BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS | BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE | CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen

D E C I S I O N
of 18 March 1997

Case Number: T 0845/94 - 3.2.2

Application Number: 87118987.4

Publication Number: 0278100

IPC: A61M 1/16

Language of the proceedings: EN

Title of invention:
A system for preparing a fluid intended for a medical procedure by mixing at least one concentrate in powder form with water and a cartridge intended to be used in said system

Patentee:
GAMBRO AB

Opponents:
1. TECHNO 2000 s.a.r.l.
2. Soludia, SA
3. Baxter International Inc.
4. B. Braun Melsungen Aktiengesellschaft
5. Althin Medical AB
6. RENACARE LTD.
7. Bieffe Medital S.p.A.
8. BELLCO S.p.A.
9. Fresenius AG
10. Kahn, Wolfgang

Headword:
-

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no)"

Decisions cited:
-

Catchword:

-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0845/94 - 3.2.2

D E C I S I O N
of the Technical Board of Appeal 3.2.2
of 18 March 1997

Appellant: (Proprietor of the patent)
GAMBRO AB
Post Box 10101
S-220 10 Lund (SE)

Representative:
Marsh, Roy David
Hoffmann, Eitle & Partner
Patent- und Rechtsanwälte
Postfach 81 04 20
D-81904 München (DE)

Respondent: (Opponent 01)
TECHNO 2000 s.a.r.l.
122 rue de Paris
F-78470 Saint-Remy-lés-Chevreuses (FR)

Representative:
Flavenot, Bernard
Société ABRITT
17, rue du Docteur Charcot
La Norville
F-91290 Arpajon (FR)

Respondent: (Opponent 02)
Soludia, SA
Route de Revel, Fourquevaux
F-31450 Montgiscard (FR)

Representative:
Morelle, Guy Georges Alain
CABINET MORELLE & BARDOU, SC
5, Boulevard de la Méditerranée
F-31400 Toulouse (FR)

Respondent: (Opponent 03)
Baxter International Inc.
One Baxter Parkway
Deerfield, Illinois 60015 (US)

Representative:
McGregor, Gordon
ERIC POTTER CLARKSON
St. Mary's Court
St. Mary's Gate
Nottingham, NG1 1LE (GB)

.../...

Respondent:
(Opponent 04)

B. Braun Melsungen Aktiengesellschaft
Karl-Braun-Strasse 1, Postfach 1 20
D-34209 Melsungen (DE)

Representative:

Selting, Günther, Dipl. -Ing.
Patentanwälte
von Kreisler, Selting, Werner
Postfach 10 22 41
D-50462 Köln (DE)

Respondent:
(Opponent 05)

Althin Medical AB
ST. Grabrödersgatan 17 B
S-222 22 Lund (SE)

Representative:

Ström, Tore
Ström & Gulliksson AB
Studentgatan 1
P.O. Box 4188
S-203 13 Malmö (SE)

Respondent:
(Opponent 06)

RENACARE LTD
Northdale House, North Circular Road
London NW10 7UH (GB)

Representative:

Harrison, David Christopher
MEWBURN ELLIS
York House
23 Kingsway
London WC2B 6HP (GB)

Respondent:
(Opponent 07)

Bieffe Medical S.p.A.
Via Nuova Provinciale
I-23034 Grosotto (IT)

Representative:

Incollingo, Italo
Piazalle Lavater, 3
I-20129 Milano (IT)

Respondent:
(Opponent 08)

BELLCO, S.p.A.
Via Camurana 1
I-41037 Mirandola (Modena) (IT)

Representative:

Plebani, Rinaldo
STUDION TORTA S.r.l.
Via Viotti, 9
I-10121 Torino (IT)

.../...

Respondent: (Opponent 09)
Fresenius AG
D-61343 Bad homburg v.d. Höhe (DE)

Representative:
Fuchs, Luderschmidt & Partner
Patentanwälte
Postfach 46 60
D-65036 Wiesbaden (DE)

Respondent: (Opponent 10)
Kahn, Wolfgang
Marienstrasse 14
D-33142 Büren (DE)

Representative:
Hanewinkel, Lorenz, Dipl. -Phys.
Patentanwalt
Ferrariweg 17a
D-33102 Paderborn (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 31 October 1994 revoking European patent No. 0 278 100 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: H. J. Seidenschwarz
Members: M. G. Noel
J. C. M. De Preter

Summary of Facts and Submissions

I. European patent No. 0 278 100 was granted on 15 July 1992 with sixty five claims.

II. In consequence of ten oppositions filed by the Respondents against the grant of the patent, the Opposition Division decided on 31 October 1994 to revoke the European patent in its entirety for lack of inventive step of its subject-matter *vis-à-vis* the combination of the disclosures of the closest prior art documents R43 or R44 with either one of documents R3, R7, R8 and R49:

R3 EP-A-0 077 604
R7 WO-A-86/03 416
R8 WO-A-86/03 417
R43 Gambro "AK-10 System, Bicarbonate monitor BCM 10-1, Service manual", HC E-6901, Rev. 05.1983 (2 pages)
R44 B Braun Melsungen AG "Produktinformation Dialysegerät HD Secura", W01.11.84/1 (8 pages)
R49 "Traitement de l'insuffisance renale chronique", Thèse de 3ème cycle par D. Weber, Faculté des sciences de Toulouse, 6.1983, pages 1-169.

III. The reason given by the first instance was that with respect to document R43 or R44 which disclosed a system for preparing a bicarbonate fluid for hemodialysis by mixing in a container, before use, at least one concentrate in powder form with water, the subject-matter of claim 1 of either request was distinguished by the provision of a vessel containing a

concentrate in powder form, consisting of only one single substance, and by appropriate conducting means for continuously supplying water into said vessel and thus producing a concentrate fluid at the outlet thereof.

Since, however, document R3 disclosed a device for administering a dry medicine, comprising a cartridge containing a single substance in powder form and means for supplying water into the cartridge so as to dissolve the substance *in situ* by the flow of water through the cartridge and thus form a fluid concentrate, it was obvious for a skilled man to replace the liquid concentrate container disclosed in document R43 by the cartridge of powder disclosed in document R3, especially because the subject-matter of claim 1 in suit was not restricted to hemodialysis procedures but included fluid preparations for medical procedures in general.

IV. The Appellant (Proprietor of the patent) lodged an appeal against the first instance decision on 13 October 1994 and filed a statement of grounds on 10 March 1995 along with new sets of claims according to a main request and two auxiliary requests.

During the written proceedings and in response to the Respondents's submissions, the Appellant changed its requests on several occasions, and filed successively new sets of amended claims.

V. The Appellant requested, finally, that the decision under appeal be set aside and that the patent be maintained either

- on the basis of claims 1 to 39 and 41 to 57 filed with letter of 10 July 1996 and claim 40 filed with letter of 2 August 1996 (main request), or

- on the basis of claims 1 to 56 filed with letter of 28 February 1997 (auxiliary request).

The Respondents requested that the appeal be dismissed.

VI. Claim 1 according to the main request reads as follows (the identifying letters (a) to (f) having been introduced by the Board for ease of reference):

"A System for preparing a dialysis fluid for a hemodialysis procedure or a replacement fluid for a hemofiltration procedure or a hemodiafiltration procedure by mixing of at least one concentrate in powder form with water, said system being characterised by:

(a) a vessel (10) containing a concentrate (11) in powder form consisting of only one single substance and arranged as a column between a water inlet of the vessel and a concentrate outlet of the vessel;

(b) first fluid conducting means (1) having a first end for communicating with a source (2) of water to withdraw water into said first fluid conducting means and a second end for delivering said dialysis fluid or replacement fluid;

(c) second fluid conducting means (8) having a first end for communicating with a source of water (2) and a second end communicating with the inlet of said vessel (10) for introducing water into said vessel (10), the second fluid conducting means (8) and the vessel (10) being dimensioned to produce a substantially saturated solution of the powder concentrate in water which thereby provides a concentrate fluid which is at a relatively constant concentration level;

(d) third fluid conducting means (8) communicating with the outlet of said vessel (10) and with a mixing point (7) in said first fluid conducting means (1) intermediate said first and second ends for conducting said concentrate fluid from said vessel (10) into said first fluid conducting means (1) to be mixed with fluid being conducted through said first fluid conducting means (1) to thereby produce said dialysis fluid or replacement fluid in said first fluid conducting means (1) for delivery to said second end of said first fluid conducting means (1);

(e) measuring means (14) in said first fluid conducting means (1) downstream of said mixing point (7) for measuring the composition of the said dialysis fluid or replacement fluid obtained by mixing of said concentrate fluid and water in said first fluid conducting means (1), and

(f) flow regulating means (13) in said third fluid conducting means (8) responsive to said measuring means (14) for controlling the flow of said concentrate fluid from said vessel (10)"

Claim 1 according to the auxiliary request comprises the content of claim 1 of the main request and, in addition, features (a1) and (a2) to be incorporated after feature (a) of the main request:

(a1) said single substance being either sodium bicarbonate or sodium chloride;

(a2) said powder form having a particle size which, in the case of sodium bicarbonate, is greater than 100 microns;

VII. Besides fifty documents considered during the opposition proceedings, twenty eight new documents were additionally filed by the parties to support their arguments in the course of the subsequent appeal proceedings.

In a communication dated 10 January 1997 accompanying the summons to oral proceedings, the Board informed the parties of its intention to focus the discussion during oral proceedings, principally on the inventive step of the main claims according to all requests, in particular with respect to the prior art documents R42/R43, R7/R34, R19 and R49, supplemented by two references R73 (parent of R19) and R80 (percolation process), both introduced by the Board of its own motion:

R19 CA-A-1 173 795
R34 US-A-4 465 471
R42 Gambro AK-10 System, Bicarbonate monitor BCM 10-1, HC E-6410, 05.1981 (4 pages)
R73 US-A-4 479 794
R80 "Extraction and Extractives", by Peter W. Riebling, Remington's Pharmaceutical Sciences, Fifteenth edition (1975), pages 1443 and 1509-1522.

VIII. In response to the Board's communication, the Appellant submitted on 28 February 1997, among others, document R75 to support its view in relation to leaching (percolation) procedures:

R75 "Leaching", Perry's Chemical Engineer's Handbook, sixth edition, 1984, page 19-48.

On behalf of the Respondent 09, new documents R78 and R79 were filed on 17 February 1997. Although filed late these documents were discussed at the oral proceedings:

R78 US-A-4 386 634

R79 "Bicarb-o-mate RS-8000" from Renal Systems Inc., 1980

IX. Oral proceedings were held on 18 March 1997, in the absence of Respondents 06 and 07. At the beginning of the proceedings a twenty minute videotape was produced by the Appellant, which showed in a practical environment the importance of the technical features and effects of the invention.

X. In its written submissions and at the oral proceedings, the Appellant argued essentially as follows:

- All previous systems for making pre-prepared solutions of bicarbonate-containing dialysis concentrates involved adding the concentrate in powder form to a large quantity of water, e.g. normally in a canister. In the embodiment according to the closest prior art documents R42/R43, two containers comprising liquid concentrate components A and B, respectively, were provided, wherein one component (A component) basically contained all electrolytes, except sodium bicarbonate, whereas the bicarbonate was contained in another concentrate, the B component. This bicarbonate component was provided in the form of a bulk liquid concentrate prepared by mixing just before use, i.e. as a batch, before the dialysis treatment was started.

- In order to overcome the numerous disadvantages of liquid bicarbonate concentrates prepared before use, in particular chemical instability, poor sterility, handling and storing of bulky and heavy containers, the batch technology of the prior art was replaced, in accordance with the present invention, by a continuous technology for preparing a dialysis concentrate just when it was needed and in exactly the amount needed for making up the final dialysis fluid.

- More specifically, the invention resided in the finding that a source of dialysis liquid concentrate of relatively constant concentration could be provided over the entire period of a dialysis treatment, by means of a cartridge of powder as claimed. A large amount of powder was arranged as a column, in order that the powder be gradually dissolved in water, by flow of the water through the column, at a notably low rate and during the several hours of the treatment. Dissolution of the powder took place only in the upper most layer of the powder column, with liquid and powder existing in equilibrium in the remainder of the length of the column. In this way, a reservoir of substantially saturated solution occupied the cartridge, from the base up to the upper most active layer, as schematically illustrated in documents R58 and R59 filed with the Appellant's statement of 26 January 1996.

- The invention thus involved a new concept of continuously producing, from a cartridge of powder, a substantially saturated, relatively constant concentration of solution. This involved recognising the utility of the equilibrium phenomenon of the saturated solution inside the cartridge. The cartridge was self-regulating by

virtue of the structure and content of the cartridge in the sense that the concentration of the liquid outflow remained constant, irrespective of the fluctuations of concentrate volume which might be demanded by the dialysis machine downstream of the cartridge, and this over the full duration of the dialysis treatment. Typically, a flow rate of 16 ml/min was required from a cartridge of the invention filled with 600 g of sodium bicarbonate, to produce a dialysis fluid at a rate of 500 ml/min.

- Percolation was a separation or extraction process, by flowing liquid through a bed of solid particles. The insoluble bed remained at the end of the process. By contrast, the invention solved a mixing problem. At the end of the dissolution process, the dissolved part of the solid had completely disappeared. Documents R75 and R80 which generally referred to leaching procedures, made it clear that in a properly designed percolation extractor, the equilibrium of a saturated solution was never encountered. This was because saturation was incompatible with the objective of continuous separation of a soluble component from an insoluble solid mass. This procedure was contrary to preparing a concentrate which was a substantially saturated solution of a solute in water, as in the present patent.

- While a slow flow was detrimental in percolation, the rate of flow of solvent through the powder column of the invention, which was determined by the dimension of the cartridge, was such that saturation was maintained at the concentrate

outlet for as long as there was a certain amount of the powder column remaining. This was a surprising effect of the present invention, which was not achieved in percolation, extraction or other known procedures.

- Document R73 was concerned with a parenteral delivery system for the administration of a medical fluid containing a beneficial agent. There was no disclosure or suggestion in this document of forming a concentrated solution of the beneficial agent in the parenteral fluid. Since infusions of high concentration of active agents could have dangerous toxic effects on the patient, the need for concentrates of relatively high constant concentration was not a problem which was encountered or addressed in the field of drug delivery. On the contrary, document R73 was concerned precisely with endeavours to limit over-concentration of solute in parenterally administrable solutions. Even the simplest device, e.g. that of Figure 12, comprising a formulation chamber for housing a beneficial agent, included a rate-limiting structure, i.e. a film formed of a material for controlling the rate of release of the agent solution from the chamber. As different rules and considerations applied between parenteral infusion liquid and dialysis fluid, structures of parenteral administration sets could not find application in the invention as defined. The R73 technology was simply not fit to be incorporated into an R42/R43 dialysis machine.

- Should the skilled man nevertheless have considered adopting an in-line preparation technology in the dialysis field, the only teaching he would have obtained from document R73 was that the measures disclosed therein would have

been insufficient and unsuitable to solve the specific problem involved with dialysis, i.e. of continuously providing a stable source of large amounts of liquid concentrate at a substantially saturated concentration.

- Having in mind the above considerations, the skilled person, therefore, would not have arrived at the present invention by simply combining the teachings of documents R42/R43 with that of document R73. Stating that it was a routine matter of design or even common general knowledge alone, to develop a system for preparing a dialysis fluid from the cartridge disclosed in document R73 was an argument based on hindsight.

- In addition to the above, the simplicity, the commercial success of the present invention and the existence of a long felt want in dialysis field all demonstrated the inventiveness of the claimed solution over the previous conventional systems.

- As to claim 1 according to the auxiliary request, sodium chloride and sodium bicarbonate were the principal substances required in bicarbonate hemodialysis. The prior art powders used to make dialysis fluid components employed particle sizes substantially less than 100 μm, i.e about 45 μm, to meet the objective of easy and fast dissolution. With the invention, especially with sodium bicarbonate, the cartridge required larger particle sizes in order to function reliably, i.e. to avoid caking and the formation of channels throughout the powdered mass, due to incomplete mixing.

XI. In reply, most of the Respondents at the oral proceedings argued that, after the introduction of document R73 into the appeal proceedings, the alledged invention was restricted to simply replacing the container of pre-prepared bicarbonate liquid concentrate used in documents R42/R43 by a concentrate solution prepared *in situ* and in-line from a substance in powder form, in the way disclosed in document R73.

Since the embodiment described therein showed very close structural and functional similarities with that of the invention, i.e. dissolution in-line by continuous flow of liquid through a powder substance contained in a cartridge and, moreover, with the view to overcoming the same difficulties related to the hazards of handling liquid concentrates prepared batch-wise before use, it was obvious for a skilled person to combine the teachings of documents R42/R43 with that of document R73 so as to apply the same concept to the production of a dialysis fluid and thus to arrive at the subject-matter of claim 1 in suit.

As to claim 1 according to the auxiliary request, the features added to the subject-matter of claim 1 of the main request were not such as to render the feature combination inventive since the selection of sodium bicarbonate or sodium chloride and the particle size of the powder were usual for the preparation of dialysis fluid concentrates from substances in powder form, e.g. as disclosed in document R49.

Reasons for the Decision

1. The appeal is admissible.

2. *Closest prior art and novelty (claim 1, main request)*

2.1 Document R42 in conjunction with document R43 represent the state of the art which comes closest to the invention. It will be, therefore, designed as documents R42/R43 in the following. Both documents describe a system originating from the patent Proprietor for preparing a dialysis fluid for a hemodialysis procedure, by making use of a system comprising the bicarbonate monitor BCM 10-1 in the AK-10 system.

As described in document R42 with reference to the schematic representation (cf. top of page 3, left column), the function of the bicarbonate monitor (BCM) is to mix a dialysis fluid from two liquid concentrate solutions prepared before use, possibly by mixing a concentrate in powder form with water in two separate containers, the whole process being controlled by a micro-processor in order to mix up a dialysis fluid, the ionic content of which corresponds as nearly as possible to that of normal plasma water of a specific composition required for treatment. This means that even if it is called bicarbonate monitor, it can be used for other purposes, e.g. as extra sodium proportioner. The bicarbonate proportioning is made in two steps. First, electrolytes like calcium, magnesium and chloride in an acid solution (A component) are added through a proportioning pump. In the next step,

the bicarbonate solution (B component) is added through a separate proportioning pump. Concentrates with different electrolyte compositions can also be used. Only a small adjustment is needed in order to get the correct solution factor.

2.2 Document R43, which is an extract of the service manual leaflet for the bicarbonate monitor BCM 10-1, explains more explicitly the working principle of the mixing system as a whole with reference to a flow diagram. The bicarbonate monitor automatically mixes the fluids from the two concentrates referred to as A and B components with water.

The A pump first adds the A component (electrolytes and acid) to the water in the main line. The conductivity of the mixture is checked by the CC(A) section of a conductivity measuring cell and this measurement is used to control the A pump motor speed (that is the flow rate of the liquid concentrate from the A container) to obtain the correct mixture at this stage. Conductivity is controlled and monitored by the micro-processor, from the temperature of the mixture which is sensed by a first temperature transducer TEGA. As commonly known, conductivity control is necessary to achieve the desired concentration value of the diluted solution and, hence, the final composition of the dialysis solution.

The B pump then adds the liquid concentrate from the B container (bicarbonate) to the first stage mixture. Again, the conductivity of the new mixture is checked by the CC(B) section to control the B pump motor speed, the correct conductivity (concentration) of the mixture having been previously calculated by the micro-processor from a second temperature transducer TECA.

Since two liquid concentrates, one of which is a bicarbonate component, are added successively into the main line supplied with water, the BCM monitor is said to provide an on-line system for dialysis with bicarbonate (cf. R42, page 2, left column) in the sense of mixing (diluting) in-line at least one liquid concentrate solution with water. Moreover, it was acknowledged by the Appellant (cf. Statement of Grounds for appeal of 10 March 1995, page 11) that container B could be either provided with only bicarbonate, i.e. only one single substance, or supplemented with sodium chloride in order to impede bacterial growth.

2.3 Following the same terminology as that used in claim 1 according to the main request, document R42/R43 actually discloses:

- a system for preparing a dialysis fluid for a hemodialysis procedure or a replacement fluid for a hemofiltration procedure or a hemodiafiltration procedure by mixing of at least one concentrate in powder form with water (preamble)

- first fluid conducting means (water main line) having a first end for communicating with a source of water to withdraw water into said first fluid conducting means and a second end for delivering said dialysis fluid or replacement fluid (feature (b))

- third fluid conducting means (line from A or B container) communicating with the outlet of a vessel (container) and with a mixing point in said first fluid conducting means intermediate said first and second ends for conducting a concentrate fluid (A or B component) from said vessel into said first fluid conducting means to be mixed with fluid being

conducted through said first fluid conducting means to thereby produce said dialysis fluid or replacement fluid in said first fluid conducting means for delivery to said second end of said first fluid conducting means (feature (d))

- measuring means in said first fluid conducting means downstream of said mixing point for measuring the composition (through conductivity) of the said dialysis fluid or replacement fluid obtained by mixing of said concentrate fluid and water in said first fluid conducting means (feature (e))

- flow regulating means (A or B pump) in said third fluid conducting means responsive to said measuring means for controlling the flow of said concentrate fluid from said vessel (feature (f))

2.4 With respect to the closest prior art document R42/R43, the subject-matter of claim 1 according to the main request is, therefore, distinguished by the following remaining features:

- the vessel (10) containing a concentrate in powder form consisting of only one single substance and arranged as a column between a water inlet of the vessel and a concentrate outlet of the vessel (feature (a))

- second fluid conducting means (8) having a first end for communicating with the source of water (2) and a second end communicating with the inlet of said vessel (10) for introducing water into said vessel (10), the second fluid conducting means (8) and the vessel (10) being dimensioned to produce a substantially saturated solution of the powder concentrate in water which thereby provides a concentrate fluid which is at a relatively constant

concentration level (feature (c))

2.5 Since no document other than document R42/R43 comes closer to the subject-matter of claim 1, it must be regarded as novel within the meaning of Article 54(1) EPC.

3. *Problem and solution*

3.1 In the dialysis fluid preparation system described in document R42/R43, difficulties occur because the liquid concentrate solutions contained in containers A and B are prepared prior to actual use, either remotely in centralized preparation plants and then transferred to the point of treatment, or directly on the spot in large tanks or in smaller containers just before a specific treatment to be started. In both cases problems arise due to the fact that certain concentrates, in particular bicarbonate concentrates, do not always remain stable and are subject to bacteria growth and precipitation if prepared in large quantities beforehand and allowed to stand for substantial periods of time (cf. patent, page 3, lines 50-56).

The videotape produced by the Appellant at the beginning of the oral proceedings clearly showed the difficulties encountered with the conventional systems, as also summarized in the Appellant's Statement of Grounds of 10 March 1995 (cf. page 15):

- bulk and handling (transport, storage and disposal of bulky and heavy containers)

- preparation (in particular dissolving of hardly soluble bicarbonate into a highly concentrated liquid)

- stability (shelf-life of the liquid concentrate, CO_2 loss, precipitation)

- sterility (bacterial growth in the liquid concentrate itself, connecting tubes and so on)

3.2 With the view to overcome these difficulties, it has already been proposed to prepare a dialysis solution just before starting the treatment, from substances in powder form packed separately in pre-weighed small bags or sachets, i.e. containing predetermined amounts of powder sufficient for one treatment. Since, however, a complete bicarbonate-containing dialysis composition (i.e. comprising all components) was difficult to produce in powder form because of the hygroscopic properties of the Ca, Mg and K chloride components, document R49 recommended the use of pre-weighed sachets each containing a mixture of only compatible powder substances, referred to as B1 and B2 components (cf. page 94 and table No. 20, page 90), the compositions of which were close to those of the A and B components described in document R42/R43. According to document R49, the contents of the pre-weighed sachets were mixed with water and dissolved in a container to form a dialysis solution just prior to use (cf. page 50; pages 139-140 and Figure 7, page 34). One was, therefore, led back to the batchwise conventional procedure, but without the difficulties related to preparing, transporting, storing and conservating large amounts of liquid concentrates.

Another neighbouring procedure was described in document R5 (EP-A-0 177 614) referred to in the background part of the patent in suit, according to which two concentrate solutions (solutions A and B) were successively prepared from two pre-packed powder concentrate compositions (compositions A and B) by mixing separately each powder composition with water,

the B composition consisting of only one substance, namely sodium bicarbonate powder ($NaHCO_3$) (cf. example 2, page 16). Also in this case, the powder form of the A and B compositions and their packaging in pre-weighed portions avoided most of the drawbacks related to the use of pre-prepared liquid concentrates. As clearly explained in document R5 (cf. page 6): "It is a further advantage of the method of the invention that, since it occurs as a powder, the product, when packed in a hermetically sealed condition, can be stored, transported and otherwise handled in a simple and easy manner and can stably retain its constant quality during a prolonged period of time, without substantial changes in quality, such as changes in pH."

Further, in documents R75 and R79 discussed at the oral proceedings (R79 illustrates a sodium bicarbonate proportioning system which is a reduction to practice of the principle disclosed in R78), a dialysis solution was prepared continuously from a predetermined amount of dry solute concentrate such as sodium bicarbonate or a mixture of bicarbonate and other dialysis solution ingredients placed in a collapsible flexible plastic bag. The bag was then connected in the flow circuit and filled with water to dissolve the solute in-line, the concentration of the resulting solution being predetermined by the amount of dry solute originally introduced into the bag. The flexible solute container could be manufactured as a disposable unit and sold with a predetermined amount of concentrate or dry reagents included therein. Such disposable units were able to minimize the hazards of technician error and saved preparation time, in addition to avoiding problems related to shipment costs and stokage of large drums of liquid concentrates.

To sum up, all systems described above make use of powder concentrates which represent one or more components of a dialysis fluid composition , some of them are formed of only one single substance, in order to prepare on the spot and shortly before the beginning of the treatment, a liquid concentrate solution by mixing small predetermined amounts of powder concentrate with water in a suitable container or reservoir, either batchwise, i.e. manually and separately (e.g. documents R5, R49) or continuously, i.e. automatically and in-line (e.g. document R78) by incorporating the mixing reservoir in the proportioning circuit of the dialysis machine.

3.3 With respect to this state of the art, the technical problem underlying the present invention was, therefore, restricted to providing another, alternative, system, of the type of continuously preparing a dialysis fluid component solution from at least one concentrate in powder form.

3.4 The solution to this problem is given by the features which are distinguished from the system disclosed in the closest prior art document R42/R43 (cf. point 2.4 above).

Stated another way, the system according to the patent in suit differs essentially by the provision of a line arranged in parallel to the main line supplied with water, said derived line incorporating a cartridge of powder concentrate, such that water flowing through the powder in the cartridge results in producing, in-line, a substantially saturated solution at a relatively constant concentration.

4. *Inventive step (claim 1, main request)*

4.1 For the Board, the dissolution phenomena that take place within the powder column are well known. This is no doubt the reason why the patent specification is silent concerning this point and restricted simply to stating, with loose terms, that the concentrate solution at the output of the cartridge is "substantially" saturated to provide a fluid at a "relatively" constant concentration. It should be noticed here that both expressions represent a mere repetition. As a matter of fact, the concentration of a saturated solution is necessarily constant, by definition, since saturation is the maximum concentration that a substance can achieve in solution in a specified solvent, at a given temperature.

4.2 For preparing a concentrate solution, three main procedures are generally known: The simple solution, prepared by dissolving the solute in a suitable solvent, e.g. by agitating or stirring the mixture in a vessel or a container. The solution by chemical reaction, prepared by reacting two or more solutes with each other in a suitable solvent. The solution according to the present patent belongs to the third category, the solution by extraction, applying the principles of the percolation process. As explained in document R80 which reflects the common general knowledge of a person skilled in the art (cf. page 1443, top of the left column), "preparations of this type may be classified as solutions but, more often, are classified as extractives".

As was correctly contented by the Appellant, extraction differs from solution in that the presence of insoluble matter is implied in the former. However, the principle of dissolution implemented in the system according to the present patent corresponds actually to the

principle of action of the percolation process as defined in document R80 (cf. page 1510, top of right column): "When a powder placed in a cylindrical vessel with a porous diaphragm below is treated from above with a liquid capable of dissolving a portion of its substance, that portion of the fluid first in contact, in passing downward, exercises its solvent power on the successive layers of the powder, **until saturated**, and is impelled downward by the combined force of its own gravity and that of the column of liquid above it, minus the capillary force with which the powder tends to retain it."

The process of dissolution applied in the patent in suit differs therefrom only in that the whole substance (and not only a portion of it) is capable of being dissolved by the solvent. Therefore, said process can be seen as a particular type of solution by extraction in which all the substance can be dissolved by flow of the liquid through the powder. Moreover, it should be noticed that since document R80 clearly specifies that saturation can be achieved if a portion only of the substance is soluble, *a fortiori*, saturation will be obtained even more easily when all the substance is soluble.

Depending on the concentration to be obtained, the liquid concentrate (percolate) which is produced is called tincture, fluidextract or extract (cf. R80, page 1519, "Extractives"). According to this terminology, the liquid concentrate produced with the system of the invention can be classified as a fluidextract, which is more concentrated than tinctures, and may be used for making diluted preparations (cf. R80, page 1520, "Fluidextracts"). The same is true with the circuit arrangement described in relation with Figure 1 of the patent in suit.

Moreover, R80 discloses (cf. page 1515, "Rate of flow") that the success of the process of percolation largely depends on the regulation of the flow of the percolate. For fluidextracts using for example 1000 g of powder the rate of flow should not exceed 5 ml/min. It is true that the cartridge of powder used in the patent is designed for producing larger flow rates, but the scope of claim 1 in suit covers a dissolution principle in general, in which specific parameters, which all depend on the intended application, are not included. As rightly mentioned in the next paragraph of R80: "The proper rate of flow should vary with the quantity and character of the drug (powder substance) employed and the density of the menstruum (solvent poured on top of the powder)".

Physico-chemical phenomena described in document R80, that take place in the percolator, correspond substantially to the explanations given by the Appellant (cf. letter of 26 January 1996, pages 3 and 4 and letter of 28 February 1997, paragraph bridging pages 5 and 6) with reference to the cartridge schematically illustrated in documents R58/R59 filed with the letters above. In fact, document R80 clearly discloses (cf. pages 1510, "Small-Scale Percolation") that the first portion of the percolate is usually the most dense and contains the largest portion of the solute principles. As the operation proceeds, each succeding portion of percolate is less active than the one preceding it.

Furthermore, document R80 discloses that the percolation process is greatly influenced by the shape of the powder reservoir, the size of which must be in proportion to the quantity of drug extracted, and by the characteristics and fineness of the powder. As explained on page 1511, left column, in making a fluidextract a comparatively tall and narrow

percolator, such as that shown in Figure 86-2A, should be selected because it is desirable that the menstruum should traverse a higher column of powder. The rate of flow of the percolator is thereby diminished, the percolate (liquid concentrate) becomes **saturated** more rapidly and thus the operation is more easily controlled, provided the percolation limit (determined by the character of the drug) has not been exceeded. Since saturation can be achieved, the dissolution process is necessarily self-controlled in the sense given by the Appellant in relation with his invention.

Moreover, it is specified in document R80 (cf. page 1511, "Comminution") that the fineness of the powder plays an important role in the good working of the process and it should be carefully selected, according to the desired concentration, the time required to exhaust the powder, the relative proportions of solvent and powder, and so on. The fineness (particle size) should, in any case, be selected to permit uniform descent of the liquid, for fine particles offer more resistance to the passage of the solvent than coarse ones. A compromise has, therefore, to be found by the person skilled in the art, as rightly summarized on top of page 1513 (right column): "The intelligent practice of the process of percolation, therefore, requires an accurate knowledge of the constituents and physical properties of medicinal substances."

4.3 Document R73 describes a parenteral delivery system for the administration of a medical fluid containing a beneficial agent to a human patient, the administration set comprising (cf. Figure 1) a primary fluid path 16 for the flow of a pharmaceutically acceptable fluid, such as water, a parallel fluid path 19 in fluid communication with the primary fluid path and an agent

formulation chamber 21 connected in the parallel fluid path. The beneficial agent in the formulation chamber thus forms *in situ*, with the fluid that enters the chamber from the primary path, an agent solution that is conveyed back into the primary path for administration to the human patient (cf. column 2, lines 56-63).

The expression "beneficial agent" generally denotes any substance that produces a therapeutic or a beneficial result such as a drug in a solid form, powder or particles, that dissolve or undergo disintegration and dissolution in the presence of a parenteral fluid and thus does not require any reconstitution, or admixture prior to use (cf. column 5, lines 22-64). The amount of agent in the formulation made in the chamber can be a trace amount to a **saturating** amount (column 3, lines 14-20 and column 6, lines 12-14). While, preferably, saturation should be avoided in the case of releasing dry medicines supposedly because of the risks of toxicity (cf. column 6, lines 14-18), the production of a saturated solution is nevertheless possible and, therefore, can be contemplated for other applications, as need be.

The formulation chamber is designed to store an amount of agent for executing a prescribed therapeutic program, i.e. for housing a dosage unit amount of the beneficial agent to produce a therapeutic or a beneficial result (cf. column 5, lines 40-45 and column 9, lines 7-10). The chamber can have any shape but it is preferably round and its length exceeds its width, i.e. shaped as a column (cf. column 7, lines 46-49). It is manufactured at low cost, e.g. as a cartridge that can be used in the parallel path once or

replaced many times. Consequently the formulation chamber is regarded as self-contained, self-priming and self-powered (and, therefore self-regulating when saturation is achieved) (cf. column 5, lines 11-13 and column 12, lines 36-44).

Therefore, in the Board's judgement, the delivery system described in document R73 discloses all the features which were missing in the disclosure of the closest prior art document R42/R43 (cf. point 2.4 above), to arrive at the subject-matter of claim 1. These features are:

- a vessel 21 containing a concentrate in powder form consisting of only one single substance and arranged as a column between a water inlet 24 of the vessel and a concentrate outlet 25 of the vessel (feature (a))

- second fluid conducting means 19 having a first end for communicating with the source of water 11 and a second end communicating with the inlet 24 of said vessel for introducing water into said vessel 21, the second fluid conducting means and the vessel being dimensioned to produce a substantially saturated solution of the powder concentrate in water which thereby provides a concentrate fluid which is at a relatively constant concentration level (feature (c)).

4.4 Starting from the dialysis fluid preparation system disclosed in document R42/R43, the skilled person looking for alternative means for preparing in-line a liquid concentrate from a powder concentrate, was able to find suitable means in the arrangement proposed in document R73. By simply replacing the liquid concentrate line from container B in document R42/R43 by the line 19 shown in Figure 1 of document R73, which

incorporates a cartridge of powder concentrate connected upstream to the water main line, he could arrive directly at the subject-matter of claim 1. A direct suggestion to do so is to be seen in the fact that the system disclosed in document R73 was proposed, like in the present patent, as an alternative for producing in-line concentrate solutions, with the view to replacing the conventional systems of drugs added to a fluid in a container, prior to use, (cf. column 1, line 54) or administrated by a proportioning pump (cf. column 1, line 61). Therefore, the same general solution had been adopted in the past to solve the same problem as is solved by the present patent.

4.5 Moreover, the Board observes that document R73 is not restricted to the parenteral administration of dry medicines, such as drugs, but refers more generally to the fields of administering sterile fluids such as, among others, aqueous solutions of sodium chloride or various other electrolytes, administrated either intravenously or by intraperitoneal route (cf. column 1, lines 23-39). Again, it is stressed (cf. column 13, lines 25-44) that the parallel arrangement described therein can be used for the administration of many beneficial agents and preferably in intravenous fluid replacement such as administering plasma or saline or as a method in intravenous electrolyte-balance replacement, such as supplying sodium, potassium or chloride ions to a patient in need of electrolyte restoration.

Likewise, the claimed subject-matter is not confined to a system for preparing a dialysis fluid but more generally a replacement fluid for hemodialysis or hemodiafiltration procedures, i.e. for preparing electrolyte solutions capable of restoring the electrolytic need of a patient, sodium bicarbonate and sodium chloride being the two main sources of

electrolytes commonly used in the preparation of a dialysis fluid, the composition of which must be as close as possible to the specific blood plasma composition of a patient. Moreover, the preparation system according to the invention can still be used in connection with other medical treatments or procedures such as, for example, the production of flushing fluid for cleaning of wounds or the like (cf. patent, page 3, lines 11-15).

Taking account of the numerous possible applications offered by the patent system, the skilled person will immediately conclude that the system disclosed in document R73 which is concerned with neighbouring or even similar general applications will be also suitable for preparing dialysis fluids, although not expressly mentioned in this document.

4.6 Furthermore, the Board also considered that the main object of document R73 was to provide a system for automatically constituting an agent formulation *in situ* that could be administrated at any selected time (cf. column 3, lines 9-13), i.e. at a controlled rate and according to a preselected program, comprising continuous or repeated administration as needed (cf. column 2, lines 24-32), with the view to avoiding problems such as sterility and instability of aqueous solutions reconstituted or mixed prior to use (cf. column 1, line 67 to column 2, line 12).

Since, therefore, the same difficulties as those stated in the patent in suit were addressed in document R73 and were resolved in the same way to gain the same advantages, the skilled person would have been prompted to make use of the in-line preparation and dissolution concept and system described therein to prepare dialysis fluids as well.

4.7 It is true that the embodiment disclosed in document R73 is intended primarily for the administration of medicines and for dissolving smaller amounts of powder at smaller flow rates compared with those involved for producing a dialysis fluid. However, as explained before, the known system is not restricted to one application. For a skilled person, it is self-evident that the dimensions of the cartridge of powder have to be adapted in relation to the amount and the characteristics of the solvent and the substance to be dissolved, i.e. in dependance on the contemplated application. Size adaptations are generally considered as falling within the normal competence of a person skilled in the art, and do not alter the fact that the same structure will necessarily produce the same effects, i.e. in the present case, the production in-line of a high concentrated solution by making use of the well known principle of solution by extraction (cf. document R80).

4.8 As explained above (cf. point 4.1) the subject-matter of claim 1 is drafted as a general solution, and in particular the last part of feature (c) is drafted in the form of a result with indefinite terms ("dimensioned to produce a **substantially** saturated solution ... at a **relatively** constant concentration level").

In the absence of more detailed information from the patent specification regarding the physico-chemical phenomena that occur within the cartridge, it is quite impossible to determine with certainty whether the preparation system according to the present patent actually works in a different way from that of document R73. However, in consequence of similar structural features, the teaching of document R73 leads to the claimed subject-matter.

Moreover, since feature (c) does not allow the claimed system to be clearly distinguished from the known system, the inventiveness of the solution cannot be validly based on this feature and the Appellant's arguments based on a presumed distinction of function are not accepted.

Besides, the Board observes that the concentration of the solution produced with the claimed system is not maintained rigorously constant over the whole period of the dialysis treatment, as illustrated on the diagram provided by the Appellant (R57). Also, the patent specification states (cf. page 6, lines 20-23): "In this manner, it is possible to accurately control the ultimate mixture ... even if the concentrate in powder form were to dissolve to different extents or degrees of saturation by virtue of the water being conducted through the concentrate fluid circuit".

Therefore, the importance of maintaining a constant concentration at the outlet of the cartridge should not be overvalued, the more since the concentrated solution is then diluted with water flowing from the main line and the final concentration of the diluted solution still controlled by regulating the flow rate of the concentrated solution at the cartridge outlet, by a measurement of conductivity on the main line, downstream of the mixing point.

4.9 Other indications of the presence of inventiveness such as simplicity of the system, long-felt want or commercial success are not sufficiently persuasive to reverse the above conclusion of obviousness, where the need was directly satisfied by the use of a means which clearly suggested itself as highly suitable.

Relating to this, it is pointed out that a mere investigation for so-called "indications" of the presence of an inventive step is no substitute for the technically relevant assessment of the invention *vis-à-vis* the state of the art, involving the recognition and solution of the technical problem in the case.

4.10 For all the foregoing reasons, the Board is satisfied that the subject-matter of claim 1 according to the main request lacks any inventive step in the face of the combination of the teaching of document R42/43 with the teaching of document R73, having regard to the common general knowledge of a person skilled in the art, as reflected by document R80. Therefore, the requirements of Article 56 EPC are not fulfilled.

5. *Inventive step (claim 1, auxiliary request)*

5.1 The subject-matter of claim 1 according to the auxiliary request differs from the main request by the incorporation of the two following features:

(a1) said single substance being either sodium bicarbonate or sodium chloride;

(a2) said power form having a particle size which, in the case of sodium bicarbonate, is greater than 100 microns;

5.2 The selection of substances such as sodium bicarbonate or sodium chloride fails to add any inventive matter to the features of the main request, since it is well-known that sodium bicarbonate and sodium chloride are just the two main substances of any standard bicarbonate-containing dialysis fluid composition and that said substances provide the electrolytes which are necessary to the electrolyte balance of a patient.

Now, as was already considered, document R73 specifies that the term "beneficial agent" is not restricted to a medicine but embraces as well an electrolyte and/or the like (cf. column 5, lines 50-53). The system described in document R73, therefore, appears to be appropriate for preparing also concentrate solutions of electrolytes, which is the generic expression for dialysis solutions containing sodium bicarbonate and/or sodium chloride.

Moreover, the fact that sodium bicarbonate is very little soluble in water cannot be regarded as a hindrance or a deterrent to using the in-line dissolution system disclosed in document R73 since, as demonstrated before in relation with document R80, solution by extraction (percolation) was specifically used for preparing solutions from partially soluble materials.

5.3 In the Board's view, it comes within the normal competence of the skilled person to determine the particle size which is regarded as optimum to provide good working conditions for the whole system, which implies consideration of various parameters such as, besides particle size, nature and physical-chemical characteristics of the solvent and the substance to be dissolved, design and sizing of the conducts and the cartridge, all in dependence of the amount of powder and the flow of fluid concentrate which is required. Such considerations are clearly explained in document R80 (cf. point 4.2 above) and also in document R75 (cf. section: Methods of Operation) which refers to leaching (percolation) in the following

terms: "Whatever the mechanism and the method of operation (sprayed percolation, immersed percolation, or solids dispersion), it is clear that the leaching process will be favoured by increased surface per unit volume of solids to be leached and by decreased radial distances that must be traversed within the solids, both of which are favoured by decreased particle size. Fine solids, on the other hand, cause slow percolation rate. The basis for an optimum particle size is established by these characteristics." In the Board's judgement, particle sizing is, therefore, typically a routine matter for a person skilled in the art.

Furthermore, although document R49 (cf. pages 91 and 111) refers to a powder mixture of several substances for preparing a bicarbonate-containing dialysis solution according to the conventional batch procedure, said mixture has a particle size (less than 200 microns) of the same order as that claimed (greater than 100 microns). Therefore, such particle size is nothing surprising and even regarded as usual as far as bicarbonate is concerned, whatever the dissolution system may be (batch or in-line).

5.4 For all the foregoing reasons, the Board is satisfied that the subject-matter of claim 1 according to the auxiliary request also lacks any inventive step, in the face of the same combination of documents as considered against the main request.

6. Since independent claim 1 (main or auxiliary request) which discloses the most general subject-matter is not allowable under Article 56 EPC, examination of the other claims is unnecessary.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

S. Fabiani

The Chairman:

H. Seidenschwarz