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Datasheet for the decision of 10 January 2022

Case Number: T 2522/18 - 3.3.01

Application Number: 08862982.9

Publication Number: 2234627

IPC: A61K35/74, A61K31/702, A61P37/04, A61P31/00, C12N1/20

Language of the proceedings: EN

Title of invention:
PREVENTION OF OPPORTUNISTIC INFECTIONS IN IMMUNE-COMPROMISED SUBJECTS

Patent Proprietor:
Société des Produits Nestlé S.A.

Opponents:
Abbott Laboratories
FrieslandCampina Nederland B.V.
N.V. Nutricia

Headword:
Prevention of opportunistic infections/NESTLE

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

This datasheet is not part of the Decision
It can be changed at any time and without notice

Keyword:
Amendments - allowable (yes)
Inventive step - (no)

This datasheet is not part of the Decisior
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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 2522/18 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 10 January 2022

Appellant: (Patent Proprietor)	Société des Produits Nestlé S.A. Entre-deux-Villes 1800 Vevey (CH)
Representative:	Plougmann Vingtoft a/s Strandvejen 70 2900 Hellerup (DK)
Respondent 1: (Opponent 1)	Abbott Laboratories 100 Abbott Park Rd. Abbott Park, IL 60064-6004 (US)
Representative:	Boult Wade Tennant LLP Salisbury Square House 8 Salisbury Square London EC4Y 8AP (GB)
Respondent 2: (Opponent 2)	FrieslandCampina Nederland B.V. Stationsplein 4 3818 LE Amersfoort (NL)
Representative:	FrieslandCampina Nederland B.V. IP Department Bronland 20 6708 WH Wageningen (NL)
Respondent 3: (Opponent 3)	N.V. Nutricia Eerste Stationsstraat 186 2712 HM Zoetermeer (NL)
Representative:	Nederlandsch Octrooibureau P.O. Box 29720 2502 LS The Hague (NL)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 1 August 2018 revoking European patent No. 2234627 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman A. Lindner
Members: M. Pregetter
R. Romandini

Summary of Facts and Submissions

I. European patent No. 2 234 627 is based on European patent application No. 08862982.9, filed as an international application published as WO 2009/077352.

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

(1) Experimental report, submitted on 24 February 2017, 4 pages

(2) M. Gueimonde et al., Neonatology, 2007, 92, 64-66

(19) WO 2005/055944

(23) R. LoCascio et al., J. Agric. Food Chem., 2007, 55, 8914-8919

(25) Experimental report, submitted on 31 August 2017, 2 pages

(37) T. Asahara et al., J. Appl. Microbiol., 2001, 985-996

(38) Y. M. Rokiah et al., Asia Pacific J. Clin. Nutr., 2000, 9(2), 130-135

(39) Bernet et al., Appl. Environ. Microbiol., 1993, 59(12), 4121-4128

(40) Ward et al., Mol. Nutr. Food Res., 2007, 51, 1398-1405

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

In the course of the opposition proceedings, the patent proprietor requested that the patent be maintained as amended on the basis of the sets of claims of a main request and an auxiliary request, both submitted during oral proceedings before the opposition division.

The opposition division revoked the patent. The subject-matter of claims 6 to 8 of the main request was found not to meet the requirements of Article 83 EPC. The subject-matter of the auxiliary request did not involve an inventive step (Article 56 EPC).

IV. The patent proprietor (appellant) appealed against this decision, re-submitting the sets of claims of the main and the auxiliary request. Furthermore, with the statement of grounds of appeal, it submitted documents (37) to (39). By letter dated 7 January 2022, it withdrew its main request and indicated that the former auxiliary request was its only request (new main request).

Claim 1 of this request reads as follows.

"1. A composition suitable for use in the prevention of opportunistic infections in immune-compromised individuals comprising a probiotic, wherein the probiotic is *Bifidobacterium infantis*, and a fucosylated oligosaccharide, wherein the fucosylated oligosaccharide is 2'-fucosyllactose, and wherein the

composition is an infant formula."

V. The opponents (respondents) all submitted replies to the statement of grounds of appeal. Together with its reply, respondent 3 (opponent 3) submitted document (40).

VI. Oral proceedings before the board took place on 10 January 2022.

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

Admission of document (40)

Document (40) did not add any new information over document (23) already on file, so it should not be admitted.

Amendments

Claim 1 was the result of a monodirectional restriction of the subject-matter of claims 1, 2 and 4 as filed to *Bifidobacterium infantis*.

Inventive step

Document (19) represented the closest prior art; it was directed to oligosaccharides suitable for treating infections, including opportunistic pathogens. Although 2'-fucosyllactose (2-FL) was mentioned, the focus of document (19) was not 2-FL but rather oligosaccharides bound to proteins (abstract). However, when starting from the disclosure of 2-FL in document (19), the difference between claim 1 and the disclosure of

document (19) was the presence of *Bifidobacterium infantis*. The effect of this difference was an improved, synergistic inhibition of opportunistic pathogens. Document (1) showed that oligosaccharides might stimulate the growth of certain beneficial bacteria in the intestine and that the combination of *Bifidobacterium infantis* and 2-FL inhibited *Salmonella typhimurium* more significantly than the combination of *Bifidobacterium infantis* with glucose or the combination of *Bifidobacterium infantis* with lacto-N-neotetraose. Document (25) clearly demonstrated (Figure 1) that a combination of *Bifidobacterium infantis* with 2-FL was surprisingly more effective at preventing *Salmonella typhimurium* invasion of Caco-2 cells than a combination of *Bifidobacterium infantis* with glucose. The value was 1.10e6 for glucose, 2.10e5 for the combination of glucose with *Bifidobacterium infantis*, 7.10e5 for 2-FL and 7.10e4 for the combination of 2-FL with *Bifidobacterium infantis*. There was no clear basis for basing the additive effect on the multiplication of the inhibition. The expert who had carried out the experiments in document (25) had stated that the results showed a synergistic effect (page 1, last line). Although the statistical significance was not explicitly mentioned, there was a clear trend. Furthermore, there were no doubts that *Salmonella typhimurium* was an opportunistic pathogen, as could be seen from document (37) (last three lines of abstract; legend of Figure 2). It was well established in the art that the inhibition of opportunistic pathogens, e.g. *Pseudomonas aeruginosa*, and of *Salmonella typhimurium* was due to low pH caused by the presence of *Bifidobacterium infantis*. The technical problem was thus providing an infant formula in which prebiotics and probiotics act synergistically in inhibiting infections with *Salmonella typhimurium* and, due to an

analogous mechanism of action, *Pseudomonas aeruginosa*. Starting from document (19) it was not obvious to add *Bifidobacterium infantis*. There was no document on file disclosing infant formulas containing *Bifidobacterium infantis*. As it was not known that *Bifidobacterium infantis* could metabolise 2-FL, a person skilled in the art had no reasonable expectation that these two would act synergistically.

VIII. The respondents' arguments, in so far as they are relevant to the present decision, may be summarised as follows.

Admission of document (40)

After a new claim request restricting the claim to one species of *Bifidobacteria* and to one specific human milk oligosaccharide was filed during the oral proceedings before the opposition division, document (40) had been submitted at the earliest opportunity, namely with the reply to the grounds of appeal. It related to small fucosyl derivatives and had been submitted to supplement document (23), which concerned larger fucosides.

Amendments

A purely formalistic, "mechanical" approach for assessing the requirements of Article 123(2) EPC was not justified in the case in hand since the substrate specificity of different *Bifidobacteria* species was not known at the filing date of the patent in suit. The combination of *Bifidobacterium infantis* with 2-FL led to a claim giving the patent proprietor an unwarranted advantage. There was no explicit disclosure for this specific combination in the application as filed, which

was not a reservoir from which to select features.

Inventive step

The closest prior art was document (19), which disclosed using 2-FL in infant formulas for treating or reducing the risk of infection by e.g. opportunistic pathogens such as *Candida* (claims 33 and 34; page 53, lines 21 to 25). Mechanistic explanations were given, such as inhibition by pathogen binding to a decoy binding site (page 1, lines 25 to 31) and the capability of prebiotics to act as a substrate for probiotics, which can metabolise and grow on them (page 3, lines 20 to 22). The difference between claim 1 and the disclosure of document (19) was the presence of *Bifidobacterium infantis*. No effect could be attributed to this difference. The patent did not contain any data. Document (1) did not show any benefit over the closest prior art since it contained no comparison with 2-FL alone. Document (25) should be disregarded. It related to an *in vitro* experiment with *Salmonella typhimurium*, which was not an opportunistic pathogen in accordance with paragraph [0014] of the patent in suit. *Salmonella typhimurium* was generally known to cause what is colloquially termed "food poisoning", an intestinal disease causing enteric issues. Figure 1 of document (25) merely provided single data points for *Salmonella typhimurium* and could not provide quantitative information for other pathogens/micro-organisms. However, quantitative data were indispensable in the context of synergy. Even if the data were taken into account, they did not show synergy as this cannot be shown by a set of single data points disregarding any effects of dose-response curves. The data in Figure 1 had no statistical significance either. Furthermore, it had to be taken into account

that the y-axis was presented as a logarithmic scale. The value was 1.10e6 for glucose, 2.10e5 for the combination of glucose with *Bifidobacterium infantis*, 4.10e5 for 2-FL and 1.10e5 for the combination of 2-FL with *Bifidobacterium infantis*. When basing the additive effect on the multiplication of the inhibition by a factor of 5 and 2.5, respectively, the determined inhibition by a factor of 10 obtained by the combination of 2-FL with *Bifidobacterium infantis* was even lower than the calculated additive effect. Therefore, no synergy had been shown. The technical problem was providing an alternative composition. It was obvious to add *Bifidobacterium infantis* to an infant formula; see document (2) or any of the other documents listed in the decision under appeal.

IX. The parties' final requests were as follows.

The appellant requested that the decision be set aside and the patent be maintained on the basis of the main request originally filed as auxiliary request 1 with the statement of grounds.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Admission of document (40)*

The set of claims forming the request on which this decision is based had first been submitted during oral proceedings before the opposition division. This set of claims focuses the discussion on *Bifidobacterium infantis*, but previously a list of several

Bifidobacteria had been claimed. Furthermore, 2-FL replaces a list of human milk oligosaccharides.

Document (40) was submitted together with the reply to the grounds of appeal, i.e. at the first opportunity. Consequently, the board saw no reason to exercise its discretion under Article 12(4) to hold document (40) inadmissible pursuant to Article 12(4) RPBA 2007 (applicable pursuant to Article 25(1) and (2) RPBA 2020). Document (40) forms part of the appeal proceedings.

3. *Amendments (Article 123(2) EPC)*

The subject-matter of claim 1 is the combination of the subject-matter of claims 1, 2 and 4 as filed with the single selection of one of the probiotic bacteria defined in claim 1 as filed, *Bifidobacterium infantis*. It is thus directly and unambiguously derivable from the application as filed.

The requirements of Article 123(2) EPC are met.

4. *Inventive step (Article 56 EPC)*

4.1 The patent in suit relates to preventing opportunistic infections in immune-compromised subjects, particularly premature and neo-natal infants (paragraph [0001]). It was found that co-administration of certain probiotic *Bifidobacteria* and fucosylated oligosaccharides was particularly effective in this regard (paragraph [0009]).

4.2 The decision under appeal relies on document (19) as the closest prior art. This approach was accepted by all parties.

Document (19) relates to protection against infectious diseases by administering a pharmaceutical composition containing a molecule comprising a fucose group having certain linkages (claims 1 and 33). It specifies that the composition may comprise 2-FL (claim 34). The oligosaccharidic agents may be added to an infant formula (page 42, lines 20 to 22). The percentage of infections with *Campylobacter* was found to be inversely associated with the percentage of 2-FL in milk oligosaccharides. 2-FL is thus presented as the active agent. The background section states that fucosyloligosaccharides have prebiotic properties, i.e. they selectively stimulate the growth of beneficial bacteria in the intestine, and that protection against specific pathogens has been described in literature. Furthermore, it is stated that fucosylated oligosaccharides have structural homology to cell receptors for enteropathogens and inhibit pathogen binding by blocking binding to relevant cell receptors (page 1, lines 24 to 31). The addition of probiotics is suggested (page 42, lines 11 to 13).

4.3 It was common ground that the difference between the subject-matter of claim 1 and the disclosure of document (19) is the addition of *Bifidobacterium infantis*.

It needs to be determined whether this difference has been shown to lead to a surprising effect in the context of opportunistic infections since claim 1 under consideration specifies that the compositions have to be suitable for use in preventing these infections.

4.3.1 In support of the invoked surprising effect, the appellant referred to documents (1) and (25), both of

which use *Salmonella typhimurium* SL1344 as the pathogen. The respondents contested, however, that *Salmonella typhimurium* was an opportunistic pathogen as defined in the patent. According to the definition provided in paragraph [0014], "'opportunistic pathogen' means a pathogen which has no effect on a healthy individual but which can cause a variety of infections in an immune-compromised individual". The board also doubts that *Salmonella typhimurium* is a typical representative of opportunistic pathogens. Although infection with *Salmonella typhimurium* is generally not life-threatening for healthy individuals, it does still occur and leads to considerable symptoms even in non-immune-compromised individuals. The labelling of this pathogen as "opportunistic" by document (37) cannot change this understanding.

4.3.2 In a further line of argument, the appellant pointed to certain passages in the cited documents which state that the effect of *Bifidobacterium infantis* (or other probiotics) on pathogens, whether opportunistic or not, is due to its secretion of short-chain fatty acids such as lactic acid and the resultant lowering of the pH of the medium. Therefore, according to the appellant, the results obtained for one micro-organism can be directly transferred to other micro-organisms. The board does not agree with this argument. As pointed out by the respondents, synergy is a quantitative effect, i.e. the synergistic reduction of (in this case) the number of colony-forming units per millilitre is determined. For want of any evidence that all micro-organisms relevant to the case in hand have the same degree of sensitivity towards changes in the pH of the medium, or towards a particular short-chain fatty acid such as lactic acid (or acetic acid), the data obtained for one micro-organism cannot be directly transferred to other micro-

organisms in the context of synergy.

4.3.3 Document (1) cannot show any effects related to a combination including 2-FL since it does not contain data for 2-FL alone. The closest prior art already teaches adding 2-FL to infant formulas in the context of preventing infections. The absence of any data for 2-FL alone thus means that document (1) is unsuitable for showing a surprising effect over the closest prior art. Furthermore, a synergistic effect can only be shown if the effects of the potentially synergistic constituents as such are known. Consequently, the data in document (1) are not crucial for the present decision.

4.3.4 Document (25) compares the protection against *Salmonella typhimurium* conferred by glucose, glucose in combination with *Bifidobacterium infantis*, 2-FL and 2-FL in combination with *Bifidobacterium infantis*. The data are provided in the form of a graph as Figure 1. The y-axis provides information on the colony-forming units per millilitre on a logarithmic scale. The parties have attributed different values to the various data points. Due to the logarithmic scale, reading the values is not straightforward. In addition, the logarithmic scale means that a small error/uncertainty in the reading leads to considerable differences in values. As a consequence, the board is unable to clearly establish whether the presented results show synergy. Even when considering the appellant's interpretations, the evidence for the presence of a synergistic effect is doubtful. The situation is worsened by the error bars, which indicate a large standard deviation on the logarithmic scale.

4.3.5 In view of the doubts concerning the model system (using *Salmonella typhimurium*) and the – at best – shaky data showing synergy, the board cannot accept that the data in documents (1) and (25) establish the presence of synergy.

Consequently, there is no evidence for a surprising (synergistic) effect regarding opportunistic infections.

4.4 The technical problem to be solved is thus providing a further infant formula suitable for preventing opportunistic infections.

4.5 The closest prior art already mentions the possibility of adding a probiotic. *Bifidobacteria* are known as probiotic supplements in infant formulas (document (2), page 66, left-hand column, second paragraph).

A person skilled in the art would thus have considered adding *Bifidobacteria* to the infant formulas of document (19) and would have added any species described in the context of feeding infants, including any of the species found in the samples in document (2) in relation to human breast milk, such as *Bifidobacterium longum*, *Bifidobacterium infantis*, *Bifidobacterium animalis*, *Bifidobacterium breve* and *Bifidobacterium adolescentis* (page 65, right-hand column, second paragraph). Consequently, the person skilled in the art would have arrived at the claimed subject-matter without exercising inventive skill.

When striving to provide (merely) a further infant formula, the person skilled in the art would not have been restricted to species known to be capable of

metabolising 2-FL.

4.6 The subject-matter of claim 1 of the only request on file does not involve an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated