Internal distribution code:

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

Datasheet for the decision of 19 February 2019

Case Number: T 1166/15 - 3.3.04

Application Number: 06808431.8

Publication Number: 1951300

IPC: A61K39/145, A61K39/39

Language of the proceedings: EN

Title of invention:
Changing Th1/Th2 balance in split influenza vaccines with adjuvants

Patent Proprietor:
Novartis Vaccines and Diagnostics S.r.l.

Opponent:
Glaxo Smithkline Biologicals S.A.

Headword:
Split influenza vaccines/NOVARTIS

Relevant legal provisions:
EPC Art. 100(b)

Keyword:
Sufficiency of disclosure - (yes)

Decisions cited:

Catchword:

-

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1166/15 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 19 February 2019

Appellant: (Patent Proprietor)	Novartis Vaccines and Diagnostics S.r.l. Via Fiorentina 1 53100 Siena (SI) (IT)
Representative:	Wise, Daniel Joseph Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent: (Opponent)	Glaxo Smithkline Biologicals S.A. Rue de l'Institut 89 1330 Rixensart (BE)
Representative:	Furstoss, Olivia Aline GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex, TW8 9GS (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 10 April 2015 revoking European patent No. 1951300 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	B. Claes
	L. Bühler

Summary of Facts and Submissions

I. The appeal lies from the decision of the opposition division to revoke European patent No. 1 951 300 having the title "*Changing Th1/Th2 balance in split influenza vaccines with adjuvants*".

Claim 1 of the patent as granted read:

"1. An immunogenic composition comprising a split influenza virus antigen and a Th1 adjuvant, wherein the antigen is prepared from a virus grown in cell culture and does not include any egg proteins and the Th1 adjuvant is in the form of (i) an oil-in-water emulsion which includes squalene, a tocopherol, and polysorbate 80, or (ii) a submicron emulsion of squalene, polysorbate 80, sorbitan trioleate, and an immunostimulatory oligonucleotide."

II. The patent was opposed as a whole under Article 100(a) EPC, on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), and under Article 100(b) and (c) EPC.

III. In the decision under appeal, the opposition division held that, whereas the claims of the main request (patent as granted) did not relate to added subject-matter (Article 100(c) EPC), the patent did not sufficiently disclose the invention as defined in claim 1 of the main request and of the sole auxiliary request (Articles 83 and 100(b) EPC).

IV. With the statement of grounds of appeal, the patent proprietor (hereinafter "appellant") stated that they maintained the two claim requests dealt with in the

decision under appeal and submitted arguments in favour of sufficiency of disclosure of the claimed invention.

V. In its reply to the appeal, the opponent (hereinafter "respondent") submitted arguments to the effect that the patent as granted lacked sufficiency of disclosure of the claimed invention.

VI. In a communication pursuant to Article 15(1) RPBA the board informed the parties of its preliminary opinion on claim construction and sufficiency of disclosure of the patent in relation to the invention defined in claim 1 of the main request. The board stated that it envisaged allowing the appeal, setting aside the decision under appeal and remitting the case to the opposition division for further prosecution.

VII. The respondent submitted further arguments related to sufficiency of disclosure of the patent in a further letter in advance of the oral proceedings.

VIII. Shortly before the oral proceedings, both parties informed the board in respective letters that they would not attend the oral proceedings.

IX. Oral proceedings were held in the absence of the parties. At the end of these, the chair announced the decision of the board.

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

D8: WO95/17210

D9: Baz *et al*. (2012), Clinical and Vaccine Immunology, Vol. 19, No. 2, pages 209 to 218.

XI. The appellant's arguments on sufficiency of disclosure of the invention defined in claim 1 as granted can be summarised as follows:

The opposition division had held that the expression "Th1 adjuvant" in claim 1 was unclear and that the disclosed examples did not provide evidence that the adjuvants recited in the claim worked as Th1 adjuvants. This led the opposition division to conclude that the claimed invention was not reproducible for the skilled person. The reasoning was, however, neither based on nor supported by serious doubts. Nor was it substantiated by verifiable facts as required by the established case law.

There was no ambiguity regarding the meaning of the expression "Th1 adjuvant". First, the claim itself provided a structural definition of the compounds comprised in the adjuvant. Second, a Th1 adjuvant was understood by the skilled person as an adjuvant capable of inducing a Th1 response to a given antigen and, thus, capable of biasing the immune response to a particular antigen more towards a Th1 response than a response induced by the same antigen in the absence of the Th1 adjuvant.

The proper test to determine whether the disclosure was sufficient to carry out the invention was whether the skilled person could prepare an immunogenic composition comprising a cell culture-based influenza virus antigen in combination with a Th1 adjuvant as indicated in the claim. The patent provided the skilled person with sufficient information on how to prepare the virus antigen (see e.g. paragraphs [0025] to [0030] and paragraph [0035]). The patent disclosed, and the claim

itself defined, which components the adjuvant needed to contain to be a Th1 adjuvant. All the components referred to in the claim were as such known in the art.

The data in the patent confirmed that the oil-in-water emulsion adjuvants defined in the claim and comprising squalene, a tocopherol and polysorbate 80 were "Th1 adjuvants" and could induce a Th1 response for split influenza vaccines in a patient. This function of an oil-in-water emulsion as defined in part (i) of the claim was also confirmed in the post-published documents D8 and D9.

XII. The respondent's arguments on sufficiency of disclosure of the invention defined in claim 1 as granted can be summarised as follows:

The skilled person reading the patent did not understand the term "Th1 adjuvant" to refer to an adjuvant that merely generated a Th1 immune response to the co-administered antigen, but to influence also the generation of a Th2 immune response and a possible bias (or shift) of Th1 and Th2 responses. Indeed, the patent taught the skilled person that the functional feature "Th1 adjuvant" meant an adjuvant for which the Th1/Th2 balance was shifted away from an excessive Th2 response (see title and paragraphs [0007] and [0041] of the patent).

The patent contained inconsistent and contradicting statements in relation to the meaning of the term "Th1 adjuvant" (see paragraphs [0007], [0008] and [0041]) as it contemplated all types of ranges of Th1 responses for a "Th1 adjuvant" in the sense of the invention, i.e. from partial to exclusive, including mixed forms. The skilled person could therefore not determine

whether the technical effect "Th1 adjuvant" as required by the claim was achieved.

The skilled person needed to be able to determine whether an adjuvant comprising the components structurally defined in the claim were a "Th1 adjuvant" in the sense of the patent. The patent did not however teach the skilled person how to select immunogenic compositions comprising an adjuvant falling within this structural definition of a "Th1 adjuvant" according to the claim and fulfilling the function ascribed to it in the patent.

Document D8 disclosed two adjuvants falling under the structural definition in part i) of the claim but reported that, in the context of HIV vaccines, these adjuvants "*can barely induce any Th1 response*" and were "*not sufficient to induce a shift toward a Th1 response*". Also, document D9 disclosed the use of an adjuvant falling under the structural definition in part i) of the claim, i.e. AS03, here in the context of split influenza vaccines. The response by the adjuvant was a mixed Th1/Th2-type response, the Th2 response being higher, and a shift towards the Th1 response was not detected when AS03 was used as compared to a non-adjuvanted vaccine composition.

If a "Th1 adjuvant" merely required the generation of a Th1 response irrespective of any bias or shift, then Alum fell under such a definition as it generated a Th1 immune response to the co-administered influenza antigen (see Figure 1 of the patent). However, the patent taught that Alum should not be used in the invention (see paragraphs [0008] or [0040] of the patent) because it elicited a Th2-biased immune

response (see paragraphs [0112] and [0113] of the patent).

The definition of a "Th1 adjuvant" thus involved, and relied upon, a bias or a shift in the total immune response towards a Th1-type response. The data in the table in paragraph [0120] of Example 2 of the patent led to serious doubts as to whether an adjuvant in the form of an oil-in water emulsion which comprises squalene, a tocopherol and polysorbate 80 was a "Th1 adjuvant" which provided a Th1 shift of the response as the sole conclusion which could be drawn from this table was that a Th1 response was induced. Indeed, in the experiment of Example 2 of the patent, only Th1 cytokines were measured.

XIII. The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted (main request) or, alternatively, that the patent be maintained in amended form on the basis of claims 1 to 17 of auxiliary requests 1 filed with the letter dated 13 November 2012.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. The parties were neither present nor represented during the oral proceedings as they had announced earlier. In accordance with Rule 115(2) EPC and Article 15(3) RPBA, the board decided to continue the proceedings in the absence of the parties.

Main request - claim 1 (as granted)

Claimed subject-matter

3. The claim is for a product, i.e. an immunogenic composition, comprising two constituents, namely, a "split influenza virus antigen" and a "Th1 adjuvant". The antigen constituent is defined further as being "prepared from a virus grown in cell culture" and as not including any egg proteins. The "Th1 adjuvant" constituent is further defined structurally in the claim. It is in the form of (i) an oil-in-water emulsion of particular compounds, or (ii) a submicron emulsion of particular compounds and an immunostimulatory oligonucleotide.

The decision under appeal - sufficiency of disclosure

4. The sole reason for the opposition division to revoke the patent in suit was that it failed to disclose the claimed invention in a manner sufficiently clear and complete for it to be carried out by the person skilled in the art in respect of the "Th1 adjuvant" compound of the composition.

5. The opposition division held that based on the disclosure of the patent, a "Th1 adjuvant", as referred to in the claim, was an adjuvant which was suitable "*for generating a Th1 immune response bias for vaccines that fall under the scope*" of the claim. The patent did not establish that the adjuvants recited in the claim were Th1 adjuvants in accordance with this understanding, and the patent failed to disclose a reliable teaching for the skilled person how to select for such Th1 adjuvants. The patent thus failed to teach

on how to select vaccine compositions which avoided oculorespiratory syndrome (ORS).

Claim construction

6. The pivotal issue for dealing with the requirement of sufficiency of disclosure in the present appeal case is to determine the technical meaning of the "Th1 adjuvant" feature, in terms of the required functions of such an adjuvant, in the context of the claimed invention.

7. The board has announced in the communication pursuant to Article 15(1) RPBA (see section VI) that it considers that the feature a "Th1 adjuvant" should be given the technical meaning as commonly understood by the skilled person in the technical field of vaccine preparations, i.e. a "Th1 adjuvant" is such an adjuvant that "*generates (promotes, triggers, ...) a Th1 immune response to a given co-administered antigen*".

8. The respondent has argued in essence that from various passages in the patent, the skilled person would rather understand the feature "Th1 adjuvant", for the purpose of the disclosure of the patent, to have the meaning as adhered to by the opposition division, i.e. an adjuvant suitable for generating an immune response biased towards a Th1-type immune response. The respondent referred in this context to paragraphs [0007], [0008] and [0040] in the patent.

8.1 Paragraph [0007] of the patent, which introduces the general aim of the invention states that "*the invention seeks to avoid components in split vaccines that could cause an excessive Th2 response. Th2 responses are not necessarily avoided altogether, as they can be*

important for protection, but strong Th2 polarization. If incomplete splitting occurs inadvertently during manufacture, or if a split vaccine undergoes aggregation during storage, any adverse effects (e.g. ORS) related to Th2 polarization may be avoided."

8.2 The subsequent paragraph [0008] continues that "*To avoid Th2 polarization, two approaches are followed, preferably in combination. Firstly, where a split vaccine includes an adjuvant then the adjuvant is chosen to stimulate at least a partial Th1-type response e.g. it is preferred to avoid adjuvanting a split influenza vaccine solely with aluminum salts. (...)*".

8.3 In the context of the latter remark, paragraph [0040] appears to provide a clarification for the reason why paragraph [0008] explicitly mentions avoiding aluminium salt adjuvants as it states that "*As aluminum salts (...) promote a Th2-type immune response when used on their own, the invention does not adjuvant split influenza viruses in this way. Instead, alternative adjuvants are used as described below.*"

9. However, it cannot be inferred from these paragraphs referred to by the respondent that, when considering the teaching of the patent in suit, the skilled person should deviate from the general and common technical understanding in the art of the feature "Th1 adjuvant". Indeed, whereas the three paragraphs referred to in the patent, in particular paragraphs [0007] and [0008], appear to set the tone for the disclosed invention and set out in particular the aim of the invention of avoiding excessive Th2 responses to split influenza vaccines leading, upon immunisation, to a Th2 polarisation of the immune response and thus to the

related adverse effects such as e.g. ORS. To this end, the vaccines are adjuvanted with compounds which stimulate at least a "*partial Th1-type response*". However, neither of these two passages stipulate including in the function of a "Th1 adjuvant" for the purpose of the patent, that the adjuvant must influence the generation of a Th2 immune response or of a possible bias (or shift) of Th1 and Th2 responses. Rather than re-defining the term, the referred to paragraphs describe the advantageous use of such Th1 adjuvants in split influenza vaccines - which are prone to comprising components that can cause an excessive Th2 response (see paragraph [0007]) - for shifting the balance of the Th1- and Th2-type responses of the vaccine to the former.

10. The common understanding of the function of a "Th1 adjuvant" in the art appears rather to be confirmed by the disclosure of the patent in paragraph [0041] which states: "*The distinction between Th1 and Th2 T helper cells is well known. Th1 and Th2 adjuvants cause an immune response to a co-administered antigen to be biased towards, respectively, a Th1-type or a Th2-type response. Thus Th1 adjuvants result in the production of antigen-specific T cells that release cytokines such as IL-2 and interferon-γ (leading to IgG2a antibodies) and TNF-α, whereas Th2 adjuvants result in the production of antigen-specific T cells that release cytokines such as IL-4 (leading to IgG1) and IL-5. The Th1/Th2 balance of a particular adjuvant can be assessed by known assays (see below), but can vary depending on factors such as the delivery route or the presence of co-administered substances. The adjuvants used with the invention may elicit an exclusively Th1-type response against influenza antigens when delivered to a patient, but will preferably elicit a mixed Th1/*

Th2-type response. Th0 cells may also be elicited, but a polarized Th2 response will be avoided" (emphasis added by the board).

11. Thus, this passage in fact reassures the skilled person that the term "Th1 adjuvant" is an adjuvant which generates a Th1-type immune response to a given co-administered antigen and provides the skilled person with the measures to determine such a response, i.e. the production of antigen-specific T-cells which release cytokines such as IL-2, IFN-γ and TNF-α, and confirms the general understanding in the technical field that Th1 adjuvants may not exclusively elicit a Th1-type response, but are not excluded to also, to a certain extent, elicit additional Th2-type responses.

12. The respondent has submitted that, when construing the term "Th1 adjuvant" independently of the adjuvant's influence of the Th1/Th2 response bias, Alum should also be considered a "Th1 adjuvant" as it was shown in Figure 1 of the patent to induce a Th1 response, although the disclosure of the patent advised against using Alum for the immunogenic compositions of the invention.

13. However the respondent's argument appears to lack pertinence in the context of the claimed subject-matter which does not refer to Alum as an adjuvant for defining the invention. Accordingly, this argument also fails to persuade the board that the skilled person would have been prompted by the disclosure in the patent to abandon the conventional understanding of the term "Th1 adjuvant" when reading the claims.

Sufficiency of disclosure (Article 100(b) EPC)

14. The respondent has in essence submitted two lines of argument for holding that the patent lacks sufficiency of disclosure in respect of the claimed invention.

15. As a first line of argument, it was submitted that documents D8 and D9 disclosed that adjuvants falling under the structural definition in part i) of the claim failed to induce a shift of the immune response toward a Th1 response for the same antigen.
The second line of argument was that the data in the table in paragraph [0120] of Example 2 of the patent solely demonstrated the induction of a Th1 response to the tested split influenza viruses, whereas a Th2 response was not tested.

16. However, both lines of argument appear to lack pertinence in view of the common understanding of the term "Th1 adjuvant" adhered to by the board, as they relate to an alleged lack of demonstration of influence of the adjuvant in the Th1/Th2 response bias towards an antigen. Indeed, in neither case did the respondent argue in this context that these adjuvants failed to induce a Th1 response at all.

17. Furthermore, the negative finding of the opposition division in the decision under appeal on the issue of sufficiency of disclosure was based on an understanding of the function of a "Th1 adjuvant" which deviated from that adhered to by the board. Therefore, this finding can no longer be held pertinent by the board either.

18. In view of the above considerations, and in absence of pertinent arguments submitted by the respondent to the contrary, the board is satisfied that the patent

provides sufficient disclosure to obtain the immunogenic composition of claim 1 including the adjuvants defined in parts (i) and (ii).

19. Thus, the patent in fact discloses the invention in claim 1, i.e. the particular immunogenic composition comprising a split influenza virus antigen and a Th1 adjuvant in accordance with the requirements referred to in Article 100(b) EPC.

Remittal to the opposition division (Article 111(1) EPC)

20. Article 111(1) EPC provides that the decision on whether to remit a case to the department which was responsible for the decision appealed is at the board's discretion and is to be taken on the basis of the facts and circumstances of the particular case (see generally "Case Law of the Boards of Appeal of the European Patent Office", 8th edition, IV.E.7.1).

21. The decision of the opposition division was based on the grounds for opposition in Article 100(b) EPC and Article 100(c) EPC, and found, respectively, against and for, the appellant.

The board holds in the appeal that the decision of the opposition division under Article 100(b) EPC was wrong and, accordingly, decides in favour of the appellant in this matter. Furthermore, the respondent has not submitted arguments of to the effect that the decision was wrong in the context of Article 100(c) EPC.

22. The opposition division did not decide on the grounds of opposition invoked on by the respondent when opposing the patent under Article 100(a) EPC, here lack of novelty and lack of inventive step.

23. The board's communication in preparation of the oral proceedings foreshadowed that, if the board concluded that sufficiency of disclosure was given, the decision under appeal would be set aside, and the case would be remitted to the opposition division for further prosecution to consider the issues of novelty and inventive step.

24. The parties have not objected to this announced course of the procedure and, accordingly, the board considers it appropriate to make use of its discretion under Article 111(1) EPC and order the remittal of the case to the opposition division for further prosecution on the basis of the main request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division for further prosecution.

The Registrar: The Chair:

S. Lichtenvort G. Alt

Decision electronically authenticated