellants did not submit any evidence for this argument or produce any comparison of the stability of the claimed vaccine composition with that of known vaccine compositions (see point 15. above).

28. Consequently, the board is not persuaded that the stability recited in the claim can justify a finding of inventive step.

29. The board is thus not convinced by the reasons submitted by the appellants and concludes that the skilled person would have contemplated using dissolving microneedles for a DNA rabies virus vaccine. Consequently, the subject-matter of claim 1 does not involve an inventive step (Article 56 EPC).

Auxiliary request 6

Inventive step (Article 56 EPC) - Claim 1

30. The appellants did not submit any arguments specific to claim 1 of auxiliary request 6, which comprises the additional feature that the vaccine composition is placed on a pinna of an ear of the animal, thereby piercing the animal's skin with the microneedles and releasing the vaccine (see section IV.). In the absence of any arguments to the contrary and any comparative data, the vaccination site cannot be considered to relate to a particular technical effect and thus is of

a merely arbitrary nature. Consequently, claim 1 of auxiliary request 6 does not involve an inventive step for the same reasons as set out above for claim 1 of auxiliary request 5 (see points 13. to 29.).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

I. Aperribay B. Claes

Decision electronically authenticated