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Datasheet for the decision of 5 June 2014

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Application Number: 99961418.3

Publication Number: 1143000

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Language of the proceedings: EN

Title of invention:
SCREENING METHOD

Patent Proprietor:
Takeda Pharmaceutical Company Limited

Opponent:
Boehringer Ingelheim Pharma GmbH & Co. KG

Headword:
Screening method/TAKEDA

Relevant legal provisions:
EPC Art. 54(2), 56, 83

Keyword:
Novelty - (yes)
Inventive step - (yes)
Sufficiency of disclosure - (yes)

Decisions cited:
G 0004/92

Catchword:

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Case Number: T 0163/11 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 5 June 2014

Appellant I: (Patent Proprietor)	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome Chuo-ku Osaka-shi, Osaka 541-0045 (JP)
Representative:	Weiss, Wolfgang Weickmann & Weickmann Patentanwälte Richard-Strauss-Strasse 80 81679 München (DE)
Appellant II: (Opponent)	Boehringer Ingelheim Pharma GmbH & Co. KG Birkendorfer Strasse 65 88397 Biberach an der Riss (DE)
Representative:	Stock, Wolfgang Boehringer Ingelheim Pharma GmbH & Co. KG Birkendorfer Straße 65 88397 Biberach an der Riss (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 13 December 2010 concerning maintenance of the European Patent No. 1143000 in amended form.**

Composition of the Board:

Chairman	U. Oswald
Members:	T. Sommerfeld
	R. Cramer

Summary of Facts and Submissions

I. European patent No. 1 143 000, based on European patent application No. 99961418.3, which was filed as an international application published as WO 2000/040725, was granted with 16 claims.

Independent claims 1, 2, 13, 14 and 15 as granted read as follows:

"1. A method for screening a compound or its salt that alters the binding property between a melanin concentrating hormone (MCH) or its salt and SLC-1 or its salt, which comprises measuring the amount of the MCH or its derivative bound to the SLC-1 or its salt, (i) when the MCH or its derivative is brought into contact with the SLC-1 or a salt thereof, and (ii) when a test compound and the MCH or its derivative are brought into contact with the SLC-1 or a salt thereof; and comparing (i) and (ii)."

"2. A kit for screening a compound or its salt that alters the binding property between MCH or its salt and SLC-1 or its salt, comprising the MCH or its derivative, or a salt thereof and the SLC-1 or its salt."

"13. A protein containing the amino acid sequence represented by SEQ ID NO:11, or a salt thereof."

"14. A DNA containing a DNA having a base sequence encoding the protein according to claim 13."

"15. MCH derivatized with a Bolton-Hunter reagent, or a peptide or its salt derivatized with a Bolton-Hunter reagent and containing a sequence of the 4th to the

19th or of the 5th to the 19th from the N terminus of the amino acid sequence represented by SEQ ID NO:2."

II. Opposition was filed against the granted patent, the opponent requesting revocation of the patent in its entirety on the grounds of lack of novelty and inventive step (Articles 52(1) and 54 and 56 EPC and Article 100(a) EPC) and lack of sufficiency of disclosure (Articles 83 and 100(b) EPC).

III. During the proceedings before the opposition division, the patent proprietor requested that the patent be maintained on the basis of the main request filed with letter of 8 September 2010, or alternatively according to the auxiliary request filed during oral proceedings on 10 November 2010.

Claim 1 of the auxiliary request differed from granted claim 1 as follows (insertions underlined, deletions struck through):

"1. A method for screening a compound or its salt that alters the binding property between a melanin concentrating hormone (MCH) or its salt and SLC-1 or its salt, which comprises measuring the amount of ~~the~~ MCH labeled with a Bolton-Hunter reagent or ~~its~~ of an MCH derivative labeled with a Bolton-Hunter reagent bound to the SLC-1 or its salt, (i) when the MCH labeled with a Bolton-Hunter reagent or ~~its~~ the MCH derivative labeled with a Bolton-Hunter reagent is brought into contact with the SLC-1 or a salt thereof, and (ii) when a test compound and the MCH labeled with a Bolton-Hunter reagent or ~~its~~ the MCH derivative labeled with a Bolton-Hunter reagent are brought into contact with the SLC-1 or a salt thereof; and comparing (i) and (ii)."

The same amendments as in claim 1 were also introduced into granted claim 2 (claim 3 of the auxiliary request).

A new independent claim was introduced as claim 2:

"2. A method for screening a compound or its salt that alters the binding property between a melanin concentrating hormone (MCH) or its salt and SLC-1 or its salt, which comprises measuring the amount of the MCH or its derivative bound to the SLC-1 or its salt; (i) when the MCH or its derivative is brought into contact with the SLC-1 or a salt thereof, and (ii) when a test compound and the MCH or its derivative are bought into contact with the SLC-1 or a salt thereof; and comparing (i) and (ii);
wherein the SLC-1 is a protein containing the amino acid sequence shown by SEQ ID NO:11, or a protein containing the amino acid sequence shown by SEQ ID NO: 11, of which 1 to 30, preferable 1 to 10, amino acids are deleted, the amino acid sequence shown by SEQ ID NO:11, to (or in) which 1 to 30, preferably 1 to 10, amino acids are added (or inserted); or the amino acid sequence shown by SEQ ID NO:11, in which 1 to 30, preferably 1 to 10, amino acids are substituted with other amino acids."

A new independent claim 4, directed to a kit, was also introduced, wherein the SLC-1 was defined as in claim 2 above.

Granted claim 15 (claim 14 of the auxiliary request) was amended as follows:

"14~~15~~. ~~MCH derivatized with a Bolton-Hunter reagent, or a~~ A peptide or its salt ~~derivatized with a Bolton-Hunter reagent and containing~~ consisting of a sequence of the 4th to the 19th ~~or of the 5th to the 19th~~ from the N terminus of the amino acid sequence represented by SEQ ID NO:2, derivatized with a Bolton-Hunter reagent."

IV. The documents cited during the proceedings before the opposition division and the board of appeal include the following:

D3 Kolakowski et al. FEBS Letters 398 (1996) 253-258
D4 Vaughan et al. Endocrinology 125 (1989) 1660-1665
D8 WO 96/39162
D9 EP 0 848 060
D17 Shimada et al. Nature 396 (1998) 670-674

V. By an interlocutory decision pronounced at oral proceedings on 10 November 2010 and posted on 13 December 2010, the opposition division decided that the patent be maintained in amended form on the basis of the auxiliary request filed during oral proceedings (Articles 101(3)(a) and 106(2) EPC).

The opposition division considered that the claim set according to the main request lacked novelty, while the requirements of Rule 80 EPC and Articles 123(2) and (3), 84, 54, 56 and 83 EPC were considered to be fulfilled by the auxiliary request.

As regards the main request, the opposition division considered that claims 1 and 5 to 7 were not novel over the disclosure of D1, while claim 16 lacked novelty over document D18. Documents D3 and D8 were however not

considered novelty-destroying for the claimed subject-matter (in particular, claims 15 and 1, respectively).

VI. The patent proprietor (appellant I) lodged an appeal against that decision. With the statement of the grounds of appeal, it requested that the patent be maintained according to the main request, or alternatively according to auxiliary requests 1a, 1b, 1c, 1d, 2a, 2b, 2c, 2d, 3a, 3b, 3c, 3d, 4a, 4b, 5a, 5b, 5c and 5d, all filed with the grounds of appeal. Oral proceedings were requested as an auxiliary measure.

VII. The opponent (appellant II) also lodged an appeal against the decision of the opposition division. With the statement of the grounds of appeal, it requested that the decision be set aside and the patent revoked in its entirety. Oral proceedings were requested as an auxiliary measure. A new document was submitted as document D19.

VIII. With letter dated 9 November 2011, appellant I submitted a substantive reply to the grounds of appeal of appellant II, and requested that document D19 be not admitted into the proceedings.

IX. Summons to oral proceedings before the board were issued, scheduling oral proceedings for 5 June 2014.

X. In reply to the summons, appellant I filed a letter dated 2 May 2014 and replaced the requests on file by a new main request and auxiliary requests 1 to 6, corresponding, respectively, to previous requests 1c, 2c, 2d, 2c with amendments, 3d, 4b and 5d.

XI. Appellant II informed the board, with letter dated 16 May 2014, that it would not be attending the oral proceedings.

XII. Oral proceedings before the board took place as scheduled on 5 June 2014, in the absence of appellant II as announced.

During the oral proceedings, appellant I withdrew the main request and auxiliary request 1.

Auxiliary request 2 differs from the claim request maintained by the opposition division in that claims 12 and 13 (granted claims 13 and 14, respectively) were deleted.

XIII. Appellant I's submissions, in so far as relevant to the present decision, may be summarised as follows:

Appellant II's objection under Article 84 EPC appeared to be rather an objection under Article 83 EPC. The Bolton-Hunter reagent could be used to introduce labels other than radioactive iodine (^{125}I) into a protein, as exemplified in Example 18 of the patent.

In relation to D8, it was noted that, contrary to appellant II's arguments, it did not directly and unambiguously disclose SLC-1, because, while referring to "MCH-receptor" it did not provide its identity or structure.

With regard to inventive step, the invention claimed was based on the finding that MCH was a ligand of SLC-1, which was not taught or suggested by any of the cited prior art documents. Some documents disclosed SLC-1 or similar proteins but not MCH (D3, D9), while

others disclosed MCH or similar proteins but not SLC-1 (D4-D6, D8, D10, D16-D18). Only documents published after the effective date of the contested patent disclosed both MCH and SLC-1 (D1, D12-D14). Document D9 was not the closest prior art, as it did not disclose the suitability of SLC-1 for screening compounds which could be used as antiobestic agents or as appetite modulators, i.e., the purpose of the invention (paragraph 215 of the patent), which was based on the implication of MCH in the regulation of food intake and energy balance (D17; D12, abstract). D8 or D17, which disclosed MCH and its potential implication in the regulation of feeding behaviour or energy metabolism, were more suitable as a starting point for the assessment of inventive step. Regarding the combination of D9 with D19, document D19 should not be admitted into the proceedings as it was not of high relevance, since it did not teach or suggest SLC-1 (abstract; page 246, left column, second paragraph). Lastly, D18 reported problems with Bolton-Hunter labelled MCH analogues and recommended the use of differently labelled MCH analogues (page 199, left column, last paragraph; page 199, right column, first paragraph), thus teaching away from the invention.

Claims 12 and 13 were directed to a variant of MCH consisting of amino acids 4 to 19 of the full-length MCH. Figure 8 of the patent, displaying the results of Example 22 on page 35, showed that surprisingly this variant labelled with Bolton-Hunter (BH-MCH(4-19)) had the highest binding activity, even higher than for MCH. Document D18, which disclosed analogs of MCH, was the closest prior art. This document did not provide any hint towards the specific variants claimed and actually taught away from them (*supra*). Even when starting from D8, page 21, lines 23 to 25, the technical problem

would be the provision of MCH derivatives with improved properties in SLC-1 binding assays; the solution as claimed would not be obvious because D8 did not provide any hint towards labelling with Bolton-Hunter or that the specific variant when labelled would show a higher affinity.

XIV. Appellant II's arguments, in so far as relevant to the present decision, may be summarised as follows:

All claims referring to Bolton-Hunter derivatisation were unclear: the patent taught labelling with [^{125}I] by a method using a Bolton-Hunter reagent (see paragraph 37 of pages 7 and 8 of the patent as well as Example 20) but it was not apparent how labelling with [^{3}H], [^{14}C] or [^{35}S] was possible with a Bolton-Hunter reagent.

As regards novelty, since SLC-1 was the MCH-receptor, document D8, which did refer to the MCH receptor (page 7, lines 4-7), was novelty-destroying for the claimed subject-matter.

Moreover, the claimed subject-matter was not inventive. Both SLC-1 and MCH were known in the prior art: SLC-1 from D3 and MCH from D4. The only contribution of the patent thus consisted in using both in a known screening method. D9 further disclosed that the receptor had been obtained from a brain database (page 19, lines 3 and 4) and that there was a connection between this receptor and diabetes or adiposity (D9, page 3, line 9; see also D15, page 16, line 20). D9 disclosed on page 19, lines 40-42 that brain extracts had natural ligands for the receptor. Accordingly, it would be obvious for the skilled person to test substances that interacted with the receptor in

preparations comprising MCH. Contrary to the opinion of the opposition division, it was apparent from the prior art that MCH had an autocrine action (e.g. D18, page 199, left column, lines 10-14). D18 also disclosed MCH derivatives which had been labelled with the Bolton-Hunter reagent. It would thus also be obvious to contact SLC-1 preparations (e.g. a membrane which comprised the receptor) with a labelled MCH, so as to screen for substances which interfered with the binding. D9 on the other hand disclosed the appropriate experiment, which included radioactively labelled ligand (D9, page 16 line 14); for this radioactive labelling, the Bolton-Hunter method would be the method of choice, as supported by e.g. D18.

Contrary to the argumentation of the opposition division, there was no requirement in the claims that SLC-1 should be in pure form. Also examples 21-23 of the patent used membrane preparations which contained SLC-1. There was no disclosure of special difficulties encountered when cloning SLC-1; on the contrary, SLC-1 was already known (D3). When searching for a suitable receptor, the skilled person would have used hypothalamus tissue or hypothalamus gene database from human or rat and would necessarily arrive at SLC-1, as evidenced by D3, which sequences only slightly differed from the claimed sequences.

XV. Appellant I requested that the decision under appeal be set aside and that the patent be maintained on the basis of auxiliary request 2 - sole request - filed with letter of 16 May 2014.

XVI. Appellant II requested that the decision under appeal be set aside and that the European patent No. 1143000 be revoked.

Reasons for the Decision

1. Both appeals are admissible.

2. The oral proceedings before the board took place in the absence of appellant II who had been duly summoned but decided not to attend.

The present decision is based on facts and evidence put forward during the written proceedings and on which appellant II has had an opportunity to comment. Therefore the conditions set forth in Enlarged Board of Appeal opinion G 4/92, OJ EPO 1994, 149, are met.

Moreover, as stipulated by Article 15(3) RPBA the board is not obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying only on its written case.

3. Added subject-matter

3.1 No objections have been raised by appellant II and the board is also satisfied that the requirements of Article 123(2) and (3) are fulfilled by the present claims.

4. Clarity / sufficiency of disclosure

4.1 With its grounds of appeal, appellant II raised a clarity objection concerning the Bolton-Hunter derivatisation. According to appellant II, the patent only taught labelling with [^{125}I], and it was not

apparent how labelling with [^{3}H], [^{14}C] or [^{35}S] was possible with a Bolton-Hunter reagent.

4.2 The board concurs with appellant I that this objection is rather an objection under Article 83 EPC. Moreover, the board notes that appellant II has not relied on any facts or evidence to support this objection: indeed, there is no evidence on file suggesting that it would not be possible to use the Bolton-Hunter reagent to introduce other labels into MCH; Example 18 of the patent actually provides evidence that other labels can be used with Bolton-Hunter.

4.3 The present claims are thus considered to fulfil the requirements of Article 83 EPC and, in so far as the amendments to the granted claims are concerned, also those of Article 84 EPC.

5. Novelty

5.1 In view of the amendments to these claims compared with the granted claims, none of the novelty objections raised by appellant II applies to the present claim set.

5.2 In particular, it is noted that all present claims are novel over document D8, which appellant II has argued in its statement of the grounds of appeal to be novelty-destroying for the claims maintained by the opposition division. Indeed, the present claims comprise the features of labelling with Bolton-Hunter and/or of SLC-1 being a protein containing given amino acid sequences (SEQ ID NO:5 or 11); these features are not disclosed in D8.

The requirements of Article 54 EPC are thus fulfilled.

6. Inventive step

6.1 Claims 1 to 4

6.1.1 These claims are directed to methods for screening of test compounds, or to kits for use in such methods, wherein the test compounds are assessed for their effect on binding between SLC-1 and MCH. According to the patent's general description of the invention at paragraph [0001], the invention relates to a method for screening an antiobestic agent, an appetite modulator or the like, characterised by using SLC-1 and MCH. In order to provide such methods, the inventors first had to identify MCH as ligand for the then orphan receptor SLC-1 (patent, paragraphs [0003] to [0005].

6.1.2 Appellant I considered document D8 or D17 to be the closest prior art, while for appellant II document D9 was the closest prior art. Document D8 discloses screening methods for compounds which inhibit binding of MCH to its (non-identified) receptor (e.g. page 17, line 37 to page 18, line 1; page 34, lines 29 to 39); D9 discloses the 11CB splice variant (=SLC-1 splice variant) and methods of screening agonists or antagonists of a receptor of the invention, which comprise determining the inhibition of binding of a (non-identified) ligand to cells which have the receptor on their surface, in the presence of a candidate compound (D9, page 16, lines 10 to 17). D17 discloses MCH and its correlation with feeding behaviour.

6.1.3 D8 discloses MCH's role in the regulation of eating and weight (see e.g. abstract) while D9 just mentions obesity as one among a list of several disorders

(page 3, lines 6 to 13). The board thus considers that D8 is the only document which discloses a screening method having the same purpose as the claimed method, i.e. a method for screening an antiobestic agent or an appetite modulator (*supra*). As such, D8 is the most suitable starting point for the discussion of inventive step.

6.1.4 The difference between D8 and claim 1 is that a screening method involving measuring the binding of MCH to SLC-1 is not disclosed. The technical problem is thus formulated as the provision of a further screening method for antiobestic agents and/or appetite modulators. The solution is the method as claimed, which involves testing compounds for their effect on the binding between MCH and SLC-1. In view of the examples of the patent, and the fact that MCH was known to be involved in appetite and weight regulation (D8), the board is satisfied that the problem has been plausibly solved.

6.1.5 Although both MCH and SLC-1 were known in the citable prior art, there was no hint at all that they were binding partners: indeed SLC-1 was an orphan G-protein coupled receptor (GPCR), i.e. a GPCR for which no ligand had been identified; likewise, no receptor for MCH had been identified. In order to arrive at the claimed invention, the skilled person starting from D8 would first have to identify and isolate the MCH receptor. However, it was not trivial, at the priority date, to identify binding partners for given ligands or GPCRs.

6.1.6 Appellant II's arguments are mainly based on the assumption that claim 1 does not require the use of isolated SLC-1 / MCH, but instead encompasses also the

use of cell or cell membrane preparations which endogenously express these proteins: according to appellant II, combining one of the components (MCH or SLC-1) with membrane fractions from brain or the hypothalamus would anticipate the claimed invention.

The board cannot follow this argumentation. The claimed method requires that the test substances are assessed for their effect on the binding between MCH and SLC-1: without knowing the two binding partners, the skilled person could only measure an effect on the activity of one of these proteins, which is not the same as measuring an effect on the binding affinity between a ligand and its receptor.

6.1.7 Further arguments that the skilled person would be prompted by the prior art to clone the MCH receptor from brain (hypothalamus) extracts are also not convincing. The citable documents relating to MCH do not provide any hint at all concerning its receptor. The fact that MCH has been cloned from rat hypothalamus (D4) would not lead the skilled person to assume that its receptor would also be present in the hypothalamus; and even if it did, there is no evidence on file that its cloning would be straightforward just based on this hypothesis. Document D8 refers to the MCH receptor but does not teach its structure and still less that the receptor is SLC-1. D17 suggests that MCH antagonists may be effective treatments for obesity (page 673, left column, last 3 lines) but does not provide any information or hint concerning a receptor for MCH.

6.1.8 On the other hand, none of the citable documents disclosing the cloning of SLC-1 / 11CB provide any information which would lead the skilled person to assume that this could be the receptor for MCH.

Document D3 discloses the cloning of SLC-1, and teaches that it is expressed in human brain regions, including the forebrain and hypothalamus, but also in the heart, kidney and ovary (D3, abstract); D3 does not mention MCH at all, nor does it suggest any role of SLC-1 in appetite or weight control. Document D9 discloses the 11CB splice variant (=SLC-1 splice variant), but does not provide any hint that this is the receptor for MCH. Even if D9 suggests that antagonists of 11CB might have a therapeutic activity in situations of anorexia and bulimia, these are just two among a list of several unrelated disorders (see e.g. abstract of D3) and there is no experimental data supporting this statement.

6.1.9 Claim 1 thus involves an inventive step (Article 56 EPC). The same is true for claim 3, directed to a kit which is functionally linked to the method, and to claims 2 and 4 to 11, which further define the polypeptides used in the method and in the kit.

6.2 Claims 12 and 13

6.2.1 Document D8 is the closest prior art for the subject-matter of these claims. As stated above, D8 discloses screening methods for compounds which inhibit binding of MCH to its (non-identified) receptor, and also describes the role of MCH in the regulation of eating and weight. Moreover, D8 comments on the literature disclosing fragment analogs of MCH, to conclude that the 4 N-terminal amino acids of MCH are not required for its activity (page 21, lines 12 to 25, in particular 23 to 25).

6.2.2 The difference between the claimed subject-matter and document D8 is that the latter does not disclose the specific MCH derivative, namely a MCH fragment

consisting of residues 4 to 19 and labelled with Bolton-Hunter reagent. The board can follow appellant I's arguments that this particular derivative has an increased affinity towards SLC-1 as compared to the affinity of the other tested MCH derivatives and of the labelled full length MCH: this is evidenced by Figure 8 of the patent. This enhanced affinity renders the specific derivative particularly suitable for the screening methods of the invention. The technical problem is thus formulated as the provision of an MCH derivative with an improved SLC-1 binding affinity.

6.2.3 The solution is the MCH derivative as claimed in claims 12 and 13 and, in view of the results presented in Figure 8 of the patent, the board is satisfied that the problem is plausibly solved. The board is also convinced that the solution involves an inventive step because there was no hint in D8 or in the other documents of the prior art that this particular derivative - labelled with Bolton-Hunter - would have an improved binding affinity. Instead, from the teaching of document D8, the skilled person would consider that any MCH derivative lacking 1 to 4 N-terminal residues would have the same binding affinity and would not expect that Bolton-Hunter labelling of one derivative would increase its binding affinity.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The matter is remitted to the department of first instance with the order to maintain the patent in amended form on the basis of auxiliary request 2 filed with the letter of 2 May 2014, and a description to be adapted thereto.

The Registrar: The Chairman:

N. Maslin U. Oswald

Decision electronically authenticated