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Datasheet for the decision of 18 March 2009

Case Number: T 0881/06 - 3.3.01

Application Number: 99122978.2

Publication Number: 1004594

IPC: C07J 9/00

Language of the proceedings: EN

Title of invention:
Use of phytosterol and/or phytostantol esters

Patentee:
DSM IP Assets B.V.

Opponents:
RAISIO BENECOL OY
McNeil-PPC, Inc.

Headword:
Use of phytosterol and/or phytostantol esters/DSM IP ASSETS B.V.

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

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main request - Inventive step (no) - obvious solution"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0881/06 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 18 March 2009

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 06 April 2006 rejecting the opposition filed against European patent No. 1004594 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: P. Ranguis
Members: J.-B. Ousset
C.-P. Brandt

Summary of Facts and Submissions

I. This appeal lies from the decision of the opposition division to reject the opposition filed against the European patent No. 1 004 594.

II. Claim 1 of the patent in suit reads as follows:

"1. Use of phytosterol and/or phytostanol esters with polyunsaturated fatty acids having from 18 to 22 carbon atoms and at least three unsaturated carbon-carbon double bonds and mixtures thereof for the preparation of formulations, suitable physical forms, diet supplement or food ingredients for the purpose of lowering serum cholesterol and simultaneously lowering serum triglycerides."

III. The oppositions filed by opponents I and II sought revocation of the patent in suit in its entirety for lack of novelty and lack of inventive step (Article 100(a) EPC).

IV. The opposition held that the subject-matter of the patent in suit was novel vis-à-vis the following document:

(6) Miettinen, T.A. and al., Atherosclerosis (1994), **105,** 217-226.

The opposition division considered that the measured values for the change in triglycerides after administration of the esters presented in Table 2 of document (6) was neither significant nor further discussed in document (6).

It was also concluded that the claimed subject-matter was based on an inventive step not only in view of document (6) but also in view of the following documents:

(3) US Re. 30 910
(8) Mattson, F.H. and al., J. Nutr. vol. 107 (1977), 1139-1146
(10) JP 56-122312 and its English translation
(11) Harris, W.S., J. Lipid Res. vol. 30, (1987), 18-19

Document (3) was considered as the closest prior art, since it was the only document relating to the lowering of the levels of both cholesterol and triglycerides in the blood serum. Although document (10) related to the use of esters according to claim 1 as cholesterol lowering agents and document (8) disclosed that structurally related sterol esters had the same activity and suggested an hydrolysis of the sterol esters in the intestine and additionally that document (11) described polyunsaturated fatty acids that lowered the level of triglycerides, the opposition division concluded there was no evidence of the hydrolysis of the esters of document (10) and no indication of the application of a mixture of phytosterol/phytostanol (esters) with fatty acids containing at least three carbon-carbon double bonds for lowering the cholesterol and triglyceride levels simultaneously.

V. Only opponent I (appellant) filed an appeal against the decision of the opposition division. Opponent II did not file any submissions in the appeal proceedings and did not attend oral proceedings which took place on

18 March 2009 before the board. During oral proceedings, the respondent replaced its main request (granted version of the claims) by a new and sole main request, whose claim 1 reads as follows:

"1. Use of phytosterol and/or phytostanol esters with eicosapentaenoic acid or docosahexaenoic acid and mixtures thereof for the preparation of formulations, suitable physical forms, diet supplement or food ingredients for the purpose of lowering serum cholesterol and simultaneously lowering serum triglycerides."

VI. In the appeal proceedings, the following documents were *inter alia* submitted:

(16) JP-A-61-118318 (English translation)
(17) WO-A-98/01126
(19) Demonty and al., Am. J. Clin. Nutr. 2006, 84, 1534-1542
(24) Hara and al., Ann. Nutr. Metab. vol. 37; 185-191

VII. The appellant submitted *inter alia* the following arguments to demonstrate the absence of an inventive step:

- Document (3) does not relate to phytosterol and/or phytostanol according to the patent in suit but to compounds having only similar structures. In particular, the fatty acids used therein having less than 12 carbon atoms in the chain (see column 3, line 29) are different from the ones used in the patent in suit. It cannot thus represent the closest state of the art.

- Document (10) could be considered as a relevant starting point for the person skilled in the art, because it describes also the use of esters of fatty acids to reduce the level of cholesterol. The reduction of level of triglycerides was however not mentioned therein.

- Document (11) teaches that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are constituents of fish-oil (see page 786, left-hand column, and second full paragraph) and can reduce the level of cholesterol (see page 791, left-hand column, first full paragraph) and could also be used as starting document to question the presence of an inventive step. An effect on the level of triglycerides is mentioned.

- Document (16) is also relevant, because it mentions the use of esters of EPA and DHA to reduce the level of cholesterol. Table 2 shows that both effects, lowering of cholesterol and triglyceride levels, are achieved (see "Group III"), since cholesterol and neutral lipids levels are reduced.

- Starting from document (16) as the closest state of the art, the results set out in the description of the patent in suit and more particularly those displayed in table 5 on page 9 relating to the decrease of triglycerides do not show that the problem underlying the patent in suit was credibly solved. The data provided in the patent in suit were of poor quality, mainly due to the possible

variations for each value and the absence of stabilisation of the group at "week 0". It was therefore not possible to clearly determine whether the claimed triglycerides lowering effect did actually take place. It was also disputed that the "Group 5" in paragraph [0015] of the patent in suit was a composition according to the invention but rather a mixture of sistosterol with fish-oil esters, since the presence of the sign "+" showed that sitosterol was added to a mixture of EPA/DHA ester with triglycerides.

- The post-published document (19), cited by the appellant in order to show that the claimed compositions do actually have a superior lowering effect on the levels of cholesterol and triglyceride with respect to fish oils, cannot show *a posteriori* that the problem underlying the patent in suit has actually been solved. Moreover, this document being post-published did not represent the closest prior art and the examples disclosed therein cannot be used as comparative examples. Due to the enzymatic synthesis of the fish-oil esters of plant sterol used in document (19), they contain diacylglycerols, which are known to lower the level of triglyceride (see document (24), page 189, Fig 1.). Hence, it cannot be concluded that the lowering effect on the level of triglyceride shown in Table 4, page 1539 of document (19) is exclusively due to the fish-oil esters of a plant sterol due to the presence of diacylglycerols in the compositions used therein.

VIII. The respondent (patentee) insofar as it is necessary for the outcome of this decision submitted the following arguments:

- Document (10) concerns phytosterol esters identical to those used in the patent in suit but only for lowering cholesterol. A simultaneous lowering of triglycerides is not mentioned. Moreover, its teaching is contradictory, because the use of esters of DHA in the regimen led to an increase of the level of cholesterol (see table 6 on page 5, entries F and I). Additionally, document (10) on page 6, lines 6 to 8 discloses that DHA increases the level of cholesterol. Thus, this document does not represent the closest prior art.

- There is no mention in document (11) of the possibility of treating both cholesterol and triglyceride levels in the blood. Furthermore, the figure on page 790 of this document does not show any lowering of the level of cholesterol. This document disclosed the use of fish oils to lower triglyceride levels but nothing is said in this document on any lowering effect of these oils on cholesterol levels (see page 801, right-hand column, paragraphs 2 and 3).

- Document (16) cannot either be considered as representing the closest prior art, because not esters but mixtures of phytosterols, different from those used in the patent in suit, and fish oils are tested in this document. Moreover, no

significant effect is present for the triglyceride levels (see Table 2 on page 6).

- However, the respondent strongly supported the view that document (3) represented the closest prior art, because it relates to a method for reducing the levels of cholesterol and triglycerides (see column 1, lines 16 to 19) and disclosed the use of sterols esters, the structure of which is similar to phytosterols esters to achieve this goal. It represents thus the closest prior art.

- Table 5 on page 9 of the patent in suit shows that the problem was solved by the Groups 3 to 5. Group 5 is a composition according to the invention, since it was obtained by reaction of sistosterol with a 1:1 mixture of EPA and DHA. Group 5 in Table 5 is an example according to the invention. The ratio EPA/DHA ester 1:1 corresponds to the ratio of the respective starting materials before synthesis of the esters used in the invention.

- Document (19) shows fish-oil esters of plant sterols (e.g. phytosterols esters with EPA/DHA) are significantly more potent than are equivalent doses of EPA/DHA glycerol esters from fish-oil in lowering fasting and postprandrial triglycerides levels in humans. It was not disputed that the compositions used in document (19) contained diacylglycerol but the amount thereof was so low that it has no effect on the level of triglycerides. Document (24) (see page 189, diagram on the top of the page) showed that the

amount of diacylglycerol must be important to influence the level of triacylglycerol.

IX. During oral proceedings, it was confirmed by the respondent and not disputed by the appellant that the expression "triterpenes" in document (16) (see page 2, least but one paragraph) embraces also phytosterols. The parties confirmed that the expression "Neutral lipids" found in Table 2 on page 6 of document (16) embraces also the triglycerides.

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

XI. The respondent requested that the appeal be dismissed and the patent be maintained on the basis of the main request (claims 1 to 5), dated 18 March 2008, filed during the oral proceedings.

XII. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. The appellant did not object to the main request on the basis of the requirements of Articles 123(2)(3), 84 and 54 EPC. The board is also satisfied that the main request does not contravene these Articles.

3. Determination of the closest prior art

3.1 The closest prior art must relate to the same purpose as the one of the invention and contain the minimum of differences between the structural and/or functional features with the invention (see T 606/89, point 2).

Document (3), describes compositions useful for lowering the levels of cholesterol and triglyceride. The compounds may be esters of sterols (see col. 2 with Y is acyloxy). The sterol structure set out therein (see col. 2), such as that of cholanic derivatives, does not correspond to a phytosterol and/or phytostanol structure. The hydrocarbon carboxylic moieties contain less than 12 carbon atoms (see col. 3, lines 28 to 35) and thus are different from the EPA and DHA mentioned in claim 1.

Document (10) mentions the use of a sistosterol ester made out ß-sistosterol and EPA, this document aims only at reducing the level of cholesterol. There is no mention concerning any effect of such a composition on the level of triglyceride. This document does not aim at the same purpose as the claimed invention.

Document (11) shows that fish-oil, thus containing triglycerides esters of EPA and DHA, lowers triglyceride level (See page 801, right-hand column, third paragraph) and lowers also cholesterol (see page 791, left-hand column, two first paragraphs and also page 790, left-hand column, first full paragraph).

In document (16), a mixture of fish oil containing 15.0 wt% of EPA with cycloartanol, 24-methylcycloartanol or 24-methylene cycloartanol (see page 1, "scope of the

patent") is used as a composition to improve the effect on blood serum lipids such as neutral lipids (see page 1, "Title of the invention" and page 2). Document (17) teaches that 24-methylcycloartanol is a phytosterol (see page 5, lines 27 to 32). Moreover, as acknowledged by the parties, the term "Neutral lipids" in table 2 of document (16) encompasses also triglycerides. The results displayed in Table 2 show a lowering effect on both cholesterol and triglycerides levels and in particular, the difference of level of triglycerides is quite significant. The difference between the claimed subject-matter and the disclosure of document (16) is that esters of phytosterol with polyunsaturated fatty acids are used, rather than free phytosterol and fish oil containing EPA. This document thus represents a prior art closer than document (11), which does not mention phytosterols or/and phytostanols and is more relevant than document (3), which is also directed to the same purpose but does not involve phytosterols and/or phytostanols. The board observes that Group 2 of table 5 of the patent in suit (see below) treated with 2% sistosterol mix/high oleic sunflower oil (TRISUN 80) (1:1 ratio) is not more relevant than document (16) due to the absence of EPA and/or DHA.

4. *Inventive step*

4.1 Hence, starting from document (16), the technical effects or results successfully achieved by the claimed subject-matter are to be determined for defining the objective technical problem to be solved.

In order to demonstrate an improvement, the respondent relied upon the post-published document (19) submitted with the response to the statement of grounds of appeal. This document contained the following Table 4

TABLE 4. Fasting plasma lipid, apolipoprotein, plant sterol, and thiobarbituric acid–reactive substance concentrations in overweight, hyperlipidemic subjects consuming different oil supplements varying in fatty acid and plant sterol content for 4 wk

Plasma lipid	Control olive oil	**Fish oil**	**Fish-oil esters of plant sterols**	Sunflower oil esters of plant sterols	*P*[2]
Cholesterol					
Total (mmol/L)	5.90 ± 0.22[3]	5.69 ± 0.23	5.48 ± 0.23	5.61 ± 0.21	0.0668[4]
LDL (mmol/L)	3.83 ± 0.17[a]	3.95 ± 0.18[b]	3.73 ± 0.17[b]	3.59 ± 0.16[b]	0.0321[4,5]
HDL (mmol/L)	1.29 ± 0.07	1.25 ± 0.08	1.30 ± 0.07	1.29 ± 0.07	0.2217
Total:HDL	4.75 ± 0.18[a]	4.81 ± 0.24[a]	4.38 ± 0.21[b]	4.53 ± 0.20[b]	0.0040
HDL_2 (mmol/L)	0.35 ± 0.05[a]	0.44 ± 0.06[a]	0.48 ± 0.06[b]	0.37 ± 0.05[a]	0.0032[6]
HDL_3 (mmol/L)	0.94 ± 0.04[a]	0.80 ± 0.04[b]	0.84 ± 0.04[b]	0.90 ± 0.04[a]	0.0069
HDL_2:HDL_3	0.37 ± 0.05[a]	0.56 ± 0.07[a,b]	0.60 ± 0.07[c]	0.41 ± 0.05[a]	0.0045[6]
Triacylglycerols					

Fasting (mmol/L)	1.86 ± 0.27[a]	**1.10 ± 0.13**	**0.99 ± 0.12**	1.62 ± 0.19[a]	0.0012
Postprandial (mmol/L)	2.63 ± 0.21[a]	**1.80 ± 0.27**	**1.53 ± 0.15**	2.56 ± 0.23[a]	0.0002

It is undisputed that the fish-oil esters of plant sterol tested contains diacylglycerols due to the enzymatic process of esterification used (see page 1535, right-hand column, first paragraph) and that the presence of diacylglycerol has an impact on the level of triacylglycerol in plasma (see document (24), page 189, Fig. 1). Even though this lowering effect is weak given the supposed small amount of diacylglycerols, it is to be noted that the difference in concentrations of triglycerides in the blood of the subjects treated with fish oil and fish-oil esters of plant sterols is also small (see above) and the standard deviations of both are overlapping, so that it cannot be concluded with a reasonable degree of certainty that the variations observed are only due to the nature of the fish oil or fish-oil esters of plant sterols. This document is, therefore, not relevant.

4.2 The data of table 5, page 9 of the patent in suit, show the effects of phytosterol esters on plasma triglycerides in rats.

	Week 0	week 2		week 4	
	Means ± SD	Means ± SD	%change	Means ± SD	%change
Group 1	1.08±0.23	1.09±0.21	1	1.22±013	13
Group 2	1.00±0.17	1.04±0.17	4	1.08±0.15	7
Group 3	1.25±0.26	0.83±0.13	34	0.74±0.15	41
Group 4	0.98±0.15	81±0.19	7	0.83±0.13	-15

Group 5	1.59±0.51	0.94±0.16	41	1.00±0.13	-37

The control group (Group 1) remains on the high fat diet used during the two weeks pretreatment period.
Group 2: 2% sitosterol mix / high oleic sunflower oil (TRISUN 80)(1:1 ratio);
Group 3: 2% sitostanol-DHA ester;
Group 4: 2% stigmasterol-EPA ester;
Group 5: 2% sitosterol mix + EPA/DHA ester (1:1 ratio)).

In the absence of evidence to the contrary and in view of the declaration of the respondent, the board can admit that Group 5 is treated with a mixture obtained by reaction of sitosterol with a mixture of EPA/DHA 1:1.

In response to the criticism of the appellant that the differences in plasma triglyceride levels at "week 0" could only be explained by typical variations of plasma triglycerides levels in this experimental setting and that it could be questioned if any conclusions could be made as the largest variation between the groups at "week 0" was higher (0.61) than the largest variation between groups at "week 2" (0.28) or "week 4" (0.48), the respondent submitted that possibly the two weeks pretreatment was a little bit too short and that after 4 weeks of treatment the animals had more time to stabilize. Therefore, only the results at "week 4" were to be considered and those results showed that the groups 3, 4 and 5 (according to the invention) provided a strong effect of the phytosterol esters of EPA and DHA on plasma triglyceride.

First, the board concurs with the appellant that as all rats were on the same diet for two weeks, the high differences in the level of plasma triglycerides can only be explained by typical variations of plasma triglyceride levels in this experimental setting. The fact that the variation at "week 2" and "week 4" be within the range of "week 0" renders any conclusion on the results at "week 2" and "week 4" doubtful.

Assuming nevertheless that only the variation for the different groups at "week 4" were to be considered as submitted by the respondent, it is observed that each value of this table is associated with a margin of variation. The value for Group 2 in "week 4" (1.08 +/- 0.15) thus varies from 1.23 to 0.93 whereas the corresponding value for Group 5 ranges from 1.13 to 0.87. There is thus a broad overlap between these two ranges (1.13 to 0.93). Since group 2 does not belong to the claimed invention whereas Group 5 does, the person skilled in the art cannot decide within the overlapping range (1.13 to 0.93) whether the alleged effects do actually take place. A similar reasoning can be made by comparing Group 2 to Group 4 or Group 1 (control) to Group 5.

Consequently, in view of the data provided in the description, the improvement alleged by the respondent has not been shown, namely the results set out in Table 5 do not show a lowering effect on the triglycerides level of the esters defined in claim 1.

Although the wording of claim 1 contains the effect to be achieved by the phytosterol and/or phytostanol

esters defined therein, which is actually not achieved, the board finds it appropriate to redefine the problem in less ambitious terms. The board considers that this problem can only be seen in the use of phytosterol and /or phytostanol esters in the preparation of formulation having a therapeutic application. In view, of document (10) disclosing the use of an ester made out the ß-sistotanol and EPA for reducing the level of cholesterol (see point 3.1), the person skilled in the art, starting from this document and looking for a solution to the above problem, would have arrived at the claimed subject-matter in an obvious manner.

4.3 Claim 1 of the main request is thus not inventive.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. European patent No. 1 004 594 is revoked.

The Registrar The Chairman

M. Schalow P. Ranguis