BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

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

Datasheet for the decision of 12 July 2010

Case Number: T 1139/08 - 3.3.04

Application Number: 01976216.0

Publication Number: 1317484

IPC: C07K 14/45

Language of the proceedings: EN

Title of invention:
Variants of the phleum pratense Phl p 1 allergenic protein

Patentee:
Consiglio Nazionale Delle Ricerche

Opponent:
Alk-Abello A/S

Headword:
Phleum pratense allergen/CONSIGLIO NAZIONALE

Relevant legal provisions:
EPC Art. 54, 56, 83, 123(2)(3)

Keyword:
"Admission of late-filed request (yes)"
"Main request: added matter, extension of scope (no); sufficiency of disclosure, novelty, inventive step (yes)"

Decisions cited:
-

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1139/08 **-** 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 12 July 2010

Appellant: (Opponent)	Alk-Abello A/S Böge Alle 6-8 DK-2970 Hörsholm (DK)
Representative:	Inspicos A/S Kogle Allé 2 P.O. Box 45 DK-2970 Hørsholm (DK)
Respondent: (Patent Proprietor)	Consiglio Nazionale Delle Richerche Piazzale Aldo Moro, 7 I-00185 Roma (IT)
Representative:	Banfi, Paolo Bianchetti Bracco Minoja S.r.l. Via Plinio 63 I-20129 Milano (IT)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted 3 April 2008 concerning maintenance of European patent No. 1317484 in amended form.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: G. Alt
M. Wieser

Summary of Facts and Submissions

I. This is an appeal from the opponent (hereinafter "appellant") against the decision of the opposition division by which it expressed its intention to maintain European patent No. 1 317 484 in amended form. The patent has the title "Variants of the Phleum pratense Phl p 1 allergenic protein".

II. Claims 1 and 2 as granted read:

"1. A hypoallergenic variant of the major Phl p 1 allergen, wherein at least one of the Lys residues present at positions 28, 35, 44, 48, 179, 181, 183, 185 of mature Phl p 1 protein SEQ ID No. 2 wherein residues at positions 28, 35, 44, 48, 179, 181, 183 and 185 are lysine is substituted or deleted.

2. A variant as claimed in claim 1, which is homologous to Phl p 1 allergen by more than 85% and has at the corresponding positions of the amino acid sequence the same substitution/deletion pattern as in Phl p 1."

III. The patent was opposed pursuant to Article 100(a) EPC on the grounds of lack of novelty and lack of inventive step, Article 100(b) EPC and Article 100(c) EPC. The opposition division decided that an amended form of the patent met the requirements of the EPC.

Claim 1 of the amended set of claims read:

"1. A hypoallergenic variant of the Phl p 1 allergen which is selected from:
a) The Phl p 1 protein SEQ ID NO: 2 wherein the residues present at positions 28, 35, 44, 48, 179, 181, 183, 185 are Lys, in which one or more Lys residues in the specified positions is substituted or deleted;

b) A class 1 allergenic protein of Graminaceae having sequence homology higher than 85% compared with Phl p 1 and having, at the corresponding positions of the amino acid sequence, the same substitution/deletion pattern as described above for Phl p 1."

The request contained 10 further claims being either dependent on claim 1 or referring to it either directly or indirectly. These latter claims related to a peptide comprising an immunologically active part of the variant, nucleic acid molecules, vectors, host cells transduced with the vector, and a pharmaceutical composition.

IV. During the appeal proceedings the patent proprietor (hereinafter "respondent") filed an auxiliary request with its letter dated 14 June 2010, an amended version of that request and two further auxiliary requests with its letter dated 5 July 2010, and yet three further auxiliary requests with its letter dated 7 July 2010.

V. By a communication dated 30 April 2010 the board summoned the parties for oral proceedings to take place on 12 July 2010. The appellant notified the board by a

letter dated 7 July 2010 that it would not be attending the oral proceedings.

VI. At the oral proceedings only the respondent was represented.

During the oral proceedings the respondent filed a new main request which corresponded to the previous amended auxiliary request 1.

Claim 1 of the main request read:

"1. A hypoallergenic variant of the Phl p 1 allergenic protein SEQ ID NO:2 bearing Lys residues at positions 28, 35, 44, 48, 179, 181, 183 and 185, said hypoallergenic variant being characterized in that one or more of said Lys residues are substituted or deleted."

The request contained 10 further claims being either dependent on claim 1 or referring to it either directly or indirectly. These latter claims related to a peptide comprising an immunologically active part of the variant, nucleic acid molecules, vectors, host cells transduced with the vector, and a pharmaceutical composition.

VII. The appellant's request as it appeared from its written submissions was that the decision of the opposition division be set aside and the patent be revoked.

The respondent's request at the end of the oral proceedings was that the decision under appeal be set

aside and the patent be maintained on the basis of the main request filed at the oral proceedings.

VIII. At the end of the oral proceedings the board announced its decision.

IX. The following documents are referred to in the present decision:

D1: Journal of Allergy and Clinical Immunology, vol. 94, no. 4, 1994, pages 689-698, Laffer, S. et al.

D2: WO-A-99/47680

D3: Journal of Allergy and Clinical Immunology, vol. 98, no. 2, pages 331-343, Smith, P.M. et al.

D6: Immunobiology - The immune system in health and disease; Fourth edition 1999; , pages 86-90; Janeway, C.A. et al.

D8: Experimental data filed on 8 August 2006: "IgE reactivity of the allergen Phl p 1 and four modified variants (ELISA assay)

D9: Experimental data filed on 8 August 2006: "IgE reactivity to Phl p 1 and its single modified variants (2.5 μg/ml)"

D12: Experimental data filed on 8 August 2006: "Inhibition of IgE binding to Phl p 1 allergen"

D13: Experimental data filed on 8 August 2006: "Concentration of inhibitor needed to obtain 50% reduction of IgE-binding"

D14: Experimental data filed on 8 August 2006: "IgE reactivity of the modified allergen Phl p 1 (ELISA assay)"

D15: Experimental data filed on 8 August 2006: "IgE reactivity to Phl p 1 and its hypoallergenic variants (5 μg/ml)"

D17: Journal of Allergy and Clinical Immunology, vol. 112, no. 3, September 2003, pages 599-605, Garcia-Casado, G. et al.

D21: International Archives of Allergy and Immunology, vol. 130, 2003, pages 87-107, Andersson K. and Lidholm, J.

X. The appellant's arguments submitted in writing and as far as they are relevant to the present decision may be summarised as follows:

Late-filed request

None of the claims of auxiliary request 1 (corresponding to the present main request and therefore hereinafter referred to as "main request") was identical with claims that had already been introduced into the proceedings. Hence, none of them could have been considered previous to their filing. The time period from their filing until the oral proceedings was too short for considering them

appropriately. Therefore, the main request should not be admitted.

Clarity - Article 84 EPC

It was not clear whether or not claim 1 related also to hypoallergenic variants which were modified in positions other than the eight recited ones.

Sufficiency of disclosure - Article 83 EPC

The patent did not report any threshold values for distinguishing an allergenic from a hypoallergenic protein. Thus, since the skilled person was in doubt about the meaning of the term "hypoallergenic", the invention was not disclosed in a manner that he/she could carry out.

Claim 1 related to a considerable number of variants and the patent only gave one example of a substitution variant. Therefore, it was doubtful, in particular with regard to deletion variants for which no example at all was provided, that all of the variants falling under the structural definition of claim 1 were "hypoallergenic". Thus, since predictions on the hyperallergenicity on the basis of the amino acid sequence were not possible, the skilled person had to test any variant for its hypoallergenic properties. Consequently, carrying out the invention amounted to an undue burden.

Inventive step - Article 56 EPC

Document D2 was the closest prior art document. It disclosed a strategy for modifying surface-exposed amino acid residues in an allergen in order to prepare hypoallergenic allergens. It was suggested that this strategy could inter alia be applied to reduce the allergenicity of Phl p 1.

In view of document D2, or equally document D6, the skilled person would attempt to reduce the allergenicity of an allergen by substituting surface-exposed amino acids. Therefore, variants with modifications of the residues recited in claim 1 could only involve an inventive step, if they were demonstrated to be superior to variants with substitutions of other surface-exposed amino acids. However, the respondent had not provided any evidence in this respect.

Moreover, the claims were not inventive over the whole scope. Since the patent did not indicate to which extent allergenicity had to be reduced before a structural variant would indeed be useful as allergy vaccine, the term "hypoallergenic" in claim 1 had to be interpreted as meaning "less allergenic than wild-type Phl p 1". Thus, variants still exhibiting 98% binding to IgE were embodiments of claim 1. It was unlikely that these variants solved any problem which was not already solved by a vaccine comprising wild-type Phl p 1.

XI. The respondent's arguments in writing and during the oral proceedings, can be summarized as follows:

Late-filed request

The claims of the main request did not differ substantially from those dealt with in the decision under appeal. Therefore, the main request should be admitted into the proceedings.

Clarity - Article 84 EPC

Claim 1 clearly defined the proteins for which protection was sought by reference to SEQ ID NO. 2 and the exact positions that had to be substituted or deleted in this sequence in order to prepare a hypoallergenic variant. Thus, there was no doubt about the meaning of claim 1.

Sufficiency of disclosure - Article 83 EPC

The skilled person knew what "hypoallergenic" meant and the patent provided assays for testing the reduction of allergenicity.

The patent and documents D8, D9 and D12 to D15 provided evidence that variants which were structurally modified as defined in claim 1 were hypoallergenic. The appellant had not provided any evidence that the skilled person when following the instructions in the patent would not be able to obtain hypoallergenic variants of the Phl p 1 protein. Thus, the requirements of Article 83 EPC were fulfilled.

Inventive step - Article 56 EPC

Document D6 contained the general teaching that antibodies bound to amino acids which were exposed on the surface of a protein. Document D2 disclosed a process for preparing hypoallergenic allergens by mutagenizing solvent-exposed amino acid residues. Both documents were silent about lysine residues as targets for reducing allergenicity and gave no hint to modify Phl p 1 in exactly the indicated positions. Thus, the claimed invention was not obvious.

Reasons for the decision

Late-filed request

1. By a letter dated 30 April 2010 the parties were summoned for oral proceedings to take place on 12 July 2010. The respondent filed the present main request as auxiliary request 1 with its letter dated 14 June 2010. A slightly amended version of this request, intended to align it more with the claims as granted, i.e. replacement of "and/or" by "or" in claim 1 and amendment of the definition of the peptide in claim 5 was filed on 5 July 2010. This version was submitted as main request during the oral proceedings.

2. In the appellant's view the auxiliary request 1 (corresponding to the present main request and therefore hereinafter referred to as "main request") should not be admitted since the claims are not identical to any claim on file and thus could not have been considered previously. Therefore, the time between

the filing of the request and the date of the oral proceedings was not sufficient to consider adequately the claims of the main request.

3. Pursuant to Article 13(3) RPBA amendments sought to be made after oral proceedings have been arranged shall not be admitted if they raise issues which the board or the other party or parties cannot reasonably be expected to deal with without adjournment of the oral proceedings.

4. The claims of the request dealt with in the decision under appeal related to "[a] hypoallergenic variant of the Phl p 1 allergen". The variant could be selected from two different groups, group (a) and (b). Group (a) was defined as follows: "The Phl p 1 protein SEQ ID NO: 2 wherein the residues present at positions 28, 35, 44, 48, 179, 181, 183, 185 are Lys, in which one or more Lys residues in the specified positions is substituted or deleted." The request contained ten further claims which were either dependent on or related to claim 1 (see section III above).

5. Claim 1 of the present main request relates to "[a] hypoallergenic variant of the Phl p 1 allergenic protein SEQ ID NO:2 bearing Lys residues at positions 28, 35, 44, 48, 179, 181, 183 and 185, said hypoallergenic variant being characterized in that one or more of said Lys residues are substituted or deleted."

6. Thus, claim 1 of the main request differs from claim 1 dealt with in the decision under appeal in that

a) group (b) is deleted;

b) the characterization of group (a) now reads "SEQ ID NO:2 bearing Lys residues at positions 28, 35, 44, 48, 179, 181, 183 and 185", whereas before it read "SEQ ID NO:2 where the residues present at positions 28, 35, 44, 48, 179, 181, 183, 185 are Lys";

c) the expression "said hypoallergenic variant being characterized in that" is used instead of the words "in which"; and

d) in the first part of the claim Phl p 1 is now denoted as "Phl p 1 allergenic protein" instead of "Phl p 1 allergen".

Claims 2 to 11 are the same as in the request dealt with in the decision under appeal with the exception that in claims 5 and 6 the references to claim 5 in claim 5 and the references to claim 6 in claim 6 is removed.

7. As can be seen from the comparison above, the amendments in present claim 1 are minor when compared to claim 1 dealt with in the decision under appeal. Moreover, in the board's view it is immediately apparent that, although the wording and the structure of the claim has changed, its meaning has not when compared to claim 1 before the opposition division. Finally, the amendment in claims 5 and 6 must be considered as the correction of an obvious error since a reference in a claim to the same claim in which the reference is made cannot be anything but a mistake. Hence, although the claims of the main request are

amended and thus, strictly speaking, could not have been regarded previously, the differences from the claims dealt with in the decision under appeal are so minimal that, in the board's view, the time period between the filing of the request and the oral proceedings was sufficient for the appellant and also the board to familiarise themselves with the new claims, so that an adjournment of oral proceedings was not necessary. Therefore, the main request is admitted.

Clarity - Article 84 EPC

8. Article 84 EPC is not a ground of opposition. Therefore, its requirements in relation to amendments of claims are assessed only insofar as modifications with regard to the claims as granted are concerned.

9. The features of claim 1 as granted (see section II above) are:

a) a hypoallergenic variant of the major Phl p 1 allergen;

b) wherein at least one of the Lys residues present at positions 28, 35, 44, 48, 179, 181, 183, 185 is substituted or deleted;

c) the mature Phl p 1 protein SEQ ID NO. 2 wherein residues at positions 28, 35, 44, 48, 179, 181, 183, 185 are lysine.

10. Present claim 1 (see section VI above) differs from claim 1 as granted in the following respects:

a) The term "major" in front of the term "Phl p 1" is removed.

b) Phl p 1 is termed an "allergenic protein" instead of an "allergen".

c) The definition of the non-modified Phl p 1 protein is moved to immediately after the first occurrence in the claim of the term "Phl p 1".

d) In the definition of Phl p 1 the term "mature" is removed.

e) The specific positions in the unmodified Phl p 1 protein are defined as "bearing Lys residues at positions ..." instead of "wherein residues at positions ... are lysine".

f) The modification with regard to the wild-type Phl p 1 protein is characterized in that "one or more of said Lys residues are substituted or deleted" instead of "at least one the Lys residues ... is substituted or deleted".

11. In the board's view, none of these amendments is ambiguous per se. Also the new structure of claim 1 has not affected its clarity, rather the contrary is true,

i.e. it is clear that claim 1 relates to those variants of Phl p 1 wherein at most the eight indicated lysine residues are substituted or deleted.

The requirements of Article 84 EPC are fulfilled.

Amendments - Article 123(2) EPC

12. The definition of the unmodified Phl p 1 in claim 1 as "SEQ ID NO:2 bearing Lys residues at positions 28, 35, 44, 48, 179, 181, 183 and 185" is based on page 1, lines 20 to 21 and page 2, line 14 referring to the natural form of Phl p 1 and the Genbank entry number X78813 which identifies a sequence corresponding to the definition in claim 1. The presence of a lysine residue at the indicated position in the natural Phl p 1 protein is also derivable from page 2, line 19. Hypoallergenic variants of the unmodified Phl p 1 with substitutions or deletions of the residues in positions 28, 35, 44, 48, 179, 181, 183, 185 are disclosed on page 2, lines 16 to 23.

The requirements of Article 123(2) EPC are fulfilled.

Extension of scope - Article 123(3) EPC

13. The extent of protection conferred by a European patent is determined by the content of all its claims. Thus, in order to asses whether or not the scope of protection is extended by an amendment, the protection conferred by the totality of the claims before the amendment is compared with the totality of the claims after amendment or, more simply, the claims with the broadest protection are compared.

14. Claim 1 of the present main request is the claim with the broadest scope. It relates to hypoallergenic variants derived from a Phl p 1 protein having SEQ ID NO:2 but bearing lysine residues at positions 28, 35, 44, 48, 179, 181, 183 and 185, and wherein at least one, but at most eight, residues at the specified positions are substituted or deleted (see point 11 above).

15. Claims 1 and 2 as granted read:

"1. A hypoallergenic variant of the major Phl p 1 allergen, wherein at least one of the Lys residues present at positions 28, 35, 44, 48, 179, 181, 183, 185 of mature Phl p 1 protein SEQ ID No. 2 wherein residues at positions 28, 35, 44, 48, 179, 181, 183 and 185 are lysine is substituted or deleted.

2. A variant as claimed in claim 1, which is homologous to Phl p 1 allergen by more than 85% and has at the corresponding positions of the amino acid sequence the same substitution/deletion pattern as in Phl p 1."

16. The appellant maintains that claim 1 as granted could be interpreted in two ways. Either it related to hypoallergenic variants having at the most modifications in the eight positions recited in the claim or it related to hypoallergenic variants which could, in addition, have modifications at further positions.

16.1 However, whichever of the two interpretations applies, the scope of present claim 1 is not broader than that of claim 1 as granted. Rather, it would be the same

with regard to the appellant's first and narrower with regard to its second interpretation.

17. The appellant argues that claim 2 as granted could also have two meanings. The first was that the claim related to those hypoallergenic variants according to claim 1 which were - **after** the substitution or deletion - homologous by more than 85% to unmodified Phl p 1.

17.1 However, if this interpretation was adopted claim 2 would be truly (see below point 18) dependent on claim 1 and its scope would thus be narrower than that of claim 1 as granted.

18. According to a second interpretation claim 2 would define a Phl p 1 variant which was made by a) choosing from any protein those which are homologous to the un-modified Phl p 1 by more than 85 % and b) mutating them according to the pattern recited in claim 1.

18.1 This interpretation would have the consequence that the scope of claim 2 as granted would in fact be broader than that of claim 1 as granted. However, the comparison of the scope of present claim 1 with that of the granted claim 2 as so-interpreted would result in the finding that the scope of present claim 1 is narrower. This is so because according to present claim 1 the protein to be modified is the specific protein "Phl p 1 SEQ ID NO. 2 but bearing Lys residues at positions 28, 35, 44, 48, 179, 181, 183 and 185" whereas it would be any protein "homologous to Phl p 1 allergen by more than 85%" according to claim 2 as granted.

19. Thus, the board is satisfied that the scope of claim 1 and thus of all claims of the main request is not extended over the scope of the claims as granted whatever interpretation of claims 1 and 2 as granted is adopted.

20. The requirements of Article 123(3) EPC are fulfilled.

Sufficiency of disclosure - Article 83 EPC

21. The appellant's first argument is that the skilled person cannot carry out the invention because the patent does not indicate specific values as to how large a degree of reduction in reactivity or how small a competitive capability should be in the particular test systems of the patent before a given variant is termed "hypoallergenic". In other words, the disclosure of the patent was insufficient because the skilled person cannot determine the parameter "hypoallergenic".

22. However, it is explained in the patent in the section "Background of the invention" in paragraphs [0009] to [0011] that treatment of allergy previously consisted in administering increasing doses of the substance which causes the allergy, thus inducing gradual desensitisation to said substance in the patient. This therapy, because it used the natural allergen, may however induce systemic side effects. Therefore in order to ensure a more effective and safer treatment, mutagenised recombinant allergens having reduced allergenic reactivity (reactivity to IgEs) while maintaining unaffected their capability of inducing favourable immunological changes have been used.

Thus, it is derivable from the patent, in particular the last sentence above, what "hypoallergenic" means.

23. This meaning of "hypoallergenic", i.e. reduction of IgE antibody binding without modifications of other immunological properties of the protein, coincides with that known to the skilled person from common general knowledge. In document D2, for example hypoallergenicity is paraphrased as "low IgE binding" (page 7, lines 6-7). It is also derivable from document D2 that the skilled person has specific values in mind when it comes to the determination of "hypoallergenicity". It is stated on page 15, lines 5 to 10: "Specific IgE binding to the mutated allergen is preferably reduced by at least 5%, preferably at least 10% in comparison to naturally-occurring isoallergens or similar recombinant proteins in an immuno assay with sera from source-specific IgE reactive allergic patients or pools thereof."

24. Thus, the board comes to the conclusion that in the present case the absence of a disclosure of specific range of values is not a reason for denying sufficiency of disclosure.

25. According to a second line of argument the appellant submits that on the one hand, the structural definition in the claim covers a large group of variants. On the other hand, the number of examples is so small, or examples are even absent (i.e. in the case of deletion variants) that it is not credible that all of the structural variants have the claimed function of being "hypoallergenic". Since predictions on hypo-allergenicity are not possible on the basis of the

amino acid sequence, the skilled person will thus have to test each and every new variant in order to know whether it is in fact "hypoallergenic". This amounts to an undue burden and therefore the requirements of Article 83 EPC are not fulfilled.

26. Thus, the reasons for the appellant's objection are that the group of structural variants is large and that compared to that the number of examples is too low.

27. However, firstly, the mere fact that a group of compounds is large is prima facie not a reason to assume that all members of that group do not share the same property. This is especially true in the present case where the limited number of specific instructions supports the perception that the desired property is achieved if they are followed. There is no evidence before the board that could call into doubt this prima facie perception.

28. Secondly, the number of examples necessary to make it credible that all members of a group have the same activity is dependent on the circumstances of each specific case. Thus, there even may be cases where no example at all is necessary in support of a structure-function relationship.

28.1 As regards the present circumstances, it is common general knowledge that changes in the amino acid sequence of a protein can result in changes of the tertiary structure and thus of the function of that protein.

28.2 In the present case the changes concern amino acids at maximally eight specific positions. They are substituted or deleted when compared to the native protein Phl p 1 which has 240 amino acids in toto. As already noted in point 27 above the board considers these specific instructions as indication that the positions have indeed been selected such that a change in function will occur upon their modification.

28.3 The patent discloses a Phl p 1 variant where the amino acid at each of the eight positions indicated in claim 1 is replaced by the amino acid alanine. This variant is "hypoallergenic" according to the tests in the patent (paragraph [0020] of the patent). Moreover, in the course of the opposition proceedings the respondent submitted data demonstrating that four different single replacement Phl p 1 variants and two different variants having replacements in four of the indicated positions have reduced allergenicity when compared to the parent Phl p1 compound (documents D8, D9 and D12 to D15).

28.4 There are no examples of functional, i.e. hypoallergenic, deletion variants with the structural characteristics of the claim. However, given the common knowledge (see point 28.1) the board has prima facie no reason to doubt that they are obtained as indicated in the claim.

28.5 Thus, on the evidence before it, the board considers that the present examples are sufficient to make it credible that substitution and deletion variants, when made according to the instructions in the claim, are "hypoallergenic".

28.6 Therefore, the board comes to the conclusion that no case has been made that the invention can only be carried out with undue burden since the skilled person has to test each and every variant in order to know whether it is in fact "hypoallergenic".

29. The requirements of Article 83 EPC are fulfilled.

Novelty - Article 54 EPC

30. Since claim 1 is related to a variant derived from "Phl p 1 SEQ ID NO. 2 but bearing Lys residues at positions 28, 35, 44, 48, 179, 181, 183 and 185" the subject-matter of this claim and also of the claims dependent on or related to it is novel, in particular over the disclosure of the Cyn d 1 and Sor h 1 allergens disclosed in Figure 4 of document D3.

Inventive step - Article 56 EPC

Closest prior art

31. Document D2 discloses that the alteration of the binding properties of an antibody to a protein by modification of the amino acid sequence of the protein, can be used to reduce the affinity of IgE antibodies to allergens, thus generating "hypoallergenic" allergens. The document also discloses a strategy for identifying surface-exposed amino acid residues involved in IgE binding. Specifically, document D2 discloses several hypoallergenic variants of the major birch pollen allergen, Bet v 1, and of the Vespula vulgaris venom major allergen, Ves v 5.

32. Thus, document D2 discloses subject-matter aiming at the same purpose as the claimed invention and, according to established case law, can therefore be considered as the closest prior art document.

Problem and solution

33. The problem to be solved vis-à-vis the specific disclosure in document D2 is the provision of a further hypoallergenic allergen to be used in the treatment of allergies.

34. According to claim 1 the solution to this problem is a hypoallergenic variant derived from an allergen of pollen from the grass Phleum pratense, Phl p 1 as defined in SEQ ID NO. 2 but wherein the residues at positions 28, 35, 44, 48, 179, 181, 183 and 185 are lysine. The reason for the unusual definition is that according to the patent SEQ ID NO:2 recites the sequence of a specific variant and not of the wild-type protein which, as stated in the definition according to claim 1, has lysine residues at the indicated positions. According to claim 1 at least one of these lysine residues is substituted or deleted in order to obtain a hypoallergenic variant of wild-type Phl p 1.

35. The patent discloses in paragraph [0020] that a protein having the lysine residues at all of the eight positions replaced by alanine (i.e. the protein having the sequence recited in SEQ ID No. 2) has reduced IgE binding capability when compared to the parent Phl p 1 protein and thus is "hypoallergenic". Moreover, there is also evidence that variants obtained by substituting a lysine residue at only one or at four of the

indicated positions are also hypoallergenic (see point 28.3 above). Given this evidence the board is satisfied that the solution stated in the claims is indeed a genuine solution to the problem formulated above.

Obviousness

36. In view of the closest prior art and the problem to be solved, a first issue is whether or not the skilled person would have concentrated on the Phl p 1 allergen as a candidate for allergy treatment.

37. Phl p 1 is the major allergen of Phleum pratense. It is classified as a member of the group I allergen grass pollen allergens (see the patent, paragraph [0007]). Members of group I allergens are the most prominent allergenic determinants in grass pollen extracts. About 90% of individuals allergic to grass pollen display IgE antibody reactivity to group I allergens (see post-published document D21, page 91, first column, second full paragraph citing documents referenced as 13 to 17, all published in the period between 1994 and 1997 and thus before the priority date of the patent). At the priority date of the patent the cDNA and amino acid sequence of Phl p 1 were known (see document D1). Phl p 1 is, among others, mentioned as an allergen to which the method disclosed in document D2 could be applied in order to obtain a hypoallergenic variant of it (page 16, line 6).

In the light of this evidence the board is satisfied that the skilled person would consider Phl p 1 as one of the candidates for allergy treatment.

38. The second issue arising from the problem and the claimed solution is whether or not the skilled person would have been motivated to modify the amino acid sequence of the Phl p 1 protein at the specific, surface-exposed positions recited in claim 1 in order to obtain a hypoallergenic variant thereof.

39. The appellant argues that both documents D2 and D6 teach to modify surface-exposed amino acids when aiming at preparing hypoallergenic variants of an allergen, that there is however no evidence from the proprietor demonstrating that modifications at these positions are superior in reducing IgE-binding when compared to modifications at any of the other surface-exposed amino acids and that therefore, the positions indicated in claim 1 have to be regarded as arbitrary selections among all surface-exposed amino acids. Consequently, the subject-matter of claim 1 lacks an inventive step.

40. The appellant's argumentation implies that the amino acid positions recited in claim 1 are located on the surface of Phl p 1. This is however not explicitly disclosed in the patent. Yet it is stated in paragraph [0013] of the patent that the positions were found by determining the hydrophilicity profile of Phl p 1 - this method identifies regions with high hydrophilicity which therefore will most probably appear on the surface of a protein, once it has adopted its tertiary structure. Therefore, it will be assumed that the eight amino acid positions recited in claim 1 are located on the surface of native Phl p 1.

40.1 In the native Phl p 1 protein the amino acid at each of the indicated positions is occupied by lysine. Thus,

the amino acids at the positions specified in claim 1 have in common that they are surfaced-exposed and lysines.

Document D6

41. Document D6 is a copy from a part of the third chapter of the textbook "Immunobiology - The immune system in Health and Disease". Chapter 3 is entitled "Structure of the Antibody Molecule and Immunoglobulin Genes". The part available as document D6 is entitled "The interaction of the antibody molecule with specific antigen" and has four sub-chapters entitled (i) "Localized regions of hypervariable sequence form the antigen-binding site" (chapter 3-6), (ii) "Small molecules bind to clefts between the heavy- and light-chain V domains" (chapter 3-7), (iii) "Antibodies bind to extended sites on the surfaces of native protein antigens (chapter 3-8) and (iv) "Antigen: antibody interactions involve a variety of forces" (chapter 3-9).

In chapter 3-8 it is disclosed that the antigenic determinants, i.e. regions to which antibodies bind, are situated on the surface of the antigen when folded into its three-dimensional structure. Chapter 3-9 discloses that different kinds of non-covalent forces are responsible for antigen-antibody binding and that all of them contribute to the binding. In order to illustrate this it is reported that in a high-affinity complex of hen egg-white lysozyme with an antibody two salt bridges between two basic arginines on the surface of lysozyme interact with two glutamic acids on the antibody. Lysozymes that lack one of the two arginine residues show a 1000-fold decrease in affinity.

41.1 Thus, document D6 generally teaches that antibody-binding is mediated by amino acid residues on the surface of a protein and that modification of amino acids involved in binding may alter the affinity of an antibody to its antigen.

Document D2

42. As noted in point 31 above, document D2 discloses a strategy for identifying surface-exposed amino acid residues involved in IgE binding and that the reduction of the affinity of IgE antibodies for allergens by alteration of such surface-exposed residues results in "hypoallergenic" allergens.

43. Given these teachings in documents D2 and D6 the board concludes that the skilled person would be motivated to modify surface-exposed amino acid residues of the allergen Phl p 1 in order to obtain a hypoallergenic variant thereof.

44. The next issue is whether or not the specific positions indicated in claim 1 have to be regarded as arbitrary selections either among all the surface-exposed amino acids of Phl p 1 or among all the surface-exposed amino acids taking part in IgE binding.

45. In order that this argument can succeed, the board must be convinced that the selection of the residues recited in claim 1 is indeed "arbitrary", i.e. that it is a random choice among numerous equally good options.

46. The arbitrariness of the selection is not prima facie evident.

46.1 As to the issue of the selection from the pool of surface-exposed amino acids, the board concludes from the disclosure of strategies for the determination of IgE binding sites (for example in document D2) that not all of the surface-exposed amino acids are involved in IgE antibody binding. Hence, since the properties of surface-located amino acids with regard to IgE-binding differ, the selection from the pool of surface-exposed amino acids of the subpool of amino acids taking part in IgE binding and even of particular amino acids among this subpool, cannot be regarded as a random choice.

46.2 As to the issue of the selection from the pool of surface-exposed amino acids involved in IgE-binding, there is evidence before the board that, generally, such amino acids cannot be considered to be equivalent as regards the consequences of their alteration. For example post-published document D17 reports the identification of IgE binding epitopes of the major peach allergen Pru p 3. Regions around amino acids in positions 23 to 36, 39 to 44 and 80 to 91, particularly residues at positions 39, 40, 44, 80 and 91 were predicted as potential antibody recognition sites. Yet, variants having point mutations in positions 80 and 91 were found to have an IgE binding capacity similar to that of parent protein, recombinant Pru p 3. Thus, although positions 80 and 91 were predicted as being involved in antibody binding, their mutation had no effect on the affinity of the antibodies.

47. Thus, since the positions recited in claim 1 have not prima facie been selected arbitrarily and following the principle that any one who alleges a fact has the onus of proving his allegation, it would be for the appellant to refute this prima facie perception. However, nothing has been submitted in this respect.

48. Hence, it follows from the observations in points 45 to 47 that the appellant's argument set out in point 39 above does not convince the board.

49. The board has considered whether the application of methods for the theoretical prediction of potential antibody-binding regions would possibly have motivated the skilled person in a straightforward manner to prepare Phl p 1 variants with alterations at the indicated positions.

49.1 In fact, at the priority date of the patent different methods existed, relying for example on the analysis of the molecular surface on the basis of X-ray and NMR data (see document D2, page 23, lines 33-36 in combination with the title of the document referenced 17 in document D2) or the determination of the hydrophilicity of the amino acids in the folded protein (see the patent paragraph [0013]).

49.2 However, document D2 discloses (page 8, lines 33 to page 9, lines 6) that, while it may not be surprising that substitution of a surface-exposed amino acid has the capacity to modify the binding characteristics of a monoclonal antibody, this must not necessarily be the consequence with respect to polyclonal antibodies such as serum IgE antibodies of allergic patients.

49.3 With reference to a further publication it is observed in document D2 that although the authors of the document attempted to reduce IgE binding, the algorithm used did not ensure that amino acids selected for mutations were actually exposed to the molecular surface. In fact, only one of the described mutants lead to reduction of IgE binding, but only because it had a disrupted tertiary structure (page 9, lines 8 to 21).

49.4 To the board these disclosures indicate that predictions of antibody-binding sites made on a theoretical basis were at the priority date of the patent not of such a quality that the actual modification at the predicted positions necessarily resulted in proteins with altered, in particular reduced, antibody binding capabilities.

49.5 This view is supported by the post-published document D17 (see above point 46.2; cited here in the sense of an expert's opinion) and it seems also to be shared by the appellant who stated in the context of its written submissions on Article 83 EPC (statement of the grounds of appeal, page 9, fifth paragraph) that "it cannot be predicted whether or not a given structural variant will prove to be hypoallergenic".

49.6 Thus, on the evidence before it, the board does not come to the conclusion that the skilled person, wanting to provide hypoallergenic variants of the Phl p 1 allergen and applying one of the known methods for the theoretical prediction of antibody binding sites, would

have identified the positions recited in the claim 1 in a straightforward manner.

50. As mentioned above in point 40.1 the amino acids at the positions recited in claim 1 do not only have in common that they are situated on the surface of the Phl p 1 protein, but also that they are all lysines. However, there is no tangible evidence before the board suggesting that the skilled person would have specifically identified lysines as candidates for substitution or deletion if the IgE binding capacity of a protein is to be reduced.

51. And even if it is assumed that the skilled person identified lysines as preferred amino acid residues on the basis of common general knowledge - the appellant has submitted in opposition proceedings (notice of opposition, point 5.2.5) that it is expected that lysine due to its length and hydrophilic character will have a tendency to be located on the surface - this would not inevitably motivate the skilled person to change those residues recited in claim 1, because in fact native Phl p 1 comprises altogether twenty seven lysine residues.

52. The board concludes that the subject-matter of claim 1 and also that of the claims dependent on it or related thereto is not obvious.

Problem solved over the whole breadth

53. The appellant argues that claim 1 relates to variants with only slightly reduced immunogenicity and that these variants would, if they were used for vaccination,

have in principle the same effect as the unmodified protein. These variants would thus not solve the problem underlying the invention.

53.1 As explained above the skilled person would understand the term "hypoallergenic variant" to denote proteins having an IgE binding capacity which is reduced when compared to the parent protein and maintaining at the same time the capability of inducing favourable immunological changes. Thus, by definition a hypoallergenic variant" is considered as a "hypoallergenic variant" only if it performs better than the natural protein. Since the claim only relates to hypoallergenic variants, the issue of variants that do not solve the problem does not arise. Thus, no case has been made that the problem is not solved over the whole breadth of the claim.

54. The requirements of Article 56 EPC are fulfilled.

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 maintain the patent on the basis of claims 1-11 of the main request filed at the oral proceedings, pages 3-6 and figures 1 and 2 of the patent as granted and page 2 filed at the oral proceedings.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith