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**Datasheet for the decision  
of 16 December 2009**

**Case Number:** T 0139/06 - 3.3.09

**Application Number:** 99913195.6

**Publication Number:** 1065947

**IPC:** A23L 1/305

**Language of the proceedings:** EN

**Title of invention:**

Use of a composition for providing glutamine

**Patentee:**

SOCIETE DES PRODUITS NESTLE S.A.

**Opponent:**

Friesland Brands B.V.

**Headword:**

-

**Relevant legal provisions:**

EPC Art. 54, 56

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

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**Keyword:**

"Novelty, inventive step (yes): Second medical use:  
Therapeutic effect neither explicitly disclosed nor rendered  
obvious"

**Decisions cited:**

-

**Catchword:**

-



Case Number: T 0139/06 - 3.3.09

**DECISION**  
of the Technical Board of Appeal 3.3.09  
of 16 December 2009

**Appellant:** SOCIETE DES PRODUITS NESTLE S.A.  
(Patent Proprietor) Case postale 353  
CH-1800 Vevey (CH)

**Representative:** Marchant, James Ian  
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**Respondent:** Friesland Brands B.V.  
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**Representative:** Prins, Adrianus Willem  
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**Decision under appeal:** Decision of the Opposition Division of the  
European Patent Office orally announced  
8 November 2005 and posted 29 November 2005  
revoking European patent No. 1065947 pursuant  
to Article 102(1) EPC 1973.

**Composition of the Board:**

**Chairman:** W. Ehrenreich  
**Members:** J. Jardón Álvarez  
M.-B. Tardo-Dino

## Summary of Facts and Submissions

- I. Mention of the grant of European patent No. 1 065 947 in respect of European patent application No. 99 913 195.6 filed as International application No. PCT/EP99/01274 in the name of Société des Produits Nestlé S.A. on 22 February 1999 and published as WO-A 99/049741 on 7 October 1999 was announced on 23 April 2003 (Bulletin 2003/17).

The patent entitled "*Use of a composition for providing glutamine*" was granted with ten claims. Independent Claims 1 to 3 read as follows:

"1. The use of whey protein or a protein source comprising 80% to 90% by weight casein, 0.5% to 2% by weight isoleucine, 2% to 8% by weight leucine, 1% to 5% by weight cysteine and 1% to 5% by weight lysine in the preparation of a enterally administrable nutritional composition for therapeutically increasing plasma glutamine concentration in a stressed mammal".

"2. The use of whey protein or a protein source comprising 80% to 90% by weight casein, 0.5% to 2% by weight isoleucine, 2% to 8% by weight leucine, 1% to 5% by weight cysteine and 1% to 5% by weight lysine in the preparation of a enterally administrable nutritional composition for therapeutically increasing muscle glutamine concentrations in a mammal".

"3. The use of whey protein or a protein source comprising 80% to 90% by weight casein, 0.5% to 2% by weight isoleucine, 2% to 8% by weight leucine, 1% to 5% by weight cysteine and 1% to 5% by weight lysine in the

preparation of a enterally administrable nutritional composition for therapeutically providing glutamine to a mammal suffering from under-developed intestines".

Claims 4 to 10 were, either directly or indirectly, dependent on one or more of the independent Claims 1 to 3.

II. Notice of opposition against the patent was filed by

*Friesland Brands B.V.*

on 22 January 2004.

The opposition was based on Article 100(a) EPC, namely that the claimed subject-matter was not novel and was not based on an inventive step. Revocation of the patent in its entirety was requested.

In support of its objections the Opponent, *inter alia*, cited the following documents:

- D1 D.K. Rassin et al.: "*Milk Protein Quantity and Quality in Low-Birth-Weight Infants: II. Effects on Selected Aliphatic Amino Acids in Plasma and Urine*" in *Pediatrics* vol. 59 No. 3, pp. 407-422, March 1977;
- D6 J. Rigo and J. Senterre: "*Metabolic balance studies and plasma amino acid concentrations in preterm infants fed experimental protein hydrolysate preterm formulas*" in *Acta Paediatr. Suppl.* 405: 98-104, 1994;

D7 J. Rigo et al.: "*Nutritional evaluation of protein hydrolysate formulas*" in European Journal of Clinical nutrition (1995) 49, Suppl. 1, S26-S38.

D6, D7 were submitted after the expiry of the opposition period.

With the letters dated 12 May 2004 and 25 October 2005 the Patent Proprietor *inter alia* filed the documents:

D5 J.J. Boza et al. "*Protein hydrolysate vs free amino acid-based diets on the nutritional recovery of the starved rat*" in Eur. J. Nutr., vol. 39, (2000), pp. 237-243;

D9 F. Ziegler et al.: "*Efficiency of enteral nitrogen support in surgical patients: small peptides vs non-degraded proteins*" in Gut, 1990, 31, pp. 1277-1283.

III. With its decision orally announced 8 November 2005 and issued in writing 29 November 2005 the Opposition Division revoked the patent. The decision was based on the claims as granted (Patentee's main request) and a set of claims as basis for an auxiliary request filed with the letter dated 3 November 2005.

The claims of the auxiliary request corresponded to those of the main request with the amendment that the feature "*wherein the whey protein or protein source comprises more than 80% by weight of the protein in the nutritional composition*" was introduced at the end of each of Claims 1 to 3.

The only reason for revocation of the patent was lack of novelty of the subject-matter of the claims, which are of a second medical use type.

The Opposition Division in particular argued that D7 disclosed the use of hydrolysed whey protein formulas, *inter alia* the formula PTHF1 with 100% hydrolysed whey protein, for preparing compositions which were enterally administered to preterm infants and for which the metabolic balance and the plasma amino acid profile had been investigated. It emerged from a comparison of PTHF1 with the other protein formulas PTF (standard: whey/casein 60/40), PTHF2 (whey/casein 78/22), PTHF3 (whey/casein 78/22 plus histidine) in Table 6 on page S32 that the preprandial plasma glutamine content was in all cases statistically not significantly different. D7, therefore, demonstrated that the claimed therapeutic effect for stressed mammals did not exist. This conclusion could not be outweighed by the working examples of the patent as these examples were carried out on healthy rats, which were not stressed mammals in need of a therapeutic increase of glutamine.

Because this - non-existing - therapeutic effect was the only distinctive feature between the claimed use of whey protein and the use of whey protein according to D7, the subject-matter of Claim 1 was anticipated by the disclosure of D7.

- IV. Notice of appeal against the decision of the Opposition Division was filed by the Patent Proprietor (hereinafter: the Appellant) on 24 January 2006. The Statement of the Grounds of Appeal was submitted on 29 March 2006. Enclosed with the grounds of appeal were three sets of claims as bases for a new main request and auxiliary requests 1 and 2.

All these requests were replaced by new sets of claims according to a main and auxiliary requests 1 to 3, enclosed with the letter dated 12 November 2009 which, in response to a communication of the Board dated 20 November 2009, were again replaced by sets of claims as bases for a main and auxiliary requests 1 to 3, enclosed with a letter dated 11 December 2009.

During the oral proceedings, which took place on 16 December 2009, the Appellant, after a discussion of amendments under Rule 80 EPC, withdrew the main request dated 11 December 2009 and announced that the new main request was now the maintenance of the patent as granted.

V. The Respondent maintained its objections of lack of novelty and lack of inventive step raised in the written appeal proceedings and introduced, with the letter dated 31 July 2006, the documents

D10 *"Advanced Dairy Chemistry - 1: Proteins"*, edited by P.F. Fox, Department of Food Chemistry University College, Cork, Ireland, Elsevier Science Publishers, Ltd. (1992), page 472;

D11 M. Giovannini et al. *"Antigen-Reduced Infant Formulas Versus Human Milk: Growth and Metabolic Parameters in the First 6 Months of Life"* in *Journal of the American College of Nutrition*, vol. 13, No. 4, 357-363 (1994).

No objections against admissibility of the Appellant's new main request to maintain the patent as granted were raised.

VI. In respect of novelty and inventive step of the subject-matter according to the main request the Respondent provided the following arguments:

(a) Novelty

The wording of independent Claims 1 to 3 as granted "*The use of whey protein ... in the preparation of a ... composition*" embraced the preparation of all compositions in which at least some of the protein used was whey protein. This was also confirmed by the Appellant on page 4, point 3.4.3 of its letter dated 12 November 2009. Therefore, the preparation of all formulas used in the study of D7 were included by the above claims.

According to the study in D7, the feeding carried out was of preterm infants, who, in general, belong to the group of stressed mammals, as the Appellant itself had indicated in paragraphs [0012] and [0034] of the patent specification. Preterm infants also are humans with impaired intestinal functions, i.e. an under-developed intestine, as could be deduced from D1, page 407, right column, D7, page S37, left column, and D6, page 98, left column. D7 therefore disclosed, explicitly or at least implicitly, the use of whey protein in the preparation of a composition which was enterally administered to a stressed mammal having an under-developed intestine.

According to Table 6 of D7 the plasma amino acid profile - *inter alia* the plasma glutamine concentration - of preterm infants fed with whey-



containing protein formulations PTF (whey/casein 60/40), PTHF1 (100% whey), PTHF2 (whey/casein 78/22) and PTHF3 (whey/casein 78/22 plus histidine) was determined. The fact that the plasma glutamine concentrations for all formulations were comparable showed that the amount of whey protein in the protein formula did not significantly influence the plasma glutamine level of the preterm infant.

It could therefore be concluded from D7 that the claimed therapeutic increase of plasma glutamine, due to the use of whey protein in an enterally administrable nutritional composition, could not be achieved.

Because, as the Opposition Division correctly stated in its decision, the experiments of the patent specification had been carried out on healthy rats for which glutamine was not an essential amino acid and which were therefore not in need of a therapeutic increase of plasma/muscle glutamine, the examples could not support the alleged therapeutic effect.

As this - non-existing - therapeutic effect was the only feature which distinguished the claimed use from the disclosure in D7, the subject-matter of granted Claims 1 and 3 was not novel.

The same considerations applied to the subject-matter of Claim 2 as granted, indicating as therapeutic effect the increase of muscle

glutamine, because plasma glutamine levels were associated with glutamine levels in muscles.

(b) Inventive step

In the event that the claimed subject-matter was considered to be novel over D7, this document was representative of the closest prior art from which the claimed use differed in that in the (stressed) mammals the plasma/muscle glutamine was therapeutically increased by the use of whey protein. However, it could be deduced from D1 figure 1 at the top right of page 412 that whey-containing protein formulas in all cases increased the plasma glutamine concentrations in comparison with human milk.

A combination of D7 with D1 therefore rendered the claimed therapeutic increase of plasma and muscle glutamine, caused by the use of whey protein, obvious.

Furthermore, the alleged therapeutic effect was not achieved over the whole scope of the claims as could be deduced from the examples of the patent. A comparison of the muscle glutamine concentration provided by the control diet based on soy protein with that of the diet B comprising hydrolysed casein and whey showed that the soy diet provided more muscle glutamine (4  $\mu\text{mol/g}$ ) than diet B (3.9  $\mu\text{mol/g}$ ).

VII. The Appellant's counterarguments were as follows:

(a) Novelty

The group of animals falling under the definition "stressed mammal" according to Claim 1 was clearly defined in paragraphs [0003], [0004], [0012] and [0034] of the patent specification.

Accordingly, preterm babies having an under-developed intestine, patients who are critically ill and were suffering from sepsis, injury, burns or inflammation, patients recovering from surgery, and athletes after intense exercise belonged to this group, for which glutamine became an essential amino acid and for which a therapeutic need of glutamine therefore existed.

The experiments provided in the examples (paragraphs [0041] to [0053]) of the patent specification on healthy rats plausibly demonstrated the therapeutic of the use of whey protein in that plasma and muscle glutamine was considerably increased over groups of rats fed with other protein formulations or free amino acids, even though the initial glutamine intake was higher in the latter groups.

It could further be deduced from D5 that starved rats showed metabolic changes which led to depression of immunocompetence and alteration of digestive system functions (page 241, left column "Discussion"). The groups of starved rats used in the experiments of the patent therefore belonged to the group of stressed mammals. Moreover, it was

common practice to perform medical investigations on animals like rats. The results of the experiments in the patent were therefore realistic and transferable to other stressed mammals such as stressed humans.

The document D7 was not designed to show that the use of whey protein provided glutamine to stressed mammals for which glutamine became an essential amino acid. D7 neither mentioned that the preterm babies fed with the protein formulations had an under-developed intestine nor was there any comparison possible between non-whey protein formulas and whey protein formulas because all compositions of D7 fed to preterm infants contained whey protein.

Therefore, the results in Table 6 of D7, showing similar plasma glutamine concentrations (amongst many other amino acid concentrations), could not detract from the claimed therapeutic effect.

The same applied in principle to D6 - from which D7 was a follow-up study - and D1. In particular the figure in D1 on the top right of page 412 merely showed that all protein formulas - the whey-dominated low/high- protein compositions and the casein-dominated low/high-protein formulas - led to higher plasma glutamine than human breast milk.

(b) Inventive Step

The examples of the patent clearly showed that the therapeutic effect of the use of whey protein exists. Therefore, the distinguishing feature over the closest prior art D7 was the therapeutic increase of plasma and muscle glutamine of stressed mammals. It was neither explicitly disclosed nor rendered obvious by D7 or any of the other documents cited that whey protein or the other protein source claimed in Claims 1 to 3 of the granted patent could be used for therapeutically increasing plasma or muscle glutamine in stressed mammals.

VIII. The final requests at the end of the oral proceedings were as follows:

The Appellant requested that the decision under appeal be set aside and the patent be maintained as granted or, alternatively, on the basis of auxiliary requests 1 to 3 as filed with the letter dated 11 December 2009.

The Respondent requested that the appeal be dismissed.

## Reasons for the Decision

1. The appeal is admissible.
2. Novelty

It was not in dispute between the Parties that D7 discloses the use of whey protein for the preparation of a nutritional composition which is enterally administrable to preterm infants. In order to assess novelty of the claimed use over the disclosure in D7 the following key questions have to be answered:

- (a) does the claimed therapeutic effect, i.e. the increase of plasma/muscle glutamine in a stressed mammal, indeed exist?  
and
- (b) if (a) is answered in the affirmative: is such an effect clearly and unambiguously disclosed in D7?

### As to (a)

A basis for answering question (a) is to be found in the examples disclosed in paragraphs [0039] to [0053] of the patent specification. According to these examples five groups of eight rats each, which were starved for 72 hours, are fed with the following diets (paragraphs [0041], [0047] to [0051]):

- The group "*Control re-fed*" was fed with a control diet based on soy protein as protein source with a glutamine content of 8.99 g/100g;

- The "*Group 1*" was fed with "*Diet 1*" based on hydrolysed whey as protein source with a glutamine content of 6.2 g/100g;
- The "*Group 2*" was fed with "*Diet 2*" based on hydrolyzed whey as protein source with a glutamine content of 5.42 g/100g;
- The "*Group A*" was fed with "*Diet A*" based on free amino acids as protein source with a glutamine content of 21.63 g/100g;
- The "*Group B*" was fed with "*Diet B*" based on hydrolyzed casein and whey (ratio not defined) as protein source with a glutamine content of 8.09 g/100g.

The diets given to groups "Control re-fed" and "A" were not in accordance to the invention (no whey protein in the formulations).

As the Appellant convincingly argued (point VII(a), it emerges from D5 (cf. page 241, left column, "Discussion") that starvation of rats "*produces a series of metabolic changes that led to reduction in body weight, depression of immunocompetence, and alteration of digestive system functions, particularly of the liver and small intestine*".

This is a clear indication that starved rats are stressed mammals with an impaired intestinal function in the sense of the invention. For the above groups of rats glutamine therefore becomes an essential amino acid.

The results in the Table in paragraph [0051] of the patent specification clearly show that for the rats of Groups 1 and 2 fed with hydrolysed whey as protein source the plasma and muscle glutamine concentration is considerably higher than for the rats of the "Group control re-fed" fed with soy protein or "Group A" fed with free amino acids.

The Respondent argued (last paragraph of point VI(b)) that the "Group B" diet was also according to the invention because the rats belonging to this group were fed with a composition containing whey. However, the muscle glutamine concentration (3.9  $\mu\text{mol/g}$ ) was lower than that of the "Group Control" (4  $\mu\text{mol/g}$ ) fed with soy protein. Therefore, the alleged therapeutic effect could not be achieved over the whole scope of the claims.

The Board cannot accept this argument. The "Group Control" (first row in the Table of paragraph [0051]) represented a group of rats which were not starved and therefore were not stressed mammals. Hence, glutamine was a non-essential amino acid for this group and a therapeutic need of glutamine therefore did not exist. Due to the different metabolism of starved and non-starved rats the comparison of the glutamine production of the Control Group (non-starved) and Group B (starved) has no relevance.

In the Board's judgment, a therapeutic increase of plasma and muscle glutamine caused by the use of whey protein in an enterally administrable nutritional composition fed to stressed rats has therefore been proven by the examples in the patent specification.



The Board also accepts the argument of the Appellant (point VII (a)) that medical investigations are routinely performed on animals like rats and the Board considers the results of the examples transferable to other stressed mammals such as stressed humans. This all the more so as the Respondent has not provided evidence to the contrary.

Question (a) has therefore to be answered in the affirmative.

As to (b)

According to D7, preterm infants were fed with protein hydrolysate preterm formulas, all containing whey protein (PTF: 60% whey; PTHF1: 100% whey; PTHF2: 78% whey; PTHF3: 78% whey). It is therefore to be noted that the formulas in D7 correspond to those according to granted Claims 1 to 3 as regards the protein composition.

The Board can also accept the arguments of the Respondent (point VI (a)) that preterm infants are stressed mammals having, in general, an under-developed intestine.

Therefore, D7 explicitly discloses the use of whey protein in the preparation of an enterally administrable nutritional composition for feeding stressed mammals.

Consequently, the only issue at stake remains whether there is an unambiguous disclosure that the whey protein is used for therapeutically increasing plasma glutamine.

In Table 6 of D7 the plasma amino acid profile of preterm infants fed with the above preterm formulas is depicted. Amongst a number of amino acids, *inter alia* concentration values for glutamine are indicated. D7, however, is not focussed on plasma glutamine levels. In particular, there is no explicit indication that the glutamine concentration of preterm infants were exceptionally low before feeding them with the preterm formulas - for instance caused by metabolic stress - or that the glutamine values indicated in Table 6 represent exceptionally increased values due to the whey protein portion in the preterm compositions. The only link between whey protein and an increase or decrease of plasma amino acids is disclosed in the first paragraph of page S26 in the context of the right-hand column "*Plasma amino acid*" on page S31, where it is indicated that the whey hydrolysate formula PTHF1 comprising 100% whey increases threonine and glutamic acid and decreases valine, leucine, tyrosine, phenylalanine and histidine (emphasis by the Board). The influence of whey on glutamine, however, is not discussed.

Under these circumstances it is not decisive for the assessment of novelty whether the claimed therapeutic effect may inherently exist when applying the compositions of D7 to preterm infants.

In the Board's judgment, and contrary to the Respondent's submission, it cannot be deduced from D7 either that the claimed therapeutic effect does not exist because no appropriate comparison was made from which such a conclusion can be drawn.

Question (b) has consequently to be answered in the negative.

### Conclusion

Because the existence of the claimed therapeutic effect has been sufficiently demonstrated by the examples of the patent and D7 neither explicitly discloses nor questions such an effect, the use claimed in Claims 1 to 3 as granted is novel over D7.

The same considerations, in principle, also apply to D1, D6 and all the other of the cited documents.

The subject-matter of the claims as granted is therefore novel over the prior art.

### 3. Inventive step

As mentioned in paragraphs [0002] and [0003] of the introduction of the patent, the amino acid glutamine has many important functions in the body. During periods of illness, the metabolic rate of glutamine increases and the body is not able to synthesise sufficient glutamine to meet its needs. In these cases glutamine, although not classified as an essential amino acid, is needed to be supplemented in the diet.

The administration of glutamine supplemented diets in these stress situations, for instance to pre-term babies or to athletes, has resulted in improvement of the person's condition. Several methods of supplementation of nutritional formulas with glutamine are known. They include the use of powdered formulas

with L-glutamine, the use of gluten or gluten hydrolysates as a protein source and the use of synthetic dipeptides (see [0006] - [0007]), but these present some drawbacks such as allergy associated to the supplementation with gluten.

Starting from this prior art the problem to be solved by the patent can be seen in the provision of alternative and improved means for the therapeutic provision of glutamine to the defined subject groups, being subjects for whom glutamine is, in effect, an essential amino acid.

This problem is solved by the use of whey protein or a protein source on the basis of casein plus specific amino acids in the nutritional composition (see Claims 1 to 3).

The examples discussed above in relation with novelty show that this problem has been credibly solved by the measure taken.

In assessing inventive step of the claimed use the question has to be clarified whether there was a motivation for a skilled person to overcome a glutamine deficit of a mammal subject to certain stress by administering a nutritional composition containing whey protein or a protein source on the basis of casein plus specific amino acids as defined in Claims 1 to 3 as granted.

As mentioned above under novelty, no link can be found on the basis of the disclosure in D7 between metabolic stress, glutamine deficit caused by this stress and

whey protein as an appropriate component for overcoming this deficit.

Therefore, a skilled person intending to increase the glutamine level in mammals for which glutamine has become an essential amino acid, would not be prompted by D7 to solve this problem by applying whey protein. The same is true for the claimed alternative protein source based on casein.

The claimed therapeutic use is also not rendered obvious by combining D7 with D1.

The figure at the top right of page 412 taken in context with the second paragraph in the left-hand column at page 411 of D1 merely demonstrates that plasma glutamine was higher in preterm infants fed with synthetic whey- or casein-dominated low or high protein formulas than in infants fed with human milk. According to the left column at page 411 the only link between glutamine and the composition of the protein formulas is a higher urine glutamine concentration caused by feeding the infants with a high protein formula. From this disclosure, however, the skilled person could not conclude that the addition of whey protein is responsible for a therapeutically enhanced plasma glutamine level.

These considerations apply to Claim 1, relating to stressed mammals in general, and to Claim 3, relating to mammals (e.g. preterm infants) suffering from under-developed intestines.

Because there is a correlation between plasma and muscle glutamine, as the Respondent argued in the oral proceedings, the same considerations also apply for Claim 2 as granted.

The subject-matter of the claims as granted is therefore based on an inventive step.

The necessity to consider auxiliary requests 1 to 3 therefore does not arise.

## **Order**

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

1. The decision under appeal is set aside.
2. The patent is maintained as granted.

The Registrar

The Chairman

G. Röhn

W. Ehrenreich