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Datasheet for the decision of 2 October 2014

Case Number: T 1915/10 - 3.3.04

Application Number: 01984627.8

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Language of the proceedings: EN

Title of invention:
Vaccine against streptococcus pneumoniae

Applicant:
GlaxoSmithKline Biologicals s.a.

Headword:
Immunogenic composition/vaccine of at least two S. pneumoniae proteins/GlaxoSmithKline

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (yes)

Decisions cited:
T 0939/92, T 0964/92, T 0350/95, T 0716/08

Catchword:

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Case Number: T 1915/10 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 2 October 2014

Appellant: (Applicant)	GlaxoSmithKline Biologicals s.a. rue de l'Institut 89 1330 Rixensart (BE)
Representative:	Dalton, Marcus Jonathan William GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 18 January 2010 refusing European patent application No. 01984627.8 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman: G. Alt
Members: M. Montrone
M.-B. Tardo-Dino

Summary of Facts and Submissions

I. This appeal was lodged by the applicant (hereinafter "appellant") against the decision of the examining division to refuse the European patent application No. 01984627.8, published as international application WO 02/22168. The title of the application is "Vaccine against Streptococcus pneumoniae".

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

(D1) Ogunniyi A. D. et al; Infection and Immunity, 2000; 68(5): 3028-3033

(D2) WO 00/37105

(D5) Jedrzejas M. J.; Microbiology and Molecular Biology Reviews, 2001; 65(2): 187-207

(D6) Post-published technical data filed as point 4.2.2 of the statement of grounds of appeal concerning (i) the protection induced by immunisation with Ply and PhtD and (ii) data of a clinical trial testing the immunogenicity of different Ply and/or PhtD formulations in adults.

III. The decision under appeal was based on a main, first and second auxiliary request filed during the written proceedings and a third auxiliary request filed during the oral proceedings. The examining division found that the subject-matter of claim 1 of the main and first auxiliary request lacked novelty (Article 54 EPC) and that the subject-matter of claim 13 of the second auxiliary request lacked clarity (Article 84 EPC). In relation to the third auxiliary request the examining

division decided not to admit post-published *"supplementary technical information"* and that the subject-matter of claim 1 did not involve an inventive step (Article 56 EPC).

(i) The examining division assessed the admissibility of the *"supplementary technical information"* (which corresponds to the data of document D6 in the appeal proceedings) as follows:

The information filed on 16 August 2006 concerned post-published data about the protection induced by the immunisation of mice with Ply and PhtD. Additional post-published data filed on 25 September 2009 concerned a clinical trial testing the immunogenicity of different Ply and/or PhtD formulations in adults. According to the examining division these data were provided by the appellant to show that the immunogenic composition of PhtD and Ply *"represents a vaccine generating an unexpectedly good protective effect"*.

In the examining division's opinion neither the experimental data provided in the application as filed nor the common general knowledge represented by the prior art document (D1) provided a basis for the skilled person to conclude plausibly that the specific combination of the claimed *S. pneumoniae* antigens PhtD and Ply represented a solution to the technical problem of providing a vaccine against *S. pneumoniae* (note added by the board: as claimed in claim 10 of the third auxiliary request). The application as filed merely disclosed that native Ply and PhtD were immunogenic but a protective effect of a combination of these proteins as required for a vaccine was not shown. Moreover, document (D1) disclosing the general understanding of pneumococcal protein vaccines at the date of filing of

the present application showed that an immunogenicity *per se* of protein compositions comprising Ply together with one or two further virulence factors was not a sufficient prerequisite for such a composition to consistently induce a protective response as required for a vaccine. The "supplementary technical information" was therefore not admitted.

(ii) Regarding the lack of inventive step of the subject-matter of
claim 1 the examining division reasoned as follows:

Document (D1) was the closest prior art for the subject-matter of claim 1. It disclosed a study of detoxified Ply and the two pneumococcal virulence factors PsaA and PspA in different immunogenic combinations. The application as filed did not disclose data that supported the presence of an improved immunogenic property of the claimed combination of PhtD and detoxified Ply over the immunogenic combinations known from document (D1).

The objective technical problem to be solved in view of document (D1) was therefore the provision of an alternative immunogenic composition. According to the subject-matter of claim 1 this problem was solved by an immunogenic composition comprising at least PhtD and Ply. That this subject-matter solved the underlying technical problem was credible because the application as filed provided evidence that a composition comprising native Ply and PhtD induced Ply- and PhtD-specific antibodies.

The examining division considered this solution obvious. The skilled person looking for alternatives would combine Ply of document (D1) with other known

immunogenic pneumococcal proteins suitable for vaccine development. It would therefore turn to document (D2) disclosing such proteins, *inter alia* PhtD. The combination of Ply and PhtD was the result of *"an arbitrary selection among the solutions that can be generated on the basis of the disclosure of the antigenic proteins of both D1 and D2. Such an arbitrary selection, however, fails to represent a contribution to the prior art for which an inventive step can be acknowledged"*. The skilled person would thus have arrived in an obvious manner at the subject-matter of claim 1.

IV. With its statement of grounds of appeal the appellant filed a main request and a first auxiliary request which was identical to the third auxiliary request before the examining division, and documents (D5) and (D6). It requested that the decision under appeal be set aside and that a patent be granted on the basis of either the main or the auxiliary request. On an auxiliary basis, oral proceedings were requested.

V. The appellant was summoned to oral proceedings scheduled for 25 June 2014.

VI. In a telephone conversation on 20 May 2014 the rapporteur informed the appellant of the board's view that the auxiliary request but not the main request was allowable. The appellant then withdrew its main request and requested the *"continuation of the examination on the basis of auxiliary request 1 filed on 28 May 2010"*, *i.e.* the appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of auxiliary request 1 filed with the statement of grounds of appeal.

Claims 1 and 10 to 13 of auxiliary request 1 read:

"1. An immunogenic composition comprising at least 2 *S. pneumoniae* proteins wherein one of the proteins is PhtD and another protein is detoxified pneumolysin (Ply).

10. A vaccine comprising the immunogenic composition of claim 1-9.

11. Use of the vaccine of claim 10 in the manufacture of a medicament for prevention of pneumonia in patients over 55 years of age.

12. Use of the vaccine of claim 10 in the manufacture of a medicament for prevention of Otitis media in infants.

13. A method of making a vaccine as claimed in claim 10 comprising the steps of: selecting and isolating two different *S. pneumonia* proteins which are PhtD and detoxified pneumolysin (Ply); and mixing said proteins together with a pharmaceutically acceptable carrier."

VII. The board cancelled the oral proceedings.

VIII. The appellant's arguments, in so far as they are relevant for the present decision, may be summarized as follows:

Inventive step

Document (D1) was the closest prior art with regard to the subject-matter of claim 1, since it disclosed several immunogenic combinations of pneumococcal

proteins suitable for vaccination, including detoxified Ply. The *S. pneumoniae* protein PhtD was not mentioned.

The problem to be solved in view of the closest prior art document (D1) was the provision of a further combination of *S. pneumoniae* proteins with improved immunogenicity.

The problem was solved by the subject-matter of claim 1.

The application as filed established that it was plausible that a combination of pneumolysin and PhtD could generate a useful immune response. Example 2 showed that infants and adults developed antibodies against these two proteins upon exposure to a complete *S. pneumoniae* bacterium, *i.e.* a combination of all possible native pneumococcal antigens. A particularly strong response was induced against PhtD.

Moreover, the application disclosed on page 3, line 30 to page 4, line 3 that combinations of two proteins from different *"categories"* were preferred and explicitly indicated that the combination of PhtD and Ply in an immunogenic composition was preferred.

Decisions T 1329/04 and T 536/07 suggested that to reach the plausibility threshold all that was required was that there was no prejudice in the art against the solution put forward. This was so in the present case.

Document (D1) disclosed that all immunogenic combinations containing detoxified Ply provided some degree of protection (see table 2, page 3029, column 2, lines 30 to 32). Document (D2) described an active

protection of mice after a vaccination with PhtD (see example 6).

Under these circumstances, the post-published data of document (D6) should be taken into account for the assessment of inventive step. These data showed that the combination of PhtD and Ply was more effective than each protein alone in inducing a protective response in mice challenged with *S. pneumoniae*, and that PhtD augmented the anti-Ply antibody immune response in human adults.

To arrive at the solution of claim 1 the skilled person would have to retain one of the proteins of the different combinations disclosed in document (D1) and combine it with one of the four proteins disclosed in document (D2). However, there was no hint derivable from any of the documents that would motivate the skilled person to select the particular protein combination as claimed. If anything, the skilled person would have combined the proteins disclosed in document (D1) with a further virulence factor such as that disclosed in document (D5). However, this document did not mention PhtD.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the auxiliary request 1 filed with the statement of grounds of appeal.

Reasons for the Decision

1. The claims of the sole request before the board are the same as those of the third auxiliary request dealt with in the decision under appeal. Claims 1, 10 and 13 are

independent claims. In the decision under appeal the examining division held that the subject-matter of claims 1 to 13 of this third auxiliary request fulfilled the requirements of Articles 123(2), 84 and 54 EPC, but considered that claim 1 did not fulfil the requirements of Article 56 EPC. Hence, in its decision the examining division has considered neither the requirements of Article 56 EPC in relation to the other claims, in particular the independent claims 10 and 13, nor those of Article 83 EPC.

2. In the board's view (see below), the examining division's reasoning in finding that the subject-matter of claim 1 lacks an inventive step is not persuasive and that therefore the decision under appeal is to be set aside.

3. The board has considered remitting the case to the examining division for examination of the remaining issues, but for reasons of procedural economy has decided to deal with the case itself in accordance with Article 111(1) EPC, last half sentence. Therefore, in the following the patentability requirements of all claims are assessed.

Amendments, clarity, support and novelty - Articles 123(2), 84 and 54 EPC

4. In agreement with the examining division's reasoning and decision, the board considers that the subject-matter of claims 1 to 13 fulfils the requirements of Articles 123(2), 84 and 54 EPC.

Sufficiency of disclosure - Article 83 EPC

5. Detoxified pneumolysin (Ply) and poly-histidine triad protein D (PhtD) were known from the prior art at the priority date of the present application (see page 5, line 4 and page 7, lines 1 to 3 of the application as filed). Hence, in the board's view the skilled person is able to make the immunogenic composition of claim 1 or the vaccine of claim 10 on the basis of the disclosure provided in the application. This applies also to the subject-matter of dependent claims 2 to 9, the second medical use of the vaccine according to claims 11 and 12 and the method of making the vaccine according to claim 13.

6. With regard to the second medical use of claims 11 and 12, it is established case law that the application must also disclose the suitability of the product to be manufactured for the claimed therapeutic effect (see Case Law of the Boards of Appeal, 7th edition, II.C. 6.2, first paragraph). In the present case the claimed therapeutic effect is the treatment of pneumonia in adults over 55 years of age (claim 11) and the treatment of otitis media in infants (claim 12).

7. The application provides in example 2, and in particular in table 1 on page 22 and figures 1 to 6, serological data disclosing an anti-Ply and anti-PhtD specific immune response in adults above 55 years and in infants following a natural exposure to *S. pneumoniae*. Hence, the teaching in the present application alone and, in particular, when considered in the light of the teachings in the prior art documents (D1) and (D2) (see observations in point 15 below) discloses the suitability of the vaccine

comprising at least detoxified Ply and PhtD for the therapeutic effects referred to in claims 11 and 12.

8. Thus, the subject-matter of claims 1 to 13 fulfils the requirements of Article 83 EPC.

Inventive step - Article 56 EPC

Closest prior art

9. In assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the Boards of Appeal of the EPO normally apply the "problem-solution" approach, and so will this board in the present case. It requires as a first step the identification of the closest prior art.

The closest prior art is generally a document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most technical features in common, *i.e.* requiring the minimum of structural modifications (see Case Law of the Boards of Appeal, 7th edition 2013, I.D.3.1).

10. The application is concerned with protein-based compositions useful for the protection against a *S. pneumoniae* infection.

Claims 1 and 10

11. The board agrees with the examining division and the appellant that document (D1) is the closest prior art for the subject-matter of claim 1, and also for the subject-matter of claim 10, because it aims at the

provision of immunogenic pneumococcal protein combinations for the preparation of a *S. pneumoniae* vaccine. Moreover, some of the immunogenic compositions disclosed in this document comprise detoxified Ply (named PdB in document (D1), see abstract) including a combination of Ply and pneumococcal surface protein A (PspA) as the preferred vaccine candidate (see page 3032, column 1, second paragraph). The board considers that this combination is the closest prior art.

Problem to be solved and solution

12. According to established case law, for the purposes of the problem-solution approach the problem to be solved is formulated in view of the closest prior art on the one hand, and the claimed invention and the effects achieved by it on the other (see Case Law of the Boards of Appeal, 7th edition 2013, I.D.4.1).

The problem to be solved according to the application is the provision of an immunogenic composition and a vaccine improved over a vaccine comprising unconjugated or conjugated pneumococcal polysaccharides (see page 2, lines 1 to 17 of the application as filed).

The appellant formulates the problem to be solved as the provision of a further combination of *S. pneumoniae* proteins with improved immunogenicity.

However, since the combination of detoxified Ply and PspA of document (D1) is the closest prior art and since there is no evidence either in the application or in any other document available in these proceedings that the claimed composition is superior to the closest prior art composition, the problem to be solved is to

be reformulated as the provision of an alternative composition useful for protection against a *S. pneumoniae* infection.

The claimed solution to this problem is the immunogenic composition according to claim 1 and the vaccine according to claim 10, both comprising at least detoxified Ply and PhtD.

13. It is established case law that the assessment of inventive step using the problem-solution approach requires the consideration of whether or not the claimed subject-matter can be regarded as a credible solution to the problem posed. This has to be derivable either from the disclosure of the application as filed and/or from the common general knowledge available at the relevant date (see Case Law of the Boards of Appeal, 7th edition 2013, I.D.4.6). In the present case, whether or not the claimed solution can be considered to credibly solve the problem formulated above was an issue. It has been dealt with in the decision under appeal in the context of the admissibility of the *"supplementary technical information"* (see section III(i) above).

14. The application discloses, in particular in table 1 on page 22 and figures 1 to 6, the consistent presence of high amounts of anti-Ply and anti-PhtD antibodies in humans previously exposed to *S. pneumoniae*.

15. As concerns common general knowledge, document (D1) discloses that three different immunogenic pneumococcal protein compositions comprising detoxified Ply are **all** immunogenic (see table 1 on page 3029). Moreover, these three compositions comprising detoxified Ply significantly protect mice in **five out of six**

challenging experiments with two different pneumococcal strains when compared to a placebo group (see page 3029, column 2, lines 30 to 32; table 2 and figures 2A and 2B on page 3030; page 3031, column 1, lines 18 to 22). Document (D2) discloses the induction of a protective immune response in mice upon the administration of PhtD alone (see example 6).

Thus, the application discloses a consistent and strong antibody response against native PhtD and Ply in humans and the prior art discloses that compositions comprising detoxified Ply are immunogenic. Moreover, the large majority of these compositions and PhtD are known to induce a protective immune response.

16. The board considers that this evidence from the application and the prior art is sufficient to indicate the immunogenic character of the claimed composition and also its usefulness as a vaccine candidate, and thus that the subject-matter of claims 1 and 10 can be considered to credibly solve the problem formulated above. According to established case law, absolute proof, *i.e.* certainty that a problem has been solved, is not required for establishing that a claimed solution is credible (see for example decision T 716/08 of 19 August 2010, point 16 of the reasons).

17. Hence, the board's conclusion on this issue differs from that of the examining division (see section III(i) above). As a consequence, the board, in contrast to the examining division, takes the post-published technical data (document D6) into account. The data of document (D6) confirm that an immunogenic composition of detoxified Ply and PhtD does indeed have a protective effect and they thus demonstrate its suitability as a vaccine.

18. The essential reason for the examining division's view that the vaccine of claim 10 could not be considered a credible solution to the problem appeared to be the disclosure in document (D1) of the failure of a Ply-comprising composition to induce a protective effect in **one out of six** challenging experiments.

19. The board observes that despite this single failure the authors of document (D1) summarise their data as *"encouraging"* and as justifying a *"serious consideration of the combination vaccine approach for combating infections caused by S. pneumoniae"* (see page 3032, column 1, second paragraph). In view of these statements in document (D1) the board is not convinced by the examining division's view.

Obviousness

20. The question in the present case is whether or not the skilled person, faced with the problem of providing an alternative composition useful for protection against a *S. pneumoniae* infection, would have modified the closest prior art composition of document (D1) by combining Ply with PhtD instead with PspA.

21. Document (D1) discloses that, of the combinations disclosed in this document, especially the combination of Ply and PspA should be studied in other model systems (see page 3032, column 1, second paragraph). The document also discloses that *"further studies would necessarily include an assessment of the protective efficacies of combinations including other recently characterized virulence-associated proteins of*

S. pneumoniae such as CbpA" (see page 3032, column 2, lines 1 to 4). It is moreover derivable from document (D1) that PspA is more immunogenic than Ply (see table 1 on page 3029). In the board's view the skilled person would therefore rather be motivated to include PspA - and not Ply - in a composition and combine it with other virulence factors when looking for an alternative composition useful for protection against a *S. pneumoniae* infection. Thus, the claimed combination which comprises Ply cannot be considered as obvious in the light of the teaching of document (D1) alone.

22. Assuming that the skilled person had considered retaining Ply instead of PspA in the combination, the question is whether or not the skilled person would have been motivated to replace PspA by PhtD.

Document (D1) deals with protein-based vaccine compositions containing exclusively virulence-associated factors of this microorganism (see the references in point 21 above). PhtD is neither mentioned in this document nor is its involvement in the virulence of *S. pneumonia* derivable from it.

In fact, there is evidence suggesting that PhtD is not considered as a virulence factor. Document (D5) discloses that *S. pneumoniae* has eight different virulence factors, *inter alia* those disclosed in document (D1) (see figure 1). PhtD is not among those listed.

Document (D2) discloses four pneumococcal Pht proteins, *inter alia* PhtD. This document too neither discloses nor suggests that PhtD is a pneumococcal virulence factor.

Thus, in contrast to the decision under appeal, the board comes to the conclusion that the skilled person would not be motivated by the teachings of documents (D1) and (D2) to replace PspA by PhtD because the skilled person would not have considered PhtD to be a virulence factor. Thus, also for this reason the claimed combination is not considered as obvious.

23. With regard to the subject-matter of claim 1, the examining division declined to acknowledge an inventive step (see section III(ii) above). It formulated the problem to be solved as the provision of an alternative immunogenic composition. The examining division considered that in relation to this problem the combination of Ply and PhtD was the result of *"an arbitrary selection among the solutions that can be generated on the basis of the disclosure of the antigenic proteins of both D1 and D2. Such an arbitrary selection, however, fails to represent a contribution to the prior art for which an inventive step can be acknowledged"*. To support its view the examining division referred to decisions T 939/92 of 12 September 1995, T 964/92 of 23 August 1994 and T 350/95 of 23 July 1998.

24. The situation as described by the examining division in its decision is the one which is also derivable from the reasoning of all three decisions cited by it, *i.e.* claimed subject-matter is considered as obvious because it constitutes a choice from a larger number of alternatives, all of which the skilled person would have considered as equally suitable to solve a formulated technical problem and where the chosen compounds are not characterised by another, unexpected effect. Such a choice is denoted in the case law as "*arbitrary*".

25. In decision T 939/92, *supra*, the board, following the appellant's argumentation, formulated a *"hypothetical"* technical problem as the *"provision of further (or alternative) chemical compounds, regardless of their likely useful properties"*. The board considered that *"all structurally similar chemical compounds, irrespective of their number, that a skilled person would expect, in the light of the prior art, to be capable of being synthesised, are equally suitable candidates for solving such a hypothetical "technical problem", and would therefore all be equally "suggested" to the skilled person. It follows from these considerations that a mere arbitrary choice from this host of possible solutions of such a "technical problem" cannot involve an inventive step"* (see points 2.5 and 2.5.3 of the reasons).

26. In decision T 964/92, *supra*, the problem to be solved was formulated as *"providing further compounds having activity against angina pectoris"*. The appellant argued *inter alia* that *"the skilled person would have had to consider a host of possible alternatives"* as a solution to this problem, and that *"in the absence of any hint in the prior art towards the suitability of the relative small group of compounds defined in the present Claim 1, the selection of this group was not obvious, since the skilled person would not have chosen just this group."* The board dismissed this argument by stating that *"if, as in the present case, a number of modifications was obvious, all compounds resulting from such modifications, irrespective of their number, are equally suitable candidates for solving that technical problem and would therefore all be "suggested" to the skilled person. Any arbitrary choice among them does*

therefore not involve an inventive step" (see points 2.8 to 2.10 of the reasons).

27. In decision T 350/95, *supra*, the problem to be solved was the *"provision of a further hydrocracking process"*. The board found that by following the teaching in document D1 *"the skilled person would have obtained stabilised zeolites having unit cell sizes lying with a range which overlaps with the range specified in present claim 1. Furthermore, the stabilised zeolites of D1 are said to be suitable for use in catalyst compositions for hydrocracking operations"*. Under these circumstances the board considered that the claimed solution to the problem, constitutes *"no more than an arbitrary choice from the broad class of stabilised zeolites made available by D1"* (see points 4.2 and 4.3 of the reasons).

28. In the present case, document (D1) indicates that not all combinations containing Ply are equally immunogenic (see table 1 on page 3029). Moreover, the document points to possible *"antagonistic"* effects between the proteins, influencing their immunogenicity when used in combination (see page 3029, column 1, third paragraph). Hence, in contrast to the circumstances underlying the cited decisions, in the present case the skilled person would not perceive that all of the possibly suggested combinations are equally immunogenic. Therefore, in the light of the concept developed by the case law (see point 24 above), the choice of the particular combination claimed cannot be considered to be the result of an *"arbitrary"* choice. Thus, the examining division's view is not persuasive.

29. In summary, the board concludes that the immunogenic composition according to claim 1 and the vaccine

according to claim 10, both comprising at least detoxified Ply and PhtD, involve an inventive step (Article 56 EPC). This conclusion also applies to the subject-matter of dependent claims 2 to 9, to the subject-matter of claims 11 and 12 relating to a second medical use of the vaccine according to claim 10, and to the subject-matter of claim 13 relating to a method for producing the vaccine of claim 10.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to grant a patent on the basis of auxiliary request 1 filed with the statement of grounds of appeal and a description and figures to be adapted thereto.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated