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D E C I S I O N
of 25 July 2001

Case Number: T 0464/97 - 3.3.4

Application Number: 86112307.3

Publication Number: 0218900

IPC: A61K 37/18

Language of the proceedings: EN

Title of invention:
Osmotic agents for peritoneal dialysis

Patentee:
RESEARCH CORPORATION TECHNOLOGIES, INC.

Opponents:
Baxter International Inc.
3i RESEARCH EXPLOITATION LIMITED

Headword:
Osmotic Agents/RESEARCH CORPORATION TECHNOLOGIES

Relevant legal provisions:
EPC Art. 83, 123(2), 54, 54(3), 56

Keyword:
"Claims as maintained by the opposition division - sufficiency of disclosure (yes)"
"Novelty (yes)"
"Inventive step (no)"
"First and second auxiliary requests - inventive step (no)"

Decisions cited:
T 0990/96

Catchword:
-

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Case Number: T 0464/97 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 25 July 2001

Appellant I: (Opponent 01)
Baxter International Inc.
One Baxter Parkway
Deerfield, I11. 60015 (US)

Representative:
Dee, Ian Mark
Eric Potter Clarkson
Park View House
58 The Ropewalk
Nottingham NG1 5DD (UK)

Appellant II: (Opponent 02)
3i
RESEARCH EXPLOITATION LIMITED
91 Waterloo Road
London SE1 8XP (GB)

Representative:
Eyles, Christopher Thomas
W.P. THOMPSON & CO.
Celcon House
289-293 High Holborn
London WC1V 7HU (GB)

Respondent: (Proprietor of the patent)
RESEARCH CORPORATION TECHNOLOGIES, INC.
6840 East Broadway Boulevard
Tucson
Arizona 85710-2815 (US)

Representative:
Dr Vogelsang-Wenke, H.
Grünecker, Kinkeldey,
Stockmair & Schwanhäusser
Anwaltssozietät
Maximilianstrasse 58
D-80538 München (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 10 March 1997 concerning maintenance of European patent No. 0 218 900 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: A. L. L. Marie
S. C. Perryman

Summary of Facts and Submissions

I. The appeals were lodged by the opponents against the interlocutory decision of the opposition division issued on 10 March 1997, by which European Patent No. 0 218 900, with the title "Osmotic agent for peritoneal dialysis", was maintained in amended form on the basis of the first auxiliary request submitted during the oral proceedings on 15 October 1996. Independent claims 1 and 10 thereof read as follows:

"1. A peritoneal dialysate which comprises as an osmotically active agent an osmotically effective amount of a mixture of peptides, the mixture consisting substantially of peptide having a molecular weight of about 300 to about 2000 daltons, and an equivalent weight between about 150 to about 1500, wherein the peritoneal dialysate is free from proteolytic enzymes."

"10. A therapeutic composition comprising a mixture of peptides produced by enzymatic hydrolysis of a high quality protein, the mixture having the following characteristics:
(a) the mixture consists substantially of peptides having a molecular weight of between 300 to 2000,
(b) the mixture contains no more than about 5 mole per cent of free amino acid,
(c) the mixture contains at least about 50% of essential amino acids,
(d) the mixture is osmotically effective when added in sufficient amount to a peritoneal dialysate solution, and
(e) the mixture consists substantially of peptides having an equivalent weight between about 150 to 1500, wherein the composition is free of proteolytic

enzymes."

Claims 1 and 10 as maintained thus differed from claims 1 and 10 as filed and/or as granted by the addition of the "...free from/of proteolytic enzymes..."-feature. Claims 2 to 9 and 11 were the same as granted.

The opposition division decided that these claims met the requirements of the EPC, in particular those of Articles 54, 56 and 83 EPC, which had been invoked by the opponents (appellants) as a ground for opposition.

II. The Board issued a communication pursuant to Article 11(2) of the rules of procedure of the boards of appeal giving the Board's preliminary, non-binding opinion.

III. Oral proceedings were held on 25 July 2001.

IV. During the oral proceedings the respondent (patentee) introduced two auxiliary requests.

Claims 1, 9 and 10 of the **first auxiliary request** read:

"1. A peritoneal dialysate which comprises as an osmotically active agent an osmotically effective amount of a mixture of peptides, the mixture consisting substantially of peptide having a molecular weight of about 300 to about 2000 daltons, and an equivalent weight between about 150 to about 1500, wherein the mixture contains less than 5 mole percent of free amino acid, wherein the peritoneal dialysate is free from proteolytic enzymes."

"9. Use of a mixture of peptides produced by enzymatic hydrolysis of a high quality protein, the mixture having the following characteristics:
(a) the mixture consists substantially of peptides having a molecular weight of between 300 to 2000,
(b) the mixture contains no more than 5 mole percent of free amino acid,
(c) the mixture contains at least 50% of essential amino acids,
(d) the mixture is osmotically effective when added in sufficient amount to a peritoneal dialysate solution, and
(e) the mixture consists substantially of peptides having an equivalent weight between about 150 to 1,500 wherein the composition is free of proteolytic enzymes, for preparing a peritoneal dialysate comprising said mixture."

"10. A process for preparing a composition comprising a mixture of peptides, the mixture having the following characteristics:
(a) the mixture consists substantially of peptides having a molecular weight of between 300 to 2000,
(b) the mixture contains no more than 5 mole percent of free amino acid,
(c) the mixture contains at least 50% of essential amino acids,
(d) the mixture is osmotically active when added in sufficient amount to a peritoneal dialysate solution, and
(e) the mixture consists substantially of peptides having an equivalent weight between about 150 to 1500, wherein the composition is free of proteolytic enzymes, which process comprises:
(a) treating a high quality protein in an aqueous

solution under hydrolysing conditions, with at least one hydrolytic enzyme, to produce a peptide-containing solution, at least some of the peptides having a low molecular weight between about 300 to about 2000,
(b) contacting the peptide containing solution with one side of a dialysis membrane capable of allowing transport of the low molecular weight peptides,
(c) simultaneously contacting the opposite side of the membrane with substantially pure water derived from a reverse osmosis unit, fed by a reservoir, said water having a sufficiently low solute concentration to allow transport of the peptides across the membrane into the water, and
(d) directing the water and transported solutes to the reservoir, and
(e) accumulating the transported peptides in the reservoir by solute retention of a reverse osmosis membrane, and, optionally
(f) repeating steps (a)-(e) by recycling the aqueous solution and the water until the concentration of the solution in the reservoir is sufficient to prevent production of pure water from the reverse osmosis unit."

Claims 2 to 7 were the same as in the set of claims maintained by the opposition division (**main request**) and claim 8 corresponding to claim 9 of said set of claims.

Claim 1 of the **second auxiliary request** read:

"1. A peritoneal dialysate which comprises as an osmotically active agent an osmotically effective amount of a mixture of peptides, wherein the peptides comprise about 1 to 15% by weight of the solution , the

mixture consisting substantially of peptide having a molecular weight of about 300 to about 2000 daltons, and an equivalent weight between about 150 to about 1500, wherein the mixture contains less than 5 mole percent of free amino acid, wherein the peritoneal dialysate is free from proteolytic enzymes."

Claims 2 to 9 were identical to claims 2 to 7, 9 and 10 of the first auxiliary request.

V. Among the documents relied on by the parties during the appeal procedure, the following ones are cited in this decision:

(1) EP-0 270 545

(1.2) Priority document of EP-0 270 545

(4) WO 82/03987

(5) US-4 339 433

(7) US-4 427 658

(9) WO 82/03773

(19) Declaration of Prof. E. Klein

(20) Handbook of Chemistry, 1972-1973, 5th edition, ed. R.C. Weast, The Chemical Rubber Co., pages F-79, F-99

(21) Textbook of Medical Physiology, 1980, 6th edition, ed. A.C. Guyton; W.B. Sanders Company, page 49.

VI. The appellants argued under Article 83 EPC that the patent in suit did not provide the skilled person with sufficient information to determine the "equivalent weight" of a mixture of peptides obtained from any protein and that, although the ionisation state of a peptide largely depended on the pH of the medium, this parameter was not mentioned in any of the claims.

The appellants objected that the expression "free from/of proteolytic enzymes" contravened the requirements of Article 123(2) EPC, because there was no basis for it in the application as filed and it was not considered as a disclaimer over document (1), since it did not meet the requirements for a disclaimer and did not help to distinguish the patent in suit from said document (1), the proteolytic enzymes of which could no longer be considered as "*enzymes*", as far as they had been inactivated by heat, the term "*enzymes*" implying the existence of a measurable activity.

After having pointed at all the imprecise terms used in the claims, such as "*comprises*", "*containing substantially*" and/or "*about*" susceptible to have an influence on the assessment of the scope of the claims, the appellants objected to the novelty of claim 1 of the main request under Article 54(3) EPC in view of document (1), which was considered as identifying the same problem (disadvantages of dialysis fluids containing glucose), suggesting the same solution (peptide hydrolysate of milk protein) and disclosing all the features of claim 1, except for the expression "*free from proteolytic enzyme*". However, document (1) disclosed on column 4, lines 16 to 20 the heat-inactivation and the removal of the enzymes present so that no proteolytic activity was transferred to the

peritoneum during dialysis. This was also supported by the disclosure of document (1.2), ie the priority document of document (1), which described on page 3, lines 18 to 23 the destruction by heat of the proteolytic enzymes. This resulting in both cases in the disappearance of the proteolytic activity as suggested by said expression. On the other hand, this expression was considered as amounting to nothing else than a description of the purity of the peptide mixture of the patent in suit, which was unable to contribute to novelty of claim 1 according to T 990/96 (OJ EPO 1998, 489). This objection was found to equally apply to claim 1 of the auxiliary requests. It was also indicated that endoproteases, such as trypsin and chymotrypsin, cannot lead to the formation of free amino acids, so that the feature referring to the content of free amino acids in the auxiliary requests was *de facto* meaningless.

Claim 10 was objected to under Article 54 EPC in view of document (7), which disclosed all the features of said claim, such as a therapeutic composition, an enzymatic hydrolysis, a molecular weight below 2000 daltons, a removal of free amino acids, an essential amino acids amount of at least 50%, an activity in osmosis and an equivalent weight between about 150 and 1500.

The appellants argued that claim 1 of the main request lacked inventive step (Article 56 EPC) in view of document (9), which was considered as the closest prior art. Document (9) was in the same technical field, ie dialysis, was confronted with the same technical problem, ie the disadvantages of sugars as osmotic agents and of the free amino acids. The solution

suggested by document (9) was to at least partly replace the sugars by amino acids or short-chain peptides, reference being made in that context to the amino acid/peptide mixtures already commonly used in the nutrition field, and to add insulin to favour the assimilation of both the glucose and the amino acids after they had crossed the peritoneal membrane. This reference to nutrition pointed to document (7), which disclosed all the features of the embodiments of the patent in suit, so that the combination of the teachings of documents (9) and (7) rendered the solution of the patent in suit obvious.

Furthermore, document (7), if not regarded by the Board as novelty-destroying for claim 10 of the main request, because it did not disclose *expressis verbis* the feature "*no more than about 5 mole percent of free amino acid*", destroyed the inventive step of said claim 10 , since it gave the skilled person a motivation to reduce the concentration of free amino acids.

Claim 11 of the main request was also considered as deprived of inventive step, since document (7) disclosed a similar process, in which reverse osmosis, a known method for concentration, could have been used.

Documents (4) and (5) were also cited in this context, since they were also concerned with a dialysis solution using amino acids or a mixture of peptides.

As far as the auxiliary requests were concerned, the appellants argued that the features introduced were not susceptible of conferring inventive step, since document (7) drew the attention to the negative effects

of free amino acids. Document (5) was again evoked, since it only used polypeptides or proteins as osmotic agents and hence taught away from the use of free amino acids. The feature corresponding to the concentration of the peptides was considered as devoid of importance for the assessment of inventive step, since the skilled person, caught between efficiency and solubility of the osmotic solution, would have without any burden rapidly determined the suitable concentration by "trial-and-error" experiments.

VII. In view of the Article 83 EPC objection, the respondent submitted that the "equivalent weight"-feature was defined in the patent in a way enabling the skilled person to determine it without any burden, as confirmed by document (19), which furthermore indicated that an equivalent weight as required in the claims of the patent in suit was ***automatically*** obtained as a consequence of the molecular weight of the peptide mixture employed.

The pH was not considered as being an important factor, since every mixture of peptides used in peritoneal dialysis had to have a pH close to neutrality, so that the pH was no longer a freely variable parameter of the process available for adjusting the ionisation state of the peptides on a case to case basis to modify the equivalent weight.

The respondent argued that the expression "*free from proteolytic enzymes*" did not contravene the requirements of Article 123(2) EPC, because it was implicitly disclosed throughout the whole application as filed, since the process described therein using reverse osmosis did not lead to the presence of

polypeptides with a molecular weight much greater than 2000 daltons, and thus excluded proteolytic enzymes. Furthermore, said expression was also to be considered as a disclaimer in view of the disclosure of document (1) in column 4, lines 16, indicating that the enzymes were ***filtered and removed***.

As far as the novelty objection against claim 1 under Article 54(3) EPC was concerned, the respondent stated that about 50% by weight of the peptides obtained in document (1) (column 3, line 65 to column 4, line 15) did not comply with the molecular weight requirement of less than about 2000 as disclosed in the patent in suit. Furthermore, if the peptide mixture was expressed in mole percent, then 83% of the peptides of document (1) at best were in the range 2-18 amino acids, which was far from the requirement of the patent in suit.

Novelty over document (1) was also considered to be introduced by the expression "*free from proteolytic enzymes*", because document (1) was prior art only for the disclosure supported by the priority document (1.2). However, said document (1.2) only described the **heat-inactivation** of the proteolytic enzyme and was silent about its **removal**. The respondent considered, in this context, that the term "*enzyme*" did not only apply to biologically active molecules.

Decision T 990/96 (supra) was not considered to apply here, since it referred to low molecular weight organic molecules and proteolytic enzymes were not to be considered as "impurities" of the peptide mixture.

In view of the novelty objection against claim 10 of the main request, the respondent argued that document

(7) in column 4, lines 41 to 53 and column 5, lines 1 to 15 referred to products of high concentration in free amino acids, which were not comparable with the "*less than 5 mole percent*"-feature of the claim. The respondent also drew attention to column 15, lines 46 to 55 which demonstrated that the peptides only represented one group of the products resulting from the enzymatic hydrolysis, so that the product of document (7) was fully different from that of the patent in suit and would probably be harmful to the patients, if used in dialysis, due to the presence of high molecular weight polypeptides susceptible of inducing immunological reactions.

Regarding the requirements of the Article 56 EPC objection, the respondent considered document (9) as the closest prior art and the technical problem to be solved was defined as the improvement of the properties of the dialysis fluid (stability of the osmotic gradient, immunologic safety, absence of negative interaction with the metabolism of the patient). Said problem was solved in a non-obvious manner by the peritoneal dialysate of the patent in suit. Indeed, the respondent argued that document (9) always contained insulin, always made reference to free amino acids (a single reference to short-chain peptides being found in the whole document) and was silent on the advantages of using a mixture of peptides and minimizing the concentration of free amino acids. The fact that document (9) contained insulin demonstrated that its concern was fully different from that of the patent in suit: the crossing of the peritoneal membrane by the solutes contained in the dialysis fluid was accepted and insulin was used to avoid metabolic disturbances in the patient, whereas the patent in suit aimed at

avoiding that the solutes of the dialysis fluid crossed the peritoneal membrane. No remedy was to be found in document (7) which was concerned with nutrition, ie with the enteric assimilation of a peptidic hydrolysate and hence was not to be combined with document (9). Furthermore, the peptidic hydrolysate of document (7) contained high molecular weight components (column 15, lines 46 to 55), which could have lead to immunological reactions. No remedy could be found in document (4), which did not aim at reducing the content of the free amino acids.

The respondent also argued that document (5) had never been cited in the appeal procedure up to the oral proceedings and that it was based on a totally different concept: the use of polyionic substances binding sodium ions, such as proteins or polypeptides containing at least 10 mole percent of aspartic acid or glutamic acid residues, which cannot diffuse through the peritoneal membrane.

VIII. The appellants requested that the decision under appeal be set aside and the patent revoked.

IX. The respondent requested as main request that the appeals be dismissed or as auxiliary requests that the decision under appeal be set aside and that the patent be maintained on the basis of the claims of the 1st or 2nd auxiliary requests respectively, submitted at the oral proceedings on 25 July 2001.

Reasons for the Decision

The claims as maintained by the opposition division (main

request)

Article 123(2)(3) EPC

1. The expression "*free from proteolytic enzymes*" (claim 1) or "*free of proteolytic enzymes"* (claim 10) is *expressis verbis* mentioned neither in the application as filed nor in the patent as granted. The Board, nevertheless, considers this expression not as a disclaimer, but as a restrictive feature having an implicit basis in the application as filed, which describes the removal of the peptides of the desired size from the reaction medium via a reverse osmosis unit, which has a cut-off value lying far below the molecular weight of any of the proteolytic enzymes listed in said application. Such an arrangement unambiguously indicates to the skilled person that the **physical presence** of high molecular weight substances, such as the proteolytic enzymes listed in the application, in the final peptide mixture is excluded and that said peptide mixture is, in that sense, free from/of proteolytic enzymes.

   Therefore, the Board is of the opinion that the requirements of Article 123(2)(3) EPC are fully met.

Article 83 EPC

2. The feature "*equivalent weight*" is defined in the application as filed on page 7 (column 12, lines 28 to 32) as the expression of the molecular weight relative to the charge (valence) of the peptides. Both can be determined without any burden by the skilled person. Confirmation of this can be found in the declaration of Prof. E. Klein (cf. document (19)), uncontested by the

appellants, which indicates how the skilled person, using the osmolality and the peptide concentration, ie two easily measurable parameters, is well able to determine the equivalent weight. Reference is made in document (19) to textbooks, such as documents (20) and (21), for the definition of "valence", "equivalent weight" and "osmolality".

The requirements of Article 83 EPC are thus met by the patent in suit.

Article 54(3) EPC

3.1 As already stated above (cf. point 1), it is beyond any doubt that the patent in suit describes a dialysis fluid, in which high molecular weight molecules, such as the proteolytic enzymes listed in the application as filed, are not present.

3.2 Document (1) can only be novelty-destroying as far as its teachings are supported by the priority document (1.2). The latter describes a dialysis fluid for continuous ambulatory peritoneal dialysis (CAPD) based on the use, as an osmotic agent, of a mixture of peptides containing 2-10 amino acid residues on average resulting from an enzymic hydrolysis of milk protein, such as sodium caseinate, with endoproteases, such as trypsin. At the end of the process, the protease is heat-inactivated in order to avoid a transfer of the proteolytic activity to the peritoneum (page 3, lines 18 to 24). There is no explicit disclosure in document (1.2) of a **removal** of the heat-inactivated protease. This feature has only been introduced *expressis verbis* in document (1)(page 3, column 4, lines 16 to 20).

3.3 Can this feature be nevertheless implicitly found in the disclosure of document (1.2)? The Board considers that this question must be answered negatively. The reason therefor is that the purpose of the heat-inactivation in document (1.2), ie the avoidance of a transfer of the proteolytic activity to the peritoneum, is already fully achieved by the heat-inactivation and does not require any removal of the heat-inactivated protease.

3.4 Does this "*free from proteolytic enzymes*"-feature only relate to active enzymes, as suggested by the appellants, since inactivated enzymes can no longer be considered as "*enzymes*"? In other words, does the term "*enzyme*" necessarily imply the existence of a biological activity? This question must be answered negatively, because the skilled person will use the name "*enzyme*" to characterize a molecule known as such, even if said molecule is, in that particular moment, inactive. This implies that an enzyme is not only defined by reference to its biological activity, but also in relation to other parameters, such as its amino acid sequence, for instance. Therefore, the said feature should not be understood as simply meaning the disappearance of the proteolytic activity, but much more as implying the **physical absence** of said (active or inactive) proteolytic enzymes.

3.5 This "*free from proteolytic enzymes*"-feature is of importance in the context of CAPD, since it aims at avoiding potential immunological risks due to the presence of epitopes on the proteolytic enzymes whether in active or in inactive form. It has to be kept in mind that, in first approximation, the antigenicity of a protein is related to its length, since the

probability of the presence of an (sequential and/or spatial) epitope increases with the length of the protein. Furthermore, CAPD is a repetitive procedure, in which the presence of an epitope repetitively presented to the immune system of a CAPD-patient may lead to rather deleterious consequences for said patient. Also in this context, this "*free from proteolytic enzymes*"-feature cannot even be considered as being implicitly disclosed in document (1.2), since said document (1.2) has apparently not recognized this problem, as shown by the fact that it is absolutely silent about it.

3.6 It can thus be concluded that the priority document (1.2) neither explicitly nor implicitly discloses or suggests the **removal** of the heat-inactivated enzymes and document (1), as far as it enjoys the priority of document (1.2), differs from the patent in suit in the absence of a removal of the proteolytic enzymes and cannot be considered as novelty-destroying within the meaning of Article 54(3) EPC.

Article 54 EPC

4. Document (7) describes the total enzymatic hydrolysis of whey protein with proteolytic enzymes for use in nutrition or intensive care medicine (column 11, lines 43 to 63) using an enzyme reactor, in which a membrane separates the reaction mixture from the peptides obtained (column 11, lines 10 to 15, column 10, lines 21 to 28, column 13, lines 6 to 15). The peptide mixture contains no residual protein and at least 50% of the peptides contain 2 to 5 amino acids (column 6, lines 23 to 28). In a preferred embodiment the hydrolysate contains 70 to 90% nitrogen in the form

of peptides having a number of amino acids less than 10 (column 6, lines 28 to 32). The amount of free amino acids is mentioned in three different places in document (7) and is said to be "10-15%" (column 6, line 66), "less than 15%" (claim 1) and "less than 10%" (column 16, lines 35 to 37). The fact that these values are not so precisely defined and are not in so close agreement with each other suggests that the free amino acid content is not considered as an important feature in document (7) and is, in all events, definitively higher than the value mentioned in the patent in suit. Thus, document (7) does not disclose feature (b) of claim 10 at issue, which, in consequence, fulfils the requirements of Article 54 EPC.

Article 56 EPC

5.1 The Board considers document (4) as the closest prior art.

5.2 Document (4) is, as the patent in suit, concerned with CAPD (page 1, lines 3 to 7) and the drawbacks of glucose on the metabolism of the CAPD-patients. In order to get rid of these disadvantages, it replaces glucose by glycerol (page 3, lines 7 to 16). As a positive "side-effect", the use of glycerol, by allowing a sterilisation of the dialysis fluid at neutral pH, makes the use of an amino acid source possible. Said amino acid source, being used for both nutrition and osmotic purposes (page 5, lines 6 to 17), is defined as a protein hydrolysate containing (poly)peptides (page 5, lines 22 to 25) and reference is made to the hydrolysates currently available as

parenteral solutions (page 7, lines 8 to 12). The amino acid source material may substitute for a portion of the glycerol to raise the osmolarity of the peritoneal dialysis fluid (page 6, lines 6 to 13).

5.3 Document (4) is, in the opinion of the Board, more suitable as the closest prior art than document (9) relied upon by the appellants and the respondent, which also proposes the use of short-chain polypeptides in peritoneal dialysis fluids, because it has already solved the first problem encountered in the field of CAPD, namely the use of glucose. It thus avoids the disadvantages of the presence of glucose in the sterilization of the dialysis fluid and in the interaction with the patient's metabolism.

5.4 In the light of the teachings of document (4), the technical problem to be solved may be defined as the provision of an alternative dialysis fluid allowing a stable, long-lasting osmotic gradient as required by CAPD.

5.5 As a solution, claim 1 of the patent in suit proposes a peritoneal dialysate defined by reference to the osmotically active agent which is a mixture of peptides having some specific features. The other ingredients of the dialysate are not defined in claim 1 and, because of the use of the term "comprises", the peritoneal dialysate of claim 1 may also contain other undefined components, such as insulin, for instance, as long as their contribution to the osmotic pressure is insignificant. Example 4 of the patent in suit demonstrates that said dialysis fluid solves the technical problem mentioned above (cf. point 5.4). The osmotically active agent of claim 1 is characterized by

and differs from that of document (4) by the following features:

(a) mixture of peptides of molecular weight from about 300 to about 2000 daltons,

(b) equivalent weight between about 150 to about 1500,

(c) free from proteolytic enzymes.

The relevant question in view of the assessment of inventive step is whether the skilled person would have arrived in an obvious manner at an osmotically active agent exhibiting these features following the teachings of document (4) considered alone or in combination with other prior art documents and/or the common general knowledge.

5.6 The first aspect of this question concerns the feature "mixture of peptides of molecular weight from about 300 to about 2000 daltons". Would the skilled person have readily considered in view of the prior art the use of such peptides to make a stable and long-lasting osmotic gradient?

As mentioned above (cf. point 5.2), document (4) already uses a so-called "amino acid source material", which is defined inter alia as "protein hydrolysates" (page 5, lines 6 to 11) containing (poly)peptides (page 5, lines 22 to 25), and makes reference (page 7, lines 8 to 12) to the protein hydrolysates used in the field of parenteral nutrition. This reference provides the skilled person with a direct link to document (7), which is in the field of nutrition (column 11, lines 43 to 63) and describes an enzymatic hydrolysate of whey

protein (as in the patent in suit) using proteolytic enzymes capable of simulating the proteic digestion which occurs *in vivo* in the human body (column 6, lines 32 to 42). Such a proteolytic hydrolysis leads to a mixture of peptides containing 2 to 5 amino acids or, in a preferred embodiment, having a number of amino acids less than 10 (column 6, lines 23 to 33). Furthermore, the process described in document (7) uses an enzyme reactor in which the peptides produced are separated from the reaction mixture (whey protein and proteolytic enzyme) by filtration on a membrane with a cut-off capacity of 2,000. This implies that peptides having a molecular weight up to 2,000 are present in said peptide mixture. This is exactly the upper limit of molecular weight mentioned in claim 1. The respondent argued that the cut-off value of a membrane only means that 90% of the molecules have a molecular weight less than or equal to said cut-off value and hence 10% have a higher molecular weight. However, claim 1 at issue does not consider the value "2,000 daltons" to be a strict limit, since it also uses the adverb "**about**", thus implying that some of the peptides present in the mixture may have a molecular weight higher than this value. Therefore, the molecular weight range mentioned in claim 1 at issue corresponds to the peptides described in and obtained by the process of document (7).

Furthermore, the osmotic pressure of a peptide strongly decreases as its molecular weight increases. Since claim 1, as already mentioned above (cf. point 5.5), does not precisely define the ingredients of the dialysis fluid other than the osmotically active ones, high molecular weight peptides may even be comprised as ingredients of the claimed dialysis fluid, as long as

they do not contribute to the osmotic pressure.

5.7 According to the respondent, Figure 5 of document (7) demonstrates that the composition described therein is unsuitable for peritoneal dialysis and would be harmful to the patient, since two of its three constituent groups (column 15, lines 38 to 55) correspond to high molecular weight molecules, susceptible to induce immune responses in a dialysis patient. Indeed, whereas the third constituent group of Figure 5 corresponds to the peptides, the second group appears to be serum albumin and the first group seems to have an even higher molecular weight. However, document (7) does not refer in Figure 5 to the **final** composition, ie the mixture of peptides which has gone through the ultrafiltration membrane, but to the reaction mixture present in the enzyme reactor after a three hour digestion. Therefore, as far as the composition of the final peptide mixture is concerned, Figure 5 is meaningless. Figures 9 and 10 should be taken into consideration therefor, since Figure 9 shows the result of a total enzymatic hydrolysis and Figure 10 the result of the use of ultrafiltration membrane, ie the final product. It is concluded from Figure 9 that all the peptides obtained have a molecular weight less than 2,000 daltons (column 16, lines 32 to 35). The respondent's misinterpretation of this aspect of document (7) is obvious in view of the statement in column 11, lines 11 to 13, where the accent is put on the fact that the hydrolysis should be conducted until enzymatic hydrolysates are obtained which contain no detectable proteins. This condition is obviously not met by the second and third constituent groups of Figure 5.

In view of the teachings of document (7) and of the cut-off value of the membrane used, it can be concluded that the peptides obtained in said document are within the molecular range defined in the patent in suit. Therefore, document (4) in combination with document (7) leads in a straightforward manner to the use of a peptide mixture of a molecular weight from about 300 to about 2000 daltons, obtained by proteolytic digestion of whey protein.

5.8 The requirement for an "equivalent weight" as mentioned in claim 1 is, according to document (19), which is a declaration made by the inventor himself, **automatically** met as a consequence of the molecular weight of the peptide mixture employed in the dialysate solution of the patent in suit. Therefore, the requirement of the "equivalent weight"-feature must be considered as met as soon as the requirement for the molecular weight has been fulfilled (see above, points 5.6 and 5.7).

5.9 The absence of proteolytic enzymes in the peptide mixture is an important concern of document (7) which is mentioned in several parts of this document. In column 6, lines 1 to 16, for instance, the enzyme reactor is described as using an ultrafiltration membrane, which retains the enzyme in solution in the reactor as well as the proteinaceous substrate so that only the products of the hydrolysis, the peptides, are eliminated as they are formed. Further, one of the requirements of the membranes is defined in column 10, lines 21 to 25 as a particular efficiency in retaining the enzyme. Therefore, it is beyond any doubt that the final composition of document (7) is free from any proteolytic enzyme.

5.11 The Board is thus of the opinion that the skilled person would have readily arrived at the solution proposed in claim 1 of the main request by combining the teachings of documents (4) and (7) and considers for this reason that claim 1 of the main request does not fulfil the requirements of Article 56 EPC.

First auxiliary request

6. Neither the appellants nor the Board have raised formal objections under Articles 84, 123(2) and 123(3) EPC against the first auxiliary request.

Article 54(3) EPC.

7. The same conclusions as for claim 1 of the main request (points 3.1 to 3.6) equally apply to claim 1 of the first auxiliary request, since it also mentions the "*free from proteolytic enzymes*"-feature.

Article 54 EPC.

8. The objection raised against claim 10 of the main request in view of document (7) could equally apply for claim 9 of the first auxiliary request, since the expression "*for preparing a peritoneal dialysate comprising said mixture"* has no limiting character on the scope of said claim. However, as for claim 10 of the main request (cf. point 4), novelty has to be acknowledged, because of the feature (b) limiting the amount of the free amino acids to a value less than 5 mole percent.

Article 56 EPC.

9. Claim 1 of the first auxiliary request differs from its counterpart of the main request by the addition of the feature "*...wherein the mixture contains less than 5 mole percent of free amino acid.*". This feature is *per se* not disclosed in document (7). However, document (7) points to the negative effects of high concentrations of free amino acids in column 4 (lines 41 to 53) and column 5 (lines 7 to 19) on human patients. Further, in three different locations (column 6, lines 66 to 68; column 16, lines 35 to 37 and claim 1) it defines the upper limit of the free amino acids amount, which is in the worst case 15%. This teaching would have prompted the skilled person to avoid high contents of free amino acids.

Moreover, this teaching concerns a composition used in nutrition and the requirements that such a composition must fulfil for such an use. The skilled person is, however, aware of the well-known considerations of physics on dialysis and the particular requirements of the peritoneal dialysis, which are slightly different from those of the nutrition field. Indeed, free amino acids, because of their low molecular weight cross the membrane very rapidly and are not suitable for the maintenance of a stable and long-lasting osmotic gradient as required by CAPD. Thus, also for this reason, the skilled person would be prompted to bring the content of the free amino acids to a level as low as possible.

The Board hence considers that the introduction of this feature relating to the content of free amino acids cannot contribute to the inventive step of claim 1 of the first auxiliary request in view of the disclosure of document (4) considered together with document (7).

Second auxiliary request

10. Neither the Board nor the appellants have raised objections in view of Articles 84, 123(2) and/or 123(3) EPC against the second auxiliary request.

Article 54 EPC.

11. The same conclusions (cf. points 3.1 to 3.6, 4, 7 and 8) as those reached for the main request and the first auxiliary request apply to the claims of the second auxiliary request, since the features justifying the acknowledgement of novelty over the prior art are again present in the claims of the second auxiliary request.

Article 56 EPC.

12. Claim 1 of the second auxiliary request differs from its counterpart of the first auxiliary request by the addition of the feature "*...wherein the peptides comprises about 1 to 15% by weight of the solution.*". Document (4) states on page 7, lines 13 to 20 that a 4% amino acid solution may be used. Document (4) goes further by stating that a 1% amino acid solution will generate an osmotic force of 84 mOsm/l, so that if only amino acids would be used in the examples of document (4), then their concentration would range from 3.3% (Example 1) to 7.2% (Example 3). However, the skilled man would also have expected to use more concentrated mixtures of peptides, since document (7) draws (column 5, lines 19 to 24) the attention to the fact that the osmolality (ie in a first approximation, the osmotic efficiency) of peptides is less than that of free amino acids. The range of peptide concentrations disclosed in claim 1 of the second auxiliary request

thus corresponds to what the prior art suggested and/or the skilled person expected. Therefore, this feature cannot confer any inventive step to claim 1 of the second auxiliary request over the disclosure of document (4) combined with that of document (7).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

U. Bultmann L. Galligani