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**Datasheet for the decision  
of 23 July 2009**

**Case Number:** T 0734/07 - 3.3.09

**Application Number:** 00912432.2

**Publication Number:** 1146794

**IPC:** A23J 3/34

**Language of the proceedings:** EN

**Title of invention:**

A hypoallergenic composition containing tolerogenic peptides inducing oral tolerance

**Patentee:**

SOCIETE DES PRODUITS NESTLE S.A.

**Opponent:**

ALK-ABELLO A/S  
Numico Research B.V.

**Headword:**

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**Relevant legal provisions:**

EPC Art. 56, 114(2)

**Relevant legal provisions (EPC 1973):**

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**Keyword:**

"Late filed experiments - non-admitted"  
"Inventive step - no"

**Decisions cited:**

T 0254/93

**Catchword:**

-





Case Number: T 0734/07 - 3.3.09

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.09  
of 23 July 2009

**Appellant:** Numico Research B.V.  
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**Respondent:** SOCIETE DES PRODUITS NESTLE S.A.  
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**Representative:** -

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**Decision under appeal:** Interlocutory decision of the Opposition  
Division of the European Patent Office posted  
23 February 2007 concerning maintenance of  
European patent No. 1146794 in amended form.

**Composition of the Board:**

**Chairman:** P. Kitzmantel  
**Members:** J. Jardón Álvarez  
K. Garnett

## Summary of Facts and Submissions

I. The grant of European patent No. 1 146 794 in respect of European patent application No. 00912432.2, filed on 17 January 2000 as International application PCT/EP00/00334(WO - 00/42863) in the name of SOCIETE DES PRODUITS NESTLE S.A., was announced on 6 August 2003 (Bulletin 2003/32) on the basis of 7 claims. Independent Claims 1, 5, 6 and 7 read as follows:

"1. A hypoallergenic composition for the induction of protein tolerance in at risk individuals of protein allergy, containing (i) a "non allergenic" protein material extensively hydrolysed basis and/or of (ii) a free amino acid basis, said composition comprising as the active ingredient at least one tolerogenic peptide of the allergenic protein, wherein said tolerogenic peptides are present in the form of (i) isolated tolerogenic peptidic fractions of the hydrolysis of proteinaceous material containing the allergenic protein and/or (ii) synthetically prepared tolerogenic peptides, in such an amount that the ratio of tolerogenic activity by residual antigenicity is at least  $2 \times 10^{-2}$ .

5. Tolerogenic peptide  $H_2N-I-D-A-L-N-E-N-K-COOH$  of  $\beta$  lactoglobulin, having the ability to induce oral tolerance to milk proteins.

6. Tolerogenic peptide  $H_2N-V-L-V-L-D-T-D-Y-K,-K-COOH$  of  $\beta$  lactoglobulin, having the ability to induce oral tolerance to milk proteins.

7. Tolerogenic peptide H<sub>2</sub>N-T-P-E-V-D-D-E-A-L-E-K-F-D-K-COOH of  $\beta$  lactoglobulin, having the ability to induce oral tolerance to milk proteins."

Claims 2 to 4 were dependent claims.

II. Two Notices of Opposition requesting the revocation of the patent in its entirety on the grounds of Article 100(a) EPC, for lack of novelty and inventive step, and Article 100(b) EPC, for lack of sufficient disclosure, were filed on 6 May 2004 against this patent by:

Alk-Abelló A/S (Opponent 01) and by

Numico Research B.V. (Opponent 02)

During the opposition proceedings *inter alia* the following documents were cited:

D1: EP - A - 0 629 350,

D5: EP - A - 0 827 697,

D7: R. Fritsché *et al.* "Immunodeficiency and other clinical immunology. Induction of systemic immunologic tolerance to  $\beta$ -lactoglobulin by oral administration of a whey protein hydrolysate." J. ALLERGY CLIN IMMUNOL, 1997, 100(2), 266 - 273,

D24: L. Businco *et al.* "Hydrolysed cow's milk formulae" *Pediatr. Allergy Immunol.*, 1993, 4: 101 - 111,

- D25: A. Muckerheide *et al.* "Immunosuppressive properties of a peptic fragment of BSA" THE JOURNAL OF IMMUNOLOGY 1977, 119(4), 1340 - 1345,
- D26: Y. Sütas *et al.* "Suppression of lymphocyte proliferation in vitro by bovine caseins hydrolyzed with *Lactobacillus casei* GG-derived enzymes" J. ALLERGY CLIN IMMUNOL 1996, 98, 216 - 224,
- D27: E. Furrie *et al.* "Partial characterization of a circulating tolerogenic moiety which, after a feed of ovalbumin, suppresses delayed-type hypersensitivity in recipient mice." Immunology, 1995, 86, 480 - 486, and
- D28: P.S. Norman, "Responses to T Cell Tolerogenic Peptides" Arbeiten aus dem Paul-Ehrlich-Institut Band 91, 8th International Paul Ehrlich Seminar Gustav Fischer Verlag 1997, 40 - 44.

III. By its interlocutory decision announced orally on 11 January 2007 and issued in writing on 23 February 2007, the Opposition Division held that the grounds for opposition raised by the Opponent did not prejudice the maintenance of the patent in amended form according to the set of claims of the auxiliary request filed by the Patent Proprietor with letter dated 11 December 2006. The claims maintained by the Opposition Division read as follows:

"1. Use of tolerogenic peptide H<sub>2</sub>N-I-D-A-L-N-E-N-K-COOH of  $\beta$ -lactoglobulin in the manufacture of a hypoallergenic composition for inducing oral tolerance

to milk proteins in mammals susceptible to cows' milk allergy.

2. Use of tolerogenic peptide H<sub>2</sub>N-V-L-V-L-D-T-D-Y-K,-K-COOH of β-lactoglobulin in the manufacture of a hypoallergenic composition for inducing oral tolerance to milk proteins in mammals susceptible to cows' milk allergy.

3. Use of tolerogenic peptide H<sub>2</sub>N-T-P-E-V-D-D-E-A-L-E-K-F-D-K-COOH of β-lactoglobulin in the manufacture of a hypoallergenic composition for inducing oral tolerance to milk proteins in mammals susceptible to cows' milk allergy."

The Opposition Division acknowledged the novelty of the claimed use because the three specific peptides of Claims 1 to 3 were not explicitly mentioned in any of the documents D1, D5 or D7.

Concerning inventive step, the Opposition Division regarded the teaching of D7, disclosing the induction of systemic immunological tolerance to β-lactoglobulin by oral administration of a whey protein hydrolysate, as the closest prior art. In its opinion, the problem underlying the patent in suit, namely the provision of an improved tolerogenic formulation was solved in an inventive manner by the use of the three specific peptides. The reason being that in its opinion, even admitting that D7 disclosed the isolation of a tolerogenic fraction, this document failed to suggest the isolation of individual peptides out of the peptide mixture.

IV. On 23 April 2007 Opponent 02 (Appellant) lodged an appeal against the decision of the Opposition Division and paid the appeal fee on the same day.

In the Statement of Grounds of Appeal filed on 27 June 2007, the Appellant requested the revocation of the patent in its entirety on the grounds of lack of novelty and lack of inventive step (Article 100(a) EPC).

V. With letter dated 2 November 2007 the Patent Proprietor (Respondent) requested that the appeal be dismissed and the patent be maintained with the claims in accordance with the decision of the Opposition Division.

VI. On 17 March 2009 the Board dispatched a summons to attend oral proceedings on 23 July 2009. In the annexed communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal, the Board drew the attention of the parties to the points to be discussed during the oral proceedings.

VII. By letter dated 23 June 2009 the Appellant filed further arguments in support of its requests.

VIII. By fax dated 17 July 2009 the Appellant presented analysis results of hydrolysed whey proteins in order to establish that the hydrolysates of D5 and D7 contained the three peptides specified in Claims 1 to 3. The Appellant justified the late filing by the difficulties encountered in identifying the peptides.

IX. By fax dated 20 July 2009 the Respondent requested that the experimental data of the Appellant be not admitted into the proceedings in particular due to its late



filing and the bad quality of the fax received by him which was not sufficient for it to be read and understood. The Respondent also requested that if the Board intended to admit these experimental data into the proceedings, the oral proceedings be adjourned.

X. The arguments presented by the Appellant in its written submissions and at the oral proceedings may be summarized as follows:

- The Appellant pointed out that the newly filed experiments would not change the course of the proceedings. They were actually triggered by the Board's preliminary comments of 17 March 2009 and merely confirmed the presence of the peptides in the hydrolysates of D5 and D7, a fact that had not been disputed by the Respondent in its letter of 2 November 2007. The Appellant regretted the late filing, which was due to the difficulties in identifying all of the specified peptides.
  
- The Appellant contested the novelty of the subject-matter of Claims 1 to 3 having regard to the disclosure of documents D5 and D7. It maintained that the whey hydrolysates of D5 obtained by trypsin hydrolysis and the infant formula BEBA-HA disclosed in D7 inherently comprised the tolerogenic peptides specified in Claims 1 to 3. As a consequence, and following the rationale of decision T 254/93, the claimed second medical uses were not novel because according to this decision the use of an ingredient of a known composition for obtaining a certain medical side effect which was apparent, albeit not explicitly disclosed in the prior art document,

anticipated the use of this ingredient for the manufacture of a medicament designed to provide this medical side effect; the reason being that this simply amounted to an explanation of the known behaviour of the known composition.

- Concerning inventive step, the Appellant, starting from D7 as closest prior art, regarded it as common practice for a skilled person working in the field of hypoallergenic compositions to take the action of identifying the active peptide(s) in the fraction. It supported this argument by the documents D24 to D28, said documents not, however, having been admitted into the proceedings by the Opposition Division.

XI. The Respondent essentially argued as follows:

- The Respondent contested the admissibility of the experimental data filed by the Appellant shortly before the oral proceedings. It pointed out that the quality was not sufficient for it to be possible to read and understand the figures and as a consequence the technical validity of the data could not be checked by the Respondent's experts. In any case, the hydrolysis treatment did not appear to be the same as the one used in the patent in suit.
- The Respondent justified the novelty of the claimed subject-matter as a selection invention within the teaching of D5 and D7. Although admitting that the present situation was not directly comparable to the situations according to the case law of the Boards of Appeal for selection inventions, it argued that

the use of each individual peptide for the purpose of inducing oral tolerance to milk proteins by analogy satisfied the criteria for an inventive selection.

- Concerning inventive step, the Respondent, also starting from D7 as the closest prior art, defined the problem underlying the patent in suit as being to identify and isolate from the complex mixture of hydrolysed peptides those molecules with improved balance of properties, that is to say those which would induce tolerance and not exceed a set limit of antigenicity. It maintained that the selected peptides showed a careful balance of these properties that justified the presence of an inventive step. In its opinion there was no hint in D7 that the individual peptides should be investigated in order to formulate a tolerogenic composition. This went beyond routine work and was the product of hindsight. Furthermore, the invention could not be reduced to one of selecting the most tolerogenic peptides, but extended to striking a balance between tolerogenic potential and residual antigenicity.

XII. Opponent 01 (Party as of right) did not file any substantial submissions or requests during the present appeal proceedings.

XIII. The Appellant requested that the decision under appeal be set aside and that the European patent No. 1 146 794 be revoked in its entirety.

The Respondent requested that

- the appeal be dismissed;
- the experimental results filed by the Appellant on 17 July 2009 be not admitted into the proceedings or, if they were admitted, that the proceedings be adjourned.

## **Reasons for the Decision**

1. The appeal is admissible.
2. *Admissibility of late filed experimental evidence*
  - 2.1 Pursuant to Article 114(2) EPC the EPO may disregard evidence which has not been submitted in time by the parties concerned. In the present case the Appellant submitted fresh experimental evidence at a very late stage of the proceedings, namely less than a week before the date scheduled for the oral proceedings. Additionally the quality of the presentation of the data was bad, some pages being hardly legible.
  - 2.2 The lateness of the filing as well as the bad quality of the copies submitted deprived the Respondent of both the possibility of assessing the relevance of this late submission in the time left before the oral proceedings and of the opportunity to prepare well-founded counter-arguments, including counter-evidence, if this would have been deemed necessary.

The admission of the experiments of the Appellant would therefore have led to an adjournment of the proceedings.

2.3 The Board, in accordance with Article 13(3) RPBA, therefore decided to exercise its discretion under Article 114(2) EPC not to admit the late filed test results of the Appellant into the proceedings. However at the same time, the Board, for the reasons which follow, also announced its conclusion that on the balance of probabilities the specific peptides which are the subjects of Claims 1 to 3 were present in the hydrolysates of D5 and D7.

3. *Novelty (Article 54 EPC)*

As stated above under points X and XI, novelty of the claimed subject-matter has been contested by the Appellant having regard to the disclosures of D5 and D7 and remained hotly disputed during the proceedings.

The Board is not convinced by the objections of the Appellant but sees no need to give detailed reasons for its position since, as set out below, the patent is to be revoked for lack of inventive step.

4. *Inventive step (Article 56 EPC)*

4.1 Closest prior art

4.1.1 The patent in suit relates to hypoallergenic compositions containing specific tolerogenic peptides. The claims, drafted as second medical use claims, are directed to the use of three specific peptides obtained from milk protein for inducing immunological tolerance to milk proteins in mammals.

4.1.2 The Board considers, in agreement with the parties and the Opposition Division, that the closest prior art is represented by D7.

In D7 the capacity of partially hydrolyzed and extensively hydrolyzed cow's milk formulae to induce tolerance to cow's milk proteins is discussed (see page 266, left column, second paragraph). According to this discussion a partially hydrolyzed cow's milk formula with reduced allergenicity induces specific oral tolerance to cow's milk when administered before and during allergen sensitization, whereas an extensively hydrolyzed formula cannot induce oral tolerance (page 266, right column, last full paragraph; see also page 271, first paragraph after "Discussion"). The partially hydrolyzed formula used in D7 is an enzymatically (trypsin) hydrolyzed whey formula (18% hydrolysis) commercialized by Nestlé (BEBA-HA, see page 267, left column, under "Milk formulas").

According to D7 the oral tolerance was induced by selected cow's milk protein peptides present in the partial hydrolysate but absent in the extensively hydrolyzed formula (page 272, left column, lines 14 - 19).

The Respondent in its letter of 2 November 2007 made the following statement with regard to the question whether or not the whey protein hydrolysate BEBA HA contained the individual peptides whose use is claimed: "We do not dispute that the specific peptides which are the subjects of Claims 1 to 3 would likely be present in the hydrolysates of D5 and D7."

In the oral proceedings before the Board the representative of the Respondent did not attempt to withdraw this admission but rather sought to temper its effect by saying that it was still uncertain whether the protein hydrolysate in fact contained these peptides and concluded that in assessing D7's disclosure one could not therefore start from the assumption that this was indeed the case.

In the Board's judgment, it is sufficiently established on the balance of probabilities, both by the Respondent's admission as well as by the fact that the patent in suit and D7 both relate to tryptic whey protein part hydrolysates prepared by analogous two-step enzymatic treatments, that the product BEBA HA of D7 contained the specific peptides now claimed.

4.1.3 The subject-matter of Claims 1 to 3 of the patent in suit differs from the disclosure of D7 by the use, instead of the partially hydrolyzed peptide mixture, of three specific peptides isolated from this mixture, namely H<sub>2</sub>N-I-D-A-L-N-E-N-K-COOH (Claim 1), H<sub>2</sub>N-V-L-V-L-D-T-D-Y-K,-K-COOH (Claim 2) and H<sub>2</sub>N-T-P-E-V-D-D-E-A-L-E-K-F-D-K-COOH (Claim 3).

4.2 Problem to be solved and its solution

4.2.1 The technical problem to be solved by the patent in suit in relation to said prior art can be formulated as being the isolation and identification of tolerogenic peptides having improved tolerogenicity and low antigenicity.

4.2.2 This problem is solved by the peptides according to Claims 1 to 3.

4.2.3 The results in the patent show that this problem has been credibly solved. The three claimed peptides isolated from the hydrolyzed mixture of over twenty peptides, present the best balance of properties showing at the same time a high tolerogenic potential associated to a very low antigenicity (see Example 1, in particular [0074] - [0076] and Example 6). This finding was not contested by the Appellant.

#### 4.3 Obviousness

4.3.1 It remains to be decided whether, in view of the available prior art documents, it would have been obvious for the skilled person to solve this technical problem by the means claimed. The relevant question in the present case is whether the prior art gave the skilled person a hint to isolate the selected peptides and to investigate their ability to induce tolerance.

4.3.2 In the Board's judgment this is indeed the case for the following reasons:

- Document D7 already gives this hint to the skilled person. This is clear from the discussion of the results in D7 (pages 271 - 272). This discussion already teaches the skilled person that the peptides which are present in the partially hydrolyzed formulation, but not in the extensively hydrolyzed formula, are responsible of the tolerogenic activity (cf. page 272, left column, lines 14 - 19 and right column, lines 42 - 44). In fact, the isolation of a



tolerogenic peptide fraction (a mixture of peptides) from BEBA-HA has already been carried out in D7, which on page 272, left column, indicates that "Further evidence of the tolerizing effect of the partial hydrolysate was obtained by the isolation of a tolerogenic peptide fraction of BEBA-HA (results not shown)."

- This information in D7 provides the skilled person with the incentive to isolate the peptides of the mixture of the partially hydrolyzed formula.
  - The isolation and identification of the peptides within the mixture of peptides is made by the skilled person without inventive activity. The skilled person would by routine experimentation find those peptides having the best balance of properties.
- 4.3.3 The Respondent argued that there was no pointer in D7 to the specific amino acid sequence of the isolated peptides. The hydrolysate of D7 included over twenty peptides, most of them not showing the desired balance of properties. According to Example 1 of the patent in suit, only those three peptides present in fraction F2 (see [0067]) presented the required improved balance of properties. Moreover the antigenicity of the fraction F2 was found to be 53 times lower than the antigenicity of the hydrolysate. In its opinion D7 even taught away from the invention because the peptide fraction mentioned on page 272 referred to peptides having a molecular weight range of 2 to 10kd while the peptides now claimed had a lower molecular weight, below 2kd.
- 4.3.4 These arguments cannot be accepted by the Board.

It is correct that D7 does not indicate that the claimed peptides show the best balance of properties. However, as explained under 4.3.2 above, D7 points to the fact that it is the individual peptides within the mixture which are responsible for its properties, thus giving the skilled person a clear hint to separate and identify the peptides in order to detect those having the best tolerogenic properties. The finding that the claimed tolerogenic peptides are those having the best properties, possibly even exceeding expectations, is nothing more than the logical consequence of the measure taken and cannot justify the presence of an inventive step; having decided to engage in the suggested investigation of the peptide mixture of D7 the skilled person will automatically and without any inventive effort end up with this result.

As to the argument that the lower molecular weight limit of 2kd of the tolerogenic peptide fraction isolated in D7 was above the molecular weight of the single peptides now claimed, the Board notes that in their analysis the skilled person would anyway have to start from the original BEBA HA trypsin hydrolysate of D7, which according to D5 included peptides of a molecular weight below 2kd, namely from 1 to 10kd (see D5, column 9, lines 21 - 22). In pursuing the investigations referred to in the previous paragraph, the skilled person looking for the "best" peptides would therefore necessarily also hit upon those having a molecular weight in the range 1 to 2kd. That these investigations might be painstaking and require sophisticated laboratory equipment and experience is not an indication of non-obviousness.

4.4 In view of the above findings, the subject-matter of Claims 1 to 3 lacks an inventive step.

## **Order**

### **For these reasons it is decided that:**

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar

The Chairman

G. Röhn

P. Kitzmantel