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Datasheet for the decision of 25 May 2018

Case Number: T 0004/14 - 3.3.04

Application Number: 04701379.2

Publication Number: 1581248

IPC: A61K38/17

Language of the proceedings: EN

Title of invention:
Modification of feeding behaviour and weight control by oxyntomodulin

Patent Proprietor:
Imperial Innovations Limited

Opponent:
Eli Lilly and Company

Headword:
Oxyntomodulin/IMPERIAL

Relevant legal provisions:
EPC Art. 83

Keyword:
All requests - sufficiency of disclosure (no)

Decisions cited:
T 0409/91, T 0435/91

Catchword:
-

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Case Number: T 0004/14 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 25 May 2018

Appellant: (Patent Proprietor)	Imperial Innovations Limited 52 Prince's Gate Exhibition Road London SW7 2PG (GB)
Representative:	Abel & Imray Westpoint Building James Street West Bath BA1 2DA (GB)
Respondent: (Opponent)	Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 (US)
Representative:	Kent, Lindsey Ruth Eli Lilly and Company Limited Lilly Research Center European Patent Operations Sunninghill Road Earl Wood Manor Windlesham Surrey GU20 6PH (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 18 October 2013 revoking European patent No. 1581248 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairwoman	G. Alt
Members:	B. Claes
	M. Blasi

Summary of Facts and Submissions

I. The appeal was lodged by the patent proprietor (hereinafter "the appellant") against the decision of the opposition division to revoke European patent No. 1 581 248, having the title "*Modification of feeding behaviour and weight control by oxyntomodulin*".

II. In the impugned decision the opposition division held *inter alia* that the patent lacked sufficiency of disclosure in relation to the invention claimed in all of the pending claim requests (Article 83 EPC).

III. With its statement of grounds of appeal the appellant submitted claims of a main request and auxiliary requests 1 to 3 and argued *inter alia* that the patent with the claims of these requests complied with the requirements of Article 83 EPC.

Claim 1 of the main request read:

"1. A pharmaceutical composition comprising **oxyntomodulin** and one or more other agent(s), each of which reduces food intake and/or reduces hunger, wherein the other agent or one of the other agents is PYY or an agonist thereof." (emphasis added by the board)

Claim 1 of auxiliary request 1 read:

"1. A pharmaceutical composition comprising **oxyntomodulin** and another agent, each of which reduces food intake and/or reduces hunger, **wherein said oxyntomodulin corresponds to the sequence of SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO: 3 and wherein the histidine residue at position 1 is maintained or**

replaced by an aromatic moiety carrying a positive charge or a derivative thereof, while 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 of the other amino acids in the above OXM sequence can be independently replaced by any other independently chosen amino acid, with the exception of histidine in position 1, and wherein the other agent or one of the other agents is PYY or an agonist thereof." (emphasis added by the board)

Claim 1 of auxiliary request 2 corresponded to claim 1 of the main request but with the wording "hunger, wherein" replaced by the wording "hunger, **wherein said oxyntomodulin corresponds to the sequence of SEQ ID NO: 1 and wherein the histidine residue at position 1 is maintained or replaced by an aromatic moiety carrying a positive charge or a derivative thereof, while 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 of the other amino acids in the above OXM sequence can be independently replaced by any other independently chosen amino acid, with the exception of histidine in position 1, and wherein the sequence has no deleted amino acid residues** wherein" (emphasis added by the board)

Claim 1 of auxiliary request 3 corresponded to claim 1 of auxiliary request 2 but with the feature "the other agents is PYY or an agonist thereof" replaced by the feature "the other agents is PYY_{3-36} or an agonist thereof".

IV. The opponent replied to the appeal and submitted, *inter alia*, that the patent based on the claims of any of the main request and auxiliary requests 1 to 3 did not comply with the requirements of Article 83 EPC.

V. The board summoned the parties to oral proceedings and informed them in a communication pursuant to

Article 15(1) RPBA of its preliminary non-binding opinion on some of the issues concerning the appeal, including sufficiency of disclosure (Article 83 EPC).

VI. Prior to the date of the oral proceedings, the appellant withdrew its conditional request for oral proceedings and requested a decision on the appeal based on the written submissions and requests. On the same day the respondent confirmed its conditional request for oral proceedings. Subsequently, the parties were informed by the registry of the board that the oral proceedings would take place as scheduled.

VII. At the oral proceedings before the board the appellant was absent. At the end of the oral proceedings the chairwoman announced the board's decision.

VIII. The following documents are referred to in this decision:

D12: WO 2006/134340

D24: Druce *et al.* (2009), Endocrinology, Vol. 150, No. 4, pages 1712 to 1721

D25: Santoprete *et al.* (2011), J. Pept. Sci., Vol. 17, pages 270 to 280

IX. The appellant's written arguments in relation to sufficiency of disclosure (Article 83 EPC) where relevant for the decision may be summarised as follows:

Main request - claim 1

The term "oxyntomodulin" and its synonym "OXM" required the compound to have the biological activity of oxyntomodulin in accordance with the meaning as understood by the skilled person. Only compounds with this activity would be recognised by a person skilled in the art as falling within the scope of the term "oxyntomodulin".

Oxyntomodulin was put forward in the patent as an appetite suppressor for use in reducing food intake and/or hunger (see for example page 2, lines 3 and 4).

Document D12 taught that a very large number of OXM analogues, including those which substantially differed structurally from the native OXM sequence, have OXM's functional feature of reducing food intake and/or hunger.

Auxiliary requests 1 to 3 - claim 1

No arguments were filed during the appeal proceedings.

X. The respondent's arguments in writing and at the oral proceedings in relation to sufficiency of disclosure (Article 83 EPC) where relevant for the decision may be summarised as follows:

Main request - claim 1

The structural definition of compounds termed "oxyntomodulin" (or its synonym "OXM") given in paragraphs [0018] to [0028] of the patent was extremely broad and provided a practically innumerable amount of analogues. Although it referred to three specific OXM peptide sequences 36 amino acids long which were known to the skilled person, the patent did not align such sequences in order to identify e.g. common sequence patterns.

The patent did not describe what was to be understood by the biological activity of oxyntomodulin. This was also not clear to the skilled person on the basis of his common general knowledge, as it could refer to activities which were unique to OXM or those which could be considered positive (such as gastric emptying) or those which were negative activities (such as anxiety). It therefore constituted an undue burden for the skilled person to filter out and identify from the bulk of oxyntomodulin analogues as structurally defined in the patent those which had oxyntomodulin functionality. Accordingly, in the absence of such guidance it likewise constituted an undue burden to identify and select those analogues which further reduced food intake/hunger from those that did not as required by the claim.

That the structural definition of oxyntomodulin provided in the patent was unreasonably broad was further illustrated by the fact that it also encompassed compounds which would not be considered by the skilled person to constitute an "oxyntomodulin". The structural definition encompassed for example a 32 amino acid peptide that had the 31 amino acid sequence of GLP-1 plus one additional amino acid at the C-terminus. Such a peptide had 96.9% identity with GLP-1 and would typically be considered to be a GLP-1 analogue. It also encompassed for example a 39 amino acid peptide that had 37 amino acids in common with exendin-4, which was a 39 amino acid GLP-1 receptor agonist. Such a peptide had 94.9% identity with exendin-4 and would typically be considered to be an exendin-4 analogue.

Post-published document D12 corroborated that, based solely on the guidance in the patent, the identification of oxyntomodulin analogues referred to in the claims and capable of reducing food intake and/or hunger constituted an undue burden for the skilled person. In fact it disclosed the results of the very research programme required to obtain the necessary guidance for the skilled person to identify oxyntomodulin analogues referred to in the claim without undue burden.

Document D12 listed numerous failures of OXM analogues to reduce food intake. By way of example:
- **Figure 22a** demonstrated that N-terminal acetylation of OXM led to suppression of the food intake reduction;
- **Figure 25a** demonstrated that replacement of amino acids at positions 27 to 33 led to non-active compounds;

- **Figure 27a** demonstrated that, whereas some C-terminal additions of amino acids led to significant maintenance of food intake reduction, this maintenance could be suppressed by the presence of one single particular other amino acid;
- **Figure 30a** demonstrated that whereas a particular replacement of amino acids at positions 27 to 30 suppressed food intake reduction, this was not the case for a replacement of amino acids e.g. at positions 27 to 31 or 33;
- **Figure 56a** demonstrated that OXM conjugates such as Lys22-palmitoyl-oxm, but also others combining the conjugation with certain amino acid replacements (here 7 amino acids), did not lead to food intake reduction; and
- **Figures 76a, 80a and 114c** demonstrated that the replacement of histidine at position 1 by a histidine analogue in combination with certain other amino acid replacements could suppress food intake reduction and even lead to increased food intake as compared to saline control.

Failures were thus encountered by modifications across the whole length of the molecule, and significant losses of activity could be caused by changes even at one sole amino acid position, and it was only after identifying the numerous failures that document D12 was able to propose the general Formula (I) Z-X-S1 (see paragraph bridging pages 4 and 5), which guided the skilled person to obtain "*a series of analogues of oxm that demonstrate the oxm like activity of reducing food intake, and with certain embodiments a greater ability to decrease food intake*" (see page 4, lines 5 to 6), i.e. it "*yielded a series of more that 160 oxm analogues of which the vast majority are more potent*

inhibitors of food intake than native oxm" (see page 7, lines 17 to 18).

Further examples of OXM analogues which failed to reduce food intake were disclosed in post-published document D24 (see page 1715, left-hand column, lines 34 to 35, and page 1718, paragraph bridging the columns) and document D25 (see Table 2).

In view of the lack of guidance in the prior art and in the patent in suit, the identification of oxyntomodulin analogues referred to in the claim thus amounted to trial-and-error experimentation.

Auxiliary requests 1 to 3 - claim 1

The scope of the term "oxyntomodulin" had been narrowed only slightly and now allowed only up to 12 amino acids rather than up to 22 amino acids to be replaced in auxiliary request 1 and in addition no longer allowed up to 5 amino acids to be deleted in auxiliary requests 2 and 3.

The reasons given as to why the patent in suit did not disclose the subject-matter of claim 1 of the main request also applied to the subject-matter now claimed.

XI. The appellant requested in writing that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of the main request or, alternatively, of one of auxiliary requests 1 to 3, all as filed with the statement of grounds of appeal.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. The appellant was duly summoned to oral proceedings but did not appear. In accordance with Rule 115(2) EPC the board decided that the proceedings were to be continued without the appellant. Furthermore, in accordance with Article 15(3) RPBA, the appellant was treated as relying on its written case.

Sufficiency of disclosure (Article 83 EPC)

3. The main issue to be decided in this appeal is whether or not the decision under appeal rightly held that the patent in suit did not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art in respect of the oxyntomodulin compound present in the claimed pharmaceutical compositions.

4. According to the case law of the Boards of Appeal, the requirements of sufficiency of disclosure are met only if the claimed invention can be performed by a person skilled in the art over the whole area claimed without undue burden, using common general knowledge and having regard to the information in the patent in suit (see e.g. decisions T 409/91, OJ EPO 1994, 653, reasons 3.5, and T 435/91, OJ EPO 1995, 188, reasons 2.2.1). A reasonable amount of trial and error is permissible, provided that a skilled person has at his disposal adequate information leading necessarily and directly towards success through the evaluation of initial failures (see Case Law of the Boards of Appeal, 8th edition 2016, II.C.5.6.1).

Main request - claim 1

5. The claimed invention relates to a pharmaceutical composition comprising as an ingredient *inter alia* "oxyntomodulin [...] which reduces food intake and/or reduces hunger" (see section III).

6. The patent, in paragraphs [0018] to [0028], provides a structural definition of the terms "oxyntomodulin" and "OXM".

7. Paragraph [0018] starts by stating that "*the term "oxyntomodulin" is the same as "OXM" and relates to any composition which includes an OXM peptide sequence or an analog thereof as follows: (...).*". Whereas the following structural definition commences by referring to three specific OXM peptide sequences 36 amino acid long which were known in the art (see paragraph [0018], i.e. derived from humans, angler fish and eels), the subsequent paragraphs generalise this specific understanding of the terms "oxyntomodulin" and "OXM" by further stating:

- that the term "*OXM used in this text also covers any analogue of the above OXM sequence, wherein the histidine residue at position 1 is maintained or replaced by an aromatic moiety carrying a positive charge or a derivative thereof, preferably wherein the moiety is an amino acid, more preferably wherein it is a histidine derivative, while 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14,15, 16, 17, 18, 19, 20, 21 or 22 of the other amino acids in the above OXM sequence can be independently replaced by any other independently chosen amino acid, with the exception of histidine in position 1*." (see paragraph [0019]);

- that "[a]*ny one or more (to 22) other alpha-amino acid residue in the sequence can be independently replaced by any other one alpha-amino acid residue. Preferably, any amino acid residue other than histidine is replaced with a conservative replacement as well known in the art i.e. replacing an amino acid with one of a similar chemical type such as replacing one hydrophobic amino acid with another.*" (see paragraph [0020]);

- that "(...). *In addition to the replacement option above, this may be by a non-essential or modified or isomeric form of an amino acid. (...) Furthermore, 1 to 22 amino acids may be replaced by a corresponding or different amino acid linked via its side chain (for example gamma-linked glutamic acid). For each of the replacements discussed above, the histidine residue at position 1 is unaltered or defined above.*" (see paragraph [0021]); and

- that "[i]*n addition, 1, 2, 3, 4 or 5 of the amino acid residues can be removed from the OXM sequence with the exception of histidine at the 1 position (or as defined above). The deleted residues may be any 2, 3, 4 or 5 contiguous residues or entirely separate residues.*" (see paragraph [0022]).

8. Accordingly, the board considers that paragraphs [0019] to [0022] do indeed generalise the specific meaning of the terms "oxyntomodulin" and "OXM" extensively in terms of structural variability. However, the structural definition in the patent in suit does not stop there, and is even further extended in the following paragraphs by stating *inter alia*

- that the C-terminus of the OXM sequence may be modified to add further amino acid residues or other moieties and that the OXM may be provided as the corresponding salt (see paragraphs [0023] and [0024]);

- that the OXM may be conjugated to one or more groups such as lipid, sugar, protein or polypeptide (see paragraphs [0025]; or

- that the amino acid side chains, the N-terminus and/or the C-terminus of the OXM may be chemically modified in a variety of ways (see paragraph [0026]).

9. The board therefore agrees with the respondent that the structural definition of the term "oxyntomodulin" contained in the patent and referred to in the claim covers a vast and practically innumerable host of OXM analogues in terms of their structural variability.

10. In order to illustrate the vast extent of the structural definition of oxyntomodulin given in paragraphs [0018] to [0028] of the patent, the respondent has submitted that it also encompasses for example a 32 amino acid peptide having 96.9% identity with the amino acid sequence of GLP-1 (see paragraph [0005] of the patent) and for example a 39 amino acid peptide having 94.9% identity with exendin-4, i.e. a 39 amino acid GLP-1 receptor agonist (see patent paragraph [0014]). The board can agree with the respondent that such peptides would not be considered by the skilled person as "oxyntomodulin" compounds, but rather as an GLP-1 analogue or an exendin-4 analogue having the respective functions and activities of GLP-1 or exendin-40.

11. The board agrees with the respondent that, *prima facie*, the skilled person would not expect all of the analogues structurally defined in the patent to exhibit the biological activity of oxyntomodulin, and it notes that the appellant has submitted in this context that the claim ought to be construed as encompassing only such oxyntomodulin analogues which also have the biological activity of oxyntomodulin in accordance with the meaning as understood by the skilled person.

12. The respondent has submitted however that the patent in suit failed to disclose what the biological activity of "oxyntomodulin" was and that, in the absence of any reference to relevant prior-art publications, it was not even sure whether or not the skilled person had knowledge of such biological activity and, if it did, what the exact understanding of this term would be.

13. The board concurs with the respondent in that respect and further notes that neither the patent in suit nor the prior art discloses any working examples of actual oxyntomodulin analogues falling within the ambit of the definition provided in the patent in suit which demonstrate the biological activity of oxyntomodulin.

14. The board therefore concludes that for this reason the skilled person seeking to work the invention as claimed was at a loss to identify from the vast and practically innumerable host of OXM analogues structurally defined in the patent as constituting "oxyntomodulin" those compounds which have the biological activity of oxyntomodulin.

15. As to obtaining oxyntomodulin compounds fulfilling the functional feature in claim 1 of being capable of reducing food intake and/or hunger, the board has seen

no evidence demonstrating that, at the relevant date of the patent in suit, a skilled person knew which compounds from the host of structurally defined oxyntomodulin analogues these would be. Thus, in order to identify this type of OXM analogue the skilled person has no option other than to test every single analogue individually.

16. In fact, the board agrees with the appellant that post-published document D12, a later patent document from the same applicant and inventors, corroborates that for the skilled person the identification of oxyntomodulin analogues referred to in the claims and capable of reducing food intake and/or hunger constitutes an undue burden when designing analogues falling within the ambit of the definition given in the patent in suit.

17. In particular, as submitted by the respondent, document D12 discloses numerous designed OXM analogues which fail to reduce food intake as required by the claim, and this for designed modifications in the analogues across the whole length of the molecule, whereby significant losses of activity could be caused by changes even at one sole amino acid position (see section X, above). Further OXM analogues failing to reduce food intake were disclosed in post-published document D24 (see page 1715, left-hand column, lines 34 to 35, and page 1718, paragraph bridging the columns) and document D25 (see Table 2).

18. The board concludes from these further considerations that the skilled person is not provided in the patent in suit with any useful guidance or information leading necessarily and directly to successful modification of oxyntomodulin to obtain functional analogues suitable as oxyntomodulin peptides which are able to display the

functional feature of being capable of reducing food intake and/or hunger as required by the claim. Therefore, for the same reason it constitutes an undue burden for the skilled person to work the claimed invention.

19. The board therefore concludes that the invention as defined in claim 1 of the main request is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art as required by Article 83 EPC.

Auxiliary requests 1 to 3 - claim 1

20. The oxyntomodulin ingredient of the pharmaceutical composition which is the subject-matter of claim 1 of the main request has been restricted to such analogues having only up to 12 amino acids replaced rather than up to 22 as in the main request. In addition, the ingredient in claim 1 of auxiliary requests 2 and 3 is not to have up to 5 amino acids deleted.

21. With reference to points 5 and 6 above, the board considers that these additional structural limitations on the total host of structurally defined analogues are not sufficient to overcome the reasons why the patent did not disclose the invention as defined in claim 1 of the main request, which therefore also apply to the inventions as defined in claim 1 of these requests.

22. The board therefore concludes that the inventions defined in claim 1 of auxiliary requests 1 to 3 are also not disclosed in a manner sufficiently clear and complete for them to be carried out by a person skilled in the art as required by Article 83 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated