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Datasheet for the decision of 21 November 2019

Case Number: T 0775/16 - 3.3.01

Application Number: 08844952.5

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Language of the proceedings: EN

Title of invention:
UNIT DOSAGE FOR BRAIN HEALTH

Patent Proprietor:
N.V. Nutricia

Opponent:
Société des Produits Nestlé S.A.

Headword:
Triple combination for brain health/NUTRICIA

Relevant legal provisions:
EPC Art. 100(a), 56

Keyword:
Inventive step - (no) - all requests

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Case Number: T 0775/16 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 21 November 2019

Appellant: (Patent Proprietor)	N.V. Nutricia Eerste Stationsstraat 186 2712 HM Zoetermeer (NL)
Representative:	Nederlandsch Octrooibureau P.O. Box 29720 2502 LS The Hague (NL)
Respondent: (Opponent)	Société des Produits Nestlé S.A. Avenue Nestlé 55 1800 Vevey (CH)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 9 February 2016 revoking European patent No. 2214683 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	M. Pregetter
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 2214683 is based on European patent application No. 08844952.5, filed as an international application published as WO2009/058005.

Claim 1 of the patent as granted (main request) reads as follows:

"1. A composition comprising per dry weight of unit dose: (i) 10 - 1000 mg uridine in nucleobase, nucleoside and/or nucleotide form; (ii) 50 - 1000 mg docosahexaenoic acid (DHA); and (iii) a tocopherol and/or tocotrienol, wherein said composition has:
a) a weight of 200 - 3000 mg per unit dose;
b) an energy content of less than 209.3 kJ [50 kcal] per unit dose; and/or
c) a volume between 0.1 and 10 ml per unit dose,
and wherein the unit dose is a tablet, gel, dragee, pill, capsule, granule, pellet, or sachet."

II. The following documents, cited during the opposition and appeal proceedings, are referred to below:

(4) WO2006/127620

(9) Ricciarelli et al., Molecular Aspects of Medicine, 2007, 28, 591-606

(10) Grundman, Am. J. Clin. Nutr., 2000, 71 (suppl), 630S-636S

(18) Savelkoul et al., J. Neurochem., 2012, 120, 631-640

(31) Sung et al., The FASEB Journal, 2004, 18, 323-325

(34) Composition of Food; Raw, Processed, Prepared; USDA National Nutrient Database for Standard Reference, Release 20, 2007, with minor update 2008, pages 1-38 and Appendices A and B

III. The patent was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and an inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by the person skilled in the art, and extended beyond the content of the application as filed.

The opposition division revoked the patent. The main request (set of claims as granted) was found to lack novelty, auxiliary request 1 to contravene Article 123(2) EPC and auxiliary request 2 not to involve an inventive step.

The patent proprietor (appellant) appealed this decision.

IV. In the course of the appeal proceedings, the appellant submitted five auxiliary requests:

- auxiliary request 1 with the statement of grounds of appeal
- auxiliary request 2 with the letter dated 10 April 2017
- auxiliary request 3 with the letter dated 7 October 2019
- auxiliary request 4, with the statement of grounds of appeal as auxiliary request 2
- auxiliary request 5, with the statement of grounds of appeal as auxiliary request 3

The respective claims 1 of auxiliary requests 1 to 3 differ from claim 1 of the main request in the definition of point (iii):

Point (iii) of claim 1 of auxiliary request 1 reads: "a tocopherol and/or tocotrienol in an amount corresponding to 1 - 40 mg alpha-tocopherol per unit dose"

Point (iii) of claim 1 of auxiliary request 2 reads: "1 - 40 mg alpha-tocopherol per unit dose"

Point (iii) of claim 1 of auxiliary request 3 reads: "a tocopherol and/or an equivalent thereof, in an amount corresponding to 1 - 40 mg alpha-tocopherol per unit dose, wherein said tocopherol and/or equivalent thereof is alpha-tocopherol"

Claim 1 of auxiliary request 4 differs from claim 1 of the main request by the introduction of the following disclaimer:
"provided that said composition is not a capsule for a patient diagnosed as a prodromal dementia patient, said capsule having a coating of a slowly dissolvable polymeric material surrounding a liquid phase, wherein the liquid is 1.1 g and comprises:
- 0.8 g of a lipid blend of vegetable oil and marine oil giving as fatty acid profile:
  - o 34 g g [sic] saturated fatty acids;
  - o 15 g oleic acid;
  - o 7 g eicosapentaenoic acid;
  - o 27 g docosahexaenoic acid;
  - o 2.6 g linoleic acid;
  - o 0.6 g alpha-linolenic acid; and
  - o other fatty acids making up to 100 g fatty acids;

- 200 mg uridine monophosphate;
- 50 mg choline; and
- 50 mg other components including folic acid, vitamin B12, vitamin B6, minerals, trace elements."

Claim 1 of auxiliary request 5 reads as follows:
"1. A composition for use in the treatment and/or prevention of Alzheimer's disease, said composition comprising per dry weight of unit dose: (i) 10 - 1000 mg uridine in nucleobase, nucleoside and/or nucleotide form; (ii) 50 - 1000 mg docosahexaenoic acid (DHA); and (iii) a tocopherol and/or tocotrienol, wherein said composition has:
a) a weight of 200 - 3000 mg per unit dose;
b) an energy content of less than 209.3 kJ [50 kcal] per unit dose; and/or
c) a volume between 0.1 and 10 ml per unit dose,
and wherein the unit dose is a tablet, gel, dragee, pill, capsule, granule, pellet, or sachet."

V. The opponent (respondent) reacted with several letters to the appellant's submissions. With letter of 8 October 2019, it submitted document (34).

VI. Oral proceedings before the board took place on 21 November 2019.

VII. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Document (4) represented the closest prior art. Starting from example 5 of document (4), there were several differences compared to claim 1 of the main request: the doses of docosahexaenoic acid (DHA) and uridine monophosphate (UMP), the small "volume" (defined by weight, caloric and/or volume

restrictions) and, most importantly, the absence of vitamin E.

The experiments of the patent in suit and document (18) showed that these differences were causally linked to technical effects. Experiment 2 of the patent in suit found synergy between DHA, UMP and vitamin E. All study arms employed the ingredients in the same concentrations. The results depicted in Figure 3 proved the synergistic effect. Document (18) provided data of the double combination DHA+UMP for comparison. From Figure 4(a) it could be clearly seen that the effects of UMP and vitamin E on receptor activation were not significantly different from the control and thus comparable to the effects of UMP and vitamin E as shown in Figure 3 of the patent in suit. Incubation with DHA led to an effect of about 160%. Figure 4(c) provided effects for combinations of actives. The first bar in Figure 4(c) depicted an effect of about 150% for the combination of DHA, UMP and choline, which was a value comparable to the effect of DHA alone. This first bar of Figure 4(c) of document (18) complemented the data of Figure 3 of the patent in suit. Since it was thus shown that the double combination DHA+UMP had no effects going beyond what was expected, synergy of the triple combination was proven. Furthermore, this first bar of Figure 4(c) of document (18) represented example 5 of document (4) (which also contained choline). Comparison of this bar with the next, relating to the combination DHA, UMP and vitamin E, provided proof of synergy in view of the closest prior art.

The problem to be solved was the provision of a composition that was more easily ingestible and led to improved receptor function linked to improved neuronal communication.

Document (4) did not discuss any effects of vitamin E, did not point to the possibility of synergy, and did not address compositions of reduced volume. None of the other documents provided such information or pointers to such information, either. Consequently, the subject-matter of claim 1 of the patent in suit was inventive.

The same line of argument also applied to the claims of the auxiliary requests.

VIII. The respondent's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Document (4) concerned the treatment of Alzheimer's disease and suggested the use of a combination of DHA and UMP (example 5).

Claim 1 of the main request differed by the doses of DHA and uridine, the "size" of the composition, and the addition of vitamin E. No effects had been invoked by the patent proprietor for the doses of the active ingredients, which were within the usual ranges. Features a) to c) of claim 1 of the main request, which concerned features restricting the size of the unit dose, were responsible for providing a better chance that a patient would ingest enough of the composition comprising the active ingredients. Concerning the addition of vitamin E, the following was pertinent. The data in experiment 2 of the patent in suit could not show synergy since comparisons with the double combinations UMP+DHA and UMP+vitamin E were missing. Furthermore, there were no data for DHA alone. It was indicated that the administration of DHA led to cell death. This indication was surprising since there was

no guidance in the literature. The cell death caused by DHA implied that a wrong dose had been used and should be ignored. The absence of control data for DHA had to be seen as a fundamental deficiency of the patent in suit. Synergy had not been shown. Figure 4(c) of document (18) did not provide any relevant comparison. The results depicted by the second bar of this figure stemmed from the addition of several further active ingredients and could not lead to the recognition of an effect due to vitamin E alone. Furthermore, it was clear from the error bars that no significant differences in effects existed between the first and the second bars of Figure 4(c).

The technical problem to be solved was the provision of an alternative pharmaceutical composition for treating Alzheimer's disease which was easier to ingest.

The usual amounts of active agents were used. The small size of the compositions was suggested by document (4) itself, which taught to formulate the composition as tablets, capsules and the like (paragraph [000211]). For such galenic forms, weights and volumes as defined in points a) and c) of claim 1 of the main request were usual and consequently obvious. The addition of vitamin E to a composition for use in the treatment of Alzheimer's disease was obvious in light of documents (9), (10) and (31). Document (9), in point 2.2, document (10), in the section headed "conclusions", and document (31), in its conclusion, described the role and use of vitamin E in the treatment of Alzheimer's disease. The subject-matter of claim 1 of the main request was not inventive.

IX. The final requests of the parties were as follows:

The appellant (patent proprietor) requested that the decision under appeal be set aside and that the patent be maintained as granted (main request), or, alternatively, that the patent be maintained in amended form on the basis of one of the following claim sets:
- auxiliary request 1 filed with the statement of grounds of appeal;
- auxiliary request 2 filed by letter dated 10 April 2017;
- auxiliary request 3 filed by letter dated 7 October 2019;
- auxiliary request 4 and 5 filed as auxiliary requests 2 and 3, respectively, with the statement of grounds of appeal.
The appellant further requested that document (34) not be admitted into the appeal proceedings.

The respondent (opponent) requested that the appeal be dismissed. It further requested that auxiliary requests 2 to 5 not be admitted into the appeal proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. Admission of auxiliary requests 2 to 5.

The respondent requested that auxiliary requests 2 to 5, which had not been submitted during opposition proceedings, be not admitted into the appeal proceedings.

The board has decided to admit all auxiliary requests into the proceedings.

In view of the outcome of the appeal, it is not necessary to provide any reasoning based on the parties' arguments for the admission of these requests.

3. Main request (patent as granted) - inventive step

3.1 The patent in suit (all passages refer to the B9-publication) pertains to compositions for treating or preventing memory dysfunction, cognitive dysfunction, Alzheimer's and dementia, and pre-dementia related conditions and/or symptoms or characteristics of such conditions (patent in suit, paragraph [0001]). It has been found that active ingredients, such as UMP (uridine monophosphate) and DHA (docosahexaenoic acid) incorporated in nutritional and pharmaceutical compositions are not ingested in sufficient amounts by, especially, elderly patients. This is due to the fact that patients with reduced appetite or disturbed eating behaviour will not ingest products having a high volume (often 100-500 ml of nutritional product) (paragraphs [0007] and [0008]). However, the addition of tocopherol and/or an equivalent thereof to combinations of DHA and UMP enables the manufacture of low-volume dosage compositions that can be effectively used for the treatment and/or prevention of memory decline and/or cognitive dysfunction and/or support of healthy brain function (paragraphs [0009] - [0011]).

3.2 The board considers, in agreement with the parties, that document (4) represents the closest state of the art.

Document (4) relates to treating a subject with a memory disorder, memory impairment, neurological disorder, or brain disease or disorder, by methods of increasing or enhancing the synthesis and levels of

phospholipids, synapses, synaptic proteins, and synaptic membranes (paragraph [0001]). To this aim, an omega-3 fatty acid is administered, optionally together with a uridine phosphate (claims 1 and 5 or paragraph [0001]). The most promising starting point is example 5, in which the combined administration of UMP and DHA is described. The actives are administered to healthy gerbils. The combined administration of UMP and DHA leads to significant increases in brain phospholipid levels (see Tables 2 and 3) while maintaining the proportions of the four structural phospholipids of membranes found in the brain. Accordingly, membrane mass was increased without disrupting the normal membrane structure and function, leading to the expectation of enhanced brain function (paragraph [000250]). In the absence of any restriction in claim 1 of the main request to a treatment influencing specific physiological processes in the brain, example 5 and its teaching relating to the enhancement of brain function by increasing phospholipid levels represents a valid starting point.

3.3 The differences between claim 1 of the main request and example 5 of document (4) are the addition of tocopherol or an equivalent thereof, the amounts of uridine and DHA and the "size" of the unit dose (i.e. either the weight of the unit dose, the energy content of the unit dose, or the volume of the unit dose as defined in points a) to c) of claim 1).

3.4 *Effects linked to the differences*

3.4.1 *Addition of tocopherol or an equivalent thereof*

The appellant has asserted that the inclusion of compounds having an activity equivalent to (alpha-)

tocopherol would provide a combination of active compounds acting synergistically. In the following, the term "vitamin E" will be used as a synonym for "a tocopherol and/or an equivalent thereof" as used in paragraph [0040] of the patent in suit. The appellant has referred to experiment 2 of the patent in suit, to be complemented with data from document (18), as providing proof of the existence of a synergistic effect.

Synergistic effects are effects that go beyond the sum of the effects of each feature taken in isolation. To determine the synergistic effects of a triple combination, the effects of each feature in isolation and the effects of the double combinations must be known. Comparable effects can only be obtained from experiments that are carried out under identical conditions.

The data of experiment 2 of the patent in suit cannot show a synergistic effect. The necessary controls are missing. From the three necessary double combinations, only one is present. The combinations DHA+UMP and UMP +vitamin E have not been tested. A closer look must be given to DHA when employed in isolation. Experiment 2 states that incubation with DHA alone led to cell death (paragraph [0066]). This is surprising since the double combination of DHA+vitamin E and the triple combination DHA+UMP+vitamin E did not lead to cell death, although, allegedly, the same concentration of DHA was used for incubation in all three cases.

Document (18) provides data obtained under conditions that differ from experiment 2 of the patent. Differences are, for example, the length of the incubation time and the type of agonist used. In the

relevant tests of document (18), carbachol was used in a concentration of 1 mM as an agonist, which differs considerably to the concentration used in experiment 2 of the patent in suit (50 µM). The influence of the differences in incubation time has not been determined. Consequently, the data of document (18) cannot be used to supplement the data of experiment 2.

A synergistic effect over example 5 of document (4) has also not been shown. Document (18) shows an improvement in receptor activation due to the addition of several antioxidants (AO: vitamin E, vitamin C and selenium) and B vitamins (Bvits: vitamin B6, vitamin B12 and folic acid) in the second bar, compared to the first bar, of Figure 4(c). The composition leading to the data in the second bar in Figure 4(c) differs not only by the presence of vitamin E but in several aspects (i.e. the further antioxidants and the B vitamins) from the composition underlying the first bar in Figure 4(c). The increase in receptor activation can thus not be linked to the addition of vitamin E alone. Having come to the conclusion that the data of Figure 4(c) cannot show a comparison to the closest prior art, it is not necessary to determine whether the difference in receptor activation between the first and the second bar of Figure 4(c) depicts a synergistic effect.

3.4.2 *Amounts of actives*

The amounts/doses of the actives seem to be in the usual ranges. The appellant has not argued that a surprising effect is linked to the amounts of actives.

3.4.3 *"Size"*

It is common ground between the parties that reduced sizes or volumes of dosage forms facilitate ingestion and thus lead to the uptake of appropriate amounts of active ingredients by the patients.

The appellant has argued that the small "size" of the composition is possible only due to the synergistic effect of the three active ingredients. No further arguments have been provided.

In the absence of a synergistic effect (see point 3.4.1 above), no surprising effect can be acknowledged to be linked to the "size" of the composition.

3.5 Consequently, the technical problem is to be seen as the provision of an alternative composition for the prevention or treatment of certain brain-related conditions, for example, Alzheimer's disease.

The problem is considered to be solved by the claimed subject-matter.

3.6 The closest prior art, in addition to suggesting to use a combination of DHA and UMP in the treatment of Alzheimer's disease, also teaches to use DHA at a dosage of 400-1000 mg/day (document (4), paragraph [000179] and uridine at a dosage of 10-500 mg/day (paragraph [000184]) and to supply the actives in the form of "tablets, capsules, pills, granules, pellets and the like" (paragraph [000211]).

The galenic forms and the doses taught by the closest prior art are thus completely in line with the subject-matter of claim 1 of the main request. The board adopts the respondent's view that the cited galenic forms usually have either a weight of less than 3000 mg per

unit dose or a volume of less than 10 ml per unit dose. The appellant has not challenged this view. Furthermore, it would be part of the skilled person's routine activities to optimise doses and dosages of active ingredients for which a pharmacological effect is already known or obvious.

It therefore remains to be established whether it would have been obvious for the skilled person to add vitamin E to a composition to be used in the treatment or prevention of certain brain-related conditions, for example, Alzheimer's disease.

The respondent has invoked documents (9), (10) and (31) to show that vitamin E was known to be effective in the treatment of Alzheimer's disease.

Document (9), in section 2.2, discusses various *in vitro* and *in vivo* tests that investigate vitamin E mediated effects in relation to Alzheimer's disease. While some interventional trials produced contradictory results, the epidemiological studies indicate a putative role of vitamin E in preventing cognitive impairment.

Document (10) points to evidence that suggests that oxidative stress is important in the pathogenesis of Alzheimer's disease. Vitamin E has been shown to prevent free radical-mediated cell death in cell culture and to diminish cognitive deterioration in animal models ("Conclusions").

Document (31) summarises that vitamin E can suppress brain lipid peroxidation and can significantly reduce Aβ levels and amyloid plaque deposition in Tg2576 mice when administered early during the evolution of their

disease phenotype. A therapeutic strategy aimed at targeting oxidative stress should be initiated at the earliest possible stage of the Alzheimer's disease ("Conclusion and significance").

When aiming at providing an alternative composition for the treatment of a certain disease, the skilled person would add further ingredients that are known to be effective in the treatment of the disease under consideration. In the present case, the skilled person, aware of documents (9), (10) and (31), would have seriously contemplated adding vitamin E to such compositions. The addition of vitamin E is thus obvious.

3.7 Consequently, no inventive step can be acknowledged (Article 56 EPC).

4. Auxiliary requests 1 to 5 - inventive step

The respective claims 1 of auxiliary requests 1 to 3 differ from claim 1 of the main request by the introduction of a dose requirement for vitamin E.

In analogy to the findings for the main request concerning the doses of DHA and UMP, the determination of the effective dose of vitamin E would also form part of the routine experiments carried out by the skilled person. Thus, the same reasoning as for the main request applies.

Claim 1 of auxiliary request 4 differs from claim 1 of the main request by a disclaimer. Since a disclaimer can have no bearing on the assessment of inventive step, the same reasoning as for the main request applies.

Claim 1 of auxiliary request 5 is worded in accordance with Article 54(5) EPC and defines the treatment and/or prevention of Alzheimer's disease with the composition defined in claim 1 of main request. The assessment of inventive step for claim 1 of the main request has been based on considerations concerning the treatment of Alzheimer's disease. Consequently, the reasoning given for the main request applies *mutatis mutandis* also to claim 1 of auxiliary request 5.

The respective claims 1 of auxiliary requests 1 to 5 do not involve an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

M. Schalow T. Sommerfeld

Decision electronically authenticated