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**Datasheet for the decision  
of 16 September 2014**

**Case Number:** T 0715/10 - 3.3.04  
**Application Number:** 00914425.4  
**Publication Number:** 1140145  
**IPC:** A61K38/22, A61K9/08, A61K9/19,  
A61P3/10, A61P5/50  
**Language of the proceedings:** EN

**Title of invention:**

Novel exendin agonist formulations and methods of  
administration thereof

**Patent Proprietor:**

Amylin Pharmaceuticals, Inc.

**Opponents:**

Sanofi-Aventis Deutschland GmbH  
Zealand Pharma A/S

**Headword:**

Stable liquid exendin formulations/Amylin Pharmaceuticals

**Relevant legal provisions:**

EPC Art. 114(2), 123(2), 123(3)  
RPBA Art. 12(1), 12(3)

**Keyword:**

Amendments -  
extension beyond the content of the application as filed (no)  
- extension of protection (no)

**Decisions cited:**

T 1721/07

**Catchword:**



**Beschwerdekammern  
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Case Number: T 0715/10 - 3.3.04

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.04**  
**of 16 September 2014**

**Appellant:** Amylin Pharmaceuticals, Inc.  
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**Decision under appeal:**      **Decision of the Opposition Division of the  
European Patent Office posted on 25 January 2010  
revoking European patent No. 1140145 pursuant to  
Article 101(3)(b) EPC.**

**Composition of the Board:**

**Chairwoman**            G. Alt  
**Members:**            M. Montrone  
                             K. Garnett

## Summary of Facts and Submissions

- I. The appeal was lodged by the patent proprietor (hereinafter "appellant") against the decision of the opposition division to revoke European patent No. 1 140 145. The patent has the title "*Novel exendin agonist formulations and methods of administration thereof*". It is based on European application No. 00914425.4, that was published as international application WO 00/41546 and which was replaced by a corrected version published on 8 March 2001. References to the "application as filed" hereinafter are references to this corrected version of WO 00/41546.
- II. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and inventive step (Article 56 EPC), under Article 100(b) EPC and under Article 100(c) EPC.
- III. In its decision the opposition division held that the subject-matter of claim 1 of the main and auxiliary requests 1, 2, 2a, 3 and 3a contravened the requirements of Article 123(2) EPC. It considered that the subject-matter of claim 1 was directed to a "stable formulation", whereas the application as filed disclosed only a composition in which the active ingredient was "stable". This resulted in a new combination of features which was not clearly and unambiguously derivable from the application as filed (see reasons of the decision under appeal, point 12.2). Auxiliary requests 4 and 5 were found not to meet the requirements of Article 123(3) EPC.
- IV. With its notice of appeal the appellant requested that the decision be set aside and that the patent be

maintained on the basis of the main request alternatively one of the auxiliary requests that were before the opposition division (being auxiliary requests 1, 2, 2a, 3, 3a, 4 and 5). With its statement of grounds of appeal the appellant submitted arguments for the compliance of the subject-matter of claim 1 of the main and the auxiliary requests 1, 2, 2a, 3, 3a with the requirements of Article 123(2) EPC and for the compliance of the subject-matter of claim 1 of auxiliary requests 4 and 5 with the requirements of Article 123(3) EPC.

- V. Two of the three opponents (hereinafter "respondent I", and "respondent III") replied to the appellant's statement of grounds of appeal and maintained the arguments relating to Articles 123(2) and (3) EPC which had been submitted before the opposition division.
  
- VI. Opponent II withdrew its opposition by its letter of 29 May 2013.
  
- VII. The parties were summoned to oral proceedings scheduled for 16 September 2014.
  
- VIII. In a communication pursuant to Article 15(1) RPBA the board indicated its preliminary view that the skilled person would interpret the feature "a stable parenteral liquid dosage form" in claim 1 in such a way that it applied to all ingredients of the formulation claimed. Furthermore, the omission of the feature "in an aqueous system" in claim 1 of all the requests on file was considered to result in subject-matter which extended beyond the content of the application as filed contrary to the requirements of Article 123(2) EPC).

- IX. In reply, with its letter of 21 August 2014 the appellant submitted a new main request and new auxiliary requests 1 and 2. The auxiliary requests 1, 2, 2a, 3, 3a, 4 and 5 filed with the statement of grounds of appeal were maintained as auxiliary requests 3 to 10 respectively.
- X. The respondents I and III announced in letters dated 1 September 2014 that they would not attend the oral proceedings.
- XI. Oral proceedings before the board took place on 16 September 2014. At the oral proceedings the appellant withdrew its main request and made its auxiliary request 1 its new main request.

Claim 1 of this request read as follows:

"1. A pharmaceutical formulation which is a stable parenteral liquid dosage form suitable for multi-use administration comprising 0.005% to 0.4 % (w/v) of an exendin in an aqueous system, 0.02% to 0.5% (w/v) of an acetate, phosphate, citrate, or glutamate buffer, alone or in combination, 1.0% to 10% (w/v) of a carbohydrate or polyhydric alcohol iso-osmolality modifier leading to an isotonic or iso-osmolar solution in an aqueous continuous phase, and 0.005 to 1.0 % (w/v) of m-cresol, said formulation having a pH between 4.0 and 6.0."

XII. The appellant's arguments, as far as they are relevant for the present decision, may be summarised as follows:

*Amendments (Article 123(2) EPC)*

*Claim 1*

The application as filed disclosed on page 43, lines 1 to 7 in combination with page 44, lines 5 and 6 a formulation in a parenteral liquid dosage form comprising a stable active ingredient, *i.e.* exendin, and excipients that maintained the overall stability of exendin in the formulation. A "stable" overall formulation was thus implicitly disclosed in these passages of the application as filed since it was the direct and unambiguous consequence of what was explicitly disclosed.

The combination of the other features of claim 1 was explicitly disclosed on page 43, line 1 to page 44, line 1 in combination with claims 14, 20, 21, 23 and 24 of the application as filed.

XIII. The respondents' arguments, as far as they are relevant for the present decision, may be summarised as follows:

*Admissibility of the new main request*

The auxiliary request 1 as filed with the appellant's letter of 21 August 2014 (*i.e.* the new main request, see sections IX and XI above) should not be admitted into proceedings as attempts to deal with the added subject-matter objections raised in the decision of the opposition division should have been filed with the statement of grounds of appeal. The objections were clearly set out in that decision and in the submissions



made during the proceedings before the opposition division. According to the case law of the Boards of Appeal, the admissibility of such late-filed claim requests should be considered with care. See decision T 1721/07, where the board had criticised the conduct of the appellant for waiting to see what was the opinion of the board before filing further requests.

*Amendments (Article 123(2) EPC)*

*Claim 1*

The application as filed only disclosed formulations in a parenteral liquid dosage form which comprised a stable active ingredient, *i.e.* exendin and excipients that maintained the stability of the active ingredient (see page 43, lines 1 to 7). However, the maintenance of conditions stabilising the active ingredient by excipients was different from excipients which were themselves stable. The application as filed did therefore not disclose a formulation which was stable as a whole.

The application as filed disclosed the multi-use administration of the formulation of claim 1 only if it was packed in a multi-use container, see page 43, lines 12, 13 and 30 to page 44, line 1 of the application as filed.

The combination of m-cresol with the other features of claim 1 was not disclosed in the application as filed.

XIV. The appellant requested that the decision under appeal be set aside and the case be remitted to the opposition division for further prosecution on the basis of its first auxiliary request as filed with its letter dated

21 August 2014 (now its main request). The requests of the respondents as made in writing were: (a) dismissal of the appeal (both respondents); (b) neither the main nor auxiliary requests 1 and 2, all filed with the appellant's letter of 21 August 2014, be admitted into the proceedings (respondent III); (c) remittal of the case to the opposition division for further prosecution if one of the appellant's requests met the requirements of Articles 123(2) and 123(3) EPC (respondent I).

## **Reasons for the Decision**

### *Admissibility of the new main request*

1. The appellant's auxiliary request 1 as filed with its letter of 21 August 2014 (*i.e.* its new main request, see sections IX and XI above) corresponds to auxiliary request 2 according to the notice of appeal and also to auxiliary request 2 which had been the subject of the decision of the opposition division, but with the following amendments in claim 1:

(1) The phrase "in an aqueous system" was inserted after the word "exendin";

(2) The phrase "leading to an isotonic or iso-osmolar solution in an aqueous continuous phase" was inserted after the term "iso-osmolality modifier".

2. In their decision, the opposition division had held auxiliary request 2 not to be allowable for the single reason that the feature "a stable parenteral liquid dosage form" was considered to extend the subject-matter claimed beyond the content of the application as

filed, in contravention of Article 123(2) EPC (see point 13 of the reasons). In its statement of grounds of appeal the appellant duly gave reasons why it considered this part of the decision to have been wrong. In its reply respondent III raised *inter alia* further objections under Article 123(2) EPC (a) concerning the omission of the phrase "in an aqueous system" and (b) arguing that in relation to the iso-osmolality modifier, the dosage form according to the disclosure in the application as filed had to be an isotonic or an iso-osmolar solution in an aqueous continuous phase. Neither point had been the subject of the decision of the opposition division. In its communication pursuant to Article 15 RPBA the board indicated that in its view the feature "a stable parenteral liquid dosage form" was to be interpreted in a sense that all of the ingredients of the formulation were stable and that respondent III was correct about the omission of the phrase "in an aqueous system" (see point (a), above). The board made no express comment on point (b), above. Auxiliary request 1 - the current new main request - was filed within the time limit set by the board for any response to its communication.

3. The board considers that the filing of the request was an appropriate response to the situation as it had developed. The request dealt with two of the points which had been raised in respondent III's reply, neither of which had played any role in the opposition division's decision, one of which the board had indicated as being possibly valid. It did not raise any new issue which could not be dealt with at the oral proceedings. The situation is quite different to that in decision T 1721/07 of 29 March 2012, point 13 of the reasons, where the board criticised the conduct of the appellant in waiting to see what the opinion of the

board was before filing further requests. The relevant part of the decision reads as follows:

*"13. Wie bereits angeführt ..., zeigen Zahl und Umfang der von den Beschwerdeführern im Laufe des Beschwerdeverfahrens eingereichten Schriftsätze, dass diese ausreichend Gelegenheit hatten, weitere Anträge zu einem früheren Zeitpunkt vorzulegen. Offenbar zogen es die Beschwerdeführer aber vor, abzuwarten, bis sie die Auffassung der Kammer zu den wenigen tatsächlich eingereichten Anträgen kannten, und erst dann - je nachdem, wie diese Auffassung ausfiel - Alternativen einzureichen. Wer als Beteiligter derart taktisch vorgeht, handelt unweigerlich auf eigenes Risiko; dies geht aus den Vorschriften der VOBK auch eindeutig hervor (wonach ein Beschwerdeführer beispielsweise mit seiner Beschwerdebegründung seinen vollständigen Sachvortrag einschließlich aller Anträge einreichen muss, Änderungen seines Vorbringens im Ermessen der Kammer stehen und eindringlich davon abgeraten wird, solche Änderungen nach Anberaumung der mündlichen Verhandlung oder gar - wie im vorliegenden Fall - während der mündlichen Verhandlung vorzunehmen (siehe Artikel 12(2), 13(1) und 13(3) VOBK)."*

4. Clearly the later a party waits before filing requests the greater the risk that they will not be admitted. However, the board does not consider that the appellant overstepped the mark in the present case and in the exercise of its discretion therefore admitted the request (Articles 114(2) EPC in combination with Articles 12(1) and 12(3) RPBA).

*Amendments (Article 123(2) EPC)*

5. It is established case law that amendments are permitted within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, from the explicit or implicit disclosure of the application as filed as a whole. An implicit disclosure is what the skilled person would consider necessarily implied by what is explicitly disclosed (see Case Law of the Boards of Appeal, 7th edition, section II.E.1, page 361, fourth paragraph and page 362, sixth paragraph).

5.1 Claim 1 relates to a pharmaceutical formulation which is defined by the following features:

(i) it is a stable parenteral liquid dosage form;

(ii) its suitability for multi-use administration;

and the presence of

(iii) 0.005% to 0.4 % (w/v) of an exendin in an aqueous system; of

(iv) 0.02% to 0.5% (w/v) of an acetate, phosphate, citrate, or glutamate buffer, alone or in combination; of

(v) 1.0% to 10% (w/v) of a carbohydrate or polyhydric alcohol iso-osmolality modifier leading to an isotonic or iso-osmolar solution in an aqueous continuous phase; of

(vi) 0.005 to 1.0 % (w/v) of m-cresol; and

(vii) a pH between 4.0 and 6.0.

Thus the pharmaceutical formulation of claim 1 is in a "stable parenteral liquid dosage form" which contains exendin as active ingredient and a buffer, an iso-osmolality modifier and m-cresol as "inactive" ingredients, *i.e.* excipients.

5.2 It is uncontested by the parties that the application as filed explicitly only discloses that the active ingredient, *i.e.* exendin, is stable in this formulation. It is however an issue in the present case whether the application as filed also discloses that the formulation as a whole is stable.

5.3 In this respect the following passage can be found in the application as filed on page 43, line 1 to page 44, line 17:

*"The formulation which best supports a parenteral liquid dosage form is one **in which the active ingredient(s) is stable** with adequate buffering capacity to maintain the pH of the solution over the intended shelf life of the product. The dosage form should be either an isotonic and/or an iso-osmolar solution to either facilitate stability of the active ingredient [...] If, however, the dosage form is packaged in a multi-use container, then a preservative is necessary. [...] Sodium chloride, as well as other excipients, may also be present, if desired. **Such excipients, however, must maintain the overall stability of the active ingredient.** Polyhydric alcohols and carbohydrates [...]. These two classes of compounds will also be effective in stabilizing protein against*

*denaturation caused by elevated temperature and by freeze-thaw or freeze-drying processes." (Emphasis added by the board).*

- 5.4 This passage explicitly discloses that the active ingredient exendin is stable and also that it is the function of the cited excipients to maintain the overall stability of the active ingredient (see the passages in bold).
- 5.5 In the board's judgement, the skilled person using common general knowledge would derive from the passage cited in point 5.3 above that the stability of exendin as active ingredient in the liquid formulation of claim 1 depends on the proper functioning of all the excipients present, or in other words, that the stability of exendin is the direct consequence of the activity of the individual excipients. This would be understood by the skilled person to mean that the formulation is stable. It follows therefore that the application as filed implicitly discloses a formulation which is stable as a whole.
6. The respondents further objected to the feature "suitable for multi-use administration" of claim 1. With reference to page 43, lines 12, 13 and 30 to page 44, line 1 of the application as filed they argued that a multi-use administration of the claimed formulation is only disclosed if it is packaged in a multi-use container (see the underlined passage in point 5.3 above).

6.1 However, the application as filed discloses on page 14, lines 3 to 8:

*"The invention also includes lyophilized and **liquid multi-dose formulations**. As with the parenteral liquid and lyophilized unit-dosage formulations described above, the lyophilized multi-unit-dosage form should contain a bulking agent to facilitate cake formation. **A preservative is included to facilitate multiple use by the patient.**"* (Emphasis added by the board).

6.2 In the board's judgement this disclosure presents a direct and unambiguous disclosure for a parenteral liquid dosage form suitable for multi-use administration according to claim 1, *i.e.* for a multi-use administration without the concomitant requirement for the packaging of the formulation in a multi-use container.

7. The respondents further objected to the combination of m-cresol with the other features of claim 1 as being not disclosed in the application as filed.

7.1 The subject-matter of claim 1 as outlined in point 5.1 above concerns a pharmaceutical formulation which is defined by features (i) to (vii).

7.2 The application as filed discloses a formulation which is a stable parenteral liquid dosage form (*i.e.* feature (i)) and suitable for multi-use administrations (*i.e.* feature (ii)) for the reasons given in points 5.3 to 6.2 above.



7.3 Moreover, the application as filed discloses in the passage cited in point 5.3 above in the context of a formulation which best supports the parental liquid dosage form of the invention:

**"0.005 to about 0.4% [...] (w/v), respectively of the active ingredient in an aqueous system"** [i.e. feature iii]; **"0.02 to 0.5% (w/v) of an acetate, phosphate, citrate or glutamate or similar buffer either alone or in combination"** [i.e. feature iv]; **"1.0 to 10% (w/v) of a carbohydrate or polyhydric alcohol iso-osmolality modifier (preferably mannitol) or up to about 0.9% saline or a combination of both leading to an isotonic or an iso-osmolar solution in an aqueous continuous phase"** [i.e. feature v], **"0.005 to 1.0% (w/v)** [i.e. feature vi] **of an anti-microbial preservative selected from the group consisting of m-cresol, benzyl alcohol, methyl ethyl, propyl and butyl parabens and phenol"**.

**M-cresol** [i.e. feature vi] is the preferred preservative in this list of preservatives (see page 14, lines 27 to 30 of the application as filed). The passage cited in point 5.4 above further discloses **"4.0 to 6.0"** [i.e. feature vii] (emphasis added by the board).

7.4 The board notes that m-cresol is not only disclosed in this passage as one of the suitable preservatives, but that it is also highlighted as the preferred one. In the board's view this passage thus discloses a combination of the features (iii) to (vii) of present claim 1 as outlined in point 5.1 above.

- 7.5 Hence, the board considers that in view of points 7.2 and 7.3 above that the application as filed discloses the combination of m-cresol with all the other features of claim 1.
8. The respondents have not raised objections pursuant to Article 123(2) EPC against the subject-matter of claims 2 to 11. Also the board has none. Thus, it is concluded that the subject-matter of claims 1 to 11 meets the requirements of Article 123(2) EPC.

*Extension of protection (Article 123(3) EPC)*

9. None of the respondents has raised an objection pursuant to Article 123(3) EPC against the amended subject-matter of claim 1. Also the board has none. The subject-matter of claim 1 thus meets the requirements of Article 123(3) EPC.

## Order

### For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance for further prosecution on the basis of the appellant's first auxiliary request as filed with its letter dated 21 August 2014.

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated