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Datasheet for the decision of 2 February 2021

Case Number: T 0906/18 - 3.3.01

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Language of the proceedings: EN

Title of invention:
NOVEL EPOPROSTENOL FORMULATION AND METHOD OF MAKING THEREOF

Patent Proprietor:
Actelion Pharmaceuticals Ltd.

Opponent:
Generics (U.K.) Limited

Headword:
Epoprostenol formulations/ACTELION

Relevant legal provisions:
EPC Art. 54(2), 56
RPBA 2020 Art. 13(2)

Keyword:

Novelty - main request (no)
Inventive step - auxiliary requests (no)

Decisions cited:

G 0007/95

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Case Number: T 0906/18 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 2 February 2021

Appellant: (Opponent)	Generics (U.K.) Limited Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Patent Proprietor)	Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 4123 Allschwil (CH)
Representative:	Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstraße 2 80538 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 5 February 2018 concerning maintenance of European Patent No. 1 993 557 in amended form**

Composition of the Board:

Chairman	A. Lindner
Members:	J. Molina de Alba
	M. Blasi

Summary of Facts and Submissions

I. This appeal by the opponent (appellant) lies from the opposition division's interlocutory decision that European patent No. 1 993 557 as amended according to the main request, and the invention to which it relates, met the requirements of the EPC. The main request is identical to the patent as granted with granted claim 17 having been deleted.

Claims 1, 8 and 14 of the main request read as follows.

"*1. A bulk solution containing (a) epoprostenol or a salt thereof, (b) arginine, and (c) sodium hydroxide, wherein the bulk solution has a pH of 13 or higher.*"

"*8. The bulk solution of claims 1 to 7, wherein the bulk solution is lyophilized.*"

"*14. A lyophilized composition according to claim 8, wherein the lyophilized composition is reconstituted with a first diluent selected from water for injection, 0.9% sodium chloride solution, lactated Ringer's solution, Ringer's solution, sodium carbonate solution, or bicarbonate solution.*"

II. The following documents are referred to in the present decision:

D1: Prescribing information Flolan® (epoprostenol sodium) for Injection, GlaxoSmithKline, September 2002

D3: EP 0 005 768

III. The patent had been opposed on the grounds of Article 100(c), (b) and (a) EPC for lack of inventive step.

In the decision under appeal, the opposition division held that the claims of the main request did not add subject-matter and that the claimed subject-matter was sufficiently disclosed and inventive starting from document D3.

IV. In the statement of grounds of appeal, the appellant submitted that the compositions in claims 8 and 14 of the main request held allowable by the opposition division were not novel over example 1 of document D3. Neither were they inventive over the teaching of documents D1 or D3.

V. With the reply to the statement of grounds of appeal, the respondent (patent proprietor) maintained the version of the patent held allowable by the opposition division as its main request. In addition, it filed the claims of auxiliary requests 1 and 2 and requested that lack of novelty, introduced by the appellant with the statement of grounds of appeal as a new ground for opposition, not be admitted into the proceedings.

Claim 1 of auxiliary request 1 reads as follows.

"*1. A bulk solution containing (a) epoprostenol sodium, (b) arginine, and (c) sodium hydroxide, wherein the bulk solution has a pH of 13 or higher and the ratio of epoprostenol sodium to the alkalinizing agent is about 1:25 to about 1:200 by weight.*"

Claims 6 and 12 of auxiliary request 1 have the same wording as claims 8 and 14 of the main request except for their dependencies, which have been adapted.

Claim 1 of auxiliary request 2 differs from claim 1 of auxiliary request 1 in that the word "*about*" has been deleted twice.

Claims 6 and 12 of auxiliary request 2 are identical to those of auxiliary request 1.

VI. The board scheduled oral proceedings in line with the parties' requests. In preparation for the oral proceedings, the board issued a preliminary opinion according to which it was inclined to consider the objection of lack of novelty vis-à-vis document D3 in the appeal proceedings and consider document D3 as the closest prior art in the assessment of inventive step.

VII. The respondent replied to the board's preliminary opinion with a letter dated 1 December 2020.

VIII. Oral proceedings were held before the board on 2 February 2021.

IX. The appellant's arguments, where relevant to the present decision, can be summarised as follows.

The lack of novelty objection against claim 8 of the main request did not introduce a new ground for opposition; the opposition division had decided on this issue in the contested decision (point 27.6.4). The fact that the issue had been decided in the context of the assessment of inventive step was irrelevant. In any case, the objection had to be considered as a step of

the problem-solution approach starting from document D3 (G 7/95).

The composition of claim 8 of the main request lacked novelty in view of example 1 of D3. The example disclosed a lyophilised composition comprising epoprostenol, arginine and sodium hydroxide prepared from a solution having a pH of 10.5. Nevertheless, the same solution could have been prepared from a composition having a pH of 13 or more because claim 8 did not contain any restriction regarding the volume of the starting solution or the weight ratio of epoprostenol:sodium hydroxide in the lyophilisate.

The respondent's argument that the composition of claim 8 was novel because it was characterised by a particular weight ratio of arginine:sodium hydroxide was submitted for the first time at the oral proceedings before the board. It should not be admitted because it raised complex issues that could not be expected to be dealt with at oral proceedings, and the respondent had not met its obligation concerning Article 13(2) RPBA 2020.

The lyophilised composition in claim 6 of auxiliary request 1 was not inventive starting from document D3, in particular from the freeze-dried composition containing arginine in example 1. The distinguishing feature was the ratio of epoprostenol:alkalinising agent. This ratio was 1:22 in example 1 of D3 and 1:25 to 1:200 in the claimed composition. This difference could not be associated to any technical effect; the evidence in example 4 of the patent did not provide for a proper comparison. Therefore, the objective technical problem was the provision of an alternative lyophilised composition. The difference between the composition of

claim 6 and the one in example 1 of D3 was so slight that it constituted an obvious, arbitrary modification. Contrary to the respondent's opinion, D3 did not teach away from increasing the amount of amino acid (arginine); it merely warned against the addition of too high amounts.

For the same reasons, the composition in claim 6 of auxiliary request 2 also lacked an inventive step.

X. The respondent's arguments, where relevant to the present decision, can be summarised as follows.

The opposition was based on the grounds for opposition of lack of inventive step, insufficiency of disclosure and added subject-matter; lack of novelty had never been introduced as a ground for opposition in the opposition proceedings. The assessment of the difference between the composition of claim 8 of the main request and the lyophilised product of document D3 in the appealed decision (point 27.6.4) had been made in the context of the examination of inventive step. The lack of novelty objection raised against claim 8 of the main request in the statement of grounds of appeal introduced a fresh ground for opposition and should not be admitted.

The composition in claim 8 of the main request was novel. First, it was obtained by lyophilisation of the bulk solution of claim 1, which had a pH of 13. Second, the claim contained the implicit limitation that, in the technical field of the invention, solutions were lyophilised in standard vials which had a volume in the order of millilitres. These restrictions characterised the claimed composition by specific weight ratios of epoprostenol:sodium hydroxide that could not be

obtained when the composition was prepared by lyophilising a standard volume of a solution having a pH of 10.5, as in example 1 of D3.

The novelty argument that the bulk solution of claim 1 was characterised by the weight ratio of arginine:sodium hydroxide, which was maintained in the composition of claim 8, should be admitted. Although the argument had been elaborated at the oral proceedings before the board, it did not change the respondent's case; the argument was based on the submission in point 2.4 of the reply to the statement of grounds of appeal which explained the relationship between the two alkalinising agents (organic and inorganic base) and the pH of 13 or higher.

The composition in claim 6 of auxiliary request 1 was inventive. D3 was not a suitable starting point because it did not deal with the same purpose as the patent. If inventive step was nevertheless assessed starting from D3, the lyophilisate in claim 6 differed from the one in example 1 of D3 by its higher amount of alkalinising agent, i.e. arginine. A comparison of formulation EPP-8 with formulations EPP-30, EPP-31 and EPP-32 in tables 8 and 9 of the patent showed that a higher amount of alkalinising agent (glycine) conferred the lyophilised composition with higher stability. This conclusion was also valid when the alkalising agent was arginine since glycine and arginine were considered equivalent in D3. Moreover, formulation EPP-25, which contained arginine, was also much more stable than EPP-8. Therefore, the objective technical problem was the provision of a lyophilised composition having higher storage stability. This problem was solved in an inventive manner by the subject-matter of claim 6 because D3 did not teach that increasing the alkalinising agent would

also increase the stability of the lyophilisate. Even if the problem was formulated as an alternative, the claimed subject-matter was inventive because D3 taught away from increasing the amount of alkalinising agent; it stated (page 5, lines 12-19, and page 7, lines 8-11) that the amount of amino acid should be as little as necessary, i.e. it should not be increased.

For the same reasons, the composition in claim 6 of auxiliary request 2 was also inventive.

XI. The parties' final requests were the following.

- The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

- The respondent requested that the appeal be dismissed, implying that the patent be maintained in amended form in the version held allowable by the opposition division (main request). Alternatively, the respondent requested that the patent be maintained in amended form on the basis of any of the sets of claims filed as auxiliary requests 1 and 2 with the reply to the statement of grounds of appeal, dated 15 October 2018. The respondent also requested that the ground for opposition of lack of novelty introduced by the appellant with the statement of grounds of appeal not be admitted into the proceedings.

XII. At the end of the oral proceedings, the board's decision was announced.

Reasons for the Decision

1. The appeal is admissible. It meets the requirements of Articles 106 to 108 and Rule 99(2) EPC.

2. *Admittance of the lack of novelty objection against claim 8 of the main request based on the closest prior art document D3*

When filing the opposition, the appellant marked in section VI of form 2300, *inter alia*, the boxes of the grounds for opposition of lack of novelty and lack of inventive step. However, while lack of inventive step was substantiated in the notice of opposition, lack of novelty was not addressed, nor was any lack of novelty objection explicitly raised during the opposition proceedings.

In the decision under appeal, the opposition division considered that document D3 was the closest prior art. In this context, it referred briefly (point 27.6.4 of the decision) to the appellant's arguments relating to a lack of difference between the composition of claim 8 of the main request and the product of D3. However, it did not make any explicit indication on the admission of the ground for opposition of lack of novelty.

In the statement of grounds of appeal, the appellant argued for the first time that the composition of claim 8 of the main request lacked novelty over one of the compositions in example 1 of document D3. Introducing a fresh ground for opposition into the appeal proceedings

is generally not possible without the agreement of the patent proprietor. In the case at issue, the respondent had not agreed.

However, in the appealed decision, D3 had been regarded as the closest prior art and in the opposition and appeal proceedings both parties provided inventive step arguments starting from it. An essential step of the problem-solution approach for assessing inventive step is establishing the difference between the claimed subject-matter and the closest prior art. A finding that there is no difference amounts to a finding of a lack of novelty, and, in line with decision G 7/95 of the Enlarged Board of Appeal (see OJ EPO 1996, 626, order), the allegation of lack of novelty in view of the closest prior art may be considered in the context of deciding upon the ground for opposition of lack of inventive step.

Since the question of a difference between the subject-matter of claim 8 and the disclosure of document D3 had already been an issue in opposition, the board admitted into the appeal proceedings, in accordance with Article 12(4) RPBA 2007, the objection of lack of a difference, i.e. lack of novelty, of the subject-matter of claim 8 in light of closest prior art document D3.

3. Claim 8 of the main request - difference over document D3/novelty (Article 54 EPC)

3.1 Claim 8 is a product-by-process claim directed to a composition obtainable by lyophilising a bulk solution according to claim 1. Thus, the composition of claim 8 is a lyophilisate containing epoprostenol, arginine and sodium hydroxide.

Example 1 of D3 discloses (page 14, lines 3-11) sterile solutions containing prostacyclin (i.e. epoprostenol) and mannitol prepared in an amino acid buffer of pH 10.5. The amino acid buffer of one of the solutions contains arginine, sodium chloride and sodium hydroxide. Subsequently (page 14, lines 17-20), 5 ml portions of the sterile solutions were freeze dried (i.e. lyophilised).

Accordingly, the lyophilised compositions of both claim 8 and example 1 of D3, contain epoprostenol, arginine and sodium hydroxide.

3.2 It was disputed between the parties whether the pH of the starting solution imposed implicit restrictions on the weight ratio of epoprostenol:sodium hydroxide which could render the lyophilisate of claim 8 different from the one in example 1 of D3.

As argued by the appellant, a lyophilisate obtained from a solution of pH 13 may also be prepared from that solution previously diluted with water to a pH of 10.5. By doing so, the weight ratio of epoprostenol:sodium hydroxide would be maintained. The only difference would be that starting from the solution of pH 10.5, higher volumes would need to be lyophilised. This would, in theory, also work the other way round, i.e. the lyophilised composition in example 1 of D3 could be obtained by freeze drying smaller volumes of a solution having a pH of 13. Therefore, the composition in example 1 of D3 would be encompassed by claim 8.

3.3 The respondent contended that the claims had to be interpreted as being limited by its context, in particular by the standard volume of medical vials used for freeze drying pharmaceutical bulk solutions. This

volume was in the order of millilitres, and it should contain the therapeutic dose of epoprostenol and the amount of sodium hydroxide required for reaching a pH of at least 13. Consequently, the pH of 13 or more in claim 1 implied restrictions in the weight ratio of epoprostenol:sodium hydroxide of the claimed composition; a lyophilisate obtained by freeze drying a standard vial of a solution having a pH of 13 or more would contain a considerably higher proportion of sodium hydroxide than a lyophilisate obtained in the same way from a solution having a pH of 10.5. Hence, the freeze-dried composition in example 1 of D3 was not encompassed by claim 8.

3.4 The board is not convinced by the respondent's argument. On the one hand, claim 1 does not specify that its bulk solution contains any specific concentration or weight ratio of components; it merely requires the presence of epoprostenol, arginine and sodium hydroxide and that the solution have a pH of 13 or more. On the other hand, claim 8 is silent on the volume of bulk solution to be lyophilised or the amount of epoprostenol that this volume should contain. Hence, the product of claim 8 is not limited by the ratio of epoprostenol:sodium hydroxide alleged by the respondent.

In view of the above, the board holds that the respondent has failed to prove that the composition according to claim 8 may be distinguished from the freeze-dried composition in example 1 of D3. As no difference can be established between the subject-matter of claim 8 and the disclosure of D3, the former cannot be regarded as novel, and claim 8 does not meet the requirements of Article 54 EPC.

4. Admission of a new line of argument in relation to novelty submitted at oral proceedings (Article 13(2) RPBA 2020)

4.1 At the oral proceedings before the board, the respondent introduced a new line of reasoning concerning the novelty of the composition of claim 8 of the main request. The respondent alleged that the pH of the bulk solution in claim 1 restricted the weight ratio of arginine:sodium hydroxide and made the composition of claim 8 different to that in example 1 of D3. According to the respondent, this additional submission did not amend its case; the argument had been introduced in point 2.4 of the reply to the statement of grounds of appeal.

4.2 In point 2.4 of the reply to the statement of grounds of appeal, the respondent described the situation that arginine and sodium hydroxide were the two alkalinising agents in the bulk solution and that sodium hydroxide was necessary to adjust the pH at 13 or above because arginine was not basic enough. In the board's view, this explanation cannot be equated with the allegation of fact that the pH defined in claim 1 required a specific weight ratio of arginine:sodium hydroxide because it does not contain any specific consideration on how the pH of claim 1 might possibly limit the weight ratio of arginine:sodium hydroxide. Hence, the new line of argument, based on a new alleged fact, constitutes a change in the respondent's case.

The respondent did not justify with cogent reasons that there were exceptional circumstances for introducing the change in the case at such a late stage of the proceedings. Therefore, the board decided not to take

the new line of argument into account pursuant to Article 13(2) RPBA 2020.

5. Claim 6 of auxiliary request 1 - inventive step (Article 56 EPC)

5.1 Claim 6 of auxiliary request 1 is directed to a lyophilised composition obtainable from a bulk solution having a pH of 13 or higher, which contains epoprostenol sodium, arginine and sodium hydroxide, and which has a weight ratio of epoprostenol sodium:alkalinising agent from about 1:25 to about 1:200.

In relation to the lyophilisate of the invention, the patent states (paragraphs [0001] and [0002]) that it is stable and can be dissolved with commercially available intravenous fluids to obtain solutions for parenteral administration to patients with cardiovascular disorders and diseases. The stability of the lyophilisate is attributed to the alkalinising agent, which provides an alkaline environment but does not contain any basic hydroxide group, e.g. arginine (paragraphs [0020] to [0022] and [0025]).

Document D3 teaches (page 2, lines 13-23) the stabilisation of pharmaceutical prostacyclin (i.e. epoprostenol) solutions by the association of epoprostenol with a pharmaceutically acceptable alkaline buffer based on an amino acid. The stability of epoprostenol is increased when the solution is freeze dried, i.e. lyophilised (page 3, lines 19-21). Before use, the lyophilised solution is reconstituted, preferably with water for injections (page 9, lines 17-20), and may be administered by intravenous infusion (page 2, lines 6-8 and 11; page 8, lines 3-4; page 9,

lines 17-20; page 10, lines 3-6 and 19-21; page 12, lines 16-17).

Hence, D3 is directed to the same purpose as the patent, namely the provision of stable lyophilisates for use in the preparation of epoprostenol solutions suitable for intravenous administration. Contrary to the respondent's opinion, D3 is a suitable starting point for the assessment of inventive step.

5.2 As explained in point 3.1 above, example 1 of D3 discloses the preparation of a lyophilised composition from a sterile solution having a pH of 10.5 which contains epoprostenol, mannitol, arginine, sodium chloride and sodium hydroxide.

It was not disputed between the parties that the alkalinising agent according to claim 6 in the lyophilisate of D3 was arginine. It was also common ground that the lyophilisate of claim 6 differed from the one of D3 by the weight ratio of epoprostenol sodium:arginine. According to the appellant's calculations, this ratio was 1:22 (see letter dated 29 January 2019, paragraph 50). The board came to a similar result, namely 1:20 (see communication dated 15 June 2020, point 13.1). The respondent neither provided a calculation nor disputed the results obtained by the appellant or the board.

Thus, the lyophilised composition of claim 6 differs from the one in example 1 of D3 in that it has a higher proportion of arginine in relation to its epoprostenol sodium content: epoprostenol sodium:arginine is 1:25 to 1:200 *versus* about 1:20.

5.3 With regard to the technical effect that this difference brings about, the respondent referred to the comparative tests in example 4 of the patent. It compared the following compositions in table 8 of the patent (quantities are in mg; EPP means epoprostenol sodium).

Batch#	EPP	Trehalose	Mannitol	NaCl	Glycine	Bulk.Sol.pH
EPP-8	0.5		50	3	3.75	10.5
EPP-30	0.5		100		97.76	11
EPP-31	0.5		100		97.76	12
EPP-32	0.5	50			97.76	11

The stability results of these compositions were displayed in table 9. They were as follows.

Batch#	Stability (%initial) stored at 40°C	
	15 days	30 days
EPP-8	40	0
EPP-30	88	
EPP-31	90	96
EPP-32	76	74

The respondent argued that all the lyophilisates in table 8 contained the same amount of epoprostenol (0.5 mg) but that EPP-30, EPP-31 and EPP-32 contained a high amount of alkalinising agent (97.76 mg glycine) while EPP-8 contained only a low amount (3.75 mg glycine). Thus, a comparison of the stability results of EPP-30, EPP-31 and EPP-32 with that of EPP-8 would be equivalent to comparing the stability of the lyophilisate of claim 6 with that of example 1 of D3. The fact that the alkalinising agent in EPP-8, EPP-30, EPP-31 and EPP-32 was glycine rather than arginine was

not detrimental to the conclusion because D3 taught that both amino acids were equivalent. As table 9 showed that compositions EPP-30, EPP-31 and EPP-32 were more stable than EPP-8 (higher amounts of epoprostenol remained in the formulation after 15 days at 40°C), it had been demonstrated that increasing the amount of alkalinising agent produced an increase in the stability of the lyophilisate. This was confirmed by formulation EPP-25, which contained arginine and was also much more stable than EPP-8.

On this point, the board concurs with the appellant that the evidence in tables 8 and 9 does not support the respondent's conclusion. Formulation EPP-8 does not differ from EPP-30, EPP-31 and EPP-32 only by its glycine content. On the one hand, EPP-8 contains NaCl, which is not present in EPP-30, EPP-31 and EPP-32, and EPP-32 contains trehalose, which is not present in EPP-8. On the other hand, EPP-8 contains different amounts of mannitol than EPP-30, EPP-31 and EPP-32. Furthermore, EPP-8 was prepared from a bulk solution having a pH of 10.5, while EPP-30, EPP-31 and EPP-32 resulted from bulk solutions having a pH of 11 or 12. In addition, the large difference (26 times) in glycine content between EPP-8 and EPP-30, EPP-31 and EPP-32, cannot reflect the slight difference in the ratio of epoprostenol sodium:arginine between example 1 of D3 and claim 6. Thus, even if it were possible to extrapolate the conclusions based on glycine to arginine, it is clear that the higher stability of formulations EPP-30, EPP-31 and EPP-32 cannot be univocally assigned to their higher glycine content. The same applies to the comparison between EPP-8 and EPP-25. Therefore, example 4 of the patent does not show the effect alleged by the respondent.

It thus follows that the objective technical problem to be solved must be formulated as the provision of an alternative epoprostenol lyophilisate.

5.4 On the issue of obviousness, the respondent argued that D3 teaches away from the invention because it states on page 5, lines 12-19, and page 7, lines 8-11, that the concentration of amino acid should be as little as is necessary to stabilise the active compound; too much amino acid would have the opposite effect.

The board disagrees. Example 1 of D3 discloses an amino acid concentration of 0.025M (page 14, line 9), but D3 generally teaches in the passage cited by the respondent on page 5, lines 12-19, that a suitable amino acid concentration range is 0.02 to 0.03M. Thus, D3 does not teach that the amino acid concentration cannot be higher than the one illustrated in example 1; it simply warns against the addition of an excessive amount of amino acid. Taking into consideration the slightly higher proportion of arginine in the lyophilisate of claim 6 compared to example 1 of D3 and the fact that D3 allows moderate increases in the amino acid content, the skilled person would have arrived at the solution proposed in claim 6. The composition of claim 6 would have been an obvious modification of the lyophilisate of the prior art to obtain an alternative composition. In consequence, claim 6 does not meet the requirements of Article 56 EPC.

6. Claim 6 of auxiliary request 2 - inventive step (Article 56 EPC)

The lyophilised composition in claim 6 of auxiliary request 2 differs from that in claim 6 of auxiliary request 1 only in that the definition of the weight

ratio of epoprostenol sodium:alkalinising agent is not modified by the word "about" (see claim 1 of auxiliary requests 1 and 2). It is therefore apparent that the reasons why the subject-matter of claim 6 of auxiliary request 1 lacks an inventive step also apply to the subject-matter of claim 6 of auxiliary request 2.

Order

For these reasons it is decided that:

1. Decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated