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Datasheet for the decision of 31 January 2023

Case Number: T 0234/20 - 3.3.07

Application Number: 15712064.3

Publication Number: 3110399

IPC: A61K9/08, A61K47/02, A61K31/137, A61L2/04

Language of the proceedings: EN

Title of invention:
PROCESS FOR PRODUCING A STABLE LOW CONCENTRATION, INJECTABLE SOLUTION OF NORADRENALINE

Patent Proprietor:
Sintetica S.A.

Opponent:
Grund, Dr., Martin

Headword:
Noradrenaline solution/SINTETICA

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (yes)

Decisions cited:
T 0230/07, T 1404/14, T 1027/08, T 2381/09, T 1152/16, T 0653/93, T 0929/00

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Case Number: T 0234/20 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 31 January 2023

Appellant: (Patent Proprietor)	Sintetica S.A. Via Penate, 5 6850 Mendrisio (CH)
Representative:	Hoefer & Partner Patentanwälte mbB Pilgersheimer Straße 20 81543 München (DE)
Respondent: (Opponent)	Grund, Dr., Martin Nikolaistr. 15 80802 Munich (DE)
Representative:	Bird & Bird LLP Maximiliansplatz 22 80333 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 19 December 2019 revoking European patent No. 3110399 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chair	A. Jimenez
Members:	M. Steendijk
	D. Boulois

Summary of Facts and Submissions

I. European patent 3 110 399 ("the patent") was granted on the basis of sixteen claims.

Independent claim 1 as granted defines:

"A process for producing a stable, injectable solution containing from 0.04 to 0.20 mg/ml noradrenaline, characterized by including the following steps:
a. dissolving noradrenaline and optionally an excipient in deoxygenated or degassed water, to obtain a concentration of noradrenaline from 0.04 to 0.20 mg/ml,
b. adjusting the pH of the resulting solution by adding hydrochloric acid until a value in the range from 3.2 to 3.6 is achieved,
c. filtrating the resulting noradrenaline solution in an inert gas current,
d. distributing the noradrenaline solution in an inert gas current,
e. sterilizing the noradrenaline solution".

Independent claim 9 as granted defines:

"A stable injectable noradrenaline solution with an amount of preservatives and/or antioxidizing agents lower than 0.005% by weight, wherein solvent is degassed or deaerated water, the concentration of noradrenaline is in the range from 0.04 to 0.2 mg/ml and pH is from 3.2 to 3.6 by hydrochloric acid."

II. The patent was opposed on the grounds that its subject-matter lacked an inventive step.

The patent proprietor filed the appeal against the decision of the opposition division to revoke the patent.

In its decision the opposition division cited *inter alia* the following documents:

D1: US 2005/0070613 A1
D2: Spectrochim Acta Part A, 2005, 61, 3139-3144
D3: Clin Chem, 1993; 39/12, 2503-2508
D4: CN102525895B
D4a: Translation of D4
D5: SPC Noradrenaline (Norepinephrine) 1 mg/ml Concentrate for Solution for Infusion
D7: Study Report: Diluted noradrenaline (RD080C), 13 November 2015
D9: Study Report: Diluted Noradrenaline, (RD080C, Addendum 3), 12 September 2019

The opposition division arrived at the following conclusions:

(a) Document D1 represented the closest prior art describing the preparation of stable injectable aqueous solutions of catecholamines, including a solution of noradrenaline in a concentration of 0.2 mg/ml, which are free of antioxidants and preservatives and in which oxidation and racemization is reduced by deoxygenation of the aqueous solution with an inert gas and adjustment of the pH to values over 3.0 and below 5.0.

The teaching of document D1 with respect to the disclosure of a concentration of 0.2 mg/ml noradrenaline could not be recognized as manifestly

erroneous and misrepresenting the intended technical reality.

(b) In line with the established jurisprudence on the assessment of novelty of sub-ranges the feature of the adjustment of the pH within the range of 3.2 to 3.6 did not represent a distinguishing feature with respect to the range of the pH of 3.0 to 5.0 described in document D1. In particular, the exemplified pH value of 3.1 in document D1 practically overlapped with the lower limit of the claimed range taking account of measurement errors. Moreover, in view of the teaching in document D1 to keep the pH at values between 3.0 and 5.0, such as 3.1 and higher, the skilled person would seriously contemplate applying the teaching of document D1 in the range of overlap. Document D9, which was in addition to document D7 relied upon by the proprietor to demonstrate effects associated with the defined pH adjustment, was admitted into the proceedings. However, even if the alleged effects were considered proven, the claimed pH range could not be distinguished from the range disclosed in document D1 by virtue of such effects.

(c) The only difference between the subject-matter of claims 1 and 9 as granted and the teaching of document D1 was the definition of HCl used to adjust the pH of the solution. The technical problem was seen in the provision of a suitable pH adjusting agent. The use of HCl was a trivial choice from commonly known pH adjusting agents. The subject-matter of claims 1 and 9 did therefore not involve an inventive step.

III. The following additional documents have been submitted during the appeal procedure:

D10: Expert Declaration by Alain Borgeat (21 April 2020)
D11: Study Report: Diluted Noradrenaline (RD080C, Addendum 4), 28 April 2020
D12: US 2013/0123298 A1
D13: WO 2004/000219 A2
D14: Drug Development and Industrial Pharmacy, 2019, Vol. 45, 379-386

The appellant filed documents D10 and D11 with the statement of grounds of appeal and document D14 with the letter of 2 March 2021.

The respondent (opponent) filed documents D12 and D13 with the reply to the appeal.

IV. The Board issued a communication pursuant to Article 15(1) RPBA on 20 June 2022.

Oral proceedings were held on 31 January 2023.

V. The arguments of the appellant relevant to the present decision are summarized as follows:

Document D1 represented the closest prior art.

As confirmed by document D10 the skilled person would recognize that the reference to a noradrenaline concentration of 0.2 mg/ml in claim 11 of document D1 was erroneous. In as far as document D1 was nevertheless considered to disclose a noradrenaline concentration of 0.2 mg/ml, the document did not disclose this concentration in combination with the

specific range of 3.2 to 3.6 for the pH and the selection of HCl for the pH adjustment as defined in the claims of the patent.

The claimed invention allowed for the preparation of a particularly stable injectable solution containing a low concentration of noradrenaline. The patent reported low levels of racemization, artenone and other impurities in exemplified solutions after sterilization and storage. The patent specifically indicated that the defined pH range was found to be critical for avoiding racemization and the formation of the degradation product arterenone. The criticality of the defined range for the pH was confirmed by the additional experimental results reported in document D9.

The prior art provided the skilled person with no suggestion that the adjustment of the pH between 3.2 and 3.6 allowed for the preparation of dilute noradrenaline solutions for injection which were particularly stable.

VI. The arguments of the respondent relevant to the present decision are summarized as follows:

Document D1 was a suitable starting point in the prior art. Documents D4 and D5 represented alternative suitable starting points.

Document D1 described in claim 11 a solution of noradrenaline in a concentration of 0.2 mg/ml, which stood by itself as a realistic teaching. The declaration in document D10 to the contrary was without justification only filed with the statement of grounds of appeal and actually lacked pertinence. Documents D12 and D13 further confirmed that dilute noradrenaline

solutions with a concentration up to 0.2 mg/ml were conventional in the art.

Starting from the embodiment of claim 11, the pH of the solution was according to the general teaching of document D1 to be adjusted to a value above 3.0 and below 5.0, preferably 3.1. The definition of the range for the pH of 3.2 to 3.6 according to the patent did not represent a distinguishing feature with respect to the values for the pH described in document D1.

The only difference between the claimed subject-matter and the teaching in document D1 concerned the definition of HCl as the pH adjusting agent. As solution to the problem of providing a suitable agent for the pH adjustment the use of HCl was conventional, as confirmed by documents D2 and D5, and therefore obvious to skilled person.

In as far as the definition of the pH range of 3.2 to 3.6 was nevertheless regarded as a further distinguishing feature, it only contributed to the solution of the partial problem of providing a further noradrenaline solution for injection. Neither the patent nor the post-published documents D7 and D9 supported the criticality of defined range for the pH of 3.2-3.6 with regard to racemization and the formation of arterenone as suggested in paragraph [0048] of the patent. Document D14, which was relied upon by the appellant to support the relevance of the data in document D9, lacked pertinence and was not to be admitted for being late filed. Document D9 actually concluded on the basis of the reported results that the arterenone levels were not affected by an increase of the pH from 3.6 to 3.7. Document D11, which was only filed with the statement of grounds of appeal and

presented further post-published evidence, should not be admitted. The post-published evidence should furthermore not be taken into account as evidence of effects that could not be deduced from the application as filed.

As solution to the problem of providing a further stable noradrenaline solution for injection the adjustment of the pH within the range of 3.2 to 3.6 defined in the claims was obvious to the skilled person in view of the warning in document D1 concerning the risk of racemization below a pH of 3.0 and the explicit instruction in document D1 to adjust the pH above 3.0 and below 5.0. Moreover, as documents D2, D3 and D5 indicated particular stability of noradrenaline solutions at pH values within the claimed range it was obvious to the skilled person to adjust the pH to such values to improve the stability.

The appellant's reliance on the post-published data justified a stay of the proceedings until the issue of a decision by the Enlarged Board of Appeal with respect to the referral pending under G 2/21.

VII. The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted (main request).

The appellant further requested that documents D10, D11 and D14 as well as the statements that document D1 does not disclose distributing the solution in an inert gas current (feature d) and that document D4 does not disclose the use of deoxygenated/degassed/deaerated water (feature a) be admitted into the appeal proceedings.

VIII. The respondent requested that the appeal be dismissed.

The respondent also requested, that documents D12 and D13 be admitted and that documents D10, D11 and D14 not be admitted into the appeal proceedings.

Moreover, the respondent requested that statements by the appellant that document D1 does not disclose feature d) of claim 1 as granted and that document D4 does not disclose feature a) of claim 1 as granted not be admitted.

The respondent further requested that the proceedings be stayed until the Enlarged Board of Appeal has issued a decision with respect to the pending referral G 2/21.

Reasons for the Decision

Main request - Inventive step

1. Closest prior art

1.1 The patent relates to the stabilisation of noradrenaline solutions at low concentration against chemical degradation, in particular racemization and oxidation, while avoiding the use of antioxidants or preservatives by using deoxygenated water in combination with the adjustment of the pH to a value within 3.2 and 3.6 (see patent paragraphs [0001],[0023] and [0027] to [0031]).

1.2 Document D1 describes the stabilisation of solutions of catecholamines without antioxidants or preservatives, including a solution of noradrenaline at 0.2 mg/ml, involving the deoxygenation of the aqueous solvent and

adjusting the pH to values above 3.0 and below 5.0 to avoid racemization, which may become significant at a pH less than 3.0 (see D1, paragraphs [0003]-[0004], [0006],[0015]-[0022], [0047]-[0049] and claims 1, 6 and 11).

1.3 Document D4 does not specifically address the stabilisation of diluted noradrenaline solutions and by requiring a pH between 2.3 and 4.3 does not recognize the relevance of a pH above 3.0 to avoid racemization (see translation D4a, claims 1 and 3). Document D5 does also not address the stabilisation of diluted noradrenaline solutions. Whilst document D5 describes a pH between 3 and 4 for a stable concentrated solution, it does not indicate a particular pH for the diluted solutions to be prepared from the concentrated solution. Moreover, document D5 does not require any deoxygenation (see D5 sections 2, 3, 6.3 and 6.6).

1.4 Documents D4 and D5 are thus decisively more remote from the claimed invention than document D1. Accordingly, the Board considers document D1 to represent the most promising starting point in the prior art.

Following these considerations the respondent's request not to admit the statements by the appellant that document D4 does not disclose feature a) of claim 1 remains without consequence.

2. Relevant differences with the closest prior art

2.1 It was not in dispute that the use of HCl for the pH adjustment represents a distinguishing feature of the claimed subject-matter with respect to the teaching of document D1.

2.2 The appellant maintained that the skilled person would recognize the disclosure of the noradrenaline concentration of 0.2 mg/ml defined in claim 11 of document D1 as erroneous and that document D1 did not describe dilute noradrenaline solutions as defined in the claims of the patent.

In this matter the Board agrees with the finding in the decision under appeal (see pages 11-13, section 2.3.1.4) that the stand-alone disclosure of a noradrenaline concentration of 0.2 mg/ml in claim 11 of document D1 does not represent an immediately recognisable erroneous disclosure and therefore cannot be ignored. The comprehensive explanations in the decision already address the arguments in the statement of grounds of appeal and document D10. The respondent's request not to admit document D10 remains therefore without consequence.

2.3 The respondent argued that starting from the disclosure of the embodiment involving a concentration of 0.2 mg/ml noradrenaline in claim 11 of document D1 the definition of the pH range of 3.2 to 3.6 would not represent a further distinguishing feature of the claimed subject-matter. The respondent referred to the principles established in the jurisprudence regarding the assessment of novelty of sub-ranges, in particular T 230/07, which according to further jurisprudence (T 1404/14, T 1027/08, T 2381/09) were also applicable for the identification of the distinguishing features in the assessment of inventive step. In accordance with these principles the claimed pH range of 3.2 to 3.6, which was not narrow with respect to range of 3.0 to 5.0 and close to the exemplified value of 3.1 described

in document D1, could not further distinguish the claimed subject-matter.

The Board observes, however, that document D1 discloses the pH value of 3.1 in the context of examples which comprise noradrenaline in a concentration of 0.2%, 0.025% and 0.1 % (see D1, paragraphs [0047] to [0057]), corresponding to 2.0, 0,25 and 1.0 mg/ml, rather than the 0.04 to 0.20 mg/ml as defined in the claims of the patent. These examples thereby illustrate that in addition to choosing HCl as pH adjusting agent the skilled person would have to select the concentration of 0.2 mg/ml noradrenaline in combination with the more narrowly defined pH range of 3.2 to 3.6 in order to arrive from the teaching in document D1 at a dilute noradrenaline solution as defined in the claims of the patent. In accordance with the established jurisprudence (see T 1152/16, section 10.5; T 653/93, section 3.6; T 929/00, section 2.6) such a combined selection of features distinguishes the claimed subject-matter in the absence of a specific pointer in the prior art towards such combination. In the present case document D1 provides in the mentioned examples at best a pointer towards a pH of 3.1, which falls outside the range for the pH as defined in the claims.

Accordingly, the Board concludes that the definition of the noradrenaline concentration of 0.04 to 0.20 mg/ml in combination with the definition of the pH ranges of 3.2 to 3.6 further distinguishes the claimed subject-matter from the closest prior art.

3. Problem to be solved

The patent presents in paragraph [0048] the following statement:

"*The Applicant has indeed verified that pH values of the solution higher than 3.6 cause an increase of the formation of arterenone, while pH values lower than 3.2 have greater incidence in the appearance of d-noradrenaline.*"

According to the Board the patent provides thereby a verifiable statement regarding the effect of the claimed invention.

The respondent did not provide any experimental results of his own to challenge this statement in the patent. The respondent relied instead on the results reported in document D9 to argue that the claimed range for the pH was contrary to the statement in paragraph [0048] of the patent not associated with the particular advantage with respect to racemization and the formation of arterenone.

In this context the Board notes that document D9 indeed reports (see D9, page 4/7, first sentence) that after storage of relevant solutions for four weeks at 60°C the arterenone percentages varied across the sub-batches at pH 3.7, 3.6, 3.2 and 3.1 between 0.1 and 0.2, which did not imply any significant difference. However, document D9 (see page 3/7, first two tables) indicates increased levels of arterenone percentages at pH 3.7 in the first two weeks of storage, which in the subsequent two weeks decreased with a concomitant increase in the total of unknown impurities. As was pointed out by the appellant this subsequent decrease of the arterenone concentration at pH 3.7 may in view of the reported increase in the total of unknown impurities well be explained by the further degradation of the initially formed arterenone to other unknown

impurities. Document D9 further apparently confirms the increased racemization rate below pH 3.2 (see D9, page 5/7, figure "Trend slopes vs pH").

The experimental results reported in document D9 do therefore not invalidate, but rather corroborate the statement in paragraph [0048] of the patent regarding the criticality of the defined pH range of 3.2 to 3.6 with respect to the stability of the diluted noradrenaline solutions. Following these considerations the respondent's request not to admit documents D11 and D14 remains without consequence.

Accordingly, the Board is satisfied that the problem to be solved in view of document D1 may be formulated as the provision of particularly stable dilute noradrenaline solutions for injection.

4. Assessment of the solution

4.1 Document D1 itself teaches in relation to the disclosed pH range of 3.0 to 5.0 that below pH 3.0 racemization may be significant (paragraph [0019]) and that in experiments carried out to fix the optimal conditions of use the pH of the solutions was adjusted to 3.1 (see D1, paragraphs [0047] to [0057]. Document D1 does thereby not provide any suggestion that particular stability of a dilute noradrenaline solution is achieved by adjusting the pH of the solution in the range of 3.2 to 3.6 as defined in the claims.

4.2 Document D2 mentions pH values of 3.4 and 3.55 in the context of the spectral behaviour of diluted noradrenaline solutions during titration over a broad pH range (see D2, item 3.1 / Figure 2 and item 3.3 / Figure 7). However document D2 does thereby not

indicate any particular stability of the noradrenaline solutions at the pH values of 3.4 and 3.55.

Document D3 recommends acidification for stabilizing catecholamines, including noradrenaline, in plasma and urine during storage prior to measurement and mentions in this context a pH of 3.2 (see page 2505, right column and page 2508, left column). The Board is not convinced that such recommendation in the context of the analyse of plasma and urine samples provides the skilled person with a relevant suggestion towards the particular stability of the dilute noradrenaline solutions for injection as defined in the claims.

Document D5 mentions a pH between 3 and 4 for a stable concentrated noradrenaline solution, but does not indicate any particular pH for the diluted solutions to be prepared from the concentrated solution, let alone any particular stability of diluted noradrenaline solutions associated with the pH range of 3.2 to 3.6 defined in the claims of the patent.

Document D12 mentions dilute noradrenaline solutions (see D12, paragraph [0049], but fails to provide any suggestion towards the particular stability of such solutions by adjustment of the pH in the range of 3.2 to 3.6.

Document D13 mentions noradrenaline as an example of alpha adrenergic receptor agonists (see D13, page 10 lines 17-20), but only mentions low concentrations (1 mg/ml or less) and specific pH values (including a pH of 3.5) for formulations of alpha adrenergic receptor antagonists (see D13, page 11, lines 11-14 and page 23, lines 5-10).

4.3 Accordingly, taking account of the prior art the claimed subject-matter was not obvious as solution to the problem of providing particularly stable dilute noradrenaline solutions for injection.

The Board therefore concludes that the claimed subject-matter involves an inventive step.

As this conclusion is not based on feature d) as a distinguishing characteristic of the claimed subject-matter, the respondent's objection to the admittance of the appellant's statement regarding this feature remains without consequence.

Request for a stay of the proceedings pending G 2/21

5. The pending referral G 2/21 relates to the questions whether post-published evidence must be disregarded if the proof of a technical effect relied upon for an inventive step rests exclusively on the post-published evidence and whether such post-published evidence can be taken into consideration depending on the plausibility of the technical effect based on the information in the patent and the common general knowledge. As explained in sections 3 and 4 above, the Board concludes that the claimed subject-matter of claim 1 involves an inventive step taking account of a technical effect which is substantiated by a verifiable statement in the patent, which is only further corroborated by post-published experimental results. Any outcome of the referral is therefore not expected to affect the Boards considerations in the present appeal proceedings.

The Board has therefore rejected the respondent's request for a stay of the proceedings pending G 2/21.

Order

For these reasons it is decided that:

1. The decision under appeal be set aside.

2. The patent is maintained as granted.

The Registrar: The Chair:

B. Atienza Vivancos A. Jimenez

Decision electronically authenticated