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Datasheet for the decision of 2 February 2006

Case Number: T 1193/03 - 3.3.04

Application Number: 93912750.2

Publication Number: 0642355

IPC: A61K 39/295

Language of the proceedings: EN

Title of invention:
Combined vaccines comprising hepatitis B surface antigen and other antigens

Patentee:
SmithKline Beecham Biologicals s.a.

Opponents:
Chiron Corporation
Sanofi Pasteur Limited

Headword:
Method of preparing a vaccine composition comprising hepatitis B surface antigen/SMITHKLINE

Relevant legal provisions:
EPC Art. 56

Keyword:
"Sole request - inventive step (no)"

Decisions cited:
T 0077/87, T 0412/91

Catchword:
-

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Case Number: T 1193/03 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 2 February 2006

Appellant: (Patent Proprietor)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 29 July 2003 revoking European patent No. 0642355 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chair: U. Kinkeldey
Members: G. Alt
S. Perryman

Summary of Facts and Submissions

I. European patent No. 0 642 355 with the title "Combined vaccines comprising hepatitis B surface antigen and other antigens" was granted with twenty-six claims on the basis of European patent application 93 912 750.2 which was derived from International application WO 93/24148.

II. Two oppositions were filed relying on the grounds in Article 100(a) EPC of lack of novelty and inventive step and on Article 100(b) EPC.

III. The opposition division revoked the patent pursuant to Article 102(1) EPC on the grounds that none of the requests before it met the requirements of the EPC, the main request then on file not complying with the requirements of Article 83 EPC, while the claims of the two auxiliary requests before it contravened the requirements of Article 123(2) EPC.

IV. The patent proprietor (appellant) lodged an appeal against the decision of the opposition division.

V. In the course of the appeal proceedings the appellant filed claim sets A to K, their claims differing from the claims rejected by the opposition division.

VI. Respondent I filed document D85, a declaration from respondent's I Korean patent attorney comprising Annex A, the thesis of Choi Chang Baek in the Korean language, Annex B, a shortened English translation of the Choi Chang Baek thesis and Annex C, a declaration of the Korea University library. With the letter dated

21 February 2005 the appellant accepted the admission of document D85, Annex A into the proceedings. Subsequently, the appellant provided a certified full-length translation of the Choi thesis.

VII. At a late stage of the oral proceedings the appellant withdrew all claim requests with the exception of request "H" containing eight claims, all of them relating to a method of preparing a vaccine composition.

Independent claim 1 read:

"1. A method of preparing a vaccine composition comprising adsorbing Hepatitis B surface antigen (HBsAg) onto aluminium phosphate (AP), adsorbing DT, DTPw or DTPa onto AP or aluminium hydroxide (AH), allowing time for complete and stable adsorption of the respective components, and combining the components."

where the following abbreviations are used:

D = vaccine containing diphteria antigen
T = vaccine containing tetanus antigen
Pw = vaccine containing whole cell pertussis antigen
Pa = vaccine containing acellular pertussis antigen
DTP = combined vaccine containig diphteria, tetanus and pertussis antigens
HBsAg = hepatitis B surface antigen
HB = hepatitis B virus
AP = aluminium phosphate
AH = aluminium hydroxide

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

D12: Develop. Biol. Standard, vol. 54, 1983, Mazert, M.C. et al.

D22: Final report on an "Informal consultation on quadrivalent diphteria-tetanus-pertussis-Hepatitis B vaccine"; meeting held on 7-8 May 1992 at the WHO Headquarters;

D85:

- Annex A: Thesis of Choi Chang Baek at the Korea University in the Korean language (hereinafter referred to as document D85);

- Annex C: Declaration of the manager of the Science Library of Korea University dated 1 April 2004 concerning the public availability of document D85

D85c: Certified Translation of document D85 entitled "Studies on the interaction of hepatitis B vaccine and other vaccines"

D107: Declaration of Dr. Natalie Garçon dated 17 February 2005.

IX. The arguments of the appellant in so far as they are relevant to the present decision may be summarized as follows:

Document D22 was the closest prior art document. Being a report of a meeting of experts in the vaccine field, it showed the "real world" state of the art two weeks

before the priority date and was therefore the most realistic springboard towards the invention.

Document D85 was not the closest prior art document. Firstly, it had been ignored by the scientific community as shown by the fact that it was not mentioned in document D22. Thus, it did not form part of the state of the art. Secondly, even if the document were considered to belong to the state of the art, the skilled person upon reading document D85 would discover some irregularities in the experimental set up and results which would have raised doubts that the method of preparing the DTP-HBsAg vaccine formulation had ever been performed as described. Indeed, document D107, a declaration filed during the appeal proceedings, corroborated that the method did not lead to a suitable vaccine formulation. However, erroneous disclosures not reflecting the technical reality did not form part of the state of the art as held in decisions T 77/87 or T 412/91. Hence, the skilled person would have disregarded document D85 or at least the part of it relating to DTP-HBsAg vaccine preparation.

If document D85 was considered as the closest prior art document and given that document D107 established that the method disclosed in document D85 did not result in a successful vaccine formulation, the problem to be solved was the provision of a method for reliably making a multivalent vaccine. A combination of document D85 with document D22 did not render the claimed method obvious. While the document established a need for a quadrivalent vaccine comprising Hepatitis B virus, diphteria, tetanus and pertussis antigens, it warned against mixing of the commercially available trivalent

adsorbed DTP vaccine and the commercially available adsorbed monovalent hepatitis B vaccine because of the possible, but unpredictable reduction of the immunogenicity of the HBsAg in the quadrivalent vaccine mixture when compared to the monovalent formulation due to impurities present in the DTP stemming from the manufacturing process.

X. The arguments of respondents I and II in so far as they are relevant to the present decision may be summarized as follows:

Document D85 was the closest prior art document because the method disclosed therein has the most features in common with the claimed method.

In the absence of evidence to improvements with regard to the method disclosed in document D85 the problem had to be formulated as the provision of an alternative process of preparing a multivalent vaccine composition.

The provided solution was the result of a routine choice as evidenced by document D22 teaching the combination of commercially available ready-prepared HBsAg monovalent vaccine with a ready-prepared DTP trivalent vaccine.

Document D22 discouraged simple mixing of the adsorbed components in a syringe just before use, but not mixing of the components per se.

XI. Requests

The appellant (patent proprietor) requested that the decision under appeal be set aside and that the patent be maintained on the basis of claim set H submitted on 5 December 2003.

The respondents (opponents) requested that the appeal be dismissed.

Reasons for the Decision

1. As set out below, the issue decisive for the outcome of the appeal is whether or not the subject-matter of claim 1 is inventive and thus the board sees no need to give reasons concerning other issues raised with respect to the sole request.

2. For assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal consistently apply the problem and solution approach requiring as the first step, prior to the formulation of the technical problem to be solved and the evaluation of the obviousness of the provided solution, the identification of the closest prior art, a document providing the most promising springboard towards the invention. The Boards of Appeal have developed in their case law certain criteria for identifying such a document. It has been repeatedly pointed out that it should be prior art relating to subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention

(cf. Case Law of the Boards of Appeal of the European Patent Office, 4th Edition 2001, chapter I.D.3).

3. Claim 1 relates to a method of preparing a vaccine composition. The method involves adsorbing HBsAg onto aluminium phosphate, adsorbing either of DT, DTPw or DTPa to either aluminium hydroxide or aluminium phosphate, allowing time for adsorption of the components and subsequently combining the adsorbed components.

4. Documents D22 and D85 are regarded as candidates for the closest prior art by the parties. Both disclose the preparation of a DTP-HBsAg vaccine and thus fulfil the above mentioned criterion.

5. If several documents relate to the same purpose, a secondary consideration for the selection of the closest prior art document is the highest degree of identity of technical features (cf. Case Law of the Boards of Appeal of the European Patent Office, 4th Edition 2001, chapter I.D.3).

6. Document D22 discloses that for the preparation of a combined DTP vaccine "diphteria and tetanus toxoids are combined, [...], adsorbed on an **aluminium or calcium adjuvant**", Bordetella pertussis bacteria are grown, harvested, inactivated and "combined with the adsorbed tetanus and diphteria toxoids into a final vaccine (page 7; emphasis added). HBsAg in the monovalent vaccine formulation is "adjuvanted with **aluminium compounds**" (page 8; emphasis added). Document D85 teaches to combine HBsAg, diphteria toxoid, tetanus toxoid, pertussis bacteria and **aluminium phosphate** in a

single vessel and to mix them by stirring to obtain adsorption to aluminium phosphate. Thus, one feature shared by claim 1 and the method disclosed in document D85 is the adsorption of all components to **aluminium** compounds, while document D22 refers to aluminium **or** calcium with regard to diphteria or tetanus and to no adjuvant with regard to pertussis antigen. Therefore, the method disclosed in document D85 has more features in common with the claimed method than the one disclosed in document D22. Hence, the board considers the teaching of document D85 as the most promising springboard towards the invention.

7. The appellant argues that the non-mentioning of document D85 in document D22 showed that the scientific community had ignored it, thus rendering it unavailable as state of the art under Article 54(2) EPC for the evaluation of inventive step.

Article 54(2) EPC stipulates that the state of the art comprises "everything made available to the public by means of a written or oral description [...] before the date of filing of the European patent application." A document is considered as having been made available if only a single member of the public is in a position to gain access to it (cf. Case Law of the Boards of Appeal of the European Patent Office, 4th Edition 2001, chapter I.C.1, 1.6). Thus, a document is not removed from the state of the art because it has not been cited in another document or because the scientific community did not take notice of it. The declaration of the manager of the Science Library of Korea University (document D85, Annex C) explaining that the thesis has been available in the library since July 1988 without

restriction and thus before the priority date of the patent in suit, confirms the possibility of access. The declaration was not contested. Therefore, document D85 must be treated as prima facie state of the art under Article 54(2) EPC.

8. The appellant further argues that even if document D85 prima facie belongs to the state of the art, it or at least that part of its teaching relevant for the evaluation of inventive step had to be disregarded on the legal view taken in decisions T 77/87 (OJ EPO 1990, 280) and T 412/91 of 27 February 1996 because the skilled person would detect certain aspects in the document that would give reason to doubt that the method described therein had ever been performed as described.

8.1 In particular, the appellant, relying on the following parts of the disclosure of document D85 argues:

- That the initial weight of the mice and guinea pigs is the same for all animals (in grams for the guinea pigs and tenth of a gram for mice; Tables 13 and 14) According to the appellant that would never be the case in practice.

- That the anti-HBsAg responses of the four experimental groups are almost identical (Figure 5) which, according to the appellant, is highly unusual given the biological variation among individual animals.

- That the antibody response continues to increase exponentially between two and five months after the

immunizations whereas one would expect, as reported in documents D12 and D107, a plateauing or decrease of the antibody response.

Moreover, the appellant relies on document D107 as evidence that the process described in document D85 does not result in a suitable vaccine.

8.2 The legal principle concerned, as summarized in point 4.6 of decision T 412/91, is that "...In principle, what constitutes the disclosure of a prior art document is governed not merely by the words actually used in its disclosure, but also by what the publication reveals to the skilled reader as a matter of technical reality. If a statement is plainly wrong, whether because of its inherent improbability or because other material shows that it is wrong, then although published it does not form part of the state of the art. Conversely, if he would not recognise that the teaching is wrong, it does belong to the state of the art." For the reasons given below, the board concludes that on the facts of this case, this legal principle is not applicable to exclude document D85 from being treated as state of the art. The appellant's line of argumentation would require that the skilled person reading document D85 would have indeed recognized the above mentioned aspects as deficiencies, and been certain that they were deficiencies sufficiently serious as to make it necessary to completely disregard the disclosure as technical reality.

i) The weight of laboratory animals

It is disclosed on page 19 of document D85 that the guinea pigs weighed **about** 350 g and the mice **about** 20 g. Thus, the skilled person would treat the indication of the same initial weight for all animals as most likely being an averaging out or a simplification for the purpose of the Table, and not as being any certain indication of a fundamental technical deficiency.

ii) Identical HBsAg response and missing plateauing of response

In document D12 the slowing down of the immune response is seen when a hepatitis B vaccine and a yellow fever or measles vaccine are injected alone or simultaneously. Since the way of application and the nature of the vaccine differ from the disclosure of document D85, the skilled person seeing the differing development of immunogenicity in document D12 and document D85 would not draw any conclusion from that difference. Document D107 was only available after the priority date of the patent in suit, and as such can only be irrelevant for the assessment of what the skilled person would have expected at that date. Therefore, the board has no reason to assume that the nearly identical responses to HBsAg or the continuous rise of the response would give a reason for distrust, and certainly they cannot be considered to indicate any fundamental technical deficiency.

8.3 Hence, the board concludes that document D85 belongs to the state of the art as it stands and is the closest prior art document.

9. No advantages have been substantiated for the claimed vaccine preparation process over that disclosed in document D85. Hence, the problem to be solved is the provision of an alternative method for preparing a vaccine composition consisting of either HBsAg-DT or HBsAg-DTPw or HBsAg-DTPa.

10. The solution to this problem is a method involving the adsorption of HBsAg onto aluminium phosphate and one of DT, DTPw or DTPa to aluminium hydroxide or aluminium phosphate and the subsequent combination of the adsorbed components.

11. The claimed method is exemplified in Examples 2 to 3. Example 2 discloses the combination of HBsAg adsorbed to AP as prepared in Example 1 with DTP adsorbed to AP or AH. Example 3 discloses the combination of a commercially available DTP vaccine in which DT is adsorbed to AH and Pw on a mixture of AH and AP with the AP-adsorbed HBsAg of Example 1. Examples 9 and 11 show data of clinical studies for the combined HBsAg-DTPw vaccines. Immune responses to HBsAG (example 9 and example 11.1 A to D), to diphteria, tetanus and pertussis antigens (Examples 11.1 A and D) are reported indicating that the formulations prepared by the claimed method are suitable as vaccines. It has not been challenged that these examples work as reported, thus the claimed subject-matter can be accepted as a solution to the problem.

12. For the assessment of inventive step is has to be considered whether the skilled person starting from document D85 is led in an obvious manner by the

teachings of document D85 or by the teachings of other prior art documents to choosing something falling within the claims.

13. Document D85 discloses the **combined** adsorption of diphteria, tetanus, pertussis and HBsAg onto aluminium phosphate and is silent on any other method of preparation.

14. Document D22 is the report of a meeting of experts who convened to discuss prospects for the development and utilization of a quadrivalent diphteria-tetanus-pertussis-Hepatitis B vaccine. In the context of vaccine production - the chapter is entitled "Technical issues related to the development of DTP-HB vaccine" - it is reported on pages 7 and 8 which DTP vaccines and HB vaccines are commercially available and how they are produced, including the compounds used for adsorption, i.e. diphteria and tetanus toxoids are adsorbed with an **aluminium or calcium adjuvant** while HBsAg is adjuvanted with **aluminium compounds**" (see point 6 above). The summary in the penultimate paragraph of this chapter reads: "Since both the inactivation and adsorption procedures used for the production of DTP and HB vaccines are similar and because there are no other basic incompatibilities between DTP and HB vaccines that would prevent their being combined into a quadrivalent product which would be safe, effective and stable, the commercial development of DTP-HB should be entirely possible."

Moreover, it is stated on page 9: "In particular, arrangements whereby bulk HB vaccine could be shipped to selected manufacturers of DTP to be combined into

quadrivalent product at the DTP production site should be investigated."

Hence, document D22 suggests that a quadrivalent DTP-HB vaccine be prepared by mixing of a ready-manufactured trivalent DTP vaccine and a ready-manufactured monovalent Hepatitis B vaccine.

15. The appellant points to the following passages in document D22:

Page 7: "**DTP adsorbed vaccines**, and especially those prepared with a whole cell pertussis vaccine component **differ significantly** in their composition. These differences in composition raise the possibility that there may be enzymes or other impurities present in the diphteria and tetanus toxoid and pertussis vaccine components, and chemicals used in the manufacture of some formulations of DTP adsorbed vaccines, which may affect the potency, stability, and ultimately the efficacy of the hepatitis B component of the DTP-HB combined vaccine." (emphasis added).

Page 8:" Therefore it is possible for the impurities in currently produced DTP to have a degrading effect on the HBsAg protein when incorporated into a quadrivalent product. Thus, some reduction in the immunogenicity of the HB component of a combined vaccine might occur when **certain DTP vaccines** are combined with the HB vaccine. Both short-term interaction and the stability of the product during long-term storage needs to be studied. This aspect needs careful attention; simple mixing of DTP vaccine and HB vaccine before use is not acceptable." (emphasis added).

Page 8 at the bottom continued on page 9: "However, because of the differences in composition of DTPs from different manufacturers, it is to be anticipated that **not all DTPs will be easily combinable** with HB vaccine and that optimization of the performance parameters of specific quadrivalent products will be the result of continuing trial and error at the product research level. It is for that reason that efforts to anticipate use of a quadrivalent product by mixing separate DTP and HB vaccine in the same syringe prior to inoculation should be discouraged." (emphasis added).

On the basis of these passages, in particular the passages underlined above, the appellant argues that document D22 discourages the skilled person from producing a quadrivalent DTP-HBsAg vaccine by mixing of pre-adsorbed components because of the expected negative effects on HBsAg immunity and vaccine stability.

16. The board disagrees. Document D22 teaches that there may be incompatibilities between certain lots of vaccines (see the passages marked in bold above) and therefore, medical staff is advised to be careful about uncontrolled mixing because, in view of the suspected, but unpredictable incompatibilities, it would not be foreseeable with a sufficient degree of certainty for the patient which combinations of pre-existing commercial formulations would be certain to work and which might not. This uncertainty is to be avoided by checking out what does work. This advice is however not to be seen as any form of discouragement, but merely as pointing out that some caution is needed in the

combination of pre-adsorbed vaccine components as not necessarily every combination will work.

17. It is stated in the passage on page 8 (second citation above) that "reduction in the immunogenicity of the HB component of a combined vaccine might occur when certain **DTP vaccines are combined with the HB vaccine"**. In the second passage on page 8 (third citation above) it is stated that "it is to be anticipated that not all DTPs will be **easily combinable** with HB vaccine". By stating that the uncontrolled way of combining pre-manufactured vaccine compositions should be avoided, the document conveys the clear message that by controlled working and checking out of various combinations, successful vaccine preparation by mixing will be possible.

18. Thus, the board finds that the skilled person seeking to modify the method of document D85, would be led by the teaching of document D22 to a method where the quadrivalent DTP-HBsAg vaccine is obtained by, first, adsorbing the four vaccine components separately to aluminium phosphate and, then subsequently, combining them to obtain the quadrivalent formulation. He/she would thus obtain a method falling under claim 1.

19. The subject-matter of claim 1 does not fulfil the requirements of article 56 EPC. Hence, claim request H is not allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

Registrar: Chair:

P. Cremona U. Kinkeldey