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Datasheet for the decision of 26 February 2015

Case Number: T 2049/09 - 3.3.07

Application Number: 98947842.5

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Language of the proceedings: EN

Title of invention:
METHOD FOR KEEPING THE QUALITY OF AQUEOUS PARENTERAL SOLUTION OF THROMBOMODULIN IN STORAGE AND DISTRIBUTION

Patent Proprietor:
Asahi Kasei Pharma Corporation

Opponent:
PAION Deutschland GmbH

Relevant legal provisions:
EPC Art. 54(2), 56, 100(a)

Keyword:
Novelty - implicit disclosure (no)
Inventive step - (yes)

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Case Number: T 2049/09 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 26 February 2015

Appellant: (Opponent)	PAION Deutschland GmbH Martinstrasse 10-12 52062 Aachen (DE)
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Respondent: (Patent Proprietor)	Asahi Kasei Pharma Corporation 9-1, Kanda Mitoshiro-cho Chiyoda-ku Tokyo 101-8481 (JP)
Representative:	Forstmeyer, Dietmar BOETERS & LIECK Oberanger 32 80331 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 4 August 2009 rejecting the opposition filed against European patent No. 1029548 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	D. Semino
	P. Schmitz

Summary of Facts and Submissions

I. The appeal of the opponent (appellant) lies from the decision of the opposition division announced at oral proceedings on 15 July 2009 to reject the opposition against European patent number EP 1 029 548.

The granted patent comprised 22 claims. Independent claim 1 read as follows:

"1. Use of an aqueous solution having a pH value in the range from 5 to 7.0 and containing a soluble thrombomodulin in an effective amount and buffer component(s) revealing a buffering action in a pH range of between 5 and 7.0, wherein the aqueous solution of thrombomodulin has either the following characteristic feature a) or b), namely,
a) that it contains further a surfactant and is filled aseptically in a container or
b) that it consists of a prefilled syringe preparation filled aseptically in a syringe container so as to exclude any substantial gas space therein for maintaining the quality of aqueous injection preparation of thrombomodulin in a non-frozen or non-freeze-dried form over its storage and transportation."

Independent claim 12 read as follows:

"12. An aqueous injection preparation of thrombomodulin in a non-frozen or non-freeze-dried liquid form, superior in the stability for long term storage and in the stability against shaking and suitable for storing/ transporting over a long period of time, **characterised in that** the aqueous injection preparation of thrombomodulin has a pH value in the range from 5 to 7.0, contains a soluble thrombomodulin in an effective

amount, buffer component(s) revealing a buffering action in a pH range between 5 and 7.0 and a surfactant and is filled in a container aseptically."

Independent claim 13 differed from claim 12 in that it was "**characterised in that** the aqueous injection preparation of thrombomodulin is a prefilled syringe preparation which has a pH value in the range from 5 to 7.0, contains a soluble thrombomodulin in an effective amount and buffer component(s) revealing a buffering action in a pH range between 5 and 7.0 and which is filled in a syringe container aseptically so as to exclude any substantial gas space therein."

Independently drafted claim 14 differed from claim 13 solely in that the aqueous injection preparation of thrombomodulin thereof was further characterised by the presence of a surfactant.

II. A notice of opposition was filed in which revocation of the patent in its entirety was requested on the grounds of lack of novelty and of inventive step, of insufficiency of disclosure and of extension of the subject-matter beyond the content of the application as filed (Article 100(a), (b) and (c) EPC).

III. In the decision under appeal, the following documents were cited, *inter alia*:

D1: EP-B-0 689 843
D2: EP-B-0 632 055

IV. The decision under appeal can be summarised as follows:

a) There was no added subject-matter in claims 13 and 14 and the requirement of sufficiency of disclosure was fulfilled.

b) As to novelty, document D1 did not disclose the pH of the aqueous thrombomodulin (TM) compositions prepared therein, while the independent claims of the patent all recited compositions having a pH in the range of from 5 to 7.0. With respect to D2, while the composition of experimental example 2 thereof had a pH of 7, it was not filled aseptically in a container as required by claim 12 and claim 1, alternative a). Claim 1, alternative b) and claims 13 and 14 were novel over said example since in addition to lacking the feature of aseptic filling, it did not disclose that the composition thereof was "filled in a syringe so as to avoid substantial gas space therein".

c) With regard to inventive step, document D1, directed to the provision of a highly stable soluble TM-containing composition, was the closest prior art. The subject-matter of the granted claims differed from the aqueous compositions provided in D1 at least in that these compositions did not have a pH between 5 and 7.0. The skilled person, aiming at manufacturing injectable TM solutions that are stable for storage and transportation, did not find an incentive in D2 to make such injectable compositions having a pH of from 5 to 7.0. Stabilisation of TM compositions was only disclosed in D2 in the context of the purification thereof from urine rather than the long term stabilisation of pharmaceutical compositions containing TM, on which D2 remained silent. None of the other available prior art

documents suggested the distinguishing feature, so that all independent claims involved an inventive step.

V. The appellant lodged an appeal against that decision. With the statement setting out the grounds of appeal, the appellant contested the decision only insofar as novelty and inventive step are concerned and submitted the followings documents:

D9: "Good Laboratory Practice Guideline", Title 21, Part 58 (Revised 1 April 2009)
D10: "Europäisches Arzneibuch", Deutscher Apotheker Verlag Stuttgart, 6th Edition 2008, page 1024
D11: "Pharmakologie und Toxikologie", Urban & Fischer Verlag, 10th Edition 2009, page 40

VI. With the reply to the statement setting out the grounds of appeal of 4 May 2010, the patent proprietor (respondent) filed four sets of claims as auxiliary requests 1 to 4, submitted the following document:

D12: "Good Laboratory Practice Guideline", Title 21, Part 58: Table of Contents, § 58.1, § 58.3

and referred to the following document, cited as being the method according to which experimental example 2 of D2 was performed:

D13: H. Ohno et al., Thrombosis Res., Volume 24, 1981, pages 445 to 452

VII. In a communication sent in preparation of oral proceedings, the Board reviewed the submissions of the parties and in particular with regard to inventive step, expressed the preliminary opinion that the problem as

formulated in the application appeared to have been solved with respect to D1 as the closest prior art. Furthermore, the view was expressed that information comprised within D1 and D2 appeared to indicate a bias against the use of aqueous TM injection preparations for storage and transport.

VIII. Oral proceedings were held on 26 February 2015 in the absence of the appellant, as announced with a letter of 8 December 2014.

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

Product claims - novelty

a) Granted claim 12 is not novel over the disclosure of D2, specifically experimental examples 1 and 2 thereof, which in particular inherently disclose compositions having a pH falling within the range of claim 12. Furthermore, although not explicitly disclosed in said examples of D2, aseptic filling is an inherent property of an injection solution, since *inter alia* it is part of the common general knowledge (as shown by D10 and D11), it is required by the guidelines concerning good laboratory practice (as shown in D9), and obeys the basic principles of scientific working.

Product claims - inventive step

b) Granted claim 12 is not inventive in view of D1 as closest prior art. D1 discloses all of the features of claim 12 with the exception of the pH range between 5 and 7.0. D2, which discloses that the thrombomodulin compounds TM1 or TM2 are stable

in compositions with a pH range between 2 and 10, would provide the skilled person with an incentive to modify the pH taught in D1 and arrive at the claimed subject-matter.

c) Granted claims 13 and 14 are not inventive in view of D1 in combination with D2 for similar reasons as those provided for claim 12. Claim 13 differs from claim 12 in that it does not include a surfactant but includes the feature that the preparation is filled in a syringe, so as to exclude any substantial gas space therein, while claim 14 corresponds to claim 12 with the added feature that the preparation is filled in a syringe, so as to exclude any substantial gas space therein. In particular, it is implicit to the skilled person that before administration, a syringe must be filled in such a way that the residual gas space is minimised.

Use claims - novelty

d) Both alternatives a) and b) of granted claim 1 lack novelty over the disclosure of D2, for similar reasons as those provided for claim 12. Furthermore, D2 relates to the problem of stability of TM, and suggests the use of the aqueous solutions disclosed therein for maintaining the quality of the preparations for storage and transportation. With respect to alternative b), it is implicit to the skilled person that before administration, a syringe must be filled in such a way that it does not contain any gas space.

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

Product claims - novelty

a) The opposition division was correct in concluding that claim 12 is novel. D2 fails to unambiguously disclose that the aqueous injection preparation has a pH value in the range 5 to 7.0, that the buffer reveals a buffering action in a pH range between 5 and 7.0, and that the composition is filled aseptically into a container. With respect to the latter feature, as the composition used according to experimental example 2 of D2 was prepared for administration to rats who were sacrificed shortly thereafter, there was no reason to believe that it had been filled aseptically. Moreover, as the example was conducted to determine basic characteristics of the novel anticoagulant substances disclosed in D2, the good laboratory practice guidelines cited by the appellant, which are only relevant for non-clinical studies conducted for the assessment of the safety of pharmaceuticals (as clear from D12), did not apply.

Product claims - inventive step

b) The products of claims 12 to 14 are inventive over D1 as closest prior art, from which they differ at least in that D1 does not disclose any TM containing composition having a pH value between 5 and 7.0. The objective problem is to provide an alternative aqueous TM containing composition, in which TM is kept in liquid form during storage and transportation as opposed to a freeze-dried form and can, therefore, be advantageously administered and produced at low cost. The skilled person would

not conclude from D1 that a stable aqueous preparation could be obtained by adjusting the pH according to said claims especially in view of the teaching in D1 that freeze-drying and the addition of stabilisers is essential for storage and transportation. D2 is not concerned with long term storage and transportation and consequently does not teach the skilled person that the pH range of 5 to 7.0 will solve the problem. On that basis claims 12 to 14 involve an inventive step.

Use claims - novelty

c) With respect to the use claims, D2 is not relevant for the assessment of novelty, since it relates to a novel anticoagulant obtained from urine, and nowhere directly and unambiguously discloses that the infusion composition of experimental example 2 could be considered for the use claimed in the patent.

XI. The appellant requested in writing that the decision under appeal be set aside and the patent be revoked.

XII. The respondent requested that the appeal be dismissed, alternatively that the patent be maintained on the basis of one of auxiliary requests 1-4 filed with letter of 4 May 2010.

Reasons for the Decision

Novelty of product claims

1. Novelty of granted claim 12 has been contested over the disclosure of D2, specifically experimental examples 1 and 2 thereof.

1.1 According to experimental example 1 (paragraph [0050] of D2), lubrol (a surfactant) was added only to the solution containing human placental TM, a non-soluble TM falling outside the scope of the term "soluble TM" as present in claim 12 (see the specification, paragraph [0021] and also D2, paragraphs [0010] and [0039]), whereas according to experimental example 2, lubrol is also added to the solutions comprising soluble TM (paragraph [0052] of D2, see also paragraphs [0023], [0038] and [0039]). Thus experimental example 1 cannot be novelty destroying, while experimental example 2 is the most relevant for the assessment of novelty.

1.2 This example, performed to test the effect of the new TM compounds of D2 in a thromboplastin-induced model in rats, discloses the preparation of a composition for infusion comprising TM1 or TM2, which are soluble in water (D2, paragraphs [0038] and [0039]), by dissolution in 0.01 M phosphate buffer (pH 7.0) containing 0.1% human serum albumin, 0.14 M NaCl and 0.01% lubrol (paragraph [0052]).

1.3 The respondent argues that this example differs from the subject-matter of granted claim 1 in that it does not disclose that the aqueous injection preparation has a pH value in the range 5 to 7.0, that it contains a buffering component revealing a buffering action in a pH range between 5 and 7.0, and that the composition is filled in a container aseptically.

1.4 The Board agrees with the respondent at least with respect to the last feature. Said feature, although defining the claimed product by a process step, implies a feature of the product, which thereby has the property of being aseptic within a container. The example in question makes no reference to the preparation of the infusion composition thereof under aseptic conditions, nor to any sterilisation step and thus said feature is clearly not explicitly disclosed. For the feature in question to be considered implicitly disclosed, it would need to be concluded that the skilled person would infer the feature directly and unambiguously from what is explicitly disclosed. The question is therefore whether the skilled person would implicitly understand that the aqueous infusion composition of experimental example 2 of D2 was carried out with aseptic filling.

1.5 According to said example, the experiment was performed according to the method of D13, which prescribes that the tested rats are bled to death shortly after the beginning of the experiment (page 446) and, consistent with experimental example 2 of D2, is silent with respect to sterilisation. Furthermore, different parts of D2 in the context of the preparation of pharmaceutical compositions suggest the use of sterilised water (paragraph [0058]), and mention solutions which are sterilised by filtration, put into sterilised vials and freeze-dried (paragraphs [0065] and [0067]), thus providing indirect evidence by omission that the infusion composition of experimental example 2 was not sterilised.

1.6 The evidence represented by documents D9 to D11 filed by the appellant cannot lead to a different conclusion for a number of reasons. Documents D10 and D11 refer to injections and parenteral treatment, but do not mention

an experimental animal model, such as the rat model in D2. Document D9, which refers to rules for good laboratory practice, mentions the necessity to define and document purity and composition for each batch (section 58.105(a)) as well as to preclude the possibility of contamination (section 58.107(b)), but does not indicate that sterilisation must take place in experimental conditions like the one in D2. Moreover, document D12, which is a part of the same guidelines, indicates that non-clinical studies do not include "field trials in animals" or "basic exploratory studies carried out to determine whether a test article has a potential utility or to determine physical or chemical characteristics of a test article", so that the document should not apply for tests as those of D2. Finally documents D9 to D11 represent post-published evidence, whose applicability to the tests of D2 is at least questionable.

1.7 It follows that experimental example 2 of D2 does not anticipate the preparation of claim 12.

1.8 The appellant did not contest the novelty of granted claims 13 and 14, which both include the feature that the composition is filled in a container aseptically and are thus novel for at least the same reason as that provided with respect to claim 12.

1.9 It follows that the product claims 12 to 14 of the patent as granted and claims dependent thereon are novel.

Inventive step of product claims

Closest prior art

2. Document D1 was considered as the closest prior art in the decision under appeal and has been used as such by both parties in their arguments. The Board sees no reason to choose a different approach.

2.1 D1 sets out to provide a highly stable soluble TM-containing composition which can be stored for a prolonged period and which does not exhibit adsorption of the soluble TM onto the surface of the container after diluting to a lower concentration (paragraph [0016]). The solution provided for the purpose of stabilising the soluble TM involves the admixing of maltose, lactose, sucrose or arginine therewith, while a nonionic surface-active agent (i.e. a surfactant) prevents adsorption of the soluble TM onto the surface of the container (paragraph [0018]). According to Experiment 1 (paragraph [0061]), lyophilised injections are prepared by dissolving the selected soluble thrombomodulin compound (in the case of experiment 1, this is UTM0) in distilled water, adding maltose or an alternative ingredient thereto, filtering the solution aseptically and filling it into a sterilised glass vial the content of which was then lyophilised (see "Preparation 1", paragraphs [0062] and [0063]). It is these lyophilised injections that were stored in an incubator at 50 °C for either 3 or 6 months (paragraph [0062]) and subsequently evaluated for their residual titer and aggregation formation rate by diluting with Tris-HCl buffer at pH 8.4 (paragraph [0072). Experiment 2 describes a similar test of the thrombomodulin compounds UTM1 and UTM2 (paragraphs [0075] and following), while Experiments 4 and 5 are carried out using physiological saline (paragraphs [0087] and following).

2.2 As conceded by the appellant (point 1.1.3 of the statement setting out the grounds of appeal), while the TM compositions of D1 are prepared aseptically, a value of the pH in the range between 5 and 7.0 is not disclosed therein (nor a buffer component revealing a buffering action in that pH range). Since claims 13 and 14 comprise the same features relating to the pH, the same consideration applies in this respect.

Problem Solved

3. According to the patent, the problem to be solved is the provision of a stable aqueous injection preparation of TM which can avoid the incorporation of a freeze-drying process, thereby eliminating the necessity of a dissolution procedure upon practical use (paragraph [0009]).

3.1 Table 3 of the patent summarises a heat stability test which provides evidence that, in the presence of a surfactant, the percentage residual titer (and thus the stability) of the aqueous TM preparations is higher at pH 5 and 6 than at pH 7.3, while table 4 provides evidence that, in the presence of a surfactant, a preparation having a pH of 7.0 (example 20) is more stable than the corresponding preparation at pH 7.3 (comparative example 8). In respect of granted claim 13 according to which a surfactant is not a requirement, table 8 provides evidence that, in the absence of a surfactant and with the same percentage proportion of gas space, an aqueous preparation having a pH of 6.0 is more stable than the corresponding preparation at pH 7.3 (compare comparative example 10 with example 46 and 50).

3.2 Thus in respect of granted claims 12, 13 and 14, the evidence on file shows that the technical problem as formulated in the patent has been solved.

Obviousness

4. With regard to obviousness, the Board cannot follow the argument of the appellant that the skilled person, starting from the disclosure of D1 and seeking a solution to said technical problem, would consult D2 in order to arrive at the solution, since this document also relates to the problem of improving the stability of pharmaceutical TM compositions.

4.1 D2 relates to a novel TM substance derived from human urine, having remarkably high activity of thrombin-catalysed protein C activation and a potent anticoagulant effect (paragraphs [0011] and [0014] to [0017]). Accordingly, the new TM compound of D2 is merely characterised by a set of physical properties (a) - (h), one of which is the stability thereof, property (g) (see claim 1). The stability of the new TM substance, while naturally a desirable characteristic thereof, does not represent, however, a problem which the inventors of D2 set out to solve *per se*. Indeed, when the problem to be solved is presented, stability is not mentioned as an issue addressed by D2 (paragraphs [0010] to [0017]).

4.2 Experimental example 2 of D2 (paragraphs [0052] to [0054]), invoked by the appellant with respect to the novelty of claim 12, describes an experiment performed in order to assess the effect of the new substances TM1 and TM2 on a thromboplastin-induced disseminated intravascular coagulation (DIC) model in rats, and discloses an aqueous solution discussed above in

relation to novelty (point 1.2). There is no indication in D2 that would lead the skilled person to suspect that the solution prepared for administration according to said example is not to be used immediately, and is thereby suitable for storage or transport. Consequently, even if it were to be acknowledged that the solution prepared according to said example has the required pH and buffer component differentiating the subject-matter of claims 12 to 14 from the disclosure of D1, there would be no reason for the skilled person to combine these features with the knowledge from D1 in order to solve the problem posed.

4.3 Furthermore, the formulations prepared for parenteral injection according to examples 2 and 3 of D2 are both freeze-dried and sterilized, indicating that the possibility of preparing aqueous injection preparations for storage had not been contemplated in D2.

4.4 In the case of the closest prior art D1, one of the objects of the invention is to provide a lyophilised soluble TM-containing composition (paragraph [0016]). It is mentioned that even if the soluble TM (of a prior art disclosure) is lyophilised, it still suffers from diminished activity (paragraph [0010]), indicating therefore that any other preparative form was considered to be even less advantageous in this respect. Furthermore, while Experiment 3 of D1 (paragraphs [0085] and [0086]) concerns an evaluation of the stability of a TM solution and states that a UTM0 solution containing maltose, lactose, sucrose or arginine hydrochloride did not exhibit significant loss of activity when stored at room temperature for 24 hours, the purpose of said experiment was to demonstrate that the lyophilised preparations of D1 shown to be stable at 50 °C after 3-6 months of storage, when dissolved prior to

administration, are sufficiently stable in solution on a short time scale (up to 24 hours) to prevent the medically undesirable formation of aggregates during the period between dissolution and administration. Thus, long term storage according to the invention of D1 is contemplated only with respect to the lyophilised preparations.

4.5 Consequently, the skilled person not only lacks any incentive to combine the closest prior art D1 with the disclosure of D2 in order to arrive at the claimed solution, but would furthermore be sensitive to the bias present in the teachings of both D1 and D2 in favour of providing only lyophilised injection preparations for the purpose of storage and/or transportation, and thereby taught away from the provision of aqueous solutions for said purpose.

4.6 It follows that the product claims 12-14 of the patent as granted and claims dependent thereon involve an inventive step.

Use claims

5. Use claim 1 corresponds in its two alternatives to the use of the aqueous preparations of independent claims 12 and 13 for maintaining the quality of an aqueous injection preparation of thrombomodulin in a non-frozen or non-freeze-dried liquid form over its storage and transportation. Since the products are novel and inventive, it follows that the use thereof according to claim 1 and claims dependent thereon equally satisfies the requirements of novelty and inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Kiehl J. Riolo

Decision electronically authenticated