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Datasheet for the decision of 16 October 2019

Case Number: T 1270/15 - 3.3.09

Application Number: 06819464.6

Publication Number: 1951064

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Language of the proceedings: EN

Title of invention:
ORAL TOLERANCE PROMOTION WITH GLYCATED PROTEINS

Patent Proprietor:
Société des Produits Nestlé S.A.

Opponent:
N.V. Nutricia

Headword:

Relevant legal provisions:
EPC Art. 100(a), 100(b)

Keyword:
main request: sufficiency of disclosure (yes), novelty (yes), inventive step (yes)

Decisions cited:
G 0002/88

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 1270/15 - 3.3.09

D E C I S I O N
of Technical Board of Appeal 3.3.09
of 16 October 2019

Appellant: (Opponent)	N.V. Nutricia Eerste Stationsstraat 186 2712 HM Zoetermeer (NL)
Representative:	Nederlandsch Octrooibureau P.O. Box 29720 2502 LS The Hague (NL)
Respondent: (Patent Proprietor)	Société des Produits Nestlé S.A. Entre-deux-Villes 1800 Vevey (CH)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 22 April 2015 concerning maintenance of the European Patent No. 1951064 in amended form.**

Composition of the Board:

Chairman	W. Sieber
Members:	N. Perakis
	E. Kossonakou

Summary of Facts and Submissions

I. This decision concerns the appeal filed by the opponent against the opposition division's interlocutory decision that European patent No. 1 951 064 as amended meets the requirements of the EPC.

II. In its notice of opposition the opponent raised objections under Articles 100(a) (lack of novelty and lack of inventive step) and 100(b) EPC.

The documents filed during the opposition proceedings included:

D1: M. Hattori *et al.*, *J. Agric. Food Chem.*, 2004, 52, pp 4546-4553

D4: K. Mizumachi *et al.*, *Biosci. Biotechnol. Biochem.*, 2002, 66(6), pp 1287-1294

D6: WO 00/18249 A1

D8: S. Pecquet *et al.*, *J. Allergy Clin. Immunol.*, 2000, 105(3), pp 514-521

The opposition division decided that:

- the subject-matter of claim 1 of the main request (claims as granted) and auxiliary request 1 lacked an inventive step

- the subject-matter of the claims of auxiliary request 2 met the requirements of the EPC

Claim 1 of auxiliary request 2, the only request relevant for this decision, reads as follows:

"1. A food product comprising glycated proteins for use in the promotion of oral tolerance to the unglycated proteins in a mammal, wherein the glycated proteins are whey proteins, wherein the glycated whey proteins are lactosylated and wherein the whey proteins comprise β-lactoglobulin."

III. The opponent (the appellant) requested that the decision under appeal be set aside and that the patent be revoked in its entirety. The appellant filed the following documents with the statement setting out the grounds of appeal:

D10: V. Fogliano *et al.*, *Bichimica et Biophysica Acta*, 1998, 1388, pp 295-304

D11: J. Leonil *et al.*, *J. Dairy Sci.*, 1997, 80 (No. 10), pp 2270-2281

IV. By letter dated 18 January 2016, the patent proprietor (the respondent) requested that the appeal be dismissed, i.e. that the patent be maintained on the basis of the claims of auxiliary request 2 filed before the opposition division and resubmitted as the "Main Request" on appeal or, alternatively, that the patent be maintained on the basis of the claims of auxiliary request 1 (auxiliary request 3 before the opposition division). The respondent also filed the following documents:

D12: R. Aschaffenburg *et al.*, *Bioch.*, 1957, 65, pp 273-277

D13: H. Enomoto *et al.*, *J. Agric. Food Chem.*, 2007, 55, pp 2392-2398

V. On 7 August 2019, the board issued a communication in preparation for the oral proceedings.

VI. By letter dated 24 September 2019, the respondent submitted further arguments with regard to sufficiency of disclosure.

VII. On 16 October 2019, oral proceedings were held before the board.

VIII. The relevant arguments put forward by the appellant in its written submissions and during the oral proceedings may be summarised as follows:

- The invention of the main request was not sufficiently disclosed because the patent would not have provided any guidance to the skilled person as to how to distinguish glycated (lactosylated) β-lactoglobulin (BLG) from unglycated BLG. This was corroborated by the fact that the BLGs identified in the examples of the patent as "unglycated" were actually glycated, admittedly at a low degree (tables 1 and 2).

- In view of the impossibility to distinguish between glycated and unglycated BLGs, it could even be argued that D4 was detrimental to the novelty of the subject-matter of claim 1. This document disclosed that continuous feeding of BLG to mice induced oral tolerance. It was "more likely than not" that the BLGs fed to the mice contained small amounts of glycated (lactosylated) BLG.

- The subject-matter of claim 1 of the main request lacked inventive step over D4, which was considered

the closest prior art. The subject-matter of claim 1 differed from D4 in that lactosylated (glycated) instead of unglycated BLGs were used to promote oral tolerance to the unglycated proteins in a mammal. As the patent in suit did not contain any evidence of an unexpected effect resulting from this difference, the technical problem consisted in the provision of an alternative whey protein for inducing oral tolerance to the unglycated proteins in mammals. D4, in the very last sentence, and also D8, linked oral tolerance to allergic response. Clearly, the two effects were interrelated, and when considering alternative sources, the skilled person would have turned to D6. D6 concerned BLG and the controlled modification of it. It touched upon allergenicity. D6 also focused on the enhanced functional properties of lactosylated whey proteins, including lactosylated BLG.

IX. The relevant arguments put forward by the respondent in its written submissions and during the oral proceedings may be summarised as follows:

- The claimed invention was sufficiently disclosed. The appellant did not file any evidence to cast doubt on the ability of the skilled person to manufacture lactosylated BLG, formulate it into a food product and use that food product for promoting oral tolerance to unglycated proteins in a mammal. The technical evidence of the patent in suit showed that all lactosylated BLGs, and even those BLGs having a very low degree of lactosylation and being designated as "unglycated", promoted oral tolerance compared with the water control.

- The subject-matter of claim 1 was novel over D4. This document did not disclose any treatment which would induce lactosylation. Nor did this document directly and unambiguously disclose that the BLGs contained lactosylated BLG, even at a low degree of lactosylation. The appellant's argument, that it was "more likely than not" that lactosylated BLG was present, was technically and legally unfounded. Furthermore, D4 ascribed the induction of oral tolerance to BLG itself and not to any glycated form thereof.

- The subject-matter of claim 1 involved an inventive step starting from D4 as the closest prior art. It differed from D4 in the use of a lactosylated BLG to promote oral tolerance to unglycated proteins in a mammal. The technical problem in view of D4 consisted in the provision of an alternative BLG product capable of inducing oral tolerance to the unglycated proteins in a mammal. The skilled person would not have found any motivation in the prior art to modify the structure of BLG by lactocylation because they would have been aware that any modification on BLG would have had unforeseeable consequences on its physiological behaviour. Furthermore, the skilled person would not have combined D6 with D4. D6 disclosed the use of lactosylated BLG to enhance certain functional properties which did not include oral tolerance to unglycated proteins in mammals. Contrary to the appellant's assertions, neither D6 nor D8 disclosed any link between oral tolerance and decrease in allergenicity. Thus, the skilled person would not have had any reason to combine D6 with D4.

X. The appellant requested that the decision under appeal be set aside and that the European patent be revoked.

XI. The respondent requested that the appeal be dismissed or, alternatively, that the patent be maintained on the basis of auxiliary request 1, filed as auxiliary request 3 in opposition proceedings and resubmitted with the reply to the statement setting out the grounds of appeal dated 18 January 2016.

Reasons for the Decision

1. The present decision concerns auxiliary request 2 of the opposition division's interlocutory decision (see point II), which is the respondent's main request in appeal.

2. The board agrees with the parties that claim 1 of this request is a second medical use claim according to Article 54(5) EPC. Furthermore, the only technically sensible understanding of claim 1 is that the therapeutic effect "for use in the promotion of oral tolerance to the unglycated proteins in a mammal" is associated with the glycated proteins, and in particular lactosylated β-lactoglobulin, which are the sole explicitly mentioned ingredients of the claimed food product.

The board does not agree with the appellant's view that the wording of claim 1 "wherein the whey proteins comprise β-lactoglobulin" does not require the β-lactoglobulin (BLG) to be lactosylated. Firstly, right up to the oral proceedings, all parties and the opposition division proceeded on the assumption that the BLG referred to in claim 1 was lactosylated.

Secondly, it is quite clear from the wording of claim 1 that everything is about glycated proteins: the glycated proteins are the effective ingredient for use in the promotion of oral tolerance, the glycated proteins are (glycated) whey proteins, and the glycated whey proteins are lactosylated. Thus, it is the only sensible reading of claim 1 that the whey protein BLG, which is comprised in the lactosylated whey proteins, must also be lactosylated.

3. Sufficiency of disclosure

3.1 The appellant argued that the claimed invention was insufficiently disclosed because it would not have provided any guidance to the skilled person on how to distinguish a glycated/lactosylated BLG which provided the claimed therapeutic effect from an unglycated BLG.

3.2 The patent in suit discloses that a lactosylated BLG is the result of a deliberate lactosylation step, either in solution or in the solid state (page 3, line 57; page 4, lines 1-2; page 5, lines 3-4; examples 1 and 3). It further discloses how such a process may be carried out (page 4, lines 32-36; examples 1 and 3). Thus, the skilled reader of the patent in suit would have got sufficient guidance to reproduce the claimed invention.

Depending on the progress of the glycation/ lactosylation reaction, different glycation/ lactosylation degrees are obtained, each degree expressed in terms of "% blocked lysine" (page 4, line 55), i.e. the percentage of lysine residues of a BLG monomer which are bound to lactose molecules, bearing in mind that a BLG monomer contains a total of 14 possible lysine residues (page 5, lines 30-32). For

instance, when one of the 14 lysine residues of a BLG monomer binds one lactose molecule, the BLG has 7% blocked lysine.

3.3 As regards the experimental evidence of the patent in suit, example 1 discloses that the deliberate lactosylation of a commercial BLG from Danisco results in 8 and 14 % blocked lysine, respectively (table 1, samples E and G). This means that, on average, one or two lysine residues of a BLG monomer are bound to lactose molecules. Samples E and G are thus examples of the lactosylated BLG referred to in claim 1. In example 2, samples E and G were fed to mice. The results presented in figures 1 and 2 show that feeding samples E and G induces oral tolerance to unglycated BLG in comparison to a water control. Thus, figures 1 and 2 illustrate that samples E and G provide the claimed medical use.

Similarly, in example 3, the commercial whey protein concentrate "Prolacta 75" was submitted to a deliberate lactosylation/glycation step for 3h and 8h resulting in 19.7% and 31.0 % blocked lysine, respectively (table 2). Thus, on average, more than one lysine residue of a BLG monomer is bound to a lactose monomer. Furthermore, figures 3 and 4 show that feeding these lactosylated Prolacta samples to mice (groups C and D) induces oral tolerance to the unglycated BLG in comparison with a water control.

3.4 Also, the commercial product Lacprodan 80 containing a high level of lactosylated BLG, namely 14% blocked lysine (table 1), induces the oral tolerance to unglycated BLG in mice fed with this product (group I in figures 1 and 2; group A in figures 3 and 4).

3.5 In fact, all BLGs used in the examples of the patent in suit have a certain percentage of blocked lysine, in some cases as little as 3% or even 1% (table 1). During the oral proceedings, the view evolved that a lactosylated BLG was not limited to a BLG subjected to a deliberate lactosylation step. The respondent explicitly confirmed that all BLGs that exhibited a degree of lactosylation, even a low one, are lactosylated BLGs within the meaning of claim 1. Thus, all BLGs used in the examples of the patent are lactosylated BLGs within the meaning of claim 1, notwithstanding that BLGs with a low lysine content were used in control tests or even labelled as "unglycated" ("Prolacta 75 unglycated" with 5% blocked lysine; table 2).

As regards "Prolacta 75 unglycated", the skilled reader would have regarded the labelling of a BLG with 5% blocked lysine as unglycated as a misnomer. In the context of example 3, this labelling might have been chosen to indicate that Prolacta 75 was used as such without any extra glycation treatment in contrast to the other two samples "Prolacta 75 3h glycation" and "Prolacta 75 8h glycation".

With regard to sample B of example 1/table 1 having 42% of blocked lysine, the patent points to a problem during lyophilisation (see the footnote to table 1). The board agrees with the respondent that this sample is an anomaly and should be ignored.

3.6 Lastly, the appellant did not provide any evidence to show that a lactosylated BLG would not provide the claimed therapeutic effect.

3.7 In view of what has been said above about lactosylated BLG, the appellant's objection concerning the absence of a clear distinction in the patent in suit between glycated and unglycated BLG is no longer relevant.

3.8 Thus, the skilled person would have found in the patent in suit clear guidance to carry out the claimed invention.

4. Novelty

4.1 The novelty of the subject-matter of claim 1 was contested only in view of D4. This study examined the immune response of mice to the potent milk allergen BLG after continuous feeding of a BLG solution or milk instead of drinking-water. It shows that such feeding significantly reduces the antibody response and T cell proliferation to β-lactoglobulin and induces the suppression of both Th1- and Th2-dependent responses. This reflects a state of oral tolerance induced by food ingestion (abstract; page 1287, right column, lines 10-20).

4.2 The relevant statement is in the section "Materials and Methods" of D4, which reads as follows:

"Bovine BLG (a genetic variant of A) was prepared from fresh raw skim milk of a Holstein cow on our dairy farm and purified by ion-exchange chromatography on DEAE-Sephacel (Pharmacia, Uppsala, Sweden) as previously described[10]. Crude bovine BLG (kindly presented by Meiji Milk Products Co. Ltd., Tokyo, Japan) and fresh raw milk from Holstein cows were used for feeding."

The appellant did not deny that bovine BLG prepared from fresh raw skim milk and purified by ion-exchange

chromatography was pure unglycated BLG, i.e. that it did not contain any lactosylated BLG. It rather relied on the second sentence of the above cited passage which refers to the feeding of crude bovine BLG. It argued that it was "more likely than not" that crude bovine BLG contained residual amounts of lactosylated BLG.

However, "more likely than not" is not a legal criterion for assessing novelty. The correct criterion developed by the case law of the boards of appeal of the EPO is "the direct and unambiguous disclosure". In this case, D4 does not directly and unambiguously disclose that the crude bovine BLG fed to the mice contained residual amounts of lactosylated BLG.

4.3 But even if, *arguendo,* the appellant's interpretation of the above disclosure of D4 were correct, it is absolutely clear from the entire disclosure of D4 that the authors of D4 ascribe the induction of oral tolerance to the BLG itself and not to any glycated form of it. D4 is entirely silent on glycation. The fact that lactosylated BLG, if residually present, would have contributed to the observed oral tolerance is irrelevant because such a "hidden" property/use was, as correctly pointed out by the respondent, not known to the public at the priority date of the patent in suit (see G2/88, Reasons 10.1).

4.4 In summary, the subject-matter of claim 1 of the main request is novel over D4.

5. Inventive step

5.1 Closest prior art

The board agrees with the parties that D4 can be considered the closest prior art. As set out above, D4 discloses the induction of oral tolerance to unglycated BLG in mice after continuous feeding of a BLG solution or milk.

The subject-matter of claim 1 differs from D4 in that the food product comprises a glycated protein, namely lactosylated BLG, for use in the promotion of oral tolerance to the unglycated proteins in a mammal.

5.2 The technical problem and its solution

There is no technical evidence on file to show any unexpected or surprising effect resulting from the use of the lactosylated BLG over BLG itself.

Thus, the technical problem underlying the claimed subject-matter in view of D4 consists in the provision of an alternative product capable of inducing oral tolerance to the unglycated proteins in a mammal.

The technical evidence of the patent in suit (examples 1 and 2, figures 1 to 4) shows that oral tolerance to the unglycated proteins in mice (mammals) is enhanced after feeding of a food containing lactosylated BLG irrespective of the percentage of blocked lysine (degree of the lactosylation) in comparison with water. The board concedes that the effect of oral tolerance might be more apparent with BLGs having a higher percentage of blocked lysine, such as group E and G with 8% and 14% blocked lysine,

respectively (table 1). However, there is nothing on file that raises doubts that the effect would not be achieved with lactosylated BLG having a lower percentage of blocked lysine. The effect might be less pronounced, but would still be present.

5.3 Obviousness

5.3.1 The skilled person starting from D4 and seeking to solve the set technical problem would not have found in D4 any motivation to modify the structure of BLG by lactosylation. D4 discloses that the structure of the antigen (BLG) among other factors has an impact on the induction of the oral tolerance (page 1287, left column, second paragraph). Furthermore, the skilled person would have been aware that any modification of the antigen structure would have unforeseeable consequences on its physiological behaviour. Therefore, the skilled person would not have expected that the modification of BLG by lactosylation would induce oral tolerance to the unglycated proteins in a mammal.

5.3.2 Furthermore, the skilled person would not have combined D6 with D4. D6 discloses lactosylated BLG and its incorporation into dairy products to produce a product with improved/enhanced functional properties and nutritional content (page 1, lines 8-10; page 7, lines 5-10 and 28-29; page 17, lines 23-25). With regard to the enhanced functional properties, D6 refers to enhanced heat stability, emulsifying activity, antioxidant activity and enterotoxin binding capacity (page 6, lines 29-31; claim 26). It does not contain any reference to the promotion of oral tolerance to the unglycated proteins in a mammal. Thus, the skilled person would not have found any motivation in D6 to replace the (unglycated) BLG of D4 with a glycated BLG

and still induce oral tolerance to β-lactoglobulin in mammals (mice).

The disclosure on page 2, lines 11-12, of D6 to which the appellant made reference does not relate to the invention of D6, namely the lactosylated BLG, but to the background art of that invention, which corresponds to D1 of the present case. According to D1 (abstract, lines 1-3), the immunogenicity of native BLG (not the oral tolerance to native β-lactoglobulin) is reduced by conjugation with acidic oligosaccharides (i.e. sugars different from lactose). Thus, D1 appears to deal with another problem and to propose a different solution. Consequently, this part of D6 is irrelevant.

Furthermore, the skilled person would not have found in D8 any motivation to combine D6 with D4. D8 discloses that oral tolerance against food proteins is achieved by using native or moderately hydrolysed proteins such as BLG hydrolysate (abstract, lines 1-3 and 23).

5.3.3 In view of the above, the subject-matter of claim 1 involves an inventive step.

6. Dependent claim 2 relates to a specific embodiment of claim 1 and, therefore, it satisfies the requirements of sufficiency of disclosure, novelty and inventive step for the reasons given for claim 1.

7. As the main request is allowable, the appeal must be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

D. Magliano W. Sieber

Decision electronically authenticated