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**Datasheet for the decision
of 18 July 2006**

Case Number: T 0723/05 - 3.3.04

Application Number: 93908252.5

Publication Number: 0587858

IPC: A61K 38/27

Language of the proceedings: EN

Title of invention:

Protein formulation comprising growth hormone

Patentee:

Pharmacia Aktiebolag

Opponent:

Genentech, Inc.

Headword:

Growth hormone/PHARMACIA AKTIEBOLAG

Relevant legal provisions:

EPC Art. 123(2), 84, 83, 54, 56

Keyword:

"Main request: added subject-matter (no)"

"Clarity (yes)"

"Sufficiency of disclosure (yes)"

"Novelty (yes)"

"Inventive step (yes)"

Decisions cited:

T 1241/03

Catchword:

-



Case Number: T 0723/05 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 18 July 2006

Appellant I: Pharmacia Aktiebolag
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Appellant II: Genentech, Inc.
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
8 April 2005 concerning maintenance of European
patent No. 0587858 in amended form.

Composition of the Board:

Chair: U. Kinkeldey
Members: R. Gramaglia
G. Weiss

Summary of Facts and Submissions

- I. European Patent No. 0 587 858 with the title "Protein formulation comprising growth hormone" was granted with 11 claims on the basis of European patent application No. 93 908 252.5 (published as WO 93/19776), filed on 1 April 1993 and claiming priority from SE 9201073-5 of 3 April 1992.
- II. Notice of opposition was filed by the opponent requesting the revocation of the European patent on the grounds of Articles 100(a), (b) and (c) EPC. By a decision dated 8 April 2005 the opposition division maintained the patent on the basis of the claims of the first auxiliary request then on file.
- III. Appellant I (patentee) and appellant II (opponent) lodged appeals against the decision of the opposition division.
- IV. During oral proceedings held on 18 July 2006 appellant I submitted a new main request and an amended description. Claim 1 of the new main request read as follows:
- "1. A stabilized injectable formulation of aqueous solutions of human growth hormone (hGH) or any functional analogue thereof being stable for at least 12 months, consisting of the human growth hormone and sodium citrate in an amount of 2-20 mM as buffer substance at a pH of about 6.0 to 7.0, to thereby stabilize said growth hormone in said formulation and optionally amino acids and/or sugar alcohol and/or glycerol and/or carbohydrates and/or preservative."

Claims 2 to 5 related to specific embodiments of the aqueous solution/formulation of claim 1. Claim 6 addressed a process for the preparation of a formulation according to any of claims 1 to 5.

V. The following documents are cited in the present decision:

D1 WO-A-89/09614;

D2 WO-A-91/18621;

D4 WO-A-92/17200;

D5 WO-A-93/22335;

D5a Manning M.C. et al., *Pharmaceutical Research*, Vol. 6, No. 11, pages 903-918 (1989);

D7 US-A-4,837,202;

D8 Schein C.H., *Bio/Technology*, Vol. 8, pages 308-317 (1990);

D11 Declaration of J.Q. Oeswein dated 12 March 2003;

D13 Akers M.J., *Pharmaceutical Technology*, pages 36-40 (May 1984);

D14 Jacox R.F., *Lab. Clin. Med.*, pages 721-727 (1951);

D15 Shephard M.D.S. et al., *Ann. Clin. Biochem.*, Vol. 29, pages 411-417 (1992).

VI. The submissions by the appellant I (patentee), insofar as they are relevant to the present decision, can be summarized as follows:

Article 84 EPC

- Claim 1 of the patent as granted contained the same definition of the formulation with respect to the terms "consisting of" and "optionally", so that this objection was not justified.
- The stabilized injectable formulation of present claim 1 was defined as consisting of two necessary components (hGH and sodium citrate in an amount of 2-20 mM as buffer substance at a pH of about 6.0 to 7.0). Said formulation could contain one or more of the optional ingredients listed in claim 1 and nothing else. Claim 1 was thus in line with the requirements of Article 84 EPC.

Article 83 EPC

- The formulations tested according to document D11, except those containing benzalkonium chloride and benzethonium chloride, also contained a surfactant. Therefore, test report D11 did not demonstrate that suitable preservatives such as meta-cresol, phenol, and benzyl alcohol were not useful when used in a formulation according to present claim 1.
- It was already known from documents D13, D14 and D15 that quaternary ammonium preservatives were not compatible with injectable proteins solutions.

- The skilled person had not to explore all the combinations of hGH with the optional ingredients, as these exerted no influence on the stability of the formulation (see paragraphs [0048] and [0051]).

Priority rights

- The wording in present claim 1 "stable for at least 12 months" had a counterpart in Table 2 and in the last section of Table 1 of the priority document, showing that the formulations of the invention were stable after 12 or 15 months storage at 5°C.

Novelty

- None of documents D2, D4, D5 and D7 disclosed all the features of present claim 1.

Inventive step

- The comparative data in the patent in suit clearly demonstrated that the technical effect set out in claim 1 (stability on storage for at least 12 months) could be produced across the whole scope of the claim, with or without the optional ingredients.

VII. The submissions by the appellant II (opponent), insofar as they are relevant to the present decision, can be summarized as follows:

Article 84 EPC

- Claim 1 was unclear because it had two different interpretations. Either the claim was completely closed in the sense that the formulation consisted of hGH, sodium citrate and one or more of the ingredients of the list of "optional" ingredients and nothing else. Or the expression "consisting of" merely applied to the obligatory ingredients of human growth hormone and the sodium citrate buffer, whereas the wording "optionally" was open as to the optional ingredients, in the sense that these could go beyond those explicitly recited in the claim.

- The latter interpretation was supported by paragraph [0028] of the patent in suit, according to which further ingredients not listed in claim 1, such as IGF-1 or IGF-2 could be present.

Article 83 EPC

- Claim 1 covered formulations including any preservative. However, experimental evidence D11 showed that a range of formulations containing certain preservatives did not provide stable solutions of human growth hormone. Therefore, the skilled person was not able to produce the invoked technical effect across the whole scope of claim 1 and, moreover, the patent did not teach the skilled person how to avoid these problems with stability and turbidity.

Priority rights

- The subject matter of claim 1 was not entitled to priority rights because the feature therein "stable for at least 12 months" could not be derived from the priority document. Consequently, documents D4 and D5 thus became prior art pursuant to Articles 54(2) and 54(3) EPC, respectively.

Novelty

- Documents D2, D4, D5 and D7 were novelty-destroying for claim 1.

Inventive step

- The technical effect set out in claim 1 at issue could not be produced across the whole scope of the claim. The evidence provided (document D11) showed that many formulations in which a preservative was included were unstable and thus did not solve any technical problem.

VIII. Appellant I (patentee) requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of claims 1 to 6 filed as new main request at the oral proceedings.

Appellant II (opponent) requested that the decision under appeal be set aside and that the European patent No. 0 587 858 be revoked.

Reasons for the Decision

Article 84 EPC

1. In the opinion of appellant II, claim 1 is unclear because it allows two different interpretations. Either the claim is completely closed in the sense that the formulation consists of hGH, sodium citrate and one or more of the ingredients of the list of "optional" ingredients and nothing else. Or the expression "consisting of" only applies to the obligatory ingredients (human growth hormone and the sodium citrate buffer), whereas the wording "optionally" was open as to the optional ingredients, in the sense that these may go beyond those explicitly recited in the claim.
2. Appellant II argues that the latter interpretation is supported by paragraph [0028] of the patent in suit, according to which further ingredients not listed in claim 1, such as IGF-1 or IGF-2 can be present. However, the last version of the description submitted by appellant I no longer comprises paragraph [0028].
3. In the board's view, the stabilized injectable formulation according to present claim 1 consists of two necessary components, namely human growth hormone and sodium citrate, and said formulation may, as optional embodiments, contain further ingredients, which are not necessary to solve the technical problem underlying the present invention (see paragraphs [0048] and [0051]). Otherwise stated, the board is convinced that the restrictive effect of the closed expression "consisting of" extends to the wording "optionally", in

the sense that the optional ingredients are those listed in claim 1, and nothing else.

4. Therefore, claim 1 covers stabilized injectable formulations which consist of only human growth hormone and sodium citrate **and** (if present) optional ingredients as listed in claim 1, i.e. amino acids, sugar alcohol, glycerol, carbohydrates and/or preservative. Hence, the argument put forward by appellant II that the requirements of Article 84 EPC is not fulfilled because the skilled person, when reading said claim was not in a position to know whether or not a given formulation fell within the scope of the claim, must fail and thus claim 1 is in line with the requirements of Article 84 EPC.

Article 123(2) EPC

5. The wording in present claim 1 "sodium citrate in an amount of 2-20 mM as buffer substance at a pH of about 6.0 to 7.0" finds a basis on page 5, lines 20 to 24 of the published WO application as filed. The feature according to which the formulation of hGH should be stable for at least 12 months has its counterpart on page 5, lines 33-34 of the published WO application as filed. Thus, there is no infringement of Article 123(2) EPC.

Article 83 EPC

6. Relying on the experimental evidence of document D11, appellant II argues that claim 1 is invalid for insufficiency of disclosure because the skilled person was not able to produce without undue burden the

- invoked technical effect across the whole scope of claim 1. Document D11 shows, in the appellant II's view, that four of the five tested preservatives failed to yield an aqueous solution of hGH, let alone a stable solution on long term storage.
7. Table 2 of document D11 indeed relates to 20 experiments investigating on the compatibility of a series of preservatives (meta-cresol, phenol, benzyl alcohol, benzalkonium chloride and benzethonium chloride) with Somatoprin[®] (recombinant hGH) in liquid formulations comprising 10 mM sodium citrate at a pH of 6.0.
 8. However, all formulations tested, except those containing benzalkonium chloride and benzethonium chloride, also contained a surfactant, namely Polysorbate 80, Polysorbate 20 or Poloxamer 188, i.e. a component not required by claim 1, either as a necessary component, or as an optional ingredient. Therefore, the test report of document D11 is not evidence that meta-cresol, phenol, and benzyl alcohol are not useful preservatives when used in a formulation according to claim 1.
 9. But even if the conclusion was drawn from document D11 that benzalkonium chloride and benzethonium chloride were not compatible with recombinant hGH, the board remarks that it was already known from document D13 (see Table V) that quaternary ammonium compounds such as benzalkonium chloride and benzethonium chloride should not be used in "injectable dosage forms". Furthermore, it was also known to the skilled person that quaternary ammonium compounds were able to

precipitate proteins from solutions (see documents D14 and D15). Therefore, it is unlikely that the skilled person would take precipitating preservatives into consideration.

10. In conclusion, the experimental test results of document D11 do not show that the skilled person was unable to produce the invoked technical effect across the whole scope of claim 1 without undue burden.

11. Appellant II relies on decision T 1241/03 of 1 September 2005 (not published in the OJ EPO) and argues that there the board found insufficiency of disclosure on the basis of the same facts and evidence as in the present case. However, the factual situation underlying decision T 1241/03 was different because the claims there related to a composition "comprising" non-specified components (see point 12 of the reasons of decision T 1241/03), which composition was thus not restricted to the components specified in the claim as in the present case, and the compositions also did not exhibit the technical effect stated in the claim when the above non-specified components were present in the formulation (see point 19 of the reasons of decision T 1241/03).

12. In contrast to this, in the present case, owing to the "closed" language of claim 1, the skilled person, when carrying out the invention, need not investigate an unduly broad range of (unspecified) components as in the situation of the formulation underlying decision T 1241/03 (supra). Rather, it is sufficient to merely combine the obligatory (c.f. "consisting of") ingredients hGH and sodium citrate in the amounts and

the pH defined to obtain an aqueous solution of hGH. Then, the skilled person may on the basis of his/her general knowledge select the preservative and/or any other optional ingredient listed in claim 1 and measure/monitor stability as defined in paragraph [0027] of the patent. This is done e.g., by opting for some preservatives among a limited list (see e.g. document D13), leaving out of consideration, of course, preservatives known to behave as protein-precipitating agents.

13. Appellant II also maintains that the skilled person has to explore all the combinations of hGH with the optional ingredients, which in his view play an important role on the stability. However, already the claim construction provides for the "technical" situation that the **optional** ingredients have no influence on the stability and this is further supported by paragraphs [0048] and [0051] of the description of the patent in suit.
14. In conclusion, no case of insufficiency of disclosure has been made out.

Priority rights

15. According to claim 1 the formulation of hGH should be stable for at least 12 months. The counterpart of this feature is to be found in paragraph [0027] of the patent in suit, stating that "the formulation according to the invention is stable for at least 12 months". Paragraph [0027] also provides a definition for this expression, according to which more than 85% hGH monomer (as measured by IEF) and less than 2% fragments

- (as measured by SDS-PAGE) should survive or turn up after at least 12 months.
16. However, the priority document does not comprise a counterpart of paragraph [0027] of the patent. The only passages in the priority document dealing with stability "for at least 12 months" relate to experimental results obtained with individualized formulations having a specific combination of parameters (concentrations of hGH and citrate buffer and pH: see page 8, solution "A" after 15 months' storage and page 9, solution "H" after 12 months' storage).
 17. Therefore, the board concludes that claim 1, covering a broad class of formulations (hGH and sodium citrate in an amount of 2-20 mM as buffer substance at a pH of about 6.0 to 7.0) associated to a well defined feature "stability for at least 12 months", is subject matter which is not disclosed in the priority document.
 18. Appellant I relies on the two experimental results in Table 1 and 2 of the priority document. However, these are merely confined to specific compositions "A" and "H", having moreover no relationship to "stability for at least 12 months" within the meaning of paragraph [0027] of the patent.
 19. In summary, claim 1 is only entitled to the filing date (1 April 1993) of the international application, which must be considered to be the effective date for the purposes of assessing the state of the art to determine novelty and inventive step. Consequently, documents D4

and D5 represent prior art pursuant to Articles 54(2) and 54(3) EPC, respectively.

Novelty

Documents D2, D4, D5 and D7

20. It is the view of appellant II that the above documents are novelty-destroying for the subject matter of claim 1.

21. Document D2 relates to formulations of growth hormone and IGF-I. It is stated on page 11, lines 2-5 that "If this mixture is to be stored, it is formulated in a buffer at a pH of about 6, such as citrate, with a surfactant that increases the solubility of the GH at this pH, such as 0.1% polysorbate 20 or poloxamer 188. The final preparation may be a stable liquid or lyophilized solid."

22. However, the mixture IGF-I, growth hormone and surfactant described in this document is excluded by the wording of claim 1 in its "closed" form (see point 3 supra). Moreover document D2 neither discloses the use of sodium citrate as the buffer substance nor the claimed concentration range of 2-40 mM.

23. Document D4 discloses hGH compositions comprising a citrate salt used in a concentration of 2.5 mM to 20 mM (page 7, lines 18-22), and having a pH of between 4 and 8 (line 25). However, the counter ion of citrate is not sodium as required by claim 1 but a divalent ion such as zinc, cobalt and copper (see the Chapter headed "Divalent Metal Ions and Molar Ratio" on page 6, line 37 to page 7, line 16).

24. Document D5 relates to the stabilisation of polypeptides by forming a liquid solution in a sodium citrate buffer having a pH of from 5.0 to about 5.5 (see page 2, lines 30 to 35 and page 5, lines 23-26). Human growth hormone is not among the polypeptides disclosed in document D5. On page 4, lines 6 and 7 of document D5, reference is made to "Manning et al." (document D5a) for the "pharmaceutically useful polypeptides". Document D5a is a review article relating to the stability of protein pharmaceuticals and refers to 13 proteins, including human growth hormone (see page 903, r-h column, last full paragraph).
25. In the board's judgement, the claimed subject matter cannot be directly and unambiguously derived from the teaching of document D5 even if read in the light of document D5a because this would imply a selection from not only the list disclosed on page 903, r-h column of document D5a but also from the considerable number of polypeptides disclosed in document D5, including those described in "U.S. Patent 4,532,212" (see page 4, line 3 of document D5).
26. Document D7 discloses animal somatotropin (growth hormone) (see column 1, lines 18-19) in an aqueous solution comprising at least 0.025 M (25 mM) sodium citrate (see column 4, lines 48-51). According to paragraph [0030] of the patent in suit, animal GH is a functional analogue of hGH. However, there is no pointer in document D7 to the specific combination somatotropin/Na citrate among the many possible aqueous vehicles listed in column 3, lines 51-60. More importantly, document D7 is silent about the pH.

27. Therefore, the subject-matter of claim 1 on file is not anticipated by any of documents D2, D4, D5 and D7.

Inventive step

28. The main issue by appellant II under inventive step is that the technical effect set out in claim 1 at issue cannot be produced across the whole scope of the claim, in the light of the evidence provided (document D11), showing that many formulations in which a preservative was included were unstable and thus did not solve any technical problem. However, claim 1 requires that the formulation should be stable for at least 12 months. Hence, since present claim 1 does not cover compositions which do not exhibit the claimed stability, the problem that some of the claimed compositions may lack an inventive step because of their instability, does not arise at all. This appellant II's argument rather seems to target the problem raised under Article 83 EPC. This was answered by the board in points 6 to 14 supra.

Closest prior art

29. The board agrees with the parties that the closest prior art is represented by document D1, which discloses an aqueous formulation of human growth hormone in sodium phosphate at a pH = 4-8, a pH = 7.4 being the most advantageous one (see page 7, lines 18-20; page 8, lines 2-3 and 32).

The objective technical problem

30. The objective technical problem underlying the invention in comparison to this closest prior art document can be seen as the provision of a stabilized injectable formulation of human growth hormone or any functional analogue thereof in an aqueous solution endowed with a stability upon storage of at least 12 months, within the meaning of paragraph [0027] of the patent in suit, i.e., more than 85 % monomer and less than 2% fragments should be present after 12 months, as determined by IEF and SDS-PAGE, respectively.

The solution of this technical problem

31. The above technical problem is solved by the specific features by which the subject-matter claimed differs from the closest prior art document D1, namely the buffer and the pH, which should be sodium citrate in an amount of 2-40 mM and the fine tuning of pH at from about 5.0 to 7.0.
32. The comparative data provided in the patent in suit (see Table 1: "A" versus "B" at 15 and 24 months and Table 2: "G" versus "H" at 12 months) show that the formulation according to present claim 1 is more stable on storage for at least 12 months than a formulation comprising a phosphate buffer or comprising a phosphate buffer at pH = 7.4. The latter formulation shows 27% degradation of hGH already after 6 months (see Table 1, "D": 73%). Therefore, the board considers that the above technical problem is solved by the claimed subject matter.

33. It remains to be established whether or not the prior art would have directed in an obvious way the skilled person to the specific features (sodium citrate in an amount of 2-40 mM and the pH from about 5.0 to 7.0) recited in present claim 1, in order to solve the technical problem emphasised under point 30 supra.

34. Claim 1 is not rendered obvious by any document of the prior art since document D2 suggested a pH =7.4-7.8 for stabilizing hGH (see page 10, line 32), document D4 used a different approach involving the divalent cation Zn^{++} and document D6 turned to a list of stabilizers different from citrate (polyols, amino acids, polymers and choline derivatives (see page 2, lines 43-54). As for document D5, this is a document pursuant to Article 54(3) EPC and thus not to be considered according to Article 56 Second Sentence EPC.

35. In conclusion, claim 1 and dependent claims satisfy the requirements of Article 56 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 with the order to maintain the patent on the basis of claims 1 to 6 filed as new main request at the oral proceedings and pages 2 to 10 of the description filed at the oral proceedings.

The Registrar:

Chair:

P. Cremona

U. M. Kinkeldey