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Datasheet for the decision of 11 March 2010

Case Number: T 1791/08 - 3.3.08

Application Number: 98911128.1

Publication Number: 1030177

IPC: G01N 33/48

Language of the proceedings: EN

Title of invention:
Method for inhibiting decomposition of natriuretic peptides and improved method for assaying natriuretic peptides with the use of the same

Patentee:
SHIONOGI & CO., LTD.

Opponent:
Karolin, Rudolf

Headword:
Natriuretic peptides/SHIONOGI

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main request: inventive step (yes)"

Decisions cited:
T 0588/93, T 0620/99

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1791/08 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 11 March 2010

Appellant: (Patent Proprietor)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 24 June 2008 revoking European patent No. 1030177 pursuant to Article 101(3)(b) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
J. Geschwind

Summary of Facts and Submissions

I. The patentee (appellant) lodged an appeal against the decision of the opposition division dated 24 June 2008, whereby European patent 1 030 177 was revoked. The patent had been granted on European patent application No. 98 911 128.1 entitled "*Method for inhibiting decomposition of natriuretic peptides and improved method for assaying natriuretic peptides with the use of the same*" claiming the priority date of 24 October 1997, and published under the international publication number WO 99/22235.

II. The patent had been opposed by one opponent (respondent). The grounds for opposition relied upon by the opponent were lack of novelty (Article 100(a) EPC), lack of an inventive step (Article 100(a) EPC) and insufficiency of disclosure (Article 100(b) EPC).

III. Basis for the revocation was the main and only request (claims 1 to 2) filed during oral proceedings on 21 April 2008 which was considered to lack inventive step.

Claim 1 of the said main request read:

"1. *A method for inhibiting the degradation of mammalian BNP in a specimen, which comprises using, upon handling the specimen, a container wherein the face coming into contact with the specimen is made of or coated with a material inhibiting the activation of a substance degrading the peptides whereby said specimen does not contain aprotinin, and wherein said material is silicone or plastic*."

IV. Together with its statement setting out the grounds of appeal dated 3 November 2008, the appellant filed a new main request and two auxiliary requests, each of them consisting of two claims.

Claim 1 of the main request differed from claim 1 as refused by the opposition division (see point III *supra*) in that the phrase "*and is allowed to stand for at least 24 hours*" had been added after the term "*aprotinin*".

Claim 1 of the first auxiliary request differed from claim 1 of the main request in that the phrase "*at room temperature*" was added after the term "*stand*".

Claim 1 of the second auxiliary request differed from claim 1 as refused by the opposition division (see point 3 *supra*) in that the phrase "*silicone or plastic*" had been replaced by the term "*polystyrene*".

V. In its letter dated 13 March 2009 filed in reply to the statement of grounds, the respondent argued that (i) claim 1 of the main and the first auxiliary requests did not satisfy the requirements of Articles 123(2), 84 and 56 EPC, and (ii) claim 1 of the second auxiliary request did not involve an inventive step (Article 56 EPC).

VI. On 11 November 2009, the board sent a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal in which provisional and non-binding opinions on the issues of admissibility of

the amendments, clarity and inventive step were expressed.

VII. In reply to that communication, the appellant filed on 11 February 2010 a new main request and a new first auxiliary request to replace all the previous requests then on file.

The main request consisted of two claims reading as follows:

"1. A method for inhibiting the degradation of mammalian BNP in a specimen, which comprises using, upon handling the specimen, a container wherein the face coming into contact with the specimen is made of or coated with a material inhibiting the activation of a substance degrading the peptides whereby said specimen does not contain aprotinin, and wherein said material is polystyrene or polyethylene terephthalate."

"2. The method as claimed in claim 1, wherein said mammal is human, dog, pig, rat and mouse."

VIII. The respondent replied to the board's communication on 1 March 2010. In its submissions, it argued that neither of the two requests of 11 February 2010 involved an inventive step. No other objections were raised.

IX. Oral proceedings took place on 11 March 2010 at which the respondent *inter alia* objected to the admissibility into the proceedings of the main request insofar as it related to the polyethylene terephthalate (PET) embodiment.

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

(D1) R. A. Nelesen et al., Circulation, Vol. 86, No. 2, 1992, pages 463 to 466

(D2) N. C. Davidson et al., Circulation, Vol. 91, No. 4, 15 February 1995, pages 1276 to 1277

(D7) B. J. Ballermann, Am. J. Phys., Vol. 254, No. 1, January 1988, pages F159 to F163

(D10) WO 93/24531 (published on 9 December 1993)

(D13) Greiner Bio One catalogue 2005/2006 section 2, HTS Microplates, pages 2, 6 and 10

XI. The submissions made by the appellant (patentee) in respect of the main request may be summarised as follows:

Admissibility

The newly raised respondent's objection that the main request should not be admitted into the proceedings, insofar as it concerns the embodiment of claim 1 relating to the use of a container made of or coated with polyethylene terephthalate, should have been raised earlier, as this limitation to a material explicitly mentioned in the description was made in advance of oral proceedings and the respondent had not objected thereto until at oral proceedings it became clear that the board was favourably inclined to

acknowledge inventive step in respect of the polystyrene embodiment. Thus, the objection was late-filed and should not be admitted.

Inventive step

Document D2, taken as the closest prior art, concerned the same technical field and purpose as the patent, i.e. a natriuretic peptide and its stabilization. It disclosed the short-term in vitro stability of the N-terminal proatrial natriuretic peptide N-ANP and of the brain natriuretic peptide BNP under different storage conditions up to a maximum of 6 hours. Blood samples were taken from patients into standard polypropylene tubes containing EDTA or EDTA with aprotinin. These standard polypropylene tubes were used for the investigation of different storage conditions: presence or absence of aprotinin; time point of separation of plasma. However, the influence of the surface of the tube material on the stability of said peptides was not part of the investigation, simply because only one tube material was used. Thus, document D2 definitively did not disclose that BNP was stabilized by the use of a particular material. It disclosed that BNP was stable in itself up to six hours.

In view of document D2, the underlying technical problem was the provision of an alternative method for ensuring stability of BNP after having taken a sample form a patient. The solution was a method of inhibiting BNP degradation according to claim 1, said method relying on the use of polystyrene or polyethylene terephthalate containers.

According to the case law of the Boards of Appeal (see point 30 of the Reasons of decision T 620/99 of 8 May 2003, which also refers to decision T 588/93 of 31 January 1996), for an inventive step to be present in claims referring to the alternative solution of a known problem, it was not necessary to show substantial or gradual improvement over the prior art. Thus, in the present case, there was no need to establish that the use of polystyrene or terephthalate containers was associated with a lower BNP degradation than that observed when using polypropylene containers as employed in documents D1 and D2.

Document D1, which was also referred to in the decision under appeal in support of the objection of lack of inventive step, investigated essentially the stability of ANP, stored in test tubes made of polypropylene, polystyrene, silanised glass or glass, under freezing conditions at -20°C, -80°C and -190°C. From the results described in document D1, it could be taken that there was less degradation if the samples were stored at a temperature of -80°C rather than at a temperature of -20°C and that only storage in liquid nitrogen resulted in an acceptable stability. It was also suggested not to store the samples in polystyrene or glass tubes. Thus, document D1 did not provide any specific hint that the choice of the tube material indeed could have an influence (except that polystyrene or glass should not be used for storage of the samples) on the stability of BNP contained in the sample.

None of the documents D7 and D10, which showed that polystyrene was commonly used for clinical containers

at the filing date, gave any indication that it might serve the purpose of inhibiting BNP degradation.

Document D13 which was post-published was irrelevant for the assessment of inventive step.

XII. The submissions made by the respondent (opponent) in respect of the main request may be summarised as follows:

Admissibility

The main request should not be admitted into the proceedings, insofar as it related to the embodiment of the method of claim 1 wherein a container made of or coated with polyethylene terephthalate was used, for the reason that said embodiment had not been specifically searched.

Inventive step

With no limitation as to the kind of handling of the specimen and no indication as to the storage conditions, claim 1 was very broad. Thus, for the assessment of inventive step, the particular conditions of Example 2 in which BNP contained in tubes made of polystyrene, polypropylene A, polypropylene B, reinforced polyethylene, acrylic resin, silicone-coated or non coated glass was measured after a long storage of 24 hours should not be taken into account. Handling of the specimen according to the description (cf. paragraph [0013]) could simply mean collecting the sample or analysing it.

Both documents D1 and D2 disclosed the advantages of using polypropylene as a container material for handling natriuretic peptide containing samples.

In document D1, it was shown that, depending on the storage conditions, the stabilising effect on ANP was equivalent when using polystyrene or polypropylene tubes (see Figure 2). Thus, notwithstanding the negative statement at the bottom of page 465, there was no prejudice in document D1 against the use of polystyrene tubes for storing clinical samples for testing the presence of ANP. As BNP was known to be more stable than ANP (see document D2, last sentence of the first paragraph), it could be expected that the same or even a better stabilising effect would have been obtained for BNP when using polystyrene tubes.

These findings of the prior art were indeed corroborated by the patent-in-suit which did not establish that the use of polystyrene or polyethylene terephthalate containers was associated with any advantage over the use of containers made of another material. In this respect, Figure 3 of the patent clearly showed that not polystyrene but polypropylene was the most suitable material for storage of natriuretic peptides.

Plastic container materials for the handling of natriuretic peptides, including polystyrene, were generally known in the art as could be derived for example from any of documents D7, D10 and D13. However, document D1 as well as the patent showed that polypropylene was the best material for natriuretic peptide storage, while other plastic materials were

inferior with regard to their stabilizing properties. Thus, the selection of polystyrene as a container material merely represented an arbitrary selection from a variety of plastic materials that were, in principle, all suitable as container materials, but however lacked the superior properties of polypropylene with regard to their capability to preserve the structural integrity of the natriuretic peptides.

The same reasoning applied to the use of polyethylene terephthalate (PET) as illustrated by a comparison of Figure 2 of document D1, which showed that silanised, i.e. silicone coated, glass worked as good as polypropylene, with Figure 2 of the patent which showed that silicone coated glass worked as good as PET.

XIII. The appellant (patentee) requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request or auxiliary request I, both filed with letter dated 11 February 2010.

XIV. The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

Main request

Procedural issue

1. As apparent from the minutes of the oral proceedings, after the discussion on the inventive step of the first embodiment of claim 1 (polystyrene) had taken place and

the board had signalled a positive finding, the respondent requested that the request not be admitted into the proceedings, insofar the method of claim 1 involved the use of a container made or coated with polyethylene terephthalate, the reason put forward for this procedural request being that said embodiment had not been specifically searched.

2. Indeed a claim directed specifically to such an embodiment had never been submitted until the main request was filed on 11 February 2010. Nevertheless, claim 1 as filed, on the basis of which the search was carried out, with the general expression "*a material inhibiting the activation of a substance degrading the peptides*", when read in the light of the description (see page 4, lines 1 to 11), included *inter alia* polyethylene terephthalate as one of the preferred materials. Thus, it can be reasonably presumed that the search was complete.

3. At any rate, it is observed that in its submissions of 1 March 2010 the respondent had commented on said embodiment without raising its present objection on the admissibility of the request. Nor was such an objection raised at the onset of the oral proceedings (see minutes).

4. Under these circumstances, the board regarded the respondent's request as a belated submission and, using its power of discretion, decided not to admit it.

Compliance with the requirements of Articles 54, 83 and 123(2)(3) EPC

5. Taking notice of the fact that the respondent has not raised any objection under these EPC articles, the board is satisfied that the main request complies with the requirements of Articles 54, 83 and 123(2)(3) EPC.

Compliance with the requirements of Articles 56 EPC

6. Claim 1 is directed to a method for inhibiting the degradation of a mammalian brain natriuretic peptide (BNP) in a specimen. A review of the available prior art documents shows that only documents D1 and D2 have dealt with the determination of conditions which favour the stability or inhibit the degradation of natriuretic peptides ANP (see D1 and D2) and BNP (see D2).

7. Document D1 reports a study the purpose of which was to examine the effects of different sample collection, processing, and storage techniques on human atrial natriuretic peptide (ANP) stability. In experiments 1 and 3, the effect of different preservatives and the effect of storage at different freezing temperatures were respectively tested. Experiment 2, which is pertinent to the present case, evaluated the possibility of non-specific binding to the collection or storage tubes. Samples were stored at -80°C with EDTA in four different types of test tubes, namely polystyrene, polystyrene, silanised glass, or glass tubes. As illustrated in Figure 2, collecting and storing the samples in polystyrene tubes resulted in the largest reduction of ANP activity, collection into polypropylene, silanised glass or glass tubes resulting

in smaller amounts of degradation. These results led the authors to the conclusion that plasma samples for ANP level determination **should not be stored in polystyrene** and to the final remark that degradation of ANP during storage could explain discrepancies between ANP levels in different studies (see page 465, right-hand column, last paragraph).

8. Document D2 reports an investigation in which the short-term *in vitro* stability of human N-terminal proatrial natriuretic peptide (N-ANP) and human BNP under different storage conditions was assessed. Blood samples were taken from ten patients with chronic heart failure into standard polypropylene tubes containing EDTA. Blood samples were divided as follows: (1) tubes containing EDTA and aprotinin, plasma separated immediately; (2) tubes containing EDTA and aprotinin, samples left for 2 hours at room temperature before separation of plasma; (3) tubes containing EDTA and aprotinin, samples left for 6 hours at room temperature before separation of plasma; (4) tubes containing EDTA alone, plasma separated immediately; (5) tubes containing EDTA alone, samples left for 2 hours at room temperature before separation of plasma; and (6) tubes containing EDTA alone, samples left for 6 hours at room temperature before separation of plasma. The authors concluded that their findings suggested that a blood sample taken into such a tube and transported to the laboratory for separation within 6 hours would provide an accurate measurement of plasma N-ANP and BNP concentrations.

9. Document D2, which specifically deals with an assessment of stability of BNP, qualifies as the closest state of the art.

10. The technical problem to be solved in view of document D2 is the provision of an alternative method for ensuring stability of BNP after having taken a sample from a patient, i.e. when handling the specimen. The solution to this problem is a method of inhibiting degradation according to claim 1, in which a container made of or coated with polystyrene (first embodiment) or polyethylene terephthalate (second embodiment) is employed when handling specimens. The examples of the patent specification show that both embodiments constitute a solution to the underlying technical problem.

11. The question to be answered is whether the skilled person would have found any incentive or hint in the available state of the art, regardless of precise storage conditions and the kind of handling the specimen, to devise a method for inhibiting the degradation of mammalian BNP in a specimen based on the concept of using polystyrene or polyethylene terephthalate tubes for handling blood samples instead of polypropylene tubes used in the experiments of document D2.

12. As regards the embodiment based on the concept of using polystyrene tubes, the following reasoning is made:

12.1 Prior art document D1 would not have escaped the attention of the skilled person faced with the underlying technical problem because it dealt with the

problem of stability of a natriuretic peptide, namely ANP (closely related to N-ANP, the other peptide referred to in document D2).

12.2 However, this document with its explicit conclusion that plasma samples for ANP level determination **should not be stored in polystyrene** because the experiment had shown in this case the largest reduction in ANP concentration, would have taught away from using this particular material for ANP as well as, by analogy, for the closely related peptide BNP.

12.3 In this respect, the respondent's argument that Figure 2 of document D1 shows that polystyrene and polypropylene behave similarly and that, thus, the skilled person would not have taken into serious account the recommendation in D1 is not tenable. As a matter of fact, from Figure 2 the skilled person would have derived that when plasma samples are stored at -80°C polypropylene performed much better than polystyrene (compare the ANP values for the same four plasma samples given for the -80PP and -80PS criteria indicated on the X-axis). Comparing, as proposed by the respondent, the values obtained for a polystyrene storage at -80°C (the only storage condition tested in relation with the use of polystyrene) with the values obtained for a polypropylene storage at -20°C is simply inadequate. The figure in question actually supports the recommendation made at the end of the discussion not to store the specimens in polystyrene (or glass) tubes.

12.4 Equally untenable is the argument that, since - as shown by prior art documents D7 and D10 (N.B.: document

D13 which is post-published is not relevant here) - polystyrene was a well-known (widely used) material for clinical containers, the skilled person, notwithstanding the recommendation in document D1, would not have hesitated in using containers made of polystyrene, thus arriving in a straighforward manner at the claimed method. From these documents the skilled person would have only derived that polystyrene tubes were indeed used respectively in a radioreceptor assay for rat-ANP (see D7) and in an immunoassay for human BNP (see D10). However, as the said documents were not concerned with the issue of stability of the ANP or BNP peptides, the skilled person would not have concluded that the recommendation in document D1 was not to be taken into serious account. On the contrary, as the latter document had examined the issue of stability of the ANP peptide in stored specimens, the skilled person would had turned his/her attention away from a material which was explicitly said to pose problems.

12.5 As for the further respondent's argument that claim 1 does not involve an inventive step for the reason that in the patent the use of polystyrene containers does not provide any improvement in terms of BNP stabilisation compared to the use of polypropylene tubes, it is observed with reference to case law of the boards of appeal (cf. in particular decisions T 588/93 of 31 January 1996 (see point 6.1. of the Reasons) and T 620/99 of 8 May 2003 (see point 30 of the Reasons)) that when assessing inventive step for claims referring to an alternative solution of a known problem, it is not necessary to show improvement over the prior art, the relevant question being only whether the alternative solution proposed is non-obvious. In the

present case, the technical situation can be summarised as follows: the skilled person, starting from a prior art document (D2) describing the positive effect of the use of polypropylene tubes on the short term stability of BNP (and N-ANP), although well knowing that polystyrene tube were commonly used as containers for clinical specimens, was confronted with a document (D1) confirming the positive effects on storage of ANP in polypropylene tubes and advising the readers not to use polystyrene tubes. In the board's judgement, under these technical circumstances, it was **not obvious** for the skilled person to propose a method for inhibiting the degradation of BNP in a specimen based on the use, upon handling, of a container made of or coated with polystyrene.

13. As regards the second embodiment of claim 1 based on the concept of using polyethylene terephthalate tubes, the following reasoning is made:

13.1 In document D1, polyethylene terephthalate is not one of the materials tested. In addition to polypropylene and polystyrene, only silanised glass and glass are tested. Thus, the skilled person would have found in D1 no incentive or hint to devise a method for inhibiting the degradation of mammalian BNP in a specimen based on the concept of using polyethylene terephthalate containers instead of polypropylene tubes as employed in document D2. Nor would he/she have found such an incentive in document D7 or document D10 for the reason that these documents do not describe the use of polyethylene terephthalate as a material for containers in which body fluid samples such as plasma samples are collected or stored for testing the presence of

natriuretic peptides, let alone the fact that, anyway, as indicated at point 12.4 *supra*, they do not deal with the determination of conditions which inhibit BNP degradation.

13.2 The respondent's argument that, at the relevant filing date, polyethylene terephthalate was commonly used to produce containers employed in the field of biology is not relevant, as it does not give any hint as to whether that particular material would have provided any interest or advantage when collecting or storing body fluid samples to be tested for the presence of any natriuretic peptides, including mammalian BNPs.

14. In view of the remarks made at points 6 to 13, the conclusion is reached that the method of claim 1 involves an inventive step. The same conclusion applies *de facto* to dependent claim 2. Thus, the main request complies with Article 56 EPC.

Concluding remark

15. Since the main request meets the requirements of the EPC, it forms the basis for the maintenance of the patent in an amended form.

Adaptation of the description

16. At the oral proceedings the appellant adapted the description to the main request. The respondent agreed to the amended description. The board is satisfied that the description was satisfactorily amended in accordance with the EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of:

   a. claims 1 and 2 of the main request filed on 11 February 2010;

   b. description pages 2, 2a, 3 and 4 as filed during the oral proceedings;

   c. figures as granted.

The Registrar The Chairman

A. Wolinski L. Galligani