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Datasheet for the decision of 8 October 2015

Case Number: T 1107/11 - 3.3.02

Application Number: 02726177.5

Publication Number: 1383514

IPC: A61K31/702, A61K39/02, A61P37/04, A61P1/00, A61K35/74, A23K1/16, A23K1/18, A23L1/30, A61K39/38, A61K45/00, A61K31/715

Language of the proceedings: EN

Title of invention:
USE OF A COMPOSITION COMPRISING A PREBIOTIC FOR DECREASING INFLAMMATORY PROCESS AND ABNORMAL ACTIVATION OF NON-SPECIFIC IMMUNE PARAMETERS

Patent Proprietor:
SOCIETE DES PRODUITS NESTLE S.A.

Opponents:
Tiense Suikerraffinaderij n.v.
N.V. Nutricia

Headword:
Use of a prebiotic for decreasing inflammatory process in elderly humans/SOCIETE DES PRODUITS NESTLE

Relevant legal provisions:
EPC Art. 54, 56, 83, 100(b), 107, 113(1)
EPC R. 115(2)
RPBA Art. 12, 15

Keyword:
Admission of documents (yes)
Main request: inventive step (no)
Auxiliary request 1: allowable (yes)

Decisions cited:
G 0005/83, G 0003/14

Catchword:

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Case Number: T 1107/11 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 8 October 2015

Appellant: (Opponent 2)	N.V. Nutricia Eerste Stationsstraat 186 NL- 2700 HM Zoetermeer (NL)
Representative:	Nederlandsch Octrooibureau P.O. Box 29720 2502 LS The Hague (NL)
Respondent: (Patent Proprietor)	SOCIETE DES PRODUITS NESTLE S.A. Case postale 353 1800 Vevey (CH)
Representative:	Kingsbury, Oliver William Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Party as of right: (Opponent 1)	Tiense Suikerraffinaderij n.v. Tervurenlaan 182 1150 Brussel (BE)
Representative:	Koster, Nico Tiense Suikerraffinaderij N.V. Patent Department Aandorenstraat 1 3300 Tienen (BE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 17 March 2011 concerning maintenance of the European Patent No. 1383514 in amended form.**

Composition of the Board:

Chairman	L. Bühler
Members:	M. C. Ortega Plaza
	T. Sommerfeld

Summary of Facts and Submissions

I. European patent No. 1 383 514, based on European patent application 02726177.5, which was filed as an international application published as WO 2002/076471, was granted with six claims. The date of publication and mention of the grant of the patent is 3 January 2007.

II. Independent claim 1 as granted reads as follows:

"1. Use of at least one prebiotic in the manufacture of a medicament or food or pet food composition for decreasing inflammatory process in an elderly human or elderly pet."

III. Oppositions were filed and revocation of the patent in its entirety was requested for grounds pursuant to Article 100(a) EPC (lack of novelty and inventive step) and Article 100(b) and (c) EPC.

IV. The patent in suit was revoked by an earlier decision of the opposition division, which was set aside with decision T 0286/09 of 9 December 2009 (same board in another composition). The board remitted the case to the department of first instance for further prosecution on the basis of the main request submitted during the oral proceedings on 9 December 2009.

The present appeal lies from an interlocutory decision of the opposition division posted on 17 March 2011 maintaining the patent in amended form on the basis of the main request filed with letter of 15 December 2010 (Articles 101(3)(a) and 106(2) EPC).

V. Claim 1 of the main request filed with the letter of 15 December 2010 reads as follows:

"1. Use of at least one prebiotic in the manufacture of a medicament for decreasing inflammatory process in an elderly human".

The main request filed with the letter of 15 December 2010 is identical to the set of claims filed on 9 December 2009.

VI. The following documents have been cited in the present decision:

D2 T. Mitsuoka, "Significance of dietary modulation of intestinal flora and intestinal environment", Bioscience Microflora, 19(1), 2000, 15-25

D15 C. De Simone et al., "Effect of *Bifidobacterium bifidum* and *Lactobacillus acidophilus* on gut mucosa and peripheral blood B lymphocytes", Immunopharmacology and Immunotoxicology, 14(1&2), 1992, 331-340

D33 G.R. Gibson, "Dietary modulation of the human gut microflora using the prebiotics oligofructose and inulin", American Society for Nutritional Sciences, 1999, 1438S-1441S

D37 M.K. Schmidl et al., "Essentials of functional food", Chapter 9 "Pre- and Probiotics", 2000, 205-216

D38 E.J. Schiffrin et al., "Immunomodulation of human blood cells following the ingestion of lactic acid bacteria", J Dairy Sci, 78, 1995, 491-497

D41 W.B. Ershler et al., "Age-associated increased interleukin-6 gene expression, late-life

diseases, and frailty", Annu. Rev. Med., 51, 2000, 245-270

D42 Y. Guigoz et al., "Effects of oligosaccharide on the faecal flora and non-specific immune system in elderly people", Nutrition Research, 22, 2002, 13-25

D43a J.E. Losa García et al., "Cyclosporin A decreases human macrophage interleukin-6 synthesis at post-transcriptional level", Mediators of Inflammation, 8, 1999, 253-259

D43b A. van den Berg et al., "Cytoskeletal architecture differentially controls post-transcriptional processing of IL-6 and IL-8 mRNA in airway epithelial-like cells", Experimental Cell Research, 312, 2006, 1496-1506

D43c G. Stoecklin et al., "Posttranscriptional mechanisms regulating the inflammatory response", Advances in Immunology, 89, 2006, 1-37

D44 L. Rector-Page, "How to be your own herbal pharmacist: herbal traditions - expert formulations", entry on burdock

D44a Information concerning the publication date of document D44

D45 WO96/31219

D46 J. Vulevic et al., "Modulation of the fecal microflora profile and immune function by a novel *trans*-galactooligosaccharide mixture (B-GOS) in healthy elderly volunteers", Am J Clin Nutr, 88, 2008, 1438-1446

VII. Opponent 2 (appellant) lodged an appeal against the interlocutory decision maintaining the patent and filed grounds therefor. With its statement of grounds of appeal the appellant requested that the decision under appeal be set aside and the patent be revoked in its

entirety. It also filed additional documents, *inter alia* documents D38 and D40.

VIII. Opponent 1 (party as of right) neither filed an appeal, nor any requests or submissions during the appeal proceedings.

IX. With letter of 15 December 2011 (wrongly dated 15 December 2010) the patentee (respondent) filed a substantive reply to the grounds of appeal. It also filed a main request, which is identical to the main request before the opposition division, and five auxiliary requests. It also filed document D41.

The respondent requested that the appeal be dismissed or, alternatively, that the patent be maintained on the basis of one of the auxiliary requests 1 to 5.

X. With its letter of 26 July 2012 the appellant objected to the subject-matter of the auxiliary requests for grounds pursuant to Articles 100(b) and 100(a) EPC (lack of novelty and inventive step). It also raised objections under Article 84 EPC. Additionally, it filed documents D42, D43a, D43b, D43c, D44 and D45.

XI. The board sent a communication pursuant to Article 15(1) RPBA as an annex to the summons to oral proceedings to be held on 8 October 2015.

XII. With its letter dated 7 September 2015 the respondent filed a response to the board's communication, wherein it submitted additional arguments. It also filed document D46. Furthermore, it objected to the admission of some of the documents on file, *inter alia* D37, D43a, D43b, D43c, D44 and D45.

XIII. With letter of 14 September 2015 the appellant submitted counter-arguments in favour of the admission of the contested documents. It also filed a further document, D44a.

XIV. Oral proceedings took place on 8 October 2015 in the absence of opponent 1, who had been duly summoned.

XV. In the course of the oral proceedings the respondent withdrew its main request, filed with letter of 15 December 2011 (which was the same main request as before the opposition division), and maintained its auxiliary requests 1 and 2, both filed with letter of 15 December 2011. Auxiliary request 1 became its new main request and auxiliary request 2 became its auxiliary request 1.
Furthermore, it withdrew auxiliary requests 3 to 5 filed also with the letter of 15 December 2011.

XVI. Claim 1 of the main request reads as follows:

"1. Use of at least one prebiotic in the manufacture of a medicament for decreasing inflammatory process in an elderly human, **wherein the medicament decreases abnormal activation of non-specific immune parameters in the elderly human.**" (emphasis added)

Claim 1 of auxiliary request 1 reads as follows:

"1. Use of at least one prebiotic in the manufacture of a medicament for decreasing inflammatory process in an elderly human, **wherein the medicament decreases expression of interleukin-6 mRNA in peripheral blood monocytes.**" (emphasis added)

XVII. The appellant's arguments, as far as relevant for the present decision, may be summarised as follows.

Admission of documents D37, D43a, D43b, D43c, D44/D44a, D45

Document D37 had been filed in the opposition procedure in response to the patentee's arguments. Moreover, the document was *prima facie* relevant since it gave an overview about prebiotics and probiotics, reflecting the knowledge of the prior art in the field. It was not redundant to document D33 since it disclosed different aspects. It had been cited in the statement of grounds of appeal and was referred to in the board's communication pursuant to Article 15(1) RPBA. Documents D43a, D43b and D43c were filed in direct response to a new argument of the respondent at appeal proceedings based on document D41. These documents could consequently not have been filed earlier and should therefore not be considered late-filed. Documents D44/(D44a) and D45 were *prima facie* highly relevant for the assessment of novelty of claim 1 of the main request pending at the moment of their filing, and should, thus, be admitted into the proceedings.

Main request - Inventive step

The appellant argued that the feature in claim 1 about "decreasing inflammatory process" was not a therapeutic application within the meaning of Enlarged Board of Appeal decision G 5/83, (OJ EPO 1985, 64), since it did not relate to the treatment of a disease. The skilled reader would then understand it as equivalent to "modulating the immune system". In this context, the appellant referred to document D2, which described that the immune system was extremely complex and

consequently the claim's language, being considered equivalent to modulating the immune system, did not restrict the intended use to a specific pathological situation, or to the treatment of systemic inflammation. Furthermore, the expression "wherein the medicament decreases abnormal activation of non-specific immune parameter" was a mere explanation of the previously mentioned expression, and did not restrict the intended use.

The appellant considered document D15 to represent the closest prior art, since it disclosed that "the regular administration of BB and LA [probiotics Bifidobacteria and Lactobacilli] leads to a modulation of the immunological and inflammatory response in elderly subjects" (abstract) and thus, it dealt with the same technical problem as the patent. The only difference between the disclosure of document D15 and the subject-matter of claim 1 lay in the use of prebiotics. The objective technical problem was the provision of an alternative to the administration of probiotics.
The person skilled in the art knew *inter alia* from documents D33 (abstract and page 1440S, Table 2 and first paragraph on right-hand column) and D2 (abstract and page 21, right-hand column, last paragraph and Figure 9) that administration of prebiotics resulted in elevated levels of beneficial bacteria, in particular of Bifidobacteria, in the gut flora and thus, the same effects would ultimately be attained. Consequently, it would have been obvious for a person skilled in the art to replace the administration of probiotics disclosed in document D15 by administration of prebiotics.

Auxiliary request 1

(a) The appellant raised objections of lack of sufficiency of disclosure (Article 83 EPC) against claim 1 of auxiliary request 1.

In particular, the appellant submitted that the expression "wherein the medicament decreases expression of interleukin-6 mRNA in peripheral blood monocytes" was a mere explanation of the expression "decreasing inflammatory process", and, thus, did not restrict the intended use. Consequently, the wording in claim 1 did not refer to a specific subgroup of patients, and did not restrict the use to a subgroup of patients having an elevated level of interleukin-6 (IL-6). Furthermore, the patent did not provide any teaching as to how the skilled person should define such an alleged subgroup of patients.

The appellant further argued that the examples of the patent did not serve as support for the claimed effect of decreasing inflammatory process in an elderly human, wherein the medicament decreases expression of interleukin-6 mRNA in peripheral blood monocytes for the following reasons. The subjects treated in example 1 were well nourished as evidenced by the "Mini Nutritional Assessment" (MNA) score (page 8, table 1) being in the normal region and they did not suffer from a disease, let alone inflammatory process, except for two men and two women (see [0060]). The example showed an improvement in the intestinal flora upon administration of prebiotics, in particular an increase of Bifidobacteria (page 9, Table 2a), but this effect was known from the prior art. The data provided by the patent concerning the alleged decreased expression of IL-6 mRNA was not credible (Figure 3b) as time point 1, representing the pretest period, was missing. Thus a dramatic increase or decrease during the pretest period

was possible. Moreover, the disclosure of documents D43a, D43b and D43c supported the view that a decrease of IL-6 mRNA was not directly linked to a decrease in the protein IL-6. Hence, the patent did not plausibly show that ingestion of prebiotics led to decreased expression of IL-6 mRNA resulting in a decrease in the inflammatory process.

At the oral proceedings the appellant stated that it no longer objected to the terms "prebiotic", "medicament" and "elderly", but, without any definition in the description, these terms should be given their broadest technically meaningful sense.

(b) The appellant contested the novelty of claim 1 of auxiliary request 1 in view of document D45. It argued that document D45 disclosed that the enteral administration of indigestible saccharides, preferably fructooligosaccharides (FOS) or xylooligosaccharides (XOS) inhibited infection by *Clostridium difficile* (*C. difficile*), decreased toxin A levels (page 22, Table 6; page 5, summary of the invention; page 17, last paragraph) and concurrently inhibited inflammation associated with *C. difficile* infection (paragraph bridging pages 2 and 3). As it was known that *C. difficile* infections were most frequent in elderly and debilitated patients (D45, page 3, last full paragraph) all technical features of claim 1 were disclosed in document D45. As already argued in connection with its objection of lack of sufficiency of disclosure, the appellant considered that the term "wherein the medicament decreases expression of interleukin-6 mRNA in peripheral blood monocytes" was a mere explanation of a mechanism of action, which did not limit the scope of the claim, since it inevitably occurred on administration of prebiotics.

(c) As regards the inventive step issue, the appellant referred essentially to the same arguments as presented for the main request, as it considered that the additional feature "wherein the medicament decreases expression of interleukin-6 mRNA in peripheral blood monocytes" was not a limitation of the use claimed.

XVIII. The respondent's arguments, as far as relevant for the present decision, may be summarised as follows.

The respondent argued that document D37 was no more relevant than document D33, already on file. Document D37 had not been relied upon in the opposition procedure and was only briefly mentioned in the statement of grounds of appeal. Moreover, document D37 should be deemed not admitted by the opposition division.

Documents D43a, D43b and D43c were late filed, given the fact that a set of claims containing the feature of "decreasing interleukin-6 mRNA level" had already been filed in opposition proceedings. Hence, these documents should have been filed earlier. Moreover, the relevance of the documents was only marginally discussed. Furthermore, documents D43b and D43c were post-published documents and not suitable for determining the background knowledge at the relevant filing date of the patent in suit.

Document D44 provided only anecdotal suggestions, but no credible disclosure and was thus *prima facie* not novelty-destroying for the subject-matter claimed.

Document D45 was not highly relevant for the assessment of novelty as the document did not disclose a clear

functional link between prebiotics and inflammatory process.

Main request - Inventive step

The respondent submitted that the subject-matter claimed was restricted to the treatment of systemic inflammatory process in elderly subjects by virtue of the feature "wherein the medicament decreases abnormal activation of non-specific immune parameter". In contrast thereto, document D15 disclosed solely that the administration of probiotics resulted in a local anti-inflammatory effect in the intestine of elderly subjects. Document D15 did not disclose that the administration of probiotics resulted in a decrease in non-specific immune parameters and consequently also did not disclose a systemic anti-inflammatory effect in the sense of a decreased inflammatory process.
The respondent acknowledged that it was known in the prior art that the count of Bifidobacteria (probiotic) was diminished in the gut flora of elderly subjects (see paragraphs [0006] and [0007] of the patent) and that the administration of prebiotics raised the count of Bifidobacteria in the gut flora of elderly humans (documents D2 and D33). Furthermore, the respondent also acknowledged that it was known that Bifidobacteria (probiotic) stimulated the immune function (documents D2, abstract, and D38, abstract). However, as there was no disclosure in the prior art that the administration of probiotics, or prebiotics, reduced the inflammatory process in the elderly due to a decrease in non-specific immune parameters, the combination of document D15 with any of the other cited prior-art documents would not render the claimed invention obvious.

Auxiliary request 1

(a) The respondent argued that the expression "wherein the medicament decreases expression of interleukin-6 mRNA in peripheral blood monocytes" was a technical feature of the use claimed in claim 1 further specifying the medical indication concerning a decrease in inflammatory process. Moreover, it was known in the art that, in elderly humans, there was a functional link between elevated levels of interleukin-6 (IL-6) and inflammatory process (document D41, abstract). Hence, the person skilled in the art was in a position to identify the particular group of patients, namely those having elevated levels of IL-6, based on the teaching of the patent and his common general knowledge.

The respondent submitted that the data in the patent made it at least plausible that following ingestion of prebiotics the technical effect of decreasing expression of IL-6 mRNA in peripheral blood monocytes was achieved. Furthermore, it was not necessary to provide clinical trials, let alone trials of human patients suffering from the therapeutic indication to be treated, in order to make a claimed effect plausible. For that purpose even *in vitro* tests were sufficient. The level of IL-6 mRNA was linked to the level of the protein IL-6, and documents D43a, D43b and D43c did not cast any significant doubt upon that. Moreover, it was common in the art to measure the mRNA level for a protein instead of the protein level itself. Additionally, the pretest point, allegedly missing in Figure 3b, was of no relevance. The same data were published in the post-published scientific paper D42, after due assessment by the publisher.

(b) As regards novelty, the respondent adhered to its argument that the expression "wherein the medicament

decreases expression of interleukin-6 mRNA in peripheral blood monocytes" was a functional limitation of the subject-matter claimed in that it defined the status of the elderly subjects as having elevated IL-6 levels. Moreover, the respondent submitted that it was incorrect to argue that this feature merely concerned an inevitable effect upon ingestion of prebiotics. Document D45 did not disclose this functional feature either explicitly or implicitly and for that reason its disclosure was not novelty-destroying.

(c) With respect to the issue of inventive step, the respondent essentially retained the reasoning it had presented for the main request, starting from document D15 as the closest prior art. It also argued that the prior art did not render obvious the technical effect of reducing expression of interleukin-6 mRNA in peripheral blood monocytes to decrease inflammation. There was no indication in the prior art connecting prebiotics and the technical effects mentioned in claim 1. The skilled person did not find any indication in the prior art (including document D41) for using prebiotics to achieve the technical effect in the claim.

XIX. The appellant (opponent 2) requested that the decision under appeal be set aside and that the patent No. 1 383 514 be revoked.

The respondent (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request or, alternatively, on the basis of auxiliary request 1, filed as auxiliary requests 1 and 2, respectively, with the reply to the statement of grounds of appeal on 15 December 2011.

Reasons for the Decision

1. The appeal is admissible.

2. The oral proceedings before the board took place in the absence of opponent 1, party as of right to the present proceedings (Article 107 EPC), who was duly summoned but decided not to attend.

According to Rule 115(2) EPC if a party duly summoned to oral proceedings does not appear as summoned, the proceedings may continue without that party. As stipulated by Article 15(3) RPBA, the board shall not be obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying on its written case.

In the present case the party as of right (opponent 1) has not filed any submissions or requests in writing during appeal proceedings. Although it had had ample opportunity to present its comments in writing to the facts and evidence on file (e.g. after the filing of respondent's written submissions and/or after the board's communication sent as annex to the summons), it decided not to do so. The provisions of Article 113(1) EPC which govern the right to be heard have been fulfilled in respect of opponent 1, since it was the party's own choice to remain silent during the whole appeal proceedings.

3. *Admission of documents D37, D43a, D43b, D43c, D44, D44a and D45*

3.1 Document D37 has been filed by opponent 2 with its letter dated 15 December 2010, i.e. at the final date for making written submissions set under Rule 116 EPC in the summons to oral proceedings before the opposition division, after the case had been remitted to the department of first instance for further prosecution following decision T 286/09 of the present board, in another composition.

The opposition division did not conclude on the admission of document D37 in its decision underlying the present appeal. Moreover, the document was cited in the statement of grounds of appeal. Correspondingly, the decision about its admission into the proceedings appertains to the exercise of discretion of the present board under Article 12(4) RPBA.

Document D37 was cited in the statement of grounds of appeal (page 4, under the heading "Inventive step") in addition to document D33 (a document already on file), in order to support the view that it was well known in the art that the use of prebiotics in elderly humans was recommended owing to the chain prebiotics-probiotics-regulation of immune function. Document D37 is a general book dedicated to the "Essentials of functional foods" which shows a complementary and general knowledge to the more specific teaching in document D33 about "Dietary modulation of the human gut microflora using the prebiotics oligofructose and inulin". Although the statement of grounds of appeal does not specifically list the relevant pages and paragraphs in document D37, the pages submitted concern chapter 9 only, which is entitled "Pre- and Probiotics"; the relevant passages are underlined.

Therefore, it is immediately evident why document D37 was cited as reinforcement of the appellant's line of argumentation regarding lack of inventive step in consideration of the general knowledge of the skilled person in the field.

Consequently, document D37 was admitted into the proceedings.

Documents D43a, D43b and D43c are late-filed documents since they were filed with the appellant's letter dated 26 July 2012. However, these documents were cited as support for the appellant's arguments concerning the differences between IL-6 mRNA level and IL-6 protein. Moreover, these documents were filed after the respondent had filed document D41 with its letter of 15 December 2011 in order to support its arguments in favour of auxiliary request 1 (filed as auxiliary request 2 with said letter). The *prima facie* relevance of documents D43a, D43b and D43c (without requiring an in-depth analysis of their contents) is given in the light of their respective abstracts. Therefore, these documents were admitted into the proceedings.

The fact that auxiliary request 1 (filed as auxiliary request 2 with the reply to the statement of grounds of appeal dated 15 December 2011) had been filed as auxiliary request 2 during opposition proceedings with a letter dated 15 December 2010 is not relevant for contesting the admission of documents D43a, D43b and D43c since the department of first instance based its decision of maintenance in amended form on the basis of the main request, and the discussions during the oral proceedings held on 15 February 2011 before the opposition division dealt with the main request only.

Document D45 is a late-filed document since it was filed with the letter dated 26 July 2012. In order to assess the *prima facie* relevance of this document the board is satisfied that it is not required to analyse in a detailed and conclusive manner its content. Thus, after a *prima facie* evaluation of the content as potentially novelty-destroying for the earlier main request (now withdrawn) the board concluded to admit it into the proceedings. The board's conclusion in relation to admission of document D45 does not include an in-depth analysis of its full content and a final conclusion regarding the novelty issue.

Document D44 is a late-filed document since it was filed with the letter dated 26 July 2012. D44 consists of one single page which is a screen print-out from the Internet under "Google books". Following the respondent's objection concerning the lack of information about the publication date of the book mentioned, the appellant filed with its letter of 14 September 2015 document D44a (a screen print-out from the Internet through amazon.com).

The *prima facie* relevance of document D44 is not given since the general passage concerning burdock (a particular root) shows no technical teaching for supporting the existence of a functional link between inulin and anti-inflammatory effects on the elderly (which are not even mentioned). Therefore, document D44 together with document D44a were not admitted into the proceedings.

4. Main request; inventive step

4.1 Claim 1 of the main request (which was filed as auxiliary request 1 with the letter of 15 December

2011) concerns a second medical use claim in Swiss-type form. It derives from incorporation of dependent claim 2 as granted into granted claim 1, for which only the medical use option for elderly humans is retained.

In this Swiss-type claim the active substance for which the use is claimed is "(at least) one prebiotic" and the medical indication is defined by means of the purpose of "decreasing inflammatory process in an elderly human". The claim has to be read as implicitly addressing therapy (or prevention) of those conditions which require a decrease or modulation of inflammatory process in elderly humans. Thus, the claim encompasses the therapy of chronic inflammation in elderly humans, but it is not specifically restricted thereto.

The claim further states that the medicament decreases abnormal activation of non-specific immune parameters in the elderly.

In the light of the description in the patent in suit, one of the non-specific immune parameters is phagocytic activity (see paragraphs [0009], [0011], [0012], [0054] and [0064]).

The patent establishes in paragraph [0069] that "We observed an important decrease in phagocytic activity. This decrease in phagocytic activity could be a reflection of decreased activation of macrophages linked to a possible reduction in pathogenic bacteria, and thus suggesting a diminution in inflammation due to lower endotoxin load". Correspondingly, a direct functional link between decrease of non-specific immune parameters, one of them being the phagocytic activity, and decreasing inflammation process is not necessarily given. The decrease in phagocytic activity may result

from a reduction in pathogenic bacteria owing to a better balance in the intestinal flora, for instance by increasing the levels of beneficial micro-organisms such as Bifidobacteria at the expense of some of the potentially harmful bacteria (see end of paragraph [0068] of the patent). This is in line with the knowledge in the art that "probiotics and prebiotics act on the intestinal flora and improve the balance of the flora by enhancing the growth of beneficial intestinal bacteria and/or inhibiting the growth of harmful ones, resulting in scavenging in the intestinal environment" (document D2, page 21, right-hand column, last paragraph). Thus, the last feature stated in claim 1 of the main request cannot be acknowledged as a valid functional limitation of the medical indication claimed to be taken into account for the assessment of inventive step. Moreover, although the expression of IL-6 mRNA in peripheral blood monocytes is an option among the non-specific immune parameters to be decreased (paragraph [0012] of the patent), claim 1 of the main request does not specify which are the parameters meant to be decreased and thus, it is not restricted to the particular technical effect related to interleukin-6 (IL-6).

4.2 Document D15 which discloses the modulation of the inflammatory response in elderly humans represents the closest prior art. In particular, document D15 discloses that the treatment of elderly individuals with probiotics (Bifidobacterium bifidum (BB) and Lactobacillus acidophilus (LA)) results in a modulation of the immunological and inflammatory response in elderly subjects (abstract).

Document D15 discloses that "The scope of our research was to verify if the regular administration of BB and

LA could be tolerated and lead to a modulation of the local and systemic immunocompetence in elderly subjects and to a modification of gut histology" (page 332, third paragraph).

Document D15 teaches that "The importance of a well functioning gastrointestinal mucosal immune system resides in the fact that it mediates immune responsiveness at mucosal sites and also in the rest of the body, via the control of the quality and quantity of antigenic substances gaining access to the immune system as a whole" (sentence bridging pages 338 and 339). Document D15 further teaches that when "intestinal bacteria are present in the small bowel in abnormal number, the mucosal inflammation becomes more pronounced" (end of the first paragraph on page 339) and explains that "In the stools of elderly people bifidobacteria are reduced significantly, whereas streptococci, coliforms and clostridia are increased" (page 339, second paragraph). Moreover, document D15 discloses that "Our results show that lyophilized BB and LA, administered in capsules (Infloran^{R}), reduce the chronic inflammatory reaction in the sigmoid colon. With respect to the placebo-treated group, the absolute number of immunocompetent cells in the colonic mucosa appeared to be reduced ($p<0.02$), without major modifications in the relative number of T, B, and NK cells. These findings suggest a 'barrier' effect of BB and LA against intestinal pathogens or their products, putatively responsible for local inflammatory response" (page 339, third paragraph).

Document D15 states that "In conclusion, our results suggest that BB and LA are well tolerated with little to no side effects, reduce the inflammatory response of

the colon and stimulate the host's humoral immunity" (page 340).

In the light of the closest prior art the problem to be solved lies in the provision of an alternative treatment for decreasing the inflammatory process in an elderly human.

The proposed solution relates to the use of at least one prebiotic.

The problem has been plausibly solved in the light of the content of the description of the patent, since it has been shown that prebiotics increase the levels of beneficial micro-organisms such as Bifidobacteria. The frail elderly subjects showed low counts of Bifidobacteria at the beginning of the study (paragraph [0067]), which means that they had an unbalanced intestinal flora before the treatment with prebiotics. Therefore, it is plausible that the beneficial growth of Bifidobacteria also accounts for a decrease in the local inflammatory process. In fact, document D15 teaches that Bifidobacteria are able to reduce colonic inflammation in the elderly.

Moreover, it has not been disputed by the respondent that it was well known at the effective date of filing of the patent that administration of prebiotics stimulates the growth of Bifidobacterium (paragraph [0004] of the patent).

Therefore, the solution to use at least one prebiotic is obvious in the light of the prior art.

The respondent's submission that the claim concerns the decrease of the systemic inflammatory process in an

elderly human achieved by decreasing the pro-inflammatory interleukin IL-6 owing to a decrease in the expression of interleukin-6 mRNA in peripheral blood monocytes cannot be retained for the main request, since claim 1 does not specify these technical effects. Thus, the claim has to be assessed in its broadest technically meaningful sense.

As regards the argument that document D38 recites an increase in the phagocytic activity which would have deterred the skilled person from the proposed solution, the following has to be said. The patent in suit does not unambiguously disclose that there is a direct functional link between decreased phagocytic activity and the prebiotic. Moreover, the patent cites document D38 as background art (see paragraph [0006]). Document D38 is in fact dedicated to a study about immunomodulation of human blood cells. It teaches that Lactobacillus acidophilus and Bifidobacterium bifidum "can be used as nutritional supplements to improve the immune function of particular age groups, i.e. the neonate or the elderly, for which these functions are diminished" (abstract). The studies in document D38 are performed on healthy human volunteers "from 23 to 62 yr [years] of age (mean 36.9)" (page 492, left-hand column under heading "Volunteers and Experimental Design"). Document D38 reports that phagocytic activity in peripheral blood was enhanced following the ingestion of fermented milk products (supplemented with LA or BB) (page 495, left-hand column under the heading "Discussion"), but it also states that "The increment in phagocytosis was coincident with fecal colonization by the lactic acid bacteria and persisted for 6 wk [six weeks] after ingestion of the fermented [milk] products" (abstract). In contrast to the study in document D38, during the whole study performed in the

patent in suit "intake of fermented diary products were restricted" (paragraph [0044]). Thus, it cannot be said that the findings in document D38 and those in the patent are contradictory, since the experimental circumstances are different.

The board is satisfied that the teaching in document D38 would not have deterred the skilled person from using a prebiotic in its aim to decrease inflammatory process in an elderly human, which does not exclude the beneficial local effect on colonic inflammation (resulting from an unbalanced intestinal flora in the elderly).

4.3 Consequently, the subject-matter claimed in claim 1 of the main request does not meet the requirements of Article 56 EPC.

4.4 Since the main request fails for lack of inventive step of the subject-matter claimed it is not necessary to conclude in relation to the other grounds for opposition submitted against the main request.

5. Auxiliary request 1

5.1 The amendment introduced in claim 1 of auxiliary request 1 relates to the definition "wherein the medicament decreases expression of interleukin-6 mRNA in peripheral blood monocytes". This amendment finds its basis on the description in the application as filed, page 3, lines 32 to 33, page 21, lines 22 to 24. Therefore, the requirements of Article 123(2) EPC have been met. Additionally, the subject-matter of claim 1 of auxiliary request 1 is more restricted than the subject-matter of claim 1 as granted. Therefore, the requirements of Article 123(3) EPC are also met.

5.2 Claim 1 of auxiliary request 1 concerns a second medical use claim in the Swiss-type form, which relates to the use of at least one prebiotic for decreasing inflammatory process in an elderly human. However, in contrast with claim 1 of the main request, the definition that the "medicament decreases expression of interleukin-6 mRNA in peripheral blood monocytes" is a valid functional feature which delimits the therapeutic indication claimed. The reasons are as follows.

Interleukin-6 was known at the effective filing date of the patent as a pro-inflammatory cytokine which is a potent mediator of inflammatory processes. Furthermore, it was also known that there is an age-associated rise in IL-6 even in the absence of infection, trauma or stress. Document D41, entitled "Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty" confirms this knowledge (see, *inter alia*, the abstract). Moreover, it is technically plausible that decreased expression of interleukin-6 mRNA in peripheral blood monocytes leads to a decrease in the production of the protein IL-6. Thus, the technical effect (decreased expression of IL-6 mRNA in peripheral blood monocytes) defined in claim 1 of auxiliary request 1 for the medicament (characterised by comprising at least one prebiotic) is functionally linked to the group of patients to be treated (elderly humans) and the inflammatory process associated to ageing.

5.3 The terms employed in the functional feature which is expressed in the claim by means of a technical effect achieved by the medicament are understood by the skilled person, and the description of the application from which the patent in suit derives (as well as the

specification in the patent) shows that the expression of IL-6 mRNA peripheral blood mononuclear cells before, during and after administration of prebiotics can be measured (page 22, second paragraph of the application, paragraph [0069] of the patent, and Figure 3). These experiments make it also credible that decreased expression of IL-6 mRNA in peripheral blood monocytes is measurable (page 21 of the application, second paragraph from the bottom, paragraph [0067] of the patent). Although they are not identical, the expressions "peripheral blood monocytes" and "peripheral mononuclear cells" were indistinguishably used in the application (and in the patent in suit). That the technical effect disclosed in paragraphs [0012] and [0067] of the patent truly concerns the "peripheral blood monocytes" becomes evident from the statement under the heading "Non-specific Immunity" (page 19 of the application and paragraph [0063] of the patent) that activated T lymphocytes and natural killer (NK) cells (which are also mononuclear cells) were not affected by the ingestion of fructooligosaccharides (FOS).

The appellant objected that Figure 3 did not show the data before the wash out period. However, Figure 3 shows the data before (start point of intake of prebiotic FOS), during (three weeks intake of prebiotic) and after administration of the prebiotic FOS. The wash out period (paragraph [0044]) was designed in order to restrict the intake of fermented dairy products and FOS containing food (onion, leek, chicory roots) so that they did not interfere with the experimental results, which are attributable to the administration of eight grams FOS *per* day (paragraph [0048]). Additionally, in the absence of any experimental data disproving the findings in the patent

on interleukin-6 mRNA expression, which are based on the experiments mentioned above (see also paragraph [0055] of the patent), it cannot be concluded that the skilled person would have had serious doubts against the sufficiency of disclosure of the invention claimed.

The experiments disclosed in the patent were designed to serve as a model for the medical indication claimed. The post-published document D42 is a scientific publication co-authored by the inventors of the present patent. D42 reflects the experiments in the patent and arrives at the same conclusions, thus confirming that the experimental design in the patent relates to an appropriate scientific model deserving acknowledgement in a scientific publication. That the experimental studies in the patent in suit are not exclusively performed on frail patients with poor score in the Mini Nutritional Assessment (MNA) does not cause lack of sufficiency of disclosure of the invention. Apart from the fact that clinical trials on actual patients are not a prerequisite for granting patents in the medical field, experiments including healthy volunteers, as is the case in the patent in suit, are common for the design of scientific models in the medical field when testing active substances. The subjects and study design in the post-published document D46 confirm this point (page 1439, left-hand column).

Additionally, contrary to the appellant's submissions, the content of document D43a does not raise serious doubts about sufficiency of disclosure for the claimed invention either. The fact that cyclosporine A (CsA) (a cyclic peptide) diminishes IL-6 production at post-transcriptional level does not allow to conclude that diminution of IL-6 levels cannot be achieved by other

means, such as, in the case of prebiotics, by decreasing IL-6 mRNA in peripheral blood monocytes.

As regards the post-published documents D43b and D43c, also cited by the appellant, they do not contradict the conclusions in the patent in suit. Apart from the fact that documents D43b and D43c do not concern the use of prebiotics in elderly humans, document D43b reflects that under certain circumstances IL-6 production may be reduced despite IL-6 mRNA stabilisation (abstract). Some substances may reduce IL-6 production by controlling post-transcriptional processing of IL-6 mRNA, or by causing cytoskeletal distortion of airway epithelial cells (see abstract of D43b), but this knowledge does not affect the plausibility of the assumption that a **decrease** of IL-6 mRNA in peripheral blood monocytes will decrease IL-6 levels. Document D43c states that post-transcriptional mechanisms play an important role in inflammatory response, since they function to dampen the expression of pro-inflammatory proteins to ensure that potentially injurious proteins are not over-expressed during an inflammatory response (abstract). However, the fact that control of IL-6 levels through post-transcriptional mechanisms may be important for homeostasis does not invalidate the generally accepted notion that decreased (IL-6) mRNA levels lead to decreased (IL-6) protein levels.

The appellant also contended that the skilled person would not be in a position to determine the boundaries of the claim in an absolute manner. However, this is always the case when inventions are defined by means of functional definitions which make use of relative terms. The board is, however, convinced that it would be possible for the skilled person to determine when the technical effect delimiting the subject-matter

claimed in auxiliary request 1 applies. Document D41 shows that the skilled person is able to determine when humans have elevated levels of IL-6, since IL-6 is a pro-inflammatory cytokine "that is normally tightly regulated and expressed at low levels" (D41, abstract). Document D41 states under the heading "Interleukin-6 and 'normal' ageing" (page 253) that "a wealth of data indicate that IL-6 gene expression, as well as tissue and serum levels, increases with age". Thus, the skilled person knows how to measure IL-6 levels using tissue and serum levels.

In view of the reasons given above, the board comes to the conclusion that auxiliary request 1 meets the requirements of Article 83 EPC.

5.4 The appellant's submissions pursuant to Article 100(b) EPC against claim 1 of auxiliary request 1 were in fact intertwined with reasons which qualify as objections under Article 84 EPC against the amendment originating from the description (feature which is incorporated at the end of claim 1). Such objections are admissible in view of the principles set out in Enlarged Board of Appeal decision G 003/14 of 24 March 2015. However, the objections put forward against claim 1 of auxiliary request 1 within the framework of discussion pursuant to Article 100(b) EPC cannot succeed, since they do not raise serious doubts about the clarity or sufficiency of disclosure of the claimed subject-matter. Moreover, the board is satisfied that amended claim 1 is allowable under Article 84 EPC for analogous reasons to those given in point 5.3 above.

5.5 As regards novelty, none of the cited prior art documents which form part of the state of the art under Article 54 EPC discloses prebiotics for decreasing

inflammatory process by decreasing expression of interleukin-6 mRNA in peripheral blood monocytes. These findings also apply in respect of the prior-art document D45, which discloses reduction of C. difficile infection with prebiotics. It is acknowledged in document D45 as forming part of the background knowledge that C. difficile produces toxin A and toxin B, and that "toxin A causes fluid secretion, mucosal damage, and intestinal inflammation when injected into rodent intestine" (passage bridging pages 2 and 3 of D45). Moreover, it was also generally known at that date that C. difficile infections were frequent in the elderly (page 3 of D45). However, document D45 does not specifically disclose that prebiotics decrease inflammatory process in the elderly humans. Document D45 investigates the detection of incidence in toxin A, following inoculation of the animals with C. difficile, as a parameter for assessing the effect of prebiotics on the evolution of C. difficile infection (page 20). The detection of a lower incidence of toxin A observed in animals treated with fructooligosaccharides and xylooligosaccharides, is attributable to the beneficial effects attained by the prebiotics in the unbalanced population of C. difficile in the intestinal flora, resulting from better control over the harmful micro-organism (D45, page 6, last full paragraph, page 9, second paragraph). If it can be assumed, for the sake of argumentation, that a lower incidence of toxin A would mean decreased incidence of local inflammation, claim 1 of auxiliary request 1 does not include the option of using prebiotics for decreasing inflammation caused by (excessive population of) C. difficile (which excretes toxin A in the intestine).

The technical effect defined in claim 1 of auxiliary request 1, which concerns the decreased expression of

interleukin-6 mRNA in peripheral blood monocytes, acts as a functional limitation for the medical indication claimed in the Swiss-type form (see also reasons given in point 5.2 above). Thus, the notional novelty of claim 1 of auxiliary request 1 can be acknowledged over document D45 by virtue of the legal fiction instituted with the Enlarged Board of Appeal decision G 5/83.

The appellant's argument that claim 1 of auxiliary request 1 lacked novelty vis-à-vis document D45, since the technical effect of a decrease in inflammatory process by decreasing expression of interleukin-6 mRNA inevitably occurred on administration of prebiotics, does not hold because it is not manifest from the disclosure in document D45, even in consideration of the general knowledge of the skilled person as reflected in the analysis of background art in D45, that such a technical effect was inevitable. Such a "hidden" effect was not directly and unambiguously disclosed in document D45.

Consequently, claim 1 of the main request is novel over the cited prior art (Article 54 EPC).

5.6 As regards the inventive step issue, document D15 remains the closest prior art since it addresses the problem of (colonic) inflammation in elderly humans. Document D41, which discloses the age-associated rise in pro-inflammatory IL-6 and frailty, does not teach how to provide a solution thereto. Therefore, document D41 does not represent a promising starting point. It is noteworthy that the post-published document D46 confirms the prior art knowledge shown in document D41, that immunosenescence (characterised *inter alia* by increased production of IL-6) is part of the ageing process (page 1438, right-hand column).

Thus, the objective problem to be solved is to provide a therapy directed to decreasing inflammatory process in elderly humans with elevated levels of pro-inflammatory interleukin IL-6.

The solution as proposed in the claim relates to the use of at least one prebiotic.

The proposed solution plausibly solves the problem since the description of the patent contains data showing the technical effect of decreased expression of IL-6 mRNA in peripheral blood mononuclear cells, in particular peripheral blood monocytes (as already explained), by administration of prebiotics. Moreover, it is also technically well-founded to support the decrease in IL-6 protein expression by measuring decrease in IL-6 mRNA levels for the reasons already given in connection with sufficiency of disclosure of the claimed invention (point 5.3 above). Moreover, the experimental studies in the patent in suit and the conclusions about decreased expression of IL-6 mRNA in peripheral blood monocytes are confirmed by the scientific publication D42.

The respondent has also submitted the post-published document D46 which shows that another prebiotic (galactooligosaccharides GOS) leads to significant reduction in the production of pro-inflammatory cytokines (*inter alia* IL-6) (abstract) in elderly persons. Thus, document D46 further confirms that the findings in the patent in suit about decreased IL-6 mRNA and its related effects are credible.

Although document D46 reports about the existence of contradictory test results concerning the modulation of

the gut microflora in the elderly by means of prebiotics (last paragraph on page 1438, right-hand column; first paragraph on page 1439, left-hand column), there is no apparent contradiction mentioned in document D46 about reduced expression of IL-6 mRNA in peripheral blood mononuclear cells.

It has now to be assessed whether the proposed solution is rendered obvious in the light of the prior art.

Document D2 relates to functional foods in general, which are classified into three groups: probiotics, prebiotics and biogenics (abstract). Figure 11 in document D2 consists of a schematic drawing which generally relates to functional foods and macrophages; Figure 11 is commented as follows: "The macrophage cell group called phagocytes seems to work mainly in the mechanism of maintaining bio-homeostasis (Fig. 11)" (passage bridging pages 22 and 23). In Figure 11, among other options, connections between macrophages, production of cytokines, overproduction of cytokines, and inflammation are schematically drawn. However, the complexity of the cytokine network and its relation to macrophages becomes evident in Figure 12. Document D2 represents a general invitation for a research program, but the skilled person has no hint to select prebiotics and pick up a particular approach within Figure 11 with a reasonable expectation of success.

The teaching in document D37 that "the basis for the improvement of mucosal defenses can be found in a direct capacity to antagonize pathogens and/or in the capacity to modulate the host's defense mechanisms, such as the immune reaction" (page 210, first paragraph) is of a general nature, and concerns probiotics, such as Lactobacilli and Bifidobacteria.

Document D37 does not indicate that probiotics such as Bifidobacteria (which increase as a result of intake of prebiotics) may decrease IL-6 production.

In view of the above, the skilled person finds no hint in the cited prior art for using at least one prebiotic in the aim to decrease the age-associated rise of IL-6 involved in the inflammatory process in an elderly human.

Therefore, the proposed solution involves an inventive step.

Consequently, claim 1 of the auxiliary request 1 meets the requirements of inventive step (Article 56).

5.7 Claims 2 to 5 are dependent on claim 1 and concern preferred embodiments of the subject-matter claimed in claim 1, these claims have not been objected to separately, and the board sees no reason to raise any objections against them. Therefore, the reasons given in favour of claim 1 of auxiliary 1 apply *mutatis mutandis* to the dependent claims. As a consequence auxiliary request 1 is allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of the following claims and a description to be adapted thereto:

Claims Nos. 1 to 5 of auxiliary request 1 filed as auxiliary

request 2 with the reply to the statement of grounds of appeal on 15 December 2011.

The Registrar: The Chairman:

N. Maslin L. Bühler

Decision electronically authenticated