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D E C I S I O N
of 2 December 1999

Case Number: T 0254/96 - 3.3.2

Application Number: 85903749.1

Publication Number: 0188573

IPC: A61K 31/23

Language of the proceedings: EN

Title of invention:
Dietary supplement for minimizing effects of infection

Patentee:
Mascioli, Edward A. et al

Opponent:
Pharmacia & Upjohn AB

Headword:
ù3 Fatty acid ohet/MASCIOLI

Relevant legal provisions:
EPC Art. 54, 56, 123(2), (3)

Keyword:
"Main request: Inventive step (no): Prior art acknowledged in the description as the closest prior art"
"Auxiliary request 1 (no): Extension of the protection after amendment"
"Auxiliary requests 2 and 3: Inventive step (no)"

Decisions cited:
-

Catchword:

-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0254/96 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 2 December 1999

Appellants: (Proprietors of the patent)
Mascioli, Edward A.
63 Dawson Drive
Needham, Massachusetts 02192 (US)

Blackburn, George L.
241 Perkins Street Suite 602 D
Jamaica Plain, Massachusetts 02130 (US)

Bistrian, Bruce R.
189 Argilla Road
Ipswich, Massachusetts 01938 (US)

Babayan, Vigan K.
178 Beethoven Avenue
Waban, Massachusetts 02168 (US)

Representative:
Smolders, Walter
Novartis AG
Geistiges Eigentum Konzern
Patent- und Markenabteilung CH
Postfach
4002 Basel (CH)

Respondent: (Opponent)
Pharmacia & Upjohn AB
112 87 Stockholm (SE)

Representative:
Luderschmidt, Schüler & Partner GbR
Patentanwälte
Postfach 3929
D-65029 Wiesbaden (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 5 February 1996**

revoking the European patent No. 0 188 573 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: P. A. M. Lançon
Members: C. Germinario
R. E. Teschemacher

Summary of Facts and Submissions

I. European patent No. 0 188 573 was granted pursuant to European patent application No. 85 903 749.1 on the basis of a set of 8 claims for all the designated Contracting States except AT and an additional set of 8 claims for AT.

The text of granted claim 1 of the first set of claims reads:

"*The use of ù3 fatty acids for the manufacture of a dietary material for minimizing the effects of infection in animals (e.g. humans) other than avians*."

II. Notice of opposition was filed by the respondent, requesting revocation of the patent under Article 100(a) EPC on the grounds of lack of inventive step.

The following documents were cited, *inter alia*, during the proceedings before the opposition division:

(2) J. Clin. Invest., Vol. 65, pages 227 to 230, (1980);

(3) Proc. Natl. Acad. Sci. USA, Vol. 76, No. 2, pages 944 to 948, (1979);

(17) Arthritis and Rheumatism, Vol. 26, No. 2 February 1993;

III. The opposition division revoked the patent for lack of

inventive step. It based its decision on document (2), disclosing that cyclo-oxygenase inhibitors blocked the formation of prostaglandins and thromboxane A_2 (TXA_2) from arachidonic acid, and on document (3) disclosing that the ù3-fatty acid eicosapentaenoate (EPA) inhibited arachidonic acid conversion to PGE_2 and TXA_2. The combination of the teachings of these two documents, would have suggested to the skilled person that the use of ù3 fatty acids in the diet decreased any manifestation mediated by the production of thromboxan, such as the effects of infections.

IV. The appellant lodged an appeal against this decision, and filed a new main request, on 28 October 1999, and auxiliary requests one to three, on 19 November 1999. Oral proceedings were held on 2 December 1999.

Claim 1 according to the different requests reads:

Main request

"*The use of ù3 fatty acids in the form of a plant oil or fish oil other than cod liver oil, said oil being rich in, or containing a substantial proportion of, ù3 fatty acids and having a higher proportion of ù3 fatty acids than ù6 fatty acids, for the manufacture of a dietary material for minimizing the effects of infection in animals (e.g. humans) other than avians*."

First auxiliary request

"*The use of ù3 fatty acids in the form of a plant oil or fish oil other than cod liver oil, said oil being*

rich in, or containing a substantial proportion of, ù3 fatty acids and having a higher proportion of ù3 fatty acids than ù6 fatty acids, for the manufacture of a dietary material for promoting survival and full recovery in human patients and animals other than avian challenged with infection, and for promoting resistance to infection in at risk animals other than avians including humans."

Second auxiliary request

"*The use of ù3 fatty acids in the form of a plant oil or fish oil other than cod liver oil, said oil being rich in, or containing a substantial proportion of, ù3 fatty acids and having a higher proportion of ù3 fatty acids than ù6 fatty acids, for the manufacture of a dietary material for promoting survival and full recovery in human patients and animals other than avians challenged with infection*."

Third auxiliary request

"*The use of ù3 fatty acids in the form of a plant oil or fish oil other than cod liver oil, said oil being rich in, or containing a substantial proportion of, ù3 fatty acids and having a higher proportion of ù3 fatty acids than ù6 fatty acids, for the manufacture of a dietary material for promoting survival and full recovery from endotoxic shock in human patients and animals other than avians*."

V. In writing and during the oral proceedings, the appellant argued that the therapeutic efficacy of

cyclo-oxygenase inhibitors in improving endotoxin shock was never shown to be uniformly beneficial. Also, the closest prior art, document (2), failed to show that cyclo-oxygenase inhibition was actually responsible for the higher rate of survival reported in the document by endotoxin shock.

On the other hand, document (3) related to a completely different therapeutic aspect, namely the treatment of heart diseases. Therefore the skilled reader had no reason at all to combine the teachings of the two documents, particularly in consideration of the fact that the *in vitro* results reported in this document did not necessarily reflect a corresponding *in vivo* efficacy.

VI. The respondent, among other arguments, raised an objection under Article 123(3) EPC as to the allowability of all the auxiliary requests. During the oral proceedings it drew the discussion to document (17), which, although not yet considered in the appeal proceedings, had already been considered in the proceedings before the opposition division.

VII. The appellant requested that the decision of the opposition division be set aside and the patent be maintained on the basis of the set of claims submitted as the main request with the letter dated 28 October 1999. Alternatively it was requested that the patent be maintained on the basis of one of the sets of claims submitted as auxiliary requests 1 to 3 with the letter dated 19 November 1999.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Main request*

2.1 The wording of claim 1 has been amended by incorporating into claim 1 the text of dependent claim 2 as granted. The other claims have been simply renumbered. Therefore, the main request does not give rise to any objection under Article 123(2) and (3) EPC.

2.2 Before considering the substantive aspects in relation to inventive step, the Board needs to define what is, in its understanding, the subject-matter covered by claim 1. The expression "for minimizing the effects of infection" implies that the purpose of the manufactured dietary material is not that of treating, curing or eliminating the infection, but that of minimizing any **effect** whatsoever directly or indirectly **related** to the infection, and therefore any possible physiological or pathological consequence of an infection.

2.3 Although novelty is not a point at issue in the present case, not being a ground of opposition, some consideration should be given to the state of the art. The description of the patent in suit cites three items of scientific literature from Dyerberg et al., in which the effects of diets high in ù3 fatty acids on heart disease were studied. The Greenland Eskimos, who have a low meat and high fish oil diet, were the test subjects. The studies provided a comparison between

high ù6 and high ù3 diets. The Eskimos with the high ù3 fatty acid diets had significantly lower incidence of heart disease than Eskimos who had high ù6 fatty acid diets. The correctness and reliability of this information, which predates by many years the priority date of the patent in suit, was confirmed, upon request by the Board, by the appellant during the oral proceedings. Yet, the taking of fish oil in the form of diet by the Eskimos of Greenland was justified by geographical, commercial and practical reasons which made of this diet the traditional and historical form of alimentation of the population of that land. In following this type of alimentation, which was in keeping with their traditions, the Eskimos were, before the study reported above, very probably unaware that said diet would to some extent have influenced their health by decreasing the likelihood of cardiovascular diseases. In other words, the necessary condition of a medical treatment represented by the existence of the conscious cause-effect relationship between the action of administering a substance and the expectation of a therapeutical effect, cannot be recognised in the case of a natural diet traditional for a given population. On the other hand, the Dyerberg's *a posteriori* observation of the effects brought about by said diet does not entail any teaching of reducing such observation to practice in the form of a technical invention. For this reason, the Dyerberg's articles are considered as the report of a discovery rather than the disclosure of an invention based on a novel medical treatment.

2.4 On the other hand, the background knowledge illustrated in the description of the patent may represent the

closest prior art for the purpose of assessing the inventive step involved in the subject-matter of claim 1. In this case the technical problem to be solved by the invention would be that of providing means to put into practice the facts observed among the Eskimo population of Greenland. The solution proposed by the invention is the use of ù3 fatty acids for the manufacture of a dietary material for a therapeutic treatment according to claim 1. The Board has no reason to doubt that this solution actually solves said problem.

In assessing whether the proposed solution was obviously derivable from the prior knowledge, the Board considers of decisive importance the fact that one of the possible effects of infection is indeed heart disease. Also during the oral proceedings, the respondent argued, without being contradicted by the appellant, that the skilled person knew very well, as a matter of common general knowledge, that heart diseases could be the result of a bacterial infection. The Board accepts this argument since descriptions of bacterial, ie infectious, endocarditis can easily be found in any text books, in the specific field, published even long before the relevant date of the patent in suit.

For these reasons, heart disease can be regarded as one of those effects of infection to be minimised according to the present invention. Thus the patentability of the subject-matter of claim 1 is to be evaluated first of all in the light of the teaching of the prior art as reported in the description of the patent itself.

In consideration of Dyerberg's observation, disclosed

before the priority date of the patent in suit, that the incidence of heart disease among the populations which practised an ù3 fatty acid diet was significantly lower than that observed among other populations, the Board considers that the skilled person needed to exercise no inventive activity when proposing the use of the same known means (ù3 fatty acid rich diet) in order to achieve the same effect (decrease of the incidence of heart disease) obtained among the Eskimo population.

With respect to granted claim 1, amended claim 1 also includes the additional wording "*in the form of a plant oil or fish oil other than cod liver oil, said oil being rich in, or containing a substantial proportion of, ù3 fatty acids and having a higher proportion of ù3 fatty acids than ù6 fatty acids*". The Board wishes to stress that the new features are the simple description of the natural material used in the practice as starting material both in the present invention and in the prior art, namely fish oil, which, as a matter of fact, is rich in ù3 fatty acids and comprises a higher amount of ù3 than ù6 fatty acids. Therefore, the Board does not see in this amendment any supplementary technical characteristic able to make any substantive contribution to the inventive step of claim 1.

Under these circumstances, the Board considers that the subject-matter of claim 1 does not involve an inventive step.

3. *First auxiliary request*

In the text of claim 1 according to the first auxiliary

request, the expression in granted claim 1 "for minimizing the effects of infection in animals (eg humans)" has been reformulated to read "for promoting survival and full recovery in human patients and animals ... challenged with infection and for promoting resistance to infection in at risk animals ... including humans" (emphasis added). The reference to "promoting resistance ... in at risk animals.." clearly identifies the use of dietary material in the prophylactic treatment of infections in itself, not the simple treatment of the effects of the infection.

The text of claim 1 as granted makes it plain that the protection conferred covers the manufacture of a dietary material intended for the symptomatic treatment of infection; what is expected to be minimised are indeed the effects that are the manifestation or the consequences of the infection. This is fully consistent with the understanding of the invention as derivable from the patent and as presented by the appellant at the oral proceedings. As illustrated in the description, the diet according to the invention is expected to increase the ù3 fatty acid content in the platelet and cell membranes. The higher availability of ù3 fatty acids competitively inhibits the conversion of arachidonic acid or other ù6 fatty acids to type 2 prostaglandins and thromboxane A_2, which are metabolic mediators of the infection. It is clear to the Board that preventing or inhibiting the production of substances which contribute to the final manifestation of the infection is not equivalent to treating the very infection for the purpose of eradicating or preventing it. This latter type of treatment would imply the use of different classes of medicaments effective directly

on the pathogens.

On the other hand, the prophylactic use of the dietary material is protected by claim 4 only in relation of patients afflicted with well specific diseases, but not in general terms.

In conclusion, the effect of the amendment is that a new general type of therapeutic treatment, not protected by the claims as granted, is now comprised within the scope of the protection.

For this reason, the amendment introduced in claim 1 of the first auxiliary request extends the protection conferred by the granted claims and contravenes the requirements of Article 123(3) EPC.

4. *Second auxiliary request*

4.1 Claim 1 of the second auxiliary request differs from claim 1 of the first auxiliary request in that the expression "promoting resistance to infection in at risk animals..." has been deleted. It remains to decide whether or not the further added expression "for promoting survival and full recovery", complies with the requirements of Article 123(2) and (3) EPC.

If the interpretation of said expression were that the dietary material is intended, after amendment, to treat and eliminate the causative factor of the "effects", thus the infection itself, then the scope of claim 1 would be completely outside the scope of claim 1 as granted. In this case the amended claims would contravene Article 123(3) EPC.

This, however, is not the Board's construction of the new expression. In fact, as submitted by both parties and accepted by the Board, the word "promoting" does not necessarily mean that survival and full recovery are actually achieved or achieved thanks to the diet, but simply that the dietary material should facilitate or contribute to survival and full recovery, also in the sense of sustaining the activity of other classes of concomitantly administered medicaments, which may act directly on the pathogens, such as antibiotics, antivirus, antifungus. For this reason the amendments merely represent a somewhat more extensive way of expressing the same concept of "minimizing the effects of infection" disclosed in the original application and in granted claim 1. Thus the wording of the claims before and after amendment is different in the drafted form but equivalent in substance.

In keeping with this interpretation, the Board considers that the new wording of claim 1 is supported, although not literally, by the application as filed and specifically by table 3, showing the higher survival rate in the group of animals treated according to the invention, and by the passages on page 6, lines 16 to 21, or on page 8, first paragraph. Based on the same consideration, the Board also judges that amended

claim 1 does not extend the protection conferred by the claims as granted.

4.2 As discussed in the preceding paragraph, the Board's view is that the difference between the subject-matter of claim 1 of the main request and the second auxiliary request is not substantive but merely in the form of the wording. This fact was also admitted by the appellant's representative during the oral proceedings. For this reason, the considerations which led the Board to conclude that claim 1 of the main request lacked an inventive step, apply *mutatis mutandis* to the subject-matter of claim 1 of the second auxiliary request, which is also regarded as lacking an inventive step.

5. *Third auxiliary request*

5.1 According to claim 1 of the third auxiliary request, the scope of the manufactured dietary material is "promoting survival and full recovery from endotoxin shock in human patients and animals other than avians".

All the considerations about compliance with Article 123(2) and (3) EPC of the main and second auxiliary requests hold valid in relation to the third auxiliary request. As to the specific reference to endotoxin shock, this reference, on the one hand, is fully supported by example 1 of the application as filed, and on the other, implies a limitation of the protection as granted to a specific manifestation of infection. For these reasons, claim 1 complies with the requirements of Article 123(2) and (3) EPC.

5.2 Among the cited prior documents, document (2) is the

only document reporting *in vivo* results in an animal model concerning survival by endotoxin shock. For this reason the Board shares the opinion of the opposition division that this document represents the closest prior art.

The document describes thromboxan A_2 (TXA_2) as the primary mediator eliciting in animal models the cascade of events caused by endotoxin shock and ultimately progressing to irreversibility. It is, however, shown that three different classes of substances which inhibit the synthesis of TXA or compete with TXA, ie cyclo-oxygenase inhibitors (indomethacin), selective thromboxane synthetase inhibitors (imidazole) and thromboxane antagonists (13-azaprostanoic acid) significantly reduce mortality by endotoxin shock. Mortality is also reduced in rats by a state of induced essential fatty acid (EFA) deficiency (see Introduction and Discussion).

5.3 With reference to this document, the technical problem to be solved by the invention is that of providing new means for promoting survival and recovery from endotoxin shock.

Example 1 of the application as filed, specifically table 3, provides evidence that the solution proposed by the invention, namely the use of ù3 fatty acids according to claim 1 for the preparation of a dietary material to be administered to human patients or animals in need, actually solves the aforementioned problem.

5.4 The essential point to be considered by the Board is

whether the prior knowledge taught by the different cited documents would have suggested to the skilled person that a dietary material rich in ù3 fatty acids and having a higher proportion of ù3 than ù6 fatty acids would have permitted the achievement *in vivo* of the desired effect. This teaching is not derivable from document (2) alone, since, there, protection is achieved either by giving medicaments or by inducing a state of EFA-deficiency in rats. This state is not elicited by a diet rich in ù3 fatty acid, but simply by a fat-free diet. Thus the EFA-deficient rats were deficient in ù3 as well as ù6 fatty acids.

In its contentions in relation to document (2), the appellant maintained that this document did not show that the inhibition of cyclo-oxygenase activity was responsible for the improved resistance to endotoxin shock, since other prior documents reported results contradicting this theory. In the Board's view, however, the precise mechanism leading to the observed enhanced shock-resistance is not the important knowledge revealed in (2). On the contrary, the relevant teaching derivable from this document is that TXA is the primary factor eliciting the early pathogenic events accompanying endotoxin shock, and that substances or circumstances inhibiting the production *in vivo* of TXA (regardless of the mechanism) improve survival.

On the other hand, document (3) shows that the ù3 fatty essential acid eicosapentanoate (EPA) effectively competes *in vitro* with arachidonate (AA) for platelet cyclooxygenase and thereby suppresses PGH_2 and TXA_2 formation (see Discussion, page 948). As illustrated in

figure 5A (page 947) a 1:1 EPA/AA mixture resulted in a 50% inhibition in the formation of TXB_2 (which is the stable metabolite of TXA_2). Thus, document (3) unambiguously suggested to the skilled person that an ù3 fatty acid was able to depress, by competitive inhibition of cyclo-oxygenase, the synthesis of the factor identified in (2) as the pathogenic factor in endotoxin shock.

In relation to this document, the appellant expressed the opinion that *in vitro* results did not necessarily reflect a corresponding *in vivo* effect and that in 1984 manipulation of the *in vivo* content of EFA with a diet was not a matter of general common knowledge.

The Board notes that, although the experimentation reported in (3) was indeed carried out *in vitro*, the illustrated results are given within a well-defined, real medical context, with clear reference to the experimental observation made on Greenland Eskimos following an ù3-rich diet (page 944, right-hand column, and page 948, left-hand column) and with the suggestion of possible medical applications (see discussion). For this reason, the high relevance of this document is not called into question by the appellant's considerations.

As to the feasibility of increasing the ù3 lipid tissue level *in vivo* by means of a suitable diet manipulation, the Board is convinced, contrary to the appellant's view, that the skilled person was well aware, at the relevant date of the patent in suit, that this way was indeed practicable, as shown by numerous prior documents. Among these, one of the most explicit is document (17), which reports not only that a dietary

enrichment with EPA is able to raise tissue level of EPA in experimental animals, but also that a diet utilising only mackerel as the source of fat and protein can increase the level of EPA in normal human volunteers (see page 138). This does indeed confirm the previous observations made on the Eskimo population of Greenland.

From the foregoing it becomes evident that before the priority date of the patent in suit, the skilled person, faced with the aforementioned technical problem and aware of the considerable amount of previous technical information on the specific matter, would have considered the solution proposed by the patent in suit to be the most obvious solution without exerting any inventive activity. Therefore the Board's judgment is that the subject-matter of claim 1 of the third auxiliary request lacks an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman

M. Dainese P. A. M. Lançon