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D E C I S I O N
of 1 September 2005

Case Number: T 1241/03 - 3.3.4

Application Number: 93918499.0

Publication Number: 0652766

IPC: A61K 38/27, A61K 47/10, A61K 47/26

Language of the proceedings: EN

Title of invention:
Human growth hormone aqueous formulation

Patentee:
GENENTECH, INC.

Opponents:
01. Grandis Biotech GmbH
02. Novo Nordisk A/S

Headword:
Human growth hormone/GENENTECH

Relevant legal provisions:
EPC Art. 56, 83, 123(2)

Keyword:
"Main request, auxiliary requests 1 and 4 - sufficiency of disclosure (no)"
"Auxiliary request 2 - admissibility (no)"
"Auxiliary request 3 - inventive step (no)"
"Ultimate claim request - added subject-matter (no), sufficiency, novelty, inventive step (yes)"

Decisions cited:
G 0001/03, T 0252/85, T 0665/90, T 0409/91, T 0522/91, T 0759/91, T 0149/93, T 0388/99, T 1098/01, T 0333/97, T 1045/98, T 0190/99, T 1126/00

Catchword:
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Case Number: T 1241/03 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 1 September 2005

Appellant I: (Proprietor of the patent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 17 October 2003 concerning maintenance of European patent No. 0652766 in amended form.

Composition of the Board:

Chair: U. Kinkeldey
Members: M. Wieser
G. Weiss

Summary of Facts and Submissions

I. Appeals were lodged by the Patent Proprietors (Appellants I), by Opponents 01 (Appellants II) and by Opponents 02 (Appellants III) against the decision of the Opposition Division whereby European Patent No. 0 652 766 was maintained in amended form pursuant to Article 102(3) EPC.

II. The patent had been opposed under Article 100(a) EPC for lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), under Article 100(b) EPC on the ground of lack of sufficient disclosure (Article 83 EPC) and under Article 100(c) EPC on the ground of added subject-matter (Article 123(2) EPC).

III. The Opposition Division had decided that the claims of the main request before them violated Article 123(2) EPC, but that the claims of the first auxiliary request met all requirements of the EPC.

IV. In response to the grounds of appeal filed by Appellants II and III, Appellants I on 20 December 2004 filed a new main request and three auxiliary request. The Board expressed their preliminary opinion in a communication dated 24 March 2005. Oral proceedings were held on 1 September 2005.

V. The Appellants I 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 14 (main request) or, alternatively, on the basis of

– claims 1 to 13 (auxiliary requests 1 or 2), or

– claims 1 to 12 (auxiliary requests 3 or 4), or

– the single claim of the "ultimate claim request", all requests filed with the letter of 18 August 2005.

The Appellants II and III requested that the decision under appeal be set aside and that the European Patent No. 0 652 766 be revoked.

VI. Claim 1 of Appellants' I main request, auxiliary requests 1, 2 and 3 read as follows:

"1. A stable aqueous liquid pharmaceutical formulation for storage for 6-18 months at 2-8°C, comprising human growth hormone, a buffer providing a pH in the range of 5.5 to 7, 0.1 to 1% by weight of a non-ionic surfactant, a neutral salt, and a preservative, wherein the preservative is phenol."

Claim 2 of the main request and of auxiliary request 1 read:

"2. A stable aqueous liquid pharmaceutical formulation for storage for 6-18 months at 2-8°C, containing human growth hormone as the sole active ingredient, the formulation comprising in addition a buffer providing a pH in the range of 5.5 to 7, 0.1 to 1% by weight of a non-ionic surfactant, and a neutral salt, but free of glycine."

Claim 2 of auxiliary request 2 differed therefrom in so far as it additionally contained the following feature: "..., and optionally containing a preservative, wherein the preservative is phenol."

Claims 1 and 2 of auxiliary request 4 were distinguished from claims 1 and 2 of the main request in so far as they each contained the following feature:

"..., wherein the neutral salt is sodium chloride, which is present between 50 to 200mM."

The sole claim of the ultimate claim request read:

"A stable aqueous liquid pharmaceutical formulation for storage for 6-18 months at 2-8°C, comprising 5 mg/ml hGH, 8.8 mg/ml sodium chloride, 2.0 mg/ml polysorbate 20, 2.5 mg/ml sodium citrate and 2.5 mg/ml phenol at pH 6.0."

VII. The present decision refers to the following documents:

(2) WO 89/09 614

(7) US 4,637,834

(22) Declaration by Dr D.B. Williams, 27 June 2000

(27) Journal of Parental Science and Technology, vol. 42, Supplement, 1988, pages S4 to S26

(34) Statutory Declaration by Dr J.Q. Oeswein, 12 March 2003

(35) Experimental Report (Versuchsbericht) by D. H.-J. Zeisel, 25 February 2004

VIII. The submissions made by Appellants I as far as they are relevant to the present decision may be summarised as follows:

The main request and all five auxiliary requests submitted on 18 August 2005 were filed in response to extensive submissions made by Appellants II. They contained only minor amendments when compared with claim requests filed in December 2004 and should therefore be allowed into the procedure.

The claims of all requests had a basis in the application as filed in agreement with the requirements of Article 123(2) EPC. The experiments reported in document (35) were not carried out by an expert in the here relevant technical field. They were not serious attempts to make the claimed invention work. On the contrary, they did not follow the instructions for producing the claimed formulations, as described in the application as filed, and had therefore to be disregarded by the Board when deciding on the question of sufficiency of disclosure (Article 83 EPC).

Document (2), representing the closest state of the art for the assessment of inventive step (Article 56 EPC), described the prior art attempts to produce storage stable hGH compositions by lyophilisation. The document did not contain any information concerning the long term storage of liquid formulations. A skilled person knew from the prior art that the production of stable aqueous protein solutions was technically unpredictable

and depended on a plethora of parameters varying from protein to protein. Thus he/she would not have considered relevant the disclosure in document (7), referring to protein solutions in general without explicitly mentioning hGH. A combination of the disclosure in documents (2) and (7) would not have allowed the skilled person to arrive at the claimed subject-matter in an obvious way.

IX. The submissions made by Appellants II and III as far as they are relevant to the present decision may be summarised as follows:

Auxiliary request 2, which had been filed by Appellants I two weeks before the oral proceedings only, referred to subject-matter which had not previously been claimed and should not be admitted.

The pharmaceutical formulations claimed had no exact basis in the application as filed, but represented combinations of parameter values taken from different passages of the description, contrary to the requirements of Article 123(2) EPC. The claims referring to pharmaceutical formulations were not restricted to a specific method of producing said formulations. Thus, any formulation having the same technical features but not giving rise to the technical effect stated in the claims, namely long-term storage stability, represented a non-working embodiment falling within the scope of the claims. As document (35) proved the existence of such non-working embodiments, the invention was not sufficiently disclosed and contravened the requirements of Article 83 EPC.

Document (2), in its introductory part, contained a statement referring to the desirable provision of long-term stable liquid hGH formulations. Exactly such formulations were the aim of document (7) which indicated all additives necessary to achieve this goal. These additives were identical to those used for the production of the claimed formulations. Although document (7) did not explicitly refer to hGH, it pointed to "growth and differentiation factors" as one of many possible proteins to be used according to its teaching. The skilled person having in mind to provide a stable liquid hGH formulation, as expressed in document (2) would therefore have considered the disclosure in document (7). Upon combining the teaching in the two documents he/she would have arrived at the claimed subject-matter in obvious way.

Reasons for the Decision

Admissibility of Appellants' I requests filed 18 August 2005

1. In response to the grounds of appeal filed by Appellants II and III, Appellants I on 20 December 2004 filed a new main request and three auxiliary requests. Claims 1 to 14 of the main request and claims 1 to 13 the first auxiliary request, both filed on 18 August 2005, are identical to the claims of the main request and the first auxiliary request filed on 20 December 2004, with the exception that a clerical error in the last claim of each request has been corrected. The term "5.5 mg/ml hGH" has been replaced by "5 mg/ml hGH" as contained in claim 15 as originally filed, corresponding to claim 16 as granted.

Claims 1 to 12 of the actual third auxiliary request (18 August 2005) correspond to claim 1 and claims 4 to 15 of the main request filed on 20 December 2004. Claims 2 and 3 have been deleted and the clerical error discussed in the paragraph above has been corrected.

Claims 1 to 12 of the fourth auxiliary request (18 August 2005), despite a marginally different wording in claims 1 and 2, correspond to claims 1 to 12 of the second auxiliary request filed on 20 December 2004, again with the correction of the clerical error in claim 12.

The single claim of the ultimate claim request (18 August 2005) corresponds to claim 15 as originally filed, respectively claim 16 as granted, respectively to claim 14 of the main request filed on 20 December 2004 with the correction of a clerical error as discussed above.

2. Although Appellants' I main request, first, third and fourth auxiliary requests and ultimate request have been filed late, namely on 18 August 2005, two weeks before the oral proceedings, the Board, considering the trivial nature of the amendments carried out with regard to the claim requests filed almost eight months before, as described in point (1) above), decides to allow these requests into the procedure. Appellants II and III had not objected to the admissibility of these requests.

3. A different situation arises with regard to auxiliary request 2. Claim 2 of this request (see section (VI)

above) refers to formulations "optionally containing a preservative, wherein the preservative is phenol". This formulation, which has not been contained in any other claim filed by Appellants I before 18 August 2005, introduces ambiguity, which makes it impossible for the Board to immediately see that it does not cause the introduction of new objections under the EPC. This ambiguity arises from the possibility of different interpretations of the formulation in question. One possible interpretation would be that the claimed formulation either contains a preservative or is free of a preservative; with the restriction that if a preservative is present it can be phenol only. The second interpretation would be that the optional presence of a preservative is restricted to phenol, which would mean that the formulation containing phenol or not may additionally contain another preservative. This ambiguity has the effect that the claim containing it does not precisely define the matter for which protection is sought, contrary to the requirements of Article 84 EPC.

Therefore, in accordance with the case law of the Boards of Appeal, the Board decides that auxiliary request 2 is not admitted in the procedure (see Case Law of the Boards of Appeal of the European Patent Office, 4th Ed. 2004, VII.D.14.2.2, pages 548 to 549, English version).

Main request

Added subject-matter - Article 123(2) EPC

4. Claims 1 and 2 refer to a stable aqueous liquid pharmaceutical combination for storage for 6-18 months at 2-8°C. In both claims the formulation is characterised by comprising (claim 1), respectively containing as the sole active ingredient (claim 2), hGH, and by further comprising a buffer providing a pH in the range of 5.5 to 7, 0.1 to 1% by weight of a non-ionic surfactant and a neutral salt. According to claim 1 the formulation additionally comprises phenol. Claim 2, not mentioning phenol, requires that the formulation is free of glycine.

According to claim 6 the formulation contains mannitol.

5. Appellants II and III argued that the application as originally filed did not explicitly disclose the claimed formulation. Rather the specific values for the different parameters were combined from different isolated sections of the description. In consequence the application as filed did not contain a relation between the structural features of the now claimed formulations and the technical concept of the claims, namely storage stability for 6 to 18 months at 2-8°C.

6. Page 3, lines 21 to 25 of the application as filed describes one aspect of the invention as being the provision of a stable pharmaceutically acceptable aqueous formulation of hGH, comprising a buffer, a non-ionic surfactant and optionally a neutral salt, mannitol and a preservative.

In lines 27 to 33 of the same page it is said that it is a further aspect of the invention to provide a method for preventing denaturation of hGH aqueous

formulations by mixing it with a non-ionic surfactant in the range of 0.1-5% (w/v). This stabilized formulation is then stored for 6-18 months at 2-8°C.

Preferred amounts of hGH are disclosed on page 5, lines 5 to 9 (1 to 20 mg/ml; 5 mg/ml). Examples for non-ionic surfactants, including poloxamer 188 or 184 and polysorbate 20 and 80, are given on page 5, lines 27 to 30. The preferred amount of 0.1 to 1% is indicated on page 5, line 33. The formulations according to the invention are said not to require glycine, which however may be present optionally (page 5, lines 20 to 22). Useful buffers, including citrate, phosphate, Tris, succinate, acetate or histidine buffer are listed on page 6, lines 1 to 5. The buffer is said to be present in the range of 2 mM to 50 mM (page 6, lines 2 to 50. The preferred pH range of 5.5 to 7 is indicated on page 6, line 17. Lines 7 to 13 on the same page contain a list of applicable preservatives, designating phenol and benzyl alcohol as being the preferred ones. Mannitol as optional ingredient of aqueous hGH formulations is mentioned on page 6, lines 21 to 23, where also a preferred amount is indicated. The optional presence of neutral salts like sodium chloride in a concentration range of 50-200 mM is mentioned on page 6, lines 28 to 34. The formulations are said to be preferably isotonic on page 7, line 18.

Finally, page 6, line 36 to page 7, line 7, discloses a precisely defined formulation being a preferred embodiment of the invention, which is the subject of claim 14 of the main request.

In example 1 (starting on page 9) storage stability of an aqueous hGH formulation at 2-8°C for up to one year is tested. The formulation comprises 5.0 mg hGH, 45.0 mg mannitol, 2.5 mg phenol, 2.0 mg polysorbate 20 and 2.5 mg sodium citrate per ml solution at pH 6.

7. In the light of this disclosure in the application as originally filed the Board comes to the conclusion that claims to formulations comprising the compounds in question in specific concentrations do not need to have a literal basis in a single passage of the application as originally filed, as long as the exact concentrations and ranges claimed for the specific substances are disclosed as such in the original application. Neither do the claims refer to a "patchwork" of parameters disclosed in non-connected parts of the description, nor have specific values been isolated from examples in a non-allowable way. In the present case, considering the general disclosure of the application as filed, the reference in a claim to a combination of compounds in specific concentrations, explicitly disclosed in different passages of the application, is not considered to be an amendment of the patent which extends beyond the content of the application as originally filed.

Accordingly, claims 1 to 14 do not contain subject-matter which extends beyond the content of the application as filed and meet the requirements of Article 123(2) EPC.

Sufficiency of disclosure - Article 83 EPC

8. Claims 1 and 2 both refer to "[a] stable aqueous liquid pharmaceutical formulation **for storage for 6-18 months at 2-8°C**." (emphasis added by the Board). The active ingredient of the formulations is hGH. In addition the formulations are defined by **comprising** several components. According to claim 1 these components are a buffer providing a defined pH, a non-ionic surfactant in a defined concentration range, a neutral salt and a preservative, wherein the preservative is phenol. The definition of the formulation according to claim 2 is distinguished therefrom in so far as it does not require the presence of a preservative, but mentions that the formulation is free of glycine.

9. According to established case law of the Boards of Appeal, a skilled person should try to arrive at an interpretation of a claim which is technically sensible and takes into account the whole disclosure of the patent. The patent must be construed by a mind willing to understand, not a mind desirous of misunderstanding (cf. decision T 190/99 of 6 March 2001).

Following this principle the Board interprets the claims as referring to aqueous liquid pharmaceutical formulations containing hGH as pharmaceutically active ingredient and other components as specified. These formulations remain stable after storage up to 18 months at 2-8°C. Thus the Board considers the storage stability (**"for storage for 6-18 months at 2-8°C**") to be a **technical effect** achieved by the claimed invention.

10. This **technical effect** is expressed in claims 1 and 2. When formulations falling under the scope of the claims do not show the **technical effect** expressed in the claims, there is lack of sufficient disclosure (Article 83 EPC), cf. decision of the Enlarged Board of Appeal G 1/03 (OJ EPO 2004, 413; point (2.5.2) of the reasons).

11. Document (35) an experimental report filed by Appellants II, describes tests that have been carried out to investigate stability of aqueous hGH containing formulations.

The tested formulations all contained 5 mg/ml hGH, either citrate or phosphate buffer and had a pH of 6.0. Polysorbate 20, Polysorbate 80 or Poloxamer 188 were used as non-ionic surfactants in the concentration range indicated in claims 1 and 2. Besides formulations not containing a neutral salt, isotonic formulations containing sodium chloride were tested. Each formulation in addition contained a preservative selected from the group benzalconium chloride, benzethonium chloride and benzyl alcohol. None of the formulations contained glycine (see document (35), points 4, 13, 15, 17, 18, 19 and tables 2 to 5).

Immediately after their preparation, by mixing the components in water, the formulations were visually examined. All of them were turbid with, partially flocculent, white precipitate (see tables 2 to 5).

12. As all tests in document (35) have been carried out with formulations containing preservatives other than

phenol, these tests are not relevant for the subject-matter of claim 1.

However, claim 2 refers to a formulation **containing** hGH as sole active ingredient and **comprising** in addition a buffer, a non-ionic surfactant and a neutral salt, while being free of glycine. While in everyday language the word "comprise" might have both the meaning "include" or "comprehend" and "consist of", in drafting patent claims legal certainty requires it to be interpreted by the broader meaning "include" or "comprehend" (cf. decisions T 759/91 and T 522/91 both of 18 November 1993, point (2.2) of the reasons).

Thus, in the present case claim 2 is interpreted as not being restricted to formulations comprising only what is specified, but as encompassing formulations comprising additional, not specified components.

Therefore, the formulations tested in document (35) fall within the scope of claim 2. The Board has to decide whether the results reported in document (35), namely the appearance of turbidity and white precipitate, immediately after mixing the components, proves that the claimed technical effect, i.e. storage stability up to 18 months at 2-8°C, cannot be achieved by formulations falling within the scope of claim 2.

13. Appellants I argued that the test report in document (35) is signed by a person, Dr Hans-Joachim Zeisel, who, at the priority date of the patent in suit was not known as being an expert working in the field of liquid protein formulations or in the area of growth hormone formulations. Therefore, the opinions expressed in

document (35) were, at best, of limited relevance to the issue of the present case.

Point (1) of document (35), which has the form of a declaration, identifies Dr Zeisel as being the CEO of Appellants II, Grandis Biotech GmbH. In point (2) Dr Zeisel states that he arranged to have a series of experiments carried out. The Board concludes therefrom that the experiments have been carried out by Appellants' II experts upon request of Dr Zeisel. Appellants' I argument, based on a lack of expertise of the author of document (35) does not convince the Board.

14. In a further line of argumentation Appellants I criticised that the experiments could not be considered as serious attempt to make the invention work. As can be seen from the experimental set up, the formulations were not prepared exactly according to the method disclosed on page 8, lines 20 to 31 of the application as filed. This method requires that hGH was eluted from a gel filtration column with an elution liquid containing either sodium chloride or mannitol, buffer and the non-ionic surfactant in their final ratios. Upon dilution to the desired hGH concentration the preservative was added and the solution was sterile filtered.

Contrary to this the formulations according to document (35) were prepared by simply mixing the different components in water.

Appellants I referred to decision T 665/90 (23 September 1992), which they considered to require

that comparative examples have to be carried out under strict adherence to the conditions given in the patent in suit.

15. The case underlying decision T 665/90 (supra) refers to a **chemical process.** The competent Board found that as proof that an invention has been insufficiently disclosed, it is required that the attempt to repeat it must fail despite following the conditions given in the examples. This requirement is not fulfilled where the **patented process** is repeated under conditions covered by claim 1 but differing in many respects from those applying in the contested patent's example (point (3) of the reasons).

Present claim 2 refers to a **product**, namely a pharmaceutical composition. The method of preparation of this product is not reflected in the claim. Therefore, claim 2 encompasses all products having the technical characterizing features indicated in the claim, irrespective of their method of production.

Since this is a different case the reasoning of decision T 665/90 does not apply to the present claims and Appellants' I argument must fail.

16. Appellants I further argued that the results obtained in document (35) did not prove that the tested formulations were unstable and could not be pharmaceutically used. Contrary to the patent in suit document (35) did not carry out HPLC analysis to determine the content of total hGH monomer and/or of degradation products indicating deamidated hGH.

Document (35) reports that all of the tested formulations were turbid and had a white, partly flocculent, precipitation. Even if these formulations might have had some residual pharmaceutical activity, they cannot be considered to be stable aqueous liquid pharmaceutical formulations which can be administered to a patient, not immediately after their preparation and not after storage for 6-18 months at 2-8°C.

17. In this respect, the Board notes that one of the present inventors, Dr James Q. Oeswein, in a declaration of 12 March 2003 (document (34)), which was filed in a patent opposition case technically related to the case in suit, reports the results of stability tests with liquid hGH formulations. These formulations contained 5-6 mg/ml hGH, 10 mM sodium citrate, pH 6.0, and varying concentrations of four different preservatives, in the absence or presence of a surfactant or mannitol (document (34), point 6). In point (12), Dr Oeswein comes to the following conclusion: *"Only those formulations containing Phenol as the preservative in the presence of a surfactant exhibited stability."*

18. Finally, Appellants I argued that the patent in suit disclosed various working embodiments, namely embodiments showing the claimed technical effect. In the light of decision T 292/85 (OJ EPO 1989, 275) an invention was sufficiently disclosed if at least one way was clearly indicated enabling the person skilled in the art to carry out the invention.

The competent Board in decision T 292/85 came to the conclusion that the non-availability of some particular

variants of a functionally defined component feature of the invention (which may be available in the future only) is immaterial to sufficiency as long as there are suitable variants known to the skilled person through the disclosure or common general knowledge, which provide the same effect for the invention (cf. point (3.1.5) of the reasons).

This situation is different from the one in the present case. The formulations tested in document (35) cannot be considered as being non-available variants of a functionally defined component feature, but are available embodiments falling within the scope of claim 2.

The Board does not accept Appellant's I submission that sufficiency should be acknowledged because one (or several) ways of performing the invention were disclosed. In the Board's judgment, the disclosure of one way of performing the invention is only sufficient within the meaning of Article 83 EPC if it allows the person skilled in the art to perform the invention in the whole range that is claimed (cf. decision T 409/91 OJ EPO 1994, 653; point (3.5) of the reasons).

19. As none of Appellants' I arguments, discussed in detail in points (7) to (12) above, is convincing, the Board comes to the conclusion that the results of the experiments carried out in document (35) provide evidence that formulations falling within the scope of claim 2 do not have the technical effect stated in the claim, namely being stable at storage for 6-18 months at 2-8°C.

Accordingly, the patent does not disclose the invention according to claim 2 in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The requirements of Article 83 EPC are not met.

Auxiliary Request 1

20. Claim 2 of this request is identical to claim 2 of the main request.

Auxiliary request 1, for the same reasons as given above for the main request, does not meet the requirements of Article 83 EPC.

Auxiliary Request 3

21. Claims 1 to 12 of this request, corresponding to claims 1 and 4 to 14 of the main request, meet the requirements of Article 123(2) EPC for the reasons given in points (4) to (7) above.

22. Appellants II and III objected to lack of sufficient disclosure of the invention according to auxiliary request 3. In view of the findings on Article 56 EPC (see points (24) to (31) below) it is not deemed to be necessary to give detailed reasons with regard to Article 83 EPC.

23. Appellants II and II did not object to the novelty of the subject-matter of claims 1 to 12. Thus, Article 54 EPC was not a point at issue.

Inventive step - (Article 56 EPC)

24. Claim 1 refers to aqueous liquid hGH formulations which are stable during long-term storage, namely 6 to 18 months at 2-8°C.

In accordance with the problem and solution approach and the relevant case law developed by the Boards of Appeal, the closest prior art which provides the best starting point for assessing inventive step should be prior art conceived for the same purpose or aiming at the same objective as the claimed invention (cf. Case Law of the Boards of Appeal of the European Patent Office, 4th Ed. 2001, Chapter I.D.3).

25. In the light of these criteria the Board considers document (2) to represent the closest state of the art. This document essentially relates to long-term storage stable lyophilized hGH formulations (page 5, lines 13 to 17; page 6, lines 20 to 28; page 9, lines 14 to 26) and to storage stability of aqueous hGH formulations waiting to be lyophilized for up to five weeks (page 10, line 33 to page 11, line 7).

However, page 3, lines 18 to 20 of document (2) reads: *"Alternatively, the composition can be provided in liquid form appropriate for immediate use. Desirable is a liquid formulation which maintains its activity in long term storage."*

26. The stabilized hGH formulations according to document (2) comprise glycine, mannitol, a buffer providing a pH of 4 to 8 and a non-ionic surfactant in an amount of

0.001 to 2% (w/v) (see claims 1, 2 and 10 and page 9, lines 19 to 21).

Document (2) does not contain data concerning the long-term storage stability of an aqueous hGH formulation.

27. In the light of this disclosure in the closest state of the art the problem underlying the patent in suit is considered to be the actual provision of an aqueous hGH formulation which remains stable during long-term storage.

28. Document (7) refers to stable aqueous protein solutions and processes for their preparation. Column 3, lines 29 to 38 indicates a list of proteins which are considered to be suitable for stabilization, comprising "*growth and differentiation factors*".

The stable aqueous formulations according to document (7) comprise a non-ionic surfactant in a amount of 0.1 to 0.2% by weight, a buffer a preservative and additives for adjusting isotonicity (claims 1, 5 and 6). According to column 2, lines 57 to 67, sodium chloride is a customary agent for adjusting isotonicity, phenol may be used as preservative and phosphate-, citrate- and acetate-buffers may be used to adjust the pH.

29. Appellants I argued that a skilled person, knowing from the prior art that the development of stable aqueous protein formulations was a risky business which did not allow to rely on untrustworthy stability predictions from lyophilized formulations or solutions containing a different protein (document (27), page S22, right

column, second paragraph), would not have had a reasonable expectation of success to arrive at the claimed subject-matter upon combination of the teaching in documents (2) and (7).

30. They also referred to document (22), a statutory declaration filed at the Australian Patent Office in the case of the corresponding Australian Patent. In point (60) of this declaration the author of document (7) is quoted, who said, upon being asked to set out the steps which he considered that he would have taken if he had been presented with the problem facing the inventors at the priority date:

"I consider that while indeed a person of ordinary skill in the art might well have taken these steps to test various components of putative formulation, it would not have been possible for such a person to ***predict*** *the results which these tests would have obtained. In other words regardless from the information available from the prior art, whether this was derived from lyophilised formulations of growth hormone or from liquid formulations of other proteins, it would not have been possible to predict what formulation components would provide a commercially useful, storage-stable preparation of growth hormone."*, (emphasis added by the Board).

31. In the Board's judgement, the skilled person, although knowing that the development of liquid stable protein formulations is technically unpredictable and does not allow to rely on stability predictions obtained from other, different samples, would not have been deterred from testing the stability of an hGH containing

solution comprising the components indicated in document (7).

Obviousness is not only at hand when the results are clearly predictable but also when there is a reasonable expectation of success (cf. decision T 149/93 of 23 March 1995; point (5.2) of the reasons). A reasonable expectation of success does not require certainty (cf. decision T 338/97, of 7 February 2000; point (14) of the reasons).

Thus, in spite of the understandable uncertainties which always characterise experiments using biologic compounds like proteins, the skilled person had no reason to adopt a sceptical attitude. He/she would have had either some expectations of success or, at worst, no particular expectations of any sort, but only a "try and see" attitude, which - as pointed out in decisions T 333/97 of 5 October 2000; point (13) of the reasons - does not equate with the absence of an reasonable expectation of success (cf. decision T 1045/98 of 22 October 2001; point (17) of the reasons).

32. Therefore, the Board is convinced that the skilled person would have arrived in an obvious way at the subject-matter of claim 1 in the light of the disclosure in document (2) in combination with document (7), which therefore lacks an inventive step.

Auxiliary request 3 is not allowable under Article 56 EPC.

Auxiliary Request 4

33. Claim 2 of this request is distinguished from claim 2 of the main request in that the neural salt is defined as being sodium chloride which is present between 50 to 200 mM (see section (VI) above).

34. The formulations tested in the experiments of document (35) contain sodium chloride in an amount between 98 and 141.5 mM (see tables 2 to 5).

35. Therefore, the reasons given in points (8) to (19) above with regard to the main request equally apply to auxiliary request 4, which therefore also does not meet the requirements of Article 83 EPC.

Ultimate claim request

36. Appellants II and III did not raise an objection against this request.

37. The sole claim of the request corresponds to claim 15 as originally filed (claim 16 as granted) and meets the requirements of Article 123(2) EPC.

The claimed formulation is defined as being a preferred embodiments of the invention (page 6, line 36 to page 7, line 7 of the application as filed). The patent discloses the invention according to the sole claim of the ultimate claim request in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC).

A formulation having the characterising features of the sole claim is not disclosed in the prior art documents on file. The subject-matter of the claim is novel (Article 54 EPC).

38. The problem underlying the invention according to the claim of the ultimate claim request is identical to the one defined in point (27) above for auxiliary request 3, namely the actual provision of an aqueous hGH formulation which remains stable during long-term storage.

The Board is convinced that this problem is solved by providing a formulation as claimed, which is defined by comprising specific concentrations of hGH, sodium chloride, polysorbate 20, sodium citrate and phenol at pH 6.0.

Neither document (2), representing the closest state of the art (see point (25) above) nor document (7) or any other prior art document on file contains information that would encourage a skilled person, trying to solve the underlying problem, to change the disclosure in the closest prior art and to arrive at the specific formulation according to the sole claim of the ultimate claim request in an obvious way.

The requirements of Article 56 EPC are met.

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 the first instance with the order to maintain the patent on the basis of the claim 1 of the "ultimate claim request" filed with the letter of 18 August 2005 and a description to be adapted thereto.

Registrar: Chair:

P. Cremona U. Kinkeldey