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Datasheet for the decision of 14 October 2021

Case Number: T 2411/18 - 3.3.07

Application Number: 08829225.5

Publication Number: 2200650

IPC: A61K47/18, A61K31/5575

Language of the proceedings: EN

Title of invention:
BUFFER SOLUTIONS HAVING SELECTIVE BACTERICIDAL ACTIVITY AGAINST GRAM NEGATIVE BACTERIA AND METHODS OF USING SAME

Patent Proprietor:
United Therapeutics Corporation

Opponents:
Teva Pharmaceutical Industries Ltd
Generics (U.K.) Limited

Headword:
BUFFER SOLUTIONS HAVING SELECTIVE BACTERICIDAL ACTIVITY AGAINST GRAM NEGATIVE BACTERIA AND METHODS OF USING SAME/ United Therapeutics Corporation

Relevant legal provisions:
RPBA Art. 12(4)
EPC Art. 123(2), 56, 53(c), 54(5)

Keyword:
Admission of a new document (Yes)
Main request - Extension beyond the content of the application as filed (Yes)
Auxiliary request 1 - Extension beyond the content of the application as filed (No)
Auxiliary request 1 - Inventive step (No)
Choice of the closest prior art
Problem Invention (No)
Auxiliary request 2 - Extension beyond the content of the application as filed (Yes)
Auxiliary request 3 - Article 53(c) EPC

Decisions cited:
T 0611/09, T 2016/11, T 0967/97, T 0021/08, T 0710/97, T 2147/18

Catchword:

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Case Number: T 2411/18 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 14 October 2021

Appellant: (Opponent 1)	Teva Pharmaceutical Industries Ltd 5 Basel Street P.O. Box 3190 49131 Petah Tiqva (IL)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Appellant: (Opponent 2)	Generics (U.K.) Limited Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	FRKelly 27 Clyde Road Dublin D04 F838 (IE)
Respondent: (Patent Proprietor)	United Therapeutics Corporation 1040 Spring Street Silver Spring Maryland 20910 (US)
Representative:	Nederlandsch Octrooibureau P.O. Box 29720 2502 LS The Hague (NL)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 9 August 2018 concerning maintenance of the European Patent No. 2200650 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	D. Boulois
	Y. Podbielski

Summary of Facts and Submissions

I. European patent No. 2 200 650 was granted on the basis of a set of 10 claims.

Independent claim 1 as granted read as follows:

"1. A solution with an effective amount of treprostinil sodium for use in a method of reducing the occurrence of a blood stream infection in a human suffering from pulmonary arterial hypertension and being treated with tresprostinil, said solution being obtainable by a process comprising diluting a starting solution of treprostinil sodium with a buffer comprising glycine and having a pH of greater than 10."

II. The patent was opposed under the grounds that its subject-matter lacked novelty and inventive step, was not sufficiently disclosed and extended beyond the content of the application as filed.

III. The appeal lies from the decision of the opposition division finding that the patent in amended form meets the requirements of the EPC. The decision was based on 4 sets of claims filed with letter of 1 December 2017 as main request and auxiliary requests 1-3.

Claim 1 of auxiliary request 3 read as follows difference(s) compared with claim 1 as granted shown in bold:

"1. A solution ~~**with an effective amount of treprostinil sodium**~~ for use in a method of reducing the occurrence of a blood stream infection in a human suffering from

pulmonary arterial hypertension and being treated with treprostinil, **wherein said method reduces the gram negative bacteria and inhibits the growth of gram positive bacteria**, said solution **comprising ~~being obtainable by a process comprising diluting a starting solution of~~** treprostinil sodium **in a concentration of between 0.001 mg/mL and 1 mg/mL and ~~with~~** a buffer comprising glycine and having a pH of greater than 10 **and a buffer capacity of 0.01 or less**."

IV. The documents cited during the opposition proceedings included the following:

D1: EP 0 347 243 A1

D2: Understanding Bacteria, Srivastava & Srivastva, p. 117-119 (2003)

D3: An Introduction to Microbiology, Hugo, W.B. et al, 2nd Ed., p. 57-59

D4: Effect of Glycine on Helicobacter pylori in Vitro, Minami M. et al., Antimicrob. Agents and Chemotherapy, 48:10, p. 3782-3788 (2004)

D6: Treprostinil for pulmonary hypertension, Skoro-Sajer et al., Vascular Health and Risk Management, June 2008, 4(3), p. 507-513

D7: Bloodstream infections among patients treated with intravenous epoprostenol or intravenous treprostinil for pulmonary arterial hypertension – Seven Sites, United States, 2003-2006, Centers for Disease Control and Prevention (CDC), Morb. Mortal. Wkly Rep., 2 March 2007, 56(08), p. 170-172

D11: Stability and preservative effectiveness of treprostinil sodium after dilution in common intravenous diluents, Phares et al., Am. J. Health Syst. Pharm., 1 May 2003, 60, p. 916-922

D15: WO 2007/092343 A2

D24: Highlights of Prescribing Information, Remodulin safety and effectivity

D25: Experimental Pharmaceutical Technology - Parrott, E.L. and Saski, W., Burgess Publishing Company, USA, Second edition 1965, p. 140
D26: Pharmaceutical Technology - Fundamental Pharmaceutics, Parrott, E.L., Burgess Publishing Company, USA, Third printing , 1971, p. 233
D27: T 611/09

V. According to the decision under appeal, the main request and auxiliary request 1 did not meet the requirements of Articles 123(2) and 123(3) EPC. Auxiliary request 2 did not meet the requirements of Article 123(2) EPC.

The subject-matter of auxiliary request 3 met the requirements of Articles 123(2) and 123(3) EPC. As regards the claimed concentration, a basis was found in original claim 8. The claimed subject-matter was novel.

The opposition division also considered that the claimed invention was sufficiently disclosed, in particular in view of the claimed medical indication.

As regards inventive step of auxiliary request 3, D1 was considered to be the closest prior art, rather than D15 which focused on another active agent. The claimed subject-matter differed in the treprostinil concentration, the buffer capacity, and in the claimed effects, namely reducing the occurrence of blood stream infection in a human and reducing the gram negative bacteria and inhibiting the growth of gram positive bacteria. The problem was defined as the provision of a composition which reduces the occurrence of blood stream infections. D24 rendered plausible that the problem was solved, and D6, D7 and D11 made clear that a problem of blood stream infections occurred in

patients treated I.V. with treprostinil. The opposition division considered that the skilled person would not have combined D2, D3 and D4 with D1. Thus, the claimed subject-matter of auxiliary request 3 was inventive.

VI. Opponents 01 and 02 (hereinafter appellants 01 and 02) filed an appeal against said decision.

VII. With its statement setting out the grounds of appeal, appellant 02 submitted the following items of evidence:
D29: EP 1 107 807 B1
D30: Copy of Board of Appeal decision in T 2251/14
D31: W. Hammes, K.H. Schleifer, O. Kandler; "Mode of Action of Glycine on the Biosynthesis of Peptidoglycan", J. Bacteriol., 1973, Nov., 116(2), pages 1029-1053.

VIII. With its statement setting out the grounds of appeal, appellant 01 submitted the following items of evidence:
D32: FDA label for Remodulin (treprostinil sodium) injection (2006), earlier publication version of D24 (original copy starts on page 3).

IX. With its reply to the appeals, the patent proprietor (hereinafter the respondent) filed a main request, corresponding to auxiliary request 3 maintained during the opposition proceedings, and auxiliary requests 1 to 3.

Claim 1 of auxiliary requests 1-3 read as follows, difference with the main request shown in bold:

Auxiliary request 1

"1. A solution for use in a method of reducing the occurrence of a blood stream infection in a human

suffering from pulmonary arterial hypertension and being treated with treprostinil, wherein said method reduces the gram negative bacteria and inhibits the growth of gram positive bacteria, said solution comprising treprostinil sodium in a concentration of between ~~**0.001 mg/mL and 1 mg/mL**~~ **0.004 mg/mL and 0.13 mg/mL** and a buffer comprising glycine and having a pH of greater than 10 and a buffer capacity of 0.01 or less."

Auxiliary request 2

"1. A method of reducing the occurrence of a blood stream infection in a human suffering from pulmonary arterial hypertension and being treated with treprostinil, wherein said method reduces the gram negative bacteria and inhibits the growth of gram positive bacteria, the method comprising administering a ~~said~~ solution comprising treprostinil sodium in a concentration of between 0.001 mg/mL and 1 mg/mL and a buffer comprising glycine and having a pH of greater than 10 and a buffer capacity of 0.01 or less."

Auxiliary request 3

"1. A method of reducing the occurrence of a blood stream infection in a human suffering from pulmonary arterial hypertension and being treated with treprostinil, wherein said method reduces the gram negative bacteria and inhibits the growth of gram positive bacteria, the method comprising administering a ~~said~~ solution comprising treprostinil sodium in a concentration of between ~~**0.001 mg/mL and 1 mg/mL**~~ **0.004 mg/mL and 0.13 mg/mL** and a buffer comprising glycine and having a pH of greater than 10 and a buffer capacity of 0.01 or less."

X. A communication from the Board, dated 1 April 2020, was sent to the parties. In it the Board expressed its preliminary opinion that the main request did not meet the requirements of Article 123(2) EPC and that D1 was the closest prior art for the assessment of inventive step. Moreover,the Board considered that auxiliary requests 2 and 3 did not meet the requirements of Article 53(c) EPC.

XI. Oral proceedings took place on 14 October 2021 in the form of a mixed mode hearing, i.e. in presence of the respondent, and with appellant 01 attending by videoconference.

XII. The arguments of the appellants, may be summarised as follows:

Admission of D31 into the appeal proceedings

D31 provided evidence of the fact that the antibacterial effects of glycine were well known in the art at the filing date and were part of the skilled person's common general knowledge.

Main request - Amendments

According to appellant 02, claim 1 comprised added matter in view in particular of the feature of "a concentration of between 0.001 mg/ml and 1 mg/ml" , which was not directly and unambiguously disclosed in the application as filed in combination with the other features.

Auxiliary request 1 - Inventive step

According to appellant 01, D1 was the closest prior art in view of example 1.

The claimed method could not be a method within the meaning of Article 53(c) EPC, in view of the lack of evidence of such effects, and therefore Article 54(5) EPC did not apply. It was apparent from the disclosure of the patent that the antibacterial effect of the glycine solution occurred outside of the human body. There was no teaching that the solution exerts an *in vivo* antibacterial effect. This view was supported by established case law, namely T 611/09 or T 2016/11.

Accordingly, the only distinguishing features over example 1 of D1 were the concentration of treprostinil (0.004 mg/mL to 0.13 mg/mL) and the buffer capacity (0.01 or less). With regard to the treprostinil concentration range this seemed entirely conventional, as shown in D11. With regard to the buffer capacity, this was a measure of the strength of a buffer system, namely the amount of acid or base that can be added before the pH of the solution shifts. In cases such as the present, where the pH of the administered solution varies significantly from physiological pH, it was well-known that the buffer capacity should be low to avoid disrupting the physiological pH, as shown in D25 and D26. As such, the subject-matter of claim 1 lacked an inventive step over D1 in light of the common general knowledge.

If the claimed method was however considered to be a method within the meaning of Article 53(c) EP, the conclusions would be the same. It was already known at the priority date that IV administration of a drug, in

particular treprostinil, was associated with an increased risk of blood stream infection, see D7, D8 or D29. It would have been obvious, based on common general knowledge alone, that the glycine buffer solution described in example 1 of D1 would reduce the occurrence of blood stream infections in the same way as described in the patent.

According to appellant 02, D1 was considered the closest prior art to the claimed subject-matter. Neither the feature relating to the concentration of treprostinil nor the buffer capacity had been demonstrated in the patent to have any effect on the reduction of blood stream infections. Therefore, these features could not be considered to contribute to the claimed solution of the objective technical problem and were, in any event, obvious for instance in view of D11 and D26. With regard to the feature that the claimed solution reduced the occurrence of blood stream infection in a human and was effective in reducing the gram negative bacteria and inhibiting the growth of gram positive bacteria, the patent failed to demonstrate a therapeutic effect in accordance with Article 54(5) EPC. Therefore, there was no "new clinical situation" which could distinguish the claimed solution from D1. There was absolutely no evidence in the patent, or on file, that the claimed solution could treat existing blood stream infections.

The antibacterial effects of the buffer were well known in the art and part of the skilled person's common general knowledge. Thus, the use of glycine and a high pH (of 10.5) in the buffer disclosed at example 1 of D1 would have been known, or at the very least suspected, to be useful in providing a sterile solution of treprostinil, which sterile solution would be expected

to reduce the occurrence of blood stream infections when administered. Moreover, in view of D2, D3, D4, and D31, the skilled person was well aware, and it was part of his/her common general knowledge, that glycine buffers and buffers of high pH have antibacterial and bacteriostatic activity, including activity against gram negative bacteria such as E. coli. For at least these reasons, the subject-matter of claim 1 could not be considered inventive in view of D1.

Auxiliary request 2 and 3

According to appellant 01, if the therapeutic indication was recognized, then claim 1 of each request could not meet the requirements of Article 53(c) EPC.

XIII. The arguments of the respondent may be summarised as follows:

Admission of D31 into the appeal proceedings

D31 was used as alleged evidence of the antibacterial nature of glycine, and could have been presented in the first instance proceedings. The document was also *prima facie* not relevant.

Main request - Amendments

The application as a whole had to be considered in determining what the skilled person would derive from it. The application described the claimed combinations in particular in original claims 1 and 2 and in paragraphs [0008]/[0009]. The skilled person would understand that these features applied to all aspects of the invention of original claim 1.

Auxiliary request 1 - Amendments

A direct basis for the concentration could be found in paragraph [0009] of the application as filed.

Auxiliary request 1 - Inventive step

The claims of auxiliary request 1 were medical use claims, since the claimed use was performed in the human and the effect in reducing the occurrence of infection was observed *in vivo*. The situation was different than in decision T 611/09 cited by the appellants, since there was an *in vivo* action of the claimed composition, as shown in document D24. Moreover, none of the appellants provided evidence that raised serious doubts, substantiated by verifiable facts that the method of the patent did not provide the effect of lowering the incidence of BSI.

If D1 was considered as the closest prior art, which had been done by the opposition division, then the claimed subject-matter was inventive in view thereof, as the opposition division had correctly decided. In view of D1, the relevant distinguishing features were: (i) the buffer capacity of 0.01 or less, and (ii) the new use of reducing the occurrence of BSI and reducing gram negative bacteria and inhibiting the growth of gram positive bacteria. The effect of the new solution was duly demonstrated experimentally, either *in vitro* in the examples of the patent, or *in vivo* with the study reported in D24.

Thus, in view of D1, the objective technical problem to be solved was to provide an improved solution of treprostinil for patients suffering from pulmonary arterial hypertension (PAH) that reduces the occurrence

of blood stream infection (BSI). Starting from D1, the skilled person would not have arrived at the claimed invention. First and foremost, D1 was completely silent as to bacterial infections associated with treprostinil solutions. Furthermore, neither the specification nor the specific examples of D1 disclosed or suggested that gram negative bacteria would be reduced or that gram positive bacteria growth would be inhibited. There was no reason for the skilled person to believe that by fine tuning the buffer capacity of the solutions of D1, such an effect would be achieved. The solutions using the glycine buffer according to the invention had shown to reduce BSI (blood stream infection). There was no comparable teaching in D1.The skilled person had no incentive whatsoever to employ such a buffer, certainly not in the expectation of reducing bacteria and blood stream infections, which effect was nowhere discussed in D1.

Thus, neither the specific buffer of claim 1, nor the claimed medical use was obvious in view of D1. Likewise, changing D1 in a manner to arrive at the present invention was not obvious since none of the cited prior art hinted to the use of the solution comprising treprostinil and the buffer as recited in claim 1 for such new use, namely reducing the gram negative bacteria and inhibiting the growth of gram positive bacteria, thereby reducing the occurrence of a blood stream infection in a human suffering from pulmonary arterial hypertension.

When applying the standards for selecting a closest prior art document, which should be in the same field of the invention and directed to the same problem, D1 should not have been selected as the closest prior art, because it was not directed to the problem of BSI; D1

related to the solution. It was established case law that a document related to the solution could not serve as the closest prior art.

The problem that the invention addressed was unknown in D1 and the present case thus amounted to a situation of a "problem invention".

The most suitable starting point for the assessment of inventive step was the solution presented in D24, namely the use of sterile water or 0.9% sodium chloride along with catheter care guidelines. However, as D24 further stipulated, this prior art solution was far from satisfactory in reducing BSI. Hence, the present invention provided an improved solution for reducing BSI in PAH patients receiving treprostinil treatment. Nothing in the art provided the skilled person with any incentive to use the buffer as recited in claim 1 for that effect. Also no such incentive was provided by D1, which was completely silent about BSI. The skilled person would thus not have modified the solution of D24, let alone use the buffer of claim 1.

During the oral proceedings, the respondent also argued that D7 could be the closest prior art and that the claimed solution was not obvious from this starting point.

Auxiliary request 2 and 3

These requests were filed in case the Board would not have considered the claims as directed to a medical use. They were based on the main request, but reworded as a non-therapeutic method.

During oral proceedings, the respondent expressed the wish to discuss the requirements of sufficiency of disclosure to establish whether a medical use was indeed disclosed, and accordingly whether the claims of auxiliary requests 2 and 3 met the requirements of Article 53(c) EPC.

XIV. Requests

Appellant 01 requested that the decision under appeal be set aside and that the patent be revoked. Appellant 02 had made the same request in writing.

The respondent requested that the appeals be dismissed and the patent be maintained in the form held allowable by the opposition division, or, alternatively, that the patent be maintained on the basis of one of auxiliary requests 1-3 submitted with the reply dated 29 April 2019. They also requested that document D31 not be admitted into to appeal proceedings.

Reasons for the Decision

1. Admission of D31

This document was filed by appellant 02 with its statement of grounds of appeal, and hence at the earliest stage of the appeal proceedings.

D31 is a journal article relating to the bacterial growth inhibition properties of glycine which has been filed to establish that it was common general knowledge that glycine had antibacterial properties at the effective date of the contested patent. D31 discloses common general knowledge which was also presented in

D2, D3 and D4. As such, D31 can therefore not be considered as presenting surprising or new information.

Moreover, it is a direct response to the decision of the opposition division which reasoned that D2, D3 and D4 could not be considered with regard to the obviousness of the claimed solution.

The document has therefore been filed in response to questions raised during the opposition proceedings and mentioned in the decision of the opposition division, which remain relevant in the appeal proceedings. They were filed to further support the evidence already presented in the opposition proceedings.

Consequently, the Board admits D31 into the appeal proceedings (Article 12(4) RPBA 2007).

2. Main request - Amendments

2.1 According to appellant 02, claim 1 comprises added matter since the claim encompasses a combination of features which had not been disclosed in the application as filed, especially with regard to the feature "a concentration of between 0.001 mg/ml and 1 mg/ml" which was disclosed in original dependent claim 8 only in combination with other features now omitted from claim 1. In addition, the features now in claim 1 were absent from claim 1 as originally filed.

2.2 The feature "treprostinil sodium in a concentration of between 0.001 mg/ml and 1 mg/ml" is disclosed only in original claim 8 which is a claim dependent on original claim 1.

The subject-matter of claim 1 as originally filed relates however to "a method of selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria **in a pharmaceutical preparation**…". Hence, said original claim 1 relates clearly to an ***ex vivo*** bacteriostatic and bactericidal activity in pharmaceutical preparations.

On the other hand, claim 1 of the main request relates now to "a solution for use in a method of reducing the occurrence of a blood stream infection in a human suffering from pulmonary arterial hypertension and being treated with treprostinil, wherein said method reduces the gram negative bacteria and inhibits the growth of gram positive bacteria", i.e. claim 1 concerns a product for use in a method involving an ***in vivo*** bacteriostatic and bactericidal action of the solution. This corresponds to the claim interpretation put forward by the respondent.

Accordingly, the feature "a concentration of between 0.001 mg/ml and 1 mg/ml" is now disclosed in claim 1 of the main request in combination with a different subject-matter than that disclosed originally in claims 1 or 8 as filed.

2.3 The respondent argued that claim 1 of the main request finds a basis in paragraphs [0008] and [0009] of the original application. However, said passage discloses a concentration comprised "between about 0.004 mg/mL to about 0.13 mg/mL treprostinil", which is different from the claimed concentration.

2.4 Consequently, the main request does not meet the requirements of Article 123(2) EPC.

2.5 The appellants also argued that the solutions defined in claim 1 of the main request did not exclude the presence of epoprostenol sodium, whereas claim 1 and paragraph [0008] of the original application specified that "the active ingredient is not epoprostenol sodium". In their view, it followed from the omission of this features that claim 1 of the main request included subject-matter extending beyond the content of the application as filed.

The Board considers that the omitted feature would be redundant in claim 1 of the main request since this claim specifies the presence of treprostinil as active ingredient of the solution and indicates that the solution is for use in a method of reducing the occurrence of blood stream infection in a patient being treated with treprostinil. Furthermore, paragraph [0009] of the original application, which describes a treprostinil solution having the same concentration of active ingredient as claim 1 of the main request, does not specify that "the active ingredient is not epoprostenol sodium".

3. Auxiliary request 1 - Amendments

Claim 1 of auxiliary request 1 has been amended by the feature "comprising treprostinil in a concentration of between 0.004 mg/mL and 0.13 mg/mL". Said feature is directly and unambiguously disclosed in paragraphs [0008] and [0009] of the original application, in combination with the remaining features of claim 1.

Consequently, auxiliary request 1 meets the requirements of Article 123(2) EPC.

4. Auxiliary request 1 - Inventive step

4.1 The invention relates to buffer solutions having bacteriostatic and/or bactericidal activity (see par. [0001]).

4.1.1 Independent claim 1 is drafted in the form of a purpose-related product claim pursuant to Article 54(5) EPC. This article acknowledges the novelty of substances or compositions, even if they form part of the prior art, provided they are claimed for a new specific use in a method, which is excluded pursuant to Article 53(c) EPC, such as a method for treatment of the human/animal body by therapy.

4.1.2 In the present case, claim 1 relates to a solution "for use in a method of reducing the occurrence of a blood stream infection in a human suffering from pulmonary arterial hypertension and being treated with treprostinil, wherein said method reduces the gram negative bacteria and inhibits the growth of gram positive bacteria...".

The respondent argued repeatedly and consistently in the opposition and appeal proceedings that claim 1 had to be considered as a "medical use claim", since the claimed use and the reduction of the occurrence of infection are observed *in vivo*. The opposition division took the same view in its decision. The drafting of claim 1 also clearly corresponds to a composition for use in a method referred to in Article 53(c) EPC.

The appellants essentially argued that the method of reducing the occurrence of a blood stream infection in a human referred to in claim 1, was not a method of treatment within the meaning of Article 53(c) EPC

because the antibacterial effect of the glycine occurred outside of the human body. This position was supported in the appellants view by decision T 611/09. It followed that claim 1 of auxiliary request 1 could not be regarded as a purpose-limited product claim pursuant to Article 54(5) EPC.

The Board does not concur with the positions expressed by the appellants. The glycine-containing treprostinil solution of claim 1 is administered to humans suffering from PAH. This administration results in a therapeutic effect on the humans, namely the prevention of blood stream infection, which, as observed by the opposition division (see point 37 of the decision) is supported by the experimental data disclosed in the patent and in document D24. The method incorporated in claim 1 is therefore of therapeutic nature in the sense of Article 53(c) EPC and limits the scope of the claim in accordance with Article 54(5) EPC.

4.1.3 As to the appellants reference to T 611/09 the following is noted. Claim 1 of the main request (drafted in the "Swiss-type" format), referred to the use of a lock solution in the treatment of a bacterial infection and in the prevention of a substantial risk of infection. In point 4.1.2 of the decision the Board came to the conclusion that the antibacterial activity of the solution took place in the lumen, i.e. in a part of the catheter that is located outside of the human or animal body. On that basis, the Board concluded that the use recited in claim 1 was not a therapeutic one in the sense of Article 52(4) EPC 1973. A fundamental aspect of the Board's reasoning was an observation based on the disclosure of the contested patent, namely that the citrate in the lock solution was "inactivated by calcium in the blood or calcium derived from body

stores...and can therefore not exert any therapeutic effect within the human or animal body".

In contrast to the situation underlying decision T 611/09 there is however no indication in the present case that the glycine composition is inactivated upon entering the human body. Moreover, no discussion is made in T 611/09 in relation to the use of the lock solution in the prevention of an infection. As explained in point 4.1.2 above, in the present case the administration of the solution results in a therapeutic effect on the humans namely the prevention of blood stream infection.

The Board notes that this conclusion is in line with T 2147/18 (see point 5.3).

4.2 The opposition division considered D1 to be the closest prior art. D1 was also the choice of appellants 01 and 02.

D1 discloses in example 1 the administration of treprostinil for the treatment of pulmonary arterial hypertension (PAH) in a glycine buffer at pH 10.5 at various doses, i.e. 100ng, 300ng, 1µg and 3µg/kg/min. D1 indicates that the injectable formulations comprise between 0.1 to 5% w/v of the active agent (see page 5, lines 48-55).

This document does not disclose the **buffer capacity** and the **effectiveness in reducing the gram negative bacteria and inhibiting the growth of gram positive bacteria, with the effect of reducing the occurrence of blood stream infection**. The respondent also considered that the **claimed concentration** was not disclosed in D1. The Board notes that the disclosed range limit of 0.1

wt% falls within the range of claim 1. However, having regard to the fact that example 1 of D1 does not contain any reference to the passage of page 5, it will be assumed that the concentration of treprostinil constitutes also a further distinguishing feature.

4.3 The respondent contested the choice of D1 as the closest prior art. Nonetheless, it failed to indicate in due time a suitable alternative document to be used as the closest prior art. Indeed, in its written submissions it relied on D24 as the closest prior art which is however a document published after the filing date of the opposed patent. Then, for the first time during the oral proceedings, it presented arguments starting from D7 as the closest prior art.

4.3.1 The Board recalls that the claimed subject-matter must involve an inventive step vis-à-vis each document of the prior art. If the person skilled in the art has *a priori* the choice between several documents of the state of the art as reasonable starting points, the inventive step can indeed only be effectively recognized after having applied the problem-solution approach to each of the options (T 967/97, T 21/08). If one of the options highlights the obviousness, then there is no inventive step. The problem-solution approach may thus need to be repeated for each of said options considered by those skilled in the art as reasonable starting points (T 710/97).

4.3.2 Regardless of whether D7 could be a considered as the closest prior art, the Board is of the view that D1 represents a reasonable starting point for the assessment of inventive step for the following reasons. The claimed invention aims at reducing the occurrence of a blood stream infection in a human suffering from

pulmonary arterial hypertension and being treated with treprostinil. Any document disclosing the treatment or prevention of pulmonary arterial hypertension with the same active ingredient is a relevant document that can potentially be used as a starting point for the assessment of inventive step. This requirement is fulfilled by a number of documents on file, including D1. Moreover, the absence of the mention of a further possible reduction of a blood stream infection in D1 does not disqualify this document as possible closest prior art, since the specific medical indication of the reduction of a blood stream infection is intrinsically linked with the general treatment of the same patients for the same general indication of PAH. There is no teaching in the contested patent that the claimed compositions have to be used for reducing the occurrence of a blood stream infection in general and in any patient, said teaching being limited to the treatment of patients suffering from PAH and being treated with treprostinil.

4.3.3 The respondent also argued that D1 was not a suitable closest prior art since it disclosed the "solution" of the invention, namely the presence of a glycine-containing buffer in the treprostinil solution. The Board understands that the inventors addressed the problem of reducing the risk of blood stream infection associated with the administration of treprostinil and solved this problem by adding a glycine containing buffer to the composition. However, as discussed above, the presence of an inventive step must be shown vis-à-vis any prior art document and in its assessment the judging body is not obliged to follow the same path taken by the inventors to arrive at the invention. Thus, the fact that a document discloses the feature regarded by the inventors as "the solution" of the

problem they wanted to solve, is not a bar to selecting this document as the closest prior art for the assessment of inventive step.

4.4 The opposition division in its decision formulated the technical problem over D1 as the provision of a composition which reduces the occurrence of blood steam infections. Appellant 01 defined the problem in an identical way during the oral proceedings before the Board.

In the written proceedings, the respondent concurred with this definition of the problem.

During the oral proceedings before the Board, the respondent however also defined the problem as the provision of a new use for the claimed buffer solution.

Having regard to the disclosure of D1, the Board agrees with the respondent that the technical problem should be seen in the provision of a new use of a glycine-containing treprostinil composition.

4.5 In the Board's view, the subject-matter of claim 1 represents an obvious solution to this problem.

4.5.1 With regard to the concentration of treprostinil, D11 discloses the preparation of solutions of treprostinil comprising 0.004 and 0.13 mg/mL treprostinil sodium in sterile water for injection and 0.9% sodium chloride injection (see e.g. Abstract). Moreover, document D1 indicates that the injectable formulations comprise between 0.1 to 5% w/v of the active agent treprostinil (see page 5, lines 48-55), with therefore an explicit disclosure of 0.1 w/v%. Thus, the concentration range of treprostinil recited in claim 1, i.e. 0.004 mg/ml to

0.13 mg/ml, is known in the art and is the usual concentration range of treprostinil when used in solutions. Moreover, this claimed feature does not contribute to the solution of any of the problems as posed.

4.5.2 With regard to the buffer capacity of 0.01 or less, D25 and D26 are textbook references which were cited by the appellants. D25 mentions on page 140 that pharmaceutical buffers for medicinal compositions for injections must have a low buffer capacity, and that in the case of high buffer capacity, they would resist change and interfere with the normal pH and buffer mechanisms of the body, in particular the blood pH. D26 confirms on page 233 that buffers for injectable solutions must have a low buffer capacity, in order to not interfere with the normal pH of body fluids. The use of a buffer with a low capacity, such as 0.01 or less is therefore a normal and a standard measure in the field of pharmaceutical solutions for injection.

4.5.3 Thus, neither the buffer capacity nor the treprostinil concentration provide an inventive contribution to the subject-matter of claim 1. In this regard the Board notes that the respondent did not present any argument as to the relevance of these features for the assessment of inventive step.

4.5.4 With regard to the effectiveness of the glycine buffer in reducing the occurrence of a blood stream infection by reducing the gram negative bacteria and inhibiting the growth of gram positive bacteria, the Board observes that glycine was already known as antibacterial agent against gram positive and gram negative bacteria.

D31 discloses the inhibitory effect of glycine on bacterial growth and shows an activity on several gram positive bacteria through an action on the biosynthesis of peptidoglycan (See Abstract, Table 1). This document mentions also that the inhibitory effect of glycine had been known for a long time and cites several bibliographic references (see page 1029, left-hand column, first par.).

D4 describes the antibacterial effect of glycine on the gram negative bacteria *Helicobacter pylori in vitro*, and mentions that glycine may be used as a non-specific antiseptic agent due to its low level toxicity in animals (see Abstract).

D2 and D3 are textbook references which both disclose that pH is an important factor influencing bacterial growth, and that pH values over 10 are not optimal for bacteria (see D2, Figure 5.13 and D3, Figure 14).

It follows that it was known to the skilled person that the use of a glycine buffer at a pH greater than 10 would have an effect on reducing the gram negative bacteria and inhibiting the growth of gram positive bacteria, and hence, an effect on reducing the occurrence of a blood stream infection when injected in a pharmaceutical solution.

Thus, the skilled person would have obviously considered using a treprostinil composition containing glycine to prevent or lessen a well known-side effect of treprostinil, namely the occurrence of bacterial infections.

4.5.5 Finally, the Board is not convinced by the respondent's argument, presented for the first time during the oral

proceedings before the Board, that the claimed invention represents a solution to an unrecognized problem and can therefore be regarded as a "problem invention". A "problem invention" relates to a situation wherein a technical problem had not been recognized previously in the prior art.

This is obviously not the case here, in view of at least document D7, which describes the occurrence of blood stream infections among patients treated with intravenous treprostinil.

4.6 Consequently, the subject-matter of claim 1 of auxiliary request 1 lacks an inventive step, and the main request does not meet the requirements of Article 56 EPC.

5. Auxiliary request 2 - Amendments

The subject-matter of claim 1 of auxiliary request 2 has been reformulated as a method claim, namely a "method of reducing the occurrence of a blood stream infection in a human suffering from pulmonary arterial hypertension and being treated with treprostinil, wherein said method reduces the gram negative bacteria and inhibits the growth of gram positive bacteria, the method comprising administering a solution comprising treprostinil sodium in a concentration between 0.001 mg/mL and 1 mg/mL...", which corresponds to the medical indication originally claimed in claim 1 of the main request. The features characterizing the composition remain the same as in claim 1 of the main request.

Auxiliary request 2 does not meet the requirements of Article 123(2) EPC for the same reason as the main request, in view of the feature "treprostinil sodium in

a concentration of between 0.001 mg/mL and 1 mg/mL" which is present in claim 1 in combination with a different subject-matter than that disclosed originally in claim 8 as filed (see points 2.2 and 2.3 above).

6. Auxiliary request 3 - Article 53(c) EPC

6.1 The subject-matter of claim 1 of this request has been reformulated in the same way as claim 1 of auxiliary request 2, namely as a "method of reducing the occurrence of a blood stream infection in a human suffering from pulmonary arterial hypertension and being treated with treprostinil, wherein said method reduces the gram negative bacteria and inhibits the growth of gram positive bacteria, the method comprising administering a solution...", with however treprostinil sodium "in a concentration of between 0.004 mg/mL and 0.13 mg/mL".

6.2 Based on the Board's conclusion that claim 1 of the main request was a purpose limited product claim under Article 54(5) EPC, it must be concluded that the method claim of auxiliary request 3 falls under the exclusion from patentability under Article 53(c) EPC. The reduction of the occurrence of blood stream infection relates indeed clearly to a method for treatment of the human or animal body by therapy, which is excluded from patentability by Article 53(c) EPC.

6.3 The respondent explained that auxiliary requests 2 and 3 were filed in case the Board would not have considered the claims of the main request and auxiliary request 1 as directed to purpose-limited product claims pursuant to Article 54(5) EPC. Auxiliary requests 2 and 3 were based on the main request and auxiliary request 1, but reworded as methods claims.

During the oral proceedings it suddenly argued that since a decision on the requirement of sufficiency had not been taken, it could not be established whether there was a therapeutic activity on the body and therefore it could not be concluded that auxiliary requests 2 and 3 related to a method of treatment of the human body by therapy.

The Board does not see why a decision on the requirement of sufficiency of disclosure would be necessary in order to establish whether the subject-matter of a claim relates to a method of treatment pursuant to Article 53(c) EPC. The respondent had constantly argued in its written submissions and for most of the time during the oral proceedings that claim 1 of the main request and of auxiliary request 1 relate to a product for use in a method of treatment of the human body by therapy. The Board (see points 4.1 to 4.1.3 above) agrees with this position and it consequently concludes that the subject-matter of auxiliary request 3 offends against Article 53(c) EPC.

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:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated