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**Datasheet for the decision
of 4 May 2018**

Case Number: T 0015/11 - 3.3.01

Application Number: 03799967.9

Publication Number: 1585531

IPC: A61K31/718, A61M1/28

Language of the proceedings: EN

Title of invention:

BIOCOMPATIBLE DIALYSIS FLUIDS CONTAINING ICODEXTRINS

Applicants:

Baxter International Inc.
Baxter Healthcare S.A.

Headword:

Icodextrin/BAXTER

Relevant legal provisions:

EPC Art. 123(2), 84, 56, 111(1)

Keyword:

main request - clarity (no)
auxiliary request 1 - clarity (no)
auxiliary requests 2, 4, 6 - added subject-matter (yes)
auxiliary requests 3, 5 - inventive step - (no)
auxiliary request 7 - added subject-matter (no)
remittal to the department of first instance (yes)

Decisions cited:

G 0002/10



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Case Number: T 0015/11 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 4 May 2018

Appellant: Baxter International Inc.
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Appellant: Baxter Healthcare S.A.
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Decision under appeal: **Decision of the Examining Division of the
European Patent Office posted on 29 July 2010
refusing European patent application No.
03799967.9 pursuant to Article 97(2) EPC**

Composition of the Board:

Chairman A. Lindner
Members: M. Pregetter
L. Bühler

Summary of Facts and Submissions

- I. The present appeals lie from the decision of the examining division refusing European patent application No. 03799967.9, published as WO2004/058277.
- II. The following documents, cited during the examination and appeal proceedings, are referred to below:
- (5) US 5,092,838
- (6) Peers et al., *Artificial Organs*, 1998, 22(1), 8-12
- (7) Martis et al., *Artificial Organs*, 1998, 22(1), 13-16
- III. The decision under appeal was based on a main request and on auxiliary requests 1 and 2. The examining division found that claim 1 of the main request lacked novelty and that the respective claims 1 of auxiliary requests 1 and 2 lacked inventive step.
- IV. With their statement of grounds of appeal, the appellants re-submitted the main request and auxiliary requests 1 and 2, and also filed auxiliary requests 3 and 4.
- V. In a communication pursuant to Article 15(1) RPBA dated 15 January 2018, the board raised objections under Article 123(2) EPC, indicated that compliance of the claims with Article 84 EPC might be an issue and gave indications on important points for the discussion of inventive step.

- VI. With a letter dated 27 April 2018 the appellants submitted a main request and 14 auxiliary requests.
- VII. Oral proceedings were held on 4 May 2018. During the oral proceedings the appellants submitted a new auxiliary request 7 and renumbered auxiliary requests 7 to 14 of 27 April 2018 as auxiliary requests 8 to 15.
- VIII. Claim 1 of the **main request** reads as follows:

"1. A peritoneal dialysis solution comprising:

a first part comprising icodextrin ranging from about 100.0 g/L to about 220.0 g/L, wherein the first part has a pH ranging from about 1.5 to about 5.0; and

a second part comprising a buffer solution having a pH ranging from about 7.0 to about 12;

and the first part and the second part being so constructed and arranged that the first part and the second part are mixed prior to infusion into a patient."

Claim 1 of **auxiliary request 1** differs from claim 1 of the main request in the definition of the "first part":

"a first part consisting of a first solution containing icodextrin ranging from about 100.0 g/L to about 220.0 g/L, wherein the first part has a pH ranging from about 1.5 to about 5 .0;"

Claim 1 of **auxiliary request 2** reads as follows:

"1. A multiple chamber container housing a two part peritoneal dialysis solution wherein

the first part is stored in a first chamber of the multiple chamber container and wherein the first part comprises icodextrin ranging from about 100.0 g/L to about 220.0 g/L, wherein the first part has a pH ranging from about 1.5 to about 5.0; and wherein

the second part is stored in a second chamber of the multiple chamber container and wherein the second part comprises a buffer solution having a pH ranging from about 7.0 to about 12; and wherein

the first part and the second part being so constructed and arranged that the first part and the second part are mixed prior to infusion into a patient."

Claim 1 of **auxiliary request 3** reads as follows:

"1. A multiple chamber container housing a two part peritoneal dialysis solution wherein

the first part is stored in a first chamber of the multiple chamber container and wherein the first part consists of a first solution containing icodextrin ranging from about 100.0 g/L to about 220.0 g/L, wherein the first part has a pH ranging from about 1.5 to about 5.0; and wherein

the second part is stored in a second chamber of the multiple chamber container and wherein the second part comprises a buffer solution having a pH ranging from about 7.0 to about 12; and wherein

the first part and the second part being so constructed and arranged that the first part and the second part are mixed prior to infusion into a patient."

Claim 1 of **auxiliary request 4** differs from claim 1 of auxiliary request 2 in that it specifies that the two-part peritoneal dialysis solution is heat-sterilised.

Claim 1 of **auxiliary request 5** differs from claim 1 of auxiliary request 3 in that it specifies that the two-part peritoneal dialysis solution is heat-sterilised.

Claim 1 of **auxiliary request 6** differs from claim 1 of auxiliary request 2 in that the second part is further defined by the inclusion of the following disclaimer:

"and wherein the buffer solution does not contain amino acids with a pK^1 between 7 and 13, glycine, alanine and histidine;"

Claim 1 of **auxiliary request 7**, filed during oral proceedings, reads as follows:

"1. A multiple chamber container housing a two part peritoneal dialysis solution wherein

the first part is stored in a first chamber of the multiple chamber container and wherein the first part consists of a first solution containing icodextrin ranging from about 100.0 g/L to about 220.0 g/L, wherein the first part has a pH ranging from about 1.5 to about 5.0; and wherein

the second part is stored in a second chamber of the multiple chamber container and wherein the second part comprises a buffer solution having a pH ranging from about 7.0 to about 12; and wherein the buffer solution does not contain amino acids with a pK^1 between 7 and 13, such as glycine, alanine and histidine; and wherein

the first part and the second part being so constructed and arranged that the first part and the second part are mixed prior to infusion into a patient."

IX. The appellants' arguments may be summarised as follows:

Claim 1 of the main request was clear. It defined a solution having two parts which were so constructed and arranged that they "are mixed prior to infusion into a patient", i.e. at some point in time in the future. Thus, when considering the claim in its entirety and also reading its last two lines it was clear that, although no containers were claimed, claim 1 of the main request defined a kit of parts. The same line of argument applied to claim 1 of auxiliary request 1.

Claim 1 of auxiliary request 2 had a basis in the application as filed. It was clear that the first part was in the form of a solution. Firstly, the preamble of claim 1 already defined a "two part solution". Secondly, the concentration of icodextrin was defined as "from about 100.0 g/L to about 220.0 g/L", the unit "g/L" clearly referring to a solution, which was corroborated by the fact that icodextrin in this concentration range would be completely dissolved in water. Furthermore, a pH was specified. The same line of argument also applied to the respective claims 1 of auxiliary requests 4 and 6.

Claim 1 of auxiliary request 3 involved an inventive step. The appellants considered document (6) to be the closest prior art, since it was the only document on file that provided a teaching concerning icodextrin. Document (5) related only to the preparation of a peritoneal dialysis solution, but did not include any

clinical data. Glucose polymers were mentioned only once (column 3, line 63). Document (5) focused entirely on peritoneal dialysis solutions based on histidine. Histidine was employed as a buffer, but the skilled person was aware that it also acted as an osmotic agent. From example 1 of document (5) it was clear that a skilled person would never add a glucose polymer in an amount as defined in claim 1 of auxiliary request 3, since the skilled person was aware that due to the high concentration (1.55 g/L) of histidine the concentration of the sugar, which was 84.08 g/L, could not be increased. There were thus two differences between claim 1 of auxiliary request 3 and document (5), the use of icodextrin and its concentration. The effects due to these differences were the improved properties of icodextrin as an osmotic agent in peritoneal dialysis (cf. document (6)) and the decrease in degradation products due to the fact that icodextrin in the chosen concentration and pH range showed only low levels of degradation during heat sterilisation (application as filed, page 7, lines 14 to 18). The technical problem was thus how to provide an improved peritoneal dialysis solution. The solution of using icodextrin in the claimed concentration range in the first solution was not obvious. Document (5) gave no hint that icodextrin was a suitable compound. The osmotic activity of various sugar derivatives was not immediately known to the skilled person, although he was aware that the osmotic concentration was important. The skilled person would not primarily consider molar concentrations, but would consider the usual g/L values as a good indication. Furthermore, document (6) too provided no motivation to use icodextrin, since it concerned a single peritoneal dialysis solution that had no downsides that would have led the skilled person to change to a two-part formulation. The application as

filed, in the paragraph bridging pages 2 and 3, related to the knowledge of the inventors of the present application and thus could not provide a hint either. The same line of argument applied to claim 1 of auxiliary request 5.

Claim 1 of auxiliary request 7 had a basis in the application as filed in line with decision G 2/10.

- X. The appellants requested as their final requests that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request, or alternatively of one of auxiliary requests 1 to 6, all filed with the letter dated 27 April 2018, or alternatively of auxiliary request 7 filed during the oral proceedings, or alternatively of auxiliary requests 8 to 15, filed as auxiliary requests 7 to 14 with the letter dated 27 April 2018.

Reasons for the Decision

1. The appeal is admissible.
2. *Main request and auxiliary request 1*

Claim 1 of the main request defines a peritoneal dialysis solution. The term "solution" is explicitly defined in the preamble. Patent protection is thus sought for a "solution". Said solution is further characterised by the following definition: "and the first part and the second part being so constructed and arranged that the first part and the second part are mixed prior to infusion into a patient". This statement is ambiguous and consequently leads to a lack of clarity: The terms "being so constructed and arranged that" are followed by a mixing step. This implies that

at one point in time the first part and the second part are separate. On the other hand, the phrase "the first part and the second part are mixed" indicates the presence of a mixing step, the occurrence of which is supported by the term "solution" in the preamble. In sum, the claim can be seen either as defining a "kit of parts" or as defining a "product-by-process". In the present case, a kit of parts would comprise two parts that are kept separate, whereas a product-by-process would seek protection for a single solution obtainable by mixing the two parts. Claim 1 can be construed in two ways which lead to different subject-matter for which protection is sought and thus to a lack of clarity.

The subject-matter of claim 1 of the main request is not clear (Article 84 EPC).

Claim 1 of auxiliary request 1 is structured in the same way as claim 1 of the main request. The same line of argument applies. The subject-matter of claim 1 of auxiliary request 1 is not clear (Article 84 EPC).

3. *Auxiliary requests 2, 4 and 6*

Claim 1 of auxiliary request 2 contains various amendments. It defines, inter alia, a two-part peritoneal dialysis solution "wherein the first part comprises icodextrin ranging from about 100.0 g/L to about 220.0 g/L, wherein the first part has a pH ranging from about 1.5 to about 5.0".

The application as filed defines in claim 1, inter alia, a "first part including a first solution containing a glucose polymer". The glucose polymer is thus contained in a solution. Similar wording is used

in the "Summary of invention". On page 3, lines 20 to 25, of the application as filed the wording is "a first solution containing a glucose polymer", which is followed by the statement "the first solution includes about 100.0 to about 220.0 (g/L) of icodextrin" (page 4, lines 2 to 5). Similar statements are found throughout the description as filed.

It thus has to be examined whether the deletion of the term "solution" in the definition of the first part of the multiple chamber container housing a two-part peritoneal dialysis solution leads to the subject-matter being extended beyond the content of the application as filed.

The appellants argued that the preamble defined a "two part peritoneal dialysis solution" and that it followed from that definition that both parts of the peritoneal dialysis solution were in the form of solutions. The board cannot follow this argument. A final solution can be obtained from mixing various matrices, e.g. by mixing a suspension and a solution.

A further argument of the appellants relates to the definition of the icodextrin concentration by the unit "g/L" and the definition of pH values. This argument can be followed only insofar as the unit "g/L" and the definition of pH values point to an aqueous liquid. Such a liquid may for example be in the form of a solution, an emulsion or a suspension.

The appellants have pointed out that 100.0 to 220.0 g/L icodextrin would be completely dissolved in an aqueous system and thus form a solution. The board notes however that the first part is defined in an open way. It allows for the presence of further substances (in

any concentration). The addition of these further substances could lead to forms of liquid that are not solutions, e.g. to the formation of an emulsion or a suspension.

In sum, liquid compositions comprising icodextrin in a concentration of 100 to 220 g/L and having a pH of 1.5 to 5.0 may be in forms other than a solution. Consequently, the omission of the term "solution" in the definition of the first part of the system of claim 1 of auxiliary request 2 leads to the subject-matter being extended beyond the content of the application as filed.

The subject-matter of claim 1 of auxiliary request 2 contravenes the requirement of Article 123(2) EPC.

The same line of argument also applies to the subject-matter of the respective claims 1 of auxiliary requests 4 and 6, which likewise contravenes the requirement of Article 123(2) EPC.

4. *Auxiliary requests 3 and 5*

4.1 None of the documents on file disclose the subject-matter of the claims of auxiliary request 3. The subject-matter of auxiliary request 3 is thus new.

4.2 The present application relates to peritoneal dialysis. A sterile dialysis solution is to be introduced into the peritoneal cavity of the patient. An exchange of solutes between the dialysate and the blood is achieved. Fluid removal is achieved by providing a suitable osmotic gradient from the blood to the dialysate to permit water outflow from the blood. This allows a proper acid-base, electrolyte and fluid

balance to be returned to the blood (application as filed, page 2, lines 8 to 20). Dextrose and glucose polymers are not stable during heat sterilisation if they are formulated at a physiologic pH. Provision of icodextrin at low pH can cause pain on infusion in some patients and is cytotoxic to peritoneal cells. The application therefore aims at the provision of improved solutions that can readily be manufactured, remain stable and sterile under storage conditions, and can be readily and effectively used (application as filed, page 2, line 31, to page 3, line 12).

As a solution, a multiple container housing a two-part peritoneal dialysis solution has been proposed. The two parts comprise a first part consisting of a solution containing about 100.0 g/L to about 220.0 g/L of icodextrin, a glucose polymer, at a low pH and a second part having a buffer solution, the two parts being mixed prior to infusion into a patient.

- 4.3 Two documents have been discussed in terms of their suitability as the closest prior art.
 - 4.3.1 Document (5) aims at providing medical solutions used to extract waste products from a patient's blood and to correct fluid and electrolyte abnormalities in patients with end-stage renal disease. It suggests using amino acid buffered solutions for peritoneal dialysis (column 1, lines 5 to 11). Document (5) mentions problems similar to those described in the present application. In column 1, lines 36 to 46, it addresses patient discomfort in the form of pain and stability problems during heat sterilisation. Document (5), under the heading "Summary of the invention", teaches generally to provide a two-part form, having a first solution comprising glucose, related sugars or glucose

polymers at a lower pH and a second solution being in a form that means the pH will be adjusted to 6.5-7.6 upon mixing (column 3, line 44, to column 4, line 2). The solutions are provided in two separate containers (claim 1). Document (5) provides no general teaching on the concentration of the glucose, related sugars or glucose polymers which are the osmotic agents. The amino acids, preferably histidine or its derivatives, are used at less than 1% (column 3, lines 45 to 49). In several instances a concentration of 0.01 to 60 millimoles per liter in the mixed solution is disclosed for histidine (e.g. claim 2, claim 9 and column 4, lines 51 to 60). Three actual two-part systems are exemplified, all three containing a first solution having 84.08g/L dextrose. The concentration of histidine in the second solution varies from 1.55 g/L to 0.779 g/L and to 3.10 g/L. Equal volumes of the first and the second solution are mixed (examples 1 and 2).

- 4.3.2 Document (6) has been considered by the appellant to be closer than document (5), since it directly mentions the use of icodextrin in peritoneal dialysis solutions and describes their advantages.

The board cannot follow this argument. A skilled person aiming to provide improved solutions that can readily be manufactured, remain stable and sterile under storage conditions, and can be readily and effectively used would look for a document that addresses these issues. Document (6) is completely silent on problems relating to the manufacture and stability of its solutions. Furthermore, no specific information on the solutions used is given, other than that they contain 7.5% icodextrin. The actual composition of the icodextrin solution is not disclosed. The document does

not specify which electrolytes are contained or what the pH of the solution is. Document (6) can thus provide no guidance to a skilled person looking for solutions related to manufacture and stability problems with peritoneal dialysis compositions.

- 4.3.3 The board concludes that document (5) is the closest prior-art document.
- 4.4 Claim 1 of the main request differs from the disclosure of document (5) by defining a specific glucose polymer, i.e. icodextrin, in a specific concentration range.
- 4.5 The appellants stated that the use of a two-part system comprising a first part including icodextrin in the defined concentration range in a solution having the low pH range claimed led to improved peritoneal dialysis solutions. It was argued that, first of all, icodextrin itself had many advantages. Icodextrin induced osmotic flow across the peritoneum in the absence of an osmotic gradient, while having limited absorption (document (6), page 9, right column, last sentence of first full paragraph). Icodextrin was also known to be well tolerated (document (6), page 10, left column, third paragraph). The appellants went on to stress that, further to these extremely positive effects due to the properties of icodextrin, the claimed system also led to more safety and stability. By selecting the concentration of icodextrin in the first part of the peritoneal dialysis system to be very high, i.e. in the range of 100 to 220 g/L, and by lowering the pH of the first part to 1.5 to 5.0, degradation due to heat sterilisation was minimised (application as filed, page 7, lines 14 to 17).

The board cannot adopt the appellants' line of

argument. Concerning the positive properties of icodextrin, the board has no reason to doubt their existence. However, these positive properties are described in the prior art and thus cannot be seen as a contribution made by the present invention. Concerning the second point, the heat sterilisation of a solution having a certain concentration of icodextrin and an acidic pH and the resulting decrease in degradation of icodextrin, the following has to be considered: Heat sterilisation of glucose polymers at low pH is already taught in the closest prior art, cf. document (5), column 3, lines 62 to 67. The document is however silent on the concentration of the glucose polymers. The only concentration disclosed for an osmotic agent is 84.04 g/L of dextrose in the specific examples. However, apart from an assertion in the application as filed, there is no information or evidence to be found on file that icodextrin at 100 g/L has a lower grade of degradation during heat sterilisation than, e.g., dextrose at a concentration of 84.04 g/L as used in the specific example of the closest prior art. No comparative data concerning the degradation of icodextrin has been submitted. There is no proof of less degradation upon heat sterilisation.

The appellants have thus not proven the presence of any surprising effect linked to the use of icodextrin at a concentration of 100 to 220 g/L in the first part of a two-part peritoneal dialysis system.

4.6 Therefore, the technical problem can be seen as how to provide a further safe and effective two-part peritoneal dialysis solution based on a glucose polymer as osmotic agent.

There is no doubt that the problem is solved. It remains to be established whether it was obvious for

the skilled person to use icodextrin in the claimed concentrations as osmotic agent.

- 4.7 Icodextrin, a glucose polymer, is known in the art for use as an osmotic agent in peritoneal dialysis solutions, see document (6) or document (7) (page 13, paragraph bridging the two columns). While document (7) mentions icodextrin only very briefly, document (6) discusses its use in peritoneal dialysis in more detail. In its abstract it identifies icodextrin 7.5% as an isosmolar solution for once-daily use in peritoneal dialysis for patients with end-stage renal failure and discloses various advantages of the use of icodextrin. A skilled person looking for a glucose polymer suitable for use as osmotic agent in a peritoneal solution would thus be guided by document (6) to use icodextrin.

It remains to be established whether the concentration of from about 100.0 to about 220.0 g/L icodextrin in the first part of the system was obvious for the skilled person. One of the most important considerations of the skilled person when trying to provide a peritoneal dialysis solution is the osmotic activity of the solution. The osmotic agent needs to be provided in an appropriate concentration. It is clear from the disclosure of the closest prior art that the glucose polymers, if employed, act as the osmotic agent (column 3, lines 62 to 67). The concentration of the histidine, or derivatives, is explicitly taught to be kept low ("less than a 1% concentration", "in a concentration ranging between 0.01 and 60 millimoles per liter of ready-to-use dialysate", see point 4.3.1 above). The examples of the closest prior art provide only limited guidance on selecting the appropriate concentrations, since they do not use a glucose polymer

as osmotic agent. Consequently, once the skilled person has selected a specific glucose polymer as osmotic agent, he necessarily has to inform himself about the suitable concentration range of this specific osmotic agent when employed in a peritoneal dialysis solution. In the present case the board has reached the conclusion that document (6) provides guidance to the skilled person to use icodextrin as glucose polymer. Document (6) relates to a 7.5% solution of icodextrin. The skilled person would adapt this concentration of icodextrin known for a one-part solution to the higher concentration required in the first part of a two-part system. Having in mind the 1:1 mixing ratio of the two parts of the peritoneal dialysis system of the closest prior art, the skilled person would consider doubling the concentration of icodextrin disclosed in document (6). The resultant concentration is 15%, i.e. either 150 g/L or 150 g/kg. Optimisation of concentration ranges is part of the routine tasks of the skilled person, who would thus consider the claimed concentration range when aiming to provide a further two-part peritoneal dialysis system based on icodextrin as the osmotic agent.

The appellants have argued that when starting from document (5) as the closest prior art the skilled person would never use such a high concentration of glucose-based active agent as claimed in claim 1 of auxiliary request 3, since he was aware that the histidine, used at a concentration of 1.55 g/L in example 1, also had a high osmotic activity. The board considers it too narrow an approach to limit the considerations of the skilled person to one example. It is noted that a range of 0.01 (!) to 60 mmol/L of histidine or its derivatives is generally disclosed. The skilled person is thus aware that document (5) also

includes embodiments having only minor osmotic activity due to the presence of histidine.

The subject-matter of claim 1 of auxiliary request 3 does not involve an inventive step (Article 56 EPC).

4.8 The same arguments apply to auxiliary request 5. The subject-matter of claim 1 of auxiliary request 5 is new but does not involve an inventive step

5. *Auxiliary request 7*

The passages cited below refer to the application as filed.

Claim 1 of auxiliary request 7 is based on claims 1 and 3 in combination with page 8, lines 25 to 29, and disclaims certain buffers based on amino acids in accordance with page 4, lines 5 to 8. The subject-matter remaining in claim 1 of auxiliary request 7 after the introduction of the disclaimer is directly and unambiguously disclosed in the application as filed. Claim 1 as filed defines any buffer solution at a pH ranging from about 7.0 to about 12.0; several examples of suitable buffers are given on page 4, lines 5 to 8, page 7, line 31, to page 8, line 2, in the examples and for instance in claims 4 and 7 as filed. There is thus a basis for buffer solutions in the defined pH range other than buffers based on certain amino acids.

The subject-matter of claim 1 of auxiliary request 7 fulfils the requirement of Article 123(2) EPC.

The board has no objections under Article 84 EPC. The subject-matter of claim 1 of auxiliary request 7 is

clear.

6. *Remittal*

The decision under appeal concerned only claim requests that did not exclude buffers based on amino acids. The closest prior art in the decision under appeal explicitly taught the use of a histidine-based buffer. Two-part peritoneal dialysis solutions having a buffer system other than amino acids were not addressed. In these circumstances the board finds it appropriate to exercise its power under Article 111(1) EPC and remit the case to the department of first instance for further prosecution.

Order

For these reasons it is decided that:

7. The decision under appeal is set aside.
2. The case is remitted to the examining division for further prosecution.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated