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# Datasheet for the decision of 14 January 2014

**Case Number:** T 0137/10 - 3.3.04

**Application Number:** 97902109.4

**Publication Number:** 889733

**IPC:** A61K38/27

**Language of the proceedings:** EN

**Title of invention:**
Stabilised growth hormone formulation and method of preparation thereof

**Patent Proprietor:**
CSL Limited
MONASH UNIVERSITY

**Opponent:**
Novo Nordisk A/S

**Headword:**
Human growth hormone/CSL, LTD; Monash Univ.

**Relevant legal provisions:**
EPC Art. 54, 123(2)

**Keyword:**
Amendments - added subject-matter (yes)
Novelty - auxiliary request (no)

**Decisions cited:**
T 0205/83

**Catchword:**

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**Case Number: T 0137/10 - 3.3.04**

# D E C I S I O N
# of Technical Board of Appeal 3.3.04
# of 14 January 2014

| | |
|---|---|
| **Appellant:** (Patent Proprietor 1) | CSL Limited<br>45 Poplar Road<br>Parkville, VIC 3052 (AU) |
| **Appellant:** (Patent Proprietor 2) | MONASH UNIVERSITY<br>1958 Wellington Road<br>Clayton<br>Victoria 3168 (AU) |
| **Representative:** | Sheard, Andrew Gregory<br>Patent Attorney<br>P.O. Box 521<br>Berkhamsted, Herts. HP4 1YP (GB) |
| **Respondent:** (Opponent) | Novo Nordisk A/S<br>Novo Alle<br>2880 Bagsvaerd (DK) |
| **Representative:** | Ford, Hazel<br>J A Kemp<br>14 South Square<br>Gray's Inn<br>London WC1R 5JJ (GB) |
| **Decision under appeal:** | **Decision of the Opposition Division of the European Patent Office posted on 23 November 2009 revoking European patent No. 889733 pursuant to Article 101(3)(b) EPC.** |

**Composition of the Board:**

**Chairman:** C. Rennie-Smith
**Members:** M. Montrone
B. Claes

## Summary of Facts and Submissions

I. The appeal was lodged by the patentees (hereinafter "appellants") against the decision of the opposition division to revoke European patent No. 0889733 entitled "Stabilised Growth Hormone Formulation and Method of Preparation thereof" (based on European application number 97902109).

II. The opposition was filed on the grounds in Articles 100(a) EPC (lack of novelty, Article 54 EPC, and lack of inventive step, Article 56 EPC), Article 100(b) EPC and Article 100(c) EPC.

III. In its decision under appeal the opposition division decided that the main request extended beyond the content of the application as filed (Article 123(2) EPC), auxiliary request 1 contravened Article 123(3) EPC, auxiliary requests 2, 4 and 5 lacked novelty (Article 54 EPC) and auxiliary request 3 lacked an inventive step (Article 56 EPC).

IV. An appeal, dated 25 January 2010, was filed by the appellants against the decision of the opposition division followed by a statement of grounds of appeal dated 1 April 2010. The appellants filed a main request and auxiliary requests 1 and 2 with the statement of grounds of appeal.

Claims 1 and 7 of the main request read:

"1. A method for the preparation of a stable, liquid formulation of growth hormone, preferably human growth hormone, comprising growth hormone, a buffer and a stabilising effective amount of at least one stabilising agent selected from the group consisting

of:
polyoxyethylene-polyoxypropylene block copolymer non-ionic surfactants,
wherein the method comprises admixing the growth hormone with the buffer and the stabilising agent(s) under conditions such that the growth hormone is not exposed to concentrations of the buffer or stabilising agent(s) which are greater than 2x the final concentrations of the buffer or stabilising agent(s) in the formulation, and wherein the final concentration of stabilising agent(s) in the formulation is 0.01-5.0% w/v; and wherein the pH of the formulation is from 5.0 to 6.8.

7. A stable, liquid formulation of growth hormone, obtainable by a method according to any of claims 1 to 6."

Claims 1 and 7 of the auxiliary request 1 read:

"1. A method for the preparation of a stable, liquid formulation of growth hormone, preferably human growth hormone, comprising growth hormone, a buffer and a stabilising effective amount of at least one stabilising agent selected from the group consisting of: Pluronic polyols,
wherein the method comprises admixing the growth hormone with the buffer and the stabilising agent(s) under conditions such that the growth hormone is not exposed to concentrations of the buffer or stabilising agent(s) which are greater than 2x the final concentrations of the buffer or stabilising agent(s) in the formulation, and wherein the final concentration of stabilising agent(s) in the formulation is 0.01-5.0% w/v; and wherein the pH of the formulation is from 5.0 to 6.8.

7. A stable, liquid formulation of growth hormone, obtainable by a method according to any of claims 1 to 6."

Claims 1 and 7 of the auxiliary request 2 read:

"1. A method for the preparation of a stable, liquid formulation of growth hormone, preferably human growth hormone, comprising growth hormone, a buffer and a stabilising effective amount of a stabilising agent which is Pluronic F-68,
wherein the method comprises admixing the growth hormone with the buffer and the stabilising agent(s) under conditions such that the growth hormone is not exposed to concentrations of the buffer or stabilising agent(s) which are greater than 2x the final concentrations of the buffer or stabilising agent(s) in the formulation, and wherein the final concentration of stabilising agent in the formulation is 0.01-5.0% w/v; and wherein the pH of the formulation is from 5.0 to 6.8.

7. A stable, liquid formulation of growth hormone, obtainable by a method according to any of claims 1 to 6."

V. The opponent (hereinafter "respondent") filed a reply to the statement of the grounds of appeal with a letter dated 23 August 2010.

VI. A summons to oral proceedings was issued on 9 August 2013.

VII. The board informed the parties of its preliminary view in its communication dated 13 December 2013.

VIII. The appellants filed on 13 December 2013 auxiliary requests A, B, C, A1, B1, B2 and C1. In addition, a further document (D30) was submitted (see point X, below).

Claims 1 and 7 of the auxiliary request A read:

"1. A method for the preparation of a stable, liquid formulation of growth hormone, preferably human growth hormone, comprising growth hormone, a buffer and a stabilising effective amount of at least one stabilising agent selected from polyoxyethylene-polyoxypropylene block copolymer non-ionic surfactants,
wherein the method comprises admixing the growth hormone with the buffer and the stabilising agent(s) under conditions such that the growth hormone is not exposed to concentrations of the buffer or stabilising agent(s) which are greater than 2x the final concentrations of the buffer or stabilising agent(s) in the formulation, and wherein the final concentration of stabilising agent(s) in the formulation is 0.01-5.0% w/v; and wherein the pH of the formulation is from 5.0 to 6.8.

7. A stable, liquid formulation of growth hormone, obtainable by a method according to any of claims 1 to 6."

Claims 1 and 7 of the auxiliary request B read:

"1. A method for the preparation of a stable, pharmaceutically acceptable liquid formulation of human growth hormone, comprising a pharmaceutically acceptable amount of human growth hormone, a buffer and

a stabilising effective amount of at least one stabilising agent selected from polyoxyethylene-polyoxypropylene block copolymer non-ionic surfactants,
wherein the method comprises admixing the growth hormone with the buffer and the stabilising agent(s) under conditions such that the growth hormone is not exposed to concentrations of the buffer or stabilising agent(s) which are greater than 2x the final concentrations of the buffer or stabilising agent(s) in the formulation, and wherein the final concentration of stabilising agent(s) in the formulation is 0.01-5.0% w/v; and wherein the pH of the formulation is from 5.0 to 6.8.

7. A stable, liquid formulation of human growth hormone, obtainable by a method according to any of claims 1 to 6, for use as a pharmaceutical."

Claims 1 and 7 of the auxiliary request C read:

"1. A method for the preparation of a stable, pharmaceutically acceptable liquid formulation of human growth hormone, comprising a pharmaceutically acceptable amount of human growth hormone, a buffer and a stabilising effective amount of at least one stabilising agent selected from polyoxyethylene-polyoxypropylene block copolymer non-ionic surfactants,
wherein the method comprises admixing the growth hormone with the buffer and the stabilising agent(s) under conditions such that the growth hormone is not exposed to concentrations of the buffer or stabilising agent(s) which are greater than 2x the final concentrations of the buffer or stabilising agent(s) in the formulation, and wherein the final concentration of

stabilising agent(s) in the formulation is 0.01-5.0% w/v; and wherein the pH of the formulation is from 5.0 to 6.8.

7. A stable, liquid formulation of human growth hormone, obtainable by a method according to any of claims 1 to 6, for use as a pharmaceutical."

Claims 1 and 7 of the auxiliary request A1 read:

"1. A method for the preparation of a stable, liquid formulation of growth hormone, preferably human growth hormone, comprising growth hormone, a buffer and a stabilising effective amount of at least one stabilising agent selected from Pluronic polyols, wherein the method comprises admixing the growth hormone with the buffer and the stabilising agent(s) under conditions such that the growth hormone is not exposed to concentrations of the buffer or stabilising agent(s) which are greater than 2x the final concentrations of the buffer or stabilising agent(s) in the formulation, and wherein the final concentration of stabilising agent(s) in the formulation is 0.01-5.0% w/v; and wherein the pH of the formulation is from 5.0 to 6.8.

7. A stable, liquid formulation of growth hormone, obtainable by a method according to any of claims 1 to 6."

Claims 1 and 7 of the auxiliary request B1 read:

"1. A method for the preparation of a stable, pharmaceutically acceptable liquid formulation of human growth hormone, comprising a pharmaceutically acceptable amount of human growth hormone, a buffer and

a stabilising effective amount of at least one stabilising agent selected from the group consisting of Pluronic polyols,
wherein the method comprises admixing the growth hormone with the buffer and the stabilising agent(s) under conditions such that the growth hormone is not exposed to concentrations of the buffer or stabilising agent(s) which are greater than 2x the final concentrations of the buffer or stabilising agent(s) in the formulation, and wherein the final concentration of stabilising agent(s) in the formulation is 0.01-5.0% w/v; and wherein the pH of the formulation is from 5.0 to 6.8.

7. A stable, liquid formulation of human growth hormone, obtainable by a method according to any of claims 1 to 6, for use as a pharmaceutical."

Claims 1 and 7 of the auxiliary request B2 read:

"1. A method for the preparation of a stable, pharmaceutically acceptable liquid formulation of human growth hormone, comprising a pharmaceutically acceptable amount of human growth hormone, a buffer and a stabilising effective amount of a stabilising agent which is Pluronic F-68,
wherein the method comprises admixing the growth hormone with the buffer and the stabilising agent(s) under conditions such that the growth hormone is not exposed to concentrations of the buffer or stabilising agent(s) which are greater than 2x the final concentrations of the buffer or stabilising agent(s) in the formulation, and wherein the final concentration of stabilising agent(s) in the formulation is 0.01-5.0% w/v; and wherein the pH of the formulation is from 5.0 to 6.8.

7. A stable, liquid formulation of human growth hormone, obtainable by a method according to any of claims 1 to 6, for use as a pharmaceutical."

Claims 1 and 7 of the auxiliary request C1 read:

"1. A method for the preparation of a stable, pharmaceutically acceptable liquid formulation of human growth hormone, comprising a pharmaceutically acceptable amount of human growth hormone, a buffer and a stabilising effective amount of at least one stabilising agent selected from Pluronic polyols, wherein the method comprises admixing the growth hormone with the buffer and the stabilising agent(s) under conditions such that the growth hormone is not exposed to concentrations of the buffer or stabilising agent(s) which are greater than 2x the final concentrations of the buffer or stabilising agent(s) in the formulation, and wherein the final concentration of stabilising agent(s) in the formulation is 0.01-5.0% w/v; and wherein the pH of the formulation is from 5.0 to 6.8.

7. A stable, liquid formulation of human growth hormone, obtainable by a method according to any of claims 1 to 6, for use as a pharmaceutical."

IX. Oral proceedings before the board were held on 14 January 2014.

X. The documents referred to in the present decision are:

D2: Katakam et al., 1995, J. Pharma. Science, vol. 84, 713-716

D5: W092/08985

D7: W094/03198
D8: W091/18621
D13: Merck Index, 12th Ed.; Monograph. 7724 (1996)
D14: Synonyms of polyethylene polypropylene glycol from www.chemindustry.com
D15: Synonyms of 1,2-Polypropyleneglycol, Ethoxylated and Propoxylated: www.environmentalchemistry.com
D16: Synonyms of polyethylene-polypropylene glycol from www.ecplaza.net
D17: Datasheet for Poloxamer 181 from ScienceLab.com
D18: Datasheet for Poloxamer 237 from Spectrum Laboratory Products Inc.
D22: Declaration of Dr. Philip Marshall
D26: Letter of Professor William Charman
D27: Declaration of Heidi Elmer
D28: Declaration of Dr. Mats Reslow
D29: Declaration of Dr. Hans-Joachim Zeisel
D30: Judgement of the Japanese IP High Court of 30 October 2013

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

*Main request*

*Amendments (Article 123(2) EPC)*

- A basis for "polyoxyethylene-polyoxypropylene block copolymer non-ionic surfactants" of claim 1 of the main request was "polyethylene-polypropylene glycol non-ionic surfactants" of the application as filed. The two surfactants were synonyms as could be seen from documents (D14) to (D18), (D22) and (D24). Moreover, the "block copolymer" feature was an inherent property of the

Pluronic non-ionic surfactants of the application as filed.

*Auxiliary request 1*

*Amendments (Article 123(2) EPC)*

- A basis for amended claim 1 with regard to the Pluronic polyols and its concentration range of 0.01-5.0% in combination with a pH range of 5.0 to 6.8 for the buffer was given in claims 1 to 4 and 7 as originally filed in combination with the disclosure on page 5, lines 14 to 25 of the application as filed.

*Novelty (Article 54 EPC)*

- The subject-matter of claim 7 was novel over the prior art in view of its process feature. The exposure of hGH to a solution of buffer and Pluronic polyols exceeding a threshold of 2 of their final concentration was detrimental to its stability. Accordingly, the avoidance of this exposure resulted in more stable human growth hormone (hGH) which was not known from the disclosure of documents (D5), (D7) or (D8). Experimental data supporting this assertion were disclosed in example 3 and figure 4 of the patent in suit showing a trend towards an increasing instability of hGH upon exposure to concentrations of buffer and Pluronic polyols at 2x their final concentration. In addition, the supplementary experimental data of document (D27) further supported the presence of a technical effect derived from the distinguishing process feature as was shown in increasing amounts of hGH aggregates

upon its exposure to increasing concentrations of buffer and Pluronic polyols during the formulation process. The supplementary experimental data submitted by the respondent in document (D28) were considered irrelevant in view of the lack of any mechanical stress exerted upon hGH during its formulation by merely shaking the samples. Furthermore, the respondent used a high pressure liquid chromatography (HPLC) based size exclusion chromatography (SEC-HPLC) instead of the more suitable asymmetric Flow-Field-Flow Fractionation (A4F) assay of document (D27). Only the latter was able to separate and to detect subvisible aggregates having the size of 50 to 100 nm. Moreover, the data of document (D29) related to a different patent and did not analyse the stability of the hGH upon storage over a longer period of time.

*Auxiliary request 2*

*Novelty (Article 54 EPC)*

- The arguments brought forward for the subject-matter of claim 7 of auxiliary request 1 applied *mutatis mutandis* to the subject-matter of claim 7 of auxiliary request 2 because the distinguishing process feature remained the same.

*Auxiliary requests A, B, C, A1, B1, B2 and C1*

*Admissibility*

- The appellants argued that the additional requests merely related to two amendments which were

introduced in response to objections raised by the respondent and should therefore be admitted.

*Novelty (Article 54 EPC)*

- The arguments brought forward for the subject-matter of claim 7 of auxiliary request 1 applied *mutatis mutandis* to the subject-matter of claim 7 of auxiliary requests A, B, C, A1, B1, B2 and C1 because the distinguishing process feature remained the same.

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

*Main request*

*Amendments (Article 123(2) EPC)*

- The amended "polyoxyethylene-polyoxypropylene block copolymer non-ionic surfactants" of claim 1 had no basis in the application as filed. In particular, the introduction of "block copolymer" restricted the manner in which the monomeric units of the surfactants could be arranged and thereby resulted in an non-allowable intermediate generalisation of the originally disclosed "polyethylene-polypropylene glycol non-ionic surfactants".

*Auxiliary request 1*

*Amendments (Article 123(2) EPC)*

- The combination of features of amended claim 1 relating to Pluronic polyols had no basis in the application as filed.

*Novelty (Article 54 EPC)*

- The process feature of claim 7 had no technical effect on the structure of the growth hormone. Hence, this feature could not be used to delimit the subject-matter of claim 7 from the known growth hormones of documents (D5), (D7) or (D8).

*Auxiliary request 2*

*Novelty (Article 54 EPC)*

- The arguments brought forward for the subject-matter of claim 7 of auxiliary request 1 applied *mutatis mutandis* to the subject-matter of claim 7 of auxiliary request 2 because the process feature remained the same.

*Auxiliary requests A, B, C, A1, B1, B2 and C1*

*Admissibility*

- The respondent argued that the requests are late filed, amended the appellants case and should therefore not be admitted into the proceedings.

*Novelty (Article 54 EPC)*

- The arguments brought forward for the subject-matter of claim 7 of auxiliary request 1 applied *mutatis mutandis* to the subject-matter of claim 7 of auxiliary requests A, B, C, A1, B1, B2 and C1 because the process feature remained the same.

XIII. The appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of its main request or one of its auxiliary requests 1 and 2 filed with its statement of grounds of appeal or one of its auxiliary requests A, B, C, A1, B1, B2 and C1 filed on 13 December 2013. The respondent requested that the appeal be dismissed.

## Reasons for the Decision

*Main request - claim 1 - added matter*

1. The appellants submitted that the feature "polyethylene-polypropylene glycol non-ionic surfactants" as used in claim 1 of the application as filed and the "poly**oxy**ethylene-poly**oxy**propylene **block copolymer** non-ionic surfactants" (emphasis added by the board) of present claim 1 related to identical surfactants, and that the difference in wording merely represented old and new nomenclature in the art. Thus they were synonyms and the appellants referred to documents (D13) to (D18), (D22) and (D26) as evidence that both terms are in fact synonymous. These surfactants are also known as poloxamers or under the trademark "Pluronic".

2. The board notes that none of the documents cited by the appellants provides a clear and unambiguous basis that both terms in fact relate to identical surfactants and can thus be regarded as synonyms.

2.1 Document (D13) relates to the term "poloxamers" and a definition thereof but does not explicitly disclose the term "poly**oxy**ethylene-poly**oxy**propylene **block copolymer**". The appellants asserted that the "α-hydro-ω hydroxypoly(oxyethylene)poly(oxypropylene)poly(oxyethylene) block copolymers" of document (D13) were a further synonym for "poly**oxy**ethylene-poly**oxy**propylene **block copolymer**" as presently claimed. However, the board notes that the latter term is silent on any positional indications, such as "α" or "ω" and does not disclose its segments "polyoxyethylene" and "polyoxypropylene" in the order and frequency as indicated in document (D13).

2.2 Moreover, the documents (D14) to (D18) disclose long lists of clearly different and non-identical specific surfactants, such as the trademarks Pluronic F68 and Pluronic L61, combined with non-ionic surfactants having different and more generic names. These lists are either headed "synonyms" (see documents (D14), (D17) or (D18)), or "synonyms"/"related" (see document (D15)) or not particularly classified at all (see document (D16)). In view of the fact that all these lists mix single specific but non-identical non-ionic surfactants together with different but more generic non-ionic surfactants, the board cannot regard the disclosure of documents (D14) to (D18) as clear and unambiguous evidence that "polyethylene-polypropylene glycol non-ionic surfactants" as originally filed and "polyoxyethylene-polyoxypropylene block copolymer non-ionic surfactants" as presently claimed are identical.

It is equally possible that these lists contain true synonyms of non-ionic surfactants together with other surfactants that are only chemically related (see heading of document (D15)).

2.3 Document (D22) is a declaration of Mr. Marshall indicating that a chemist would not have consciously distinguished between the different terms and would have therefore treated them as synonyms. The board, however, notes that this is a personal opinion of a single person which cannot in itself provide clear and unambiguous evidence that both terms are in fact identical and therefore true synonyms.

2.4 Finally, document (D26) relates to a letter of Mr. Charman, one of the inventors of the patent in suit, making the drafters of the original patent application aware of a **consistent error** relating to the use of "polyethylene-polypropylene glycol non-ionic surfactants" throughout the application as filed. However, the term "error" implies that the two terms could relate equally possibly to two different surfactants or to identical surfactants differing only as to nomenclature. Therefore the letter of Mr. Charman does not provide clear and unambiguous evidence that both terms relate to identical compounds.

3. Hence, none of the documents submitted by the appellants provides unambiguous evidence that both terms relate to identical surfactants.

4. A second line of argumentation of the appellants related to the meaning of the term "block copolymer" of the present claim 1. The term surfactant implied, according to the appellants, that the "polyoxyethylene" and the "polyoxypropylene" monomers which are either

hydrophilic or hydrophobic had to arrange themselves in blocks such that the polymer was able to function as an effective surfactant. Therefore the term "block copolymer" was an inherent feature of the originally disclosed "polyethylene-polypropylene glycol non-ionic surfactants". Hence its presence neither gave the skilled person any new information nor added any subject-matter.

5. The board cannot accept this reasoning. According to the established jurisprudence of the boards of appeal, an implicit disclosure in the patent application should be one which any person skilled in the art would consider **necessarily** implied by the patent application as a whole (see Case Law of the Boards of Appeal of the European Patent Office, 6th edition 2010, section III-A, 1, page 315). The term "block copolymer" indicates to the skilled person that the two "polyoxyethylene" and "polyoxypropylene" monomers of the non-ionic surfactant of amended claim 1 are arranged and distributed in the polymeric structure of the non-ionic surfactant in a certain defined and therefore limited way. However, the monomeric polyethylene glycol or polypropylene glycol units of the non-ionic surfactant as originally filed lack this kind of structural restriction and could therefore be arranged in many different ways, such as e.g. by alternating the different monomers or by arranging dimers of one monomeric unit followed by one monomer of the other unit without necessarily forming "blocks". Hence, in theory many different periodic or unperiodic arrangements of the two different monomeric units are possible. In addition, the argument of the appellants that there is no single commercially available Pluronic polyol available which does not form "blocks" of its monomers is not persuasive because (1) claim 1 does not

relate to "Pluronics" and (2) the non-existence of an effective commercial product without a "block" structure is no evidence that Pluronic surfactants without such a structure could exist - but only that such surfactants are not manufactured. Hence, the feature "block copolymers" is not an implicit necessity of the "polyethylene-polypropylene glycol non-ionic surfactants" as originally filed. The claimed "polyoxyethylene-polyoxypropylene block copolymer non-ionic surfactants" of claim 1 has therefore no basis in the application as filed and consequently extends beyond the content of the application, contrary to the requirements of Article 123(2) EPC.

*Auxiliary request 1 - claim 1 - added matter*

6. The respondent submitted that the subject-matter of claim 1 extended beyond the content of the application as filed because there was no basis in the application as filed for the specific combination of Pluronic polyols with all the other features of this claim.

7. The board finds that the relevant basis for the Pluronic polyols as stabilisers and its concentration range of 0.01-5.0% in combination with a pH range of 5.0 to 6.8 for the buffer of present claim 1 is claims 1 to 4 and 7 as originally filed in combination with the disclosure on page 5, lines 14 to 25 of the application as filed.

8. The board is therefore satisfied that the requirements of Article 123(2) EPC are complied with.

*Auxiliary request 1 - claim 7 - novelty*

9. The subject-matter of claim 7 relates to a stable liquid formulation of growth hormone characterized by process features, in particular, by being "obtainable by a method according to any of claims 1 to 6" (see section IV above).

10. It is established jurisprudence of the Boards of Appeal of the EPO that a claimed product characterized by its process of preparation ("product-by-process") must comply *per se* with the requirements of novelty and that the process features used to characterise further the claimed product are not to be considered as limiting unless they necessarily provide the product with features which it would not possess by a different process of preparation (see e.g. T 205/83, OJ EPO 85, 363, points 3.1 and 3.2.1 of the reasons for the decision). In addition, novelty can be established only **if evidence is provided** that modification of the process parameters results in other products. It is sufficient for this purpose if it is shown that distinct differences exist in the properties of the products claimed (see T 205/83, above, Headnote 2).

11. It is undisputed between the parties that stable liquid formulations of human growth hormone (hGH) containing the same buffers and Pluronic polyols as stabilisers in the pH range and concentrations as presently claimed are known from the art (see documents (D5), page 23, lines 33 to 37; (D7), example IV, table 3; and (D8), page 11, lines 2 to 5). Furthermore, it is undisputed that the only difference between the method of preparing the claimed formulation and those known from the above cited art is the step "wherein the method comprises admixing the growth hormone with the buffer

and the stabilising agent(s) under conditions such that the growth hormone is not exposed to concentrations of the buffer or stabilising agent(s) which are greater than 2x the final concentration of the buffer or stabilising agent(s) in the formulation" of claim 1.

12. Although the appellants admitted that the dilution of the growth hormone by concentrated stock solutions of buffers and stabilisers during the formulation process is a standard procedure, the appellants asserted that they were the first to discover that the exposure of hGH to a concentrated stock solution of buffer and Pluronic polyols exceeding a threshold of twice their final concentration was detrimental to its stability.

13. The appellants relied on figure 4 and example 3 of the patent in suit which disclosed an accelerated stability test of monomeric hGH in three different formulations stored at 40°C over a time period of 40 days. These formulations showed a different decrease of the hGH concentration over the time period analysed wherein formulations 2 and 3 were said to display a superior stability over formulation 1 (see paragraph 68 of the patent in suit).

14. Formulation 1 was prepared by adding a **two-fold** concentrate (**2x**) of excipients comprising buffer, Pluronic-F68, sodium chloride, sodium hydroxide and benzyl alcohol (see paragraph 66 of the patent in suit) to monomeric hGH. Formulations 2 and 3 were however, prepared by a buffer exchange. The monomeric hGH in the latter two formulations was thereby concentrated to the desired point by exchange into a buffer which contained all the above mentioned excipients, except for Pluronic F-68. This was only added later in sufficient solid amounts to give the required final concentration. The

difference between formulation 3 and 2 was the presence of additional EDTA. The appellants asserted that the transient exposure of hGH to **2x** the final concentration of buffer and stabilising agent (Pluronic F-68) in formulation 1 accounted for its faster decrease as observed in figure 4.

15. When considering the overall technical circumstances of the present case as disclosed in figure 4 and example 3, the board observes that the data of figure 4 and the experimental conditions of example 3 suffer from several fundamental deficiencies. It is evident that (1) formulation 1 is prepared by a different method than formulations 2 and 3 (direct mixing versus buffer exchange; see example 3); (2) formulations 2 and 3 contain different excipients (formulation 3 contains in addition EDTA, see example 3); (3) the starting concentrations of monomeric hGH in all three formulations is different (see figure 4); (4) all three formulations are exposed to buffer/ stabiliser concentrations within the limits defined in claim 1 (not greater than 2x) (see example 3); (5) there is a lack of any control data comparing the stability of monomeric hGH exposed to excipient concentrations above the claimed limit of 2x (see example 3 and figure 4); (6) excipients of all 3 formulations are not limited to buffer and Pluronic polyols as claimed, but also contain sodium chloride, sodium hydroxide and benzyl alcohol (see paragraph 66 of the patent in suit); (7) the semi logarithmic Y-axis of figure 4 lacks numerical values.

16. The board considers these deficiencies to be so fundamental as to prevent any reasoned conclusion to be drawn from the data of the patent in suit whether the exposure of hGH to buffer and Pluronic polyols

exceeding the limit of 2x of their final concentration would have a destabilising effect on hGH. This is essentially due to the lack of any control data relating to hGH formulations containing only buffer and Pluronic polyols as stabilisers (see deficiency point 6 above) and the lack of any data relating to hGH formulations which were in fact exposed to concentrations of buffer/Pluronics exceeding the 2x limit of present claim 1. Consequently, all the assertions made by the appellants are based on mere speculations because the patent in suit **does not provide any data** disclosing the alleged destabilising effect on hGH by an exposure to buffer/Pluronics above their two-fold final concentration. For this reason alone, the arguments of the appellants with regard to the data disclosed in the patent in suit have to fail.

17. Irrespective of the above considerations, the board observes that the concentration of the monomeric hGH of formulations 1 and 2 seems to decrease with even the same rate over roughly two semi logarithmic scales within the time period of 40 days (see figure 4). Only the amount of hGH of formulation 3 seems to decrease more slowly. However, as mentioned above, this formulation contains in addition EDTA which the other two formulations do not have. The board regards this difference alone to be sufficient to render any firm conclusion regarding formulation 3 and the reasons causing this effect on hGH impossible.

18. Hence, the board is not persuaded by the argument of the appellants that there is a trend towards a more stable monomeric hGH in formulations 2 and 3 versus formulation 1 which is allegedly due to the exposure of hGH to a maximum of a 2x concentration of buffer and Pluronic polyols during the formulation process.

19. Further, the board does not consider that the supplementary experimental data of document (D27) filed by the appellants with their statement of the grounds of appeal is sufficient to demonstrate that the "2x greater" feature of the buffer/Pluronics polyols does indeed change the structural identity of the hGH to render it unstable.

20. The board observes that it is not the stability of the **monomeric** hGH as determined by its amount after storage in example 3/figure 4 of the patent in suit which is analysed in document (D27) but the tendency of the hGH to **aggregate** in response to physical stress exerted by a magnetic stirrer during its formulation (see paragraphs 10, 12, 13 of document (D27), to chemical stress by exposing the hGH to increasing concentrations of excipients (1.33x; 2x; 3x and 5x; see paragraph 7 of document (D27)) and to thermal stress by storing the formulation at 40°C for up to 40 days. The board notes in this respect that the tendency of growth hormone to aggregate thereby rendering it unstable is known from the prior art (see document (D2), abstract and page 713, left column, third paragraph).

21. Again the board finds that the data disclosed in document (D27) suffer from several fundamental deficiencies: (1) the excipients of all 3 formulations are not limited to buffer and Pluronic polyols as stabilisers, but also contain sodium chloride, sodium hydroxide and benzyl alcohol (see paragraph 7 of document (D27)); (2) the results of the microphotographic inspection (see paragraphs 20 to 23 of document (D27)) and the asymmetric flow field flow fractionation chromatography (A4F) (see paragraphs 24 to 29 of document (D27)) do not contain any control

data of formulations lacking hGH; and (3) the composition of the particles/flakes or the subvisible aggregates has not been determined.

22. These deficiencies are again of such a kind that no firm conclusion can be drawn with regard to the question which excipient(s) and/or mixing condition is/ are responsible for any of the observed effects. Moreover, these deficiencies render the determination of the chemical identity of the observed particles/ flakes by the visual or microphotographic inspection or the identity of the monomeric or subvisible aggregates of the chromatographic peaks in figures 13 and 14 of the A4F analysis of document (D27) impossible. The appellants have neither directly analysed the particles/flakes or the chromatographic A4F eluates for its hGH content nor have they done it indirectly by using the appropriate controls as outlined above. This means that there is no evidence provided in document (D27) that these particles/flakes or these chromatographic peaks do in fact consist of aggregated hGH - or of any of the other excipients which are present in the analysed samples, such as for example the preservative benzyl alcohol.

23. Accordingly, in the absence of any such evidence, the appellants only have argued that it is nevertheless plausible that hGH forms these aggregates either as particles/flakes or as subvisible aggregates in view of the consistent data obtained by the three different analytical methods of document (D27) (visual inspection, microphotography and chromatographic analysis by A4F). These data are supposed to show that the exposure of the hGH to stepwise increasing concentrations of excipients (1.33x; 2x; 3x and 5x; see paragraph 7 of document (D27)) always correlates with

an increasing number of particles/flakes or subvisible aggregates in each of the methods applied.

24. The board accepts the appellant's submission that a certain consistency exists between the visual inspection (see paragraphs 18 and 19 of document (D27)) and the microphotographic analysis (see paragraphs 20 to 23 of document (D27)) with respect to an observed increased opalescence or particle/flake formation upon exposing the liquid hGH formulations to increasing concentrations of excipients. However, for the reasons outlined above (see point 22) this consistency *per se* is not sufficient because the chemical identity of the formed particles/flakes is unclear. Moreover, the data of the A4F chromatography of figures 13 and 14 of document (D27) relating to the formation of subvisible aggregates of hGH seem not even consistent. The appellants have asserted that the amount of alleged monomers/dimers of hGH eluting between 5 and 7.5 minutes decreases in proportion to an increasing amount of alleged aggregated hGH (see elution peak at 24 minutes, in particular the blow up version of figure 13 of document (D27) filed during oral proceedings). A small difference in the monomeric/dimeric amount of hGH of the three different formulations tested ("blue" exposure to 1.33x; "green" exposure to 3x; "red" exposure to 5x (see table in paragraph 25 of document (D27)) is supposed to be sufficient to explain the larger differences between the total amount of aggregated subvisible hGH formed in view of its stronger light scattering behaviour in the A4F analysis.

25. The board, independent of the fundamental deficiencies relating to the data of document (D27) as outlined above (see point 22), cannot agree with the appellants

that the amount of the monomers/dimers of hGH of the three different samples always decreases when the amount of their corresponding aggregates increases (see figures 13 and 14). The board notes that such an inverse relation is required if the monomers/dimers of hGH in document (D27) are the true building blocks of the later eluding subvisible aggregates. Consequently, the relative amount of monomers/dimers has to decrease if the relative amount their aggregates increases - or *vice versa* it has to be higher if the amount of its corresponding aggregate is lower. However, the board is not able to detect any visible differences in the relative amounts of the "green" and "red" monomers (see elution peak at about 6 minutes in either figure 13 or its blow-up version) while the amount of "red" aggregates is significantly larger than the amount of "green" aggregates (see peak eluding at 24 minutes). The same applies to all the dimers ("blue", "red" or "green") of the "shoulder" eluting between 6.5 and 7.5 minutes in these figures.

26. Consequently and contrary to the appellant's assertion, the amount of monomeric "red" hGH does not decrease relative to monomeric "green" hGH - although in theory it should - since the amount of aggregated "red" hGH is considerably larger than the amount of the "green" aggregates. The same applies to the amount of dimeric "red" hGH versus the amount of dimeric "green" hGH. Moreover, with respect to the "dimeric" shoulder in figures 13 and 14 the board observes that the amount of dimeric "blue" hGH is not larger relative to the "green" and "red" one - despite the fact that the amount of aggregated "blue" hGH is the lowest in comparison to the aggregated amount of the other two.

27. The board can, however, accept that the amount of "blue" monomers appears to be slightly bigger than the amount of "red" or "green" monomers eluting at about 6 minutes as shown in figures 13 and 14. This would fit into the theory of the appellants because the amount of aggregated "blue" hGH is the lowest relative to the amount of "red" and "green" aggregates (see peak eluting at 24 minutes in figures 13 and 14 and reasons provided in point 25, above). However, the board points in this respect to paragraph 26 of document (D27) which explicitly states that the separation conditions of the A4F chromatography were selected to focus on subvisible aggregates which resulted in a poor resolution of the monomer and dimer peaks **not allowing any reliable quantification of their relative amounts**. Hence, the A4F experiment of document (D27) was admitted by the appellants as never designed to provide the data necessary for arriving at any firm conclusion that there is in fact a true inverse relation between the amounts of monomers/dimers and the aggregates as stated by the appellants. Hence for this reason alone the observed difference in the amount of the alleged monomers between the "blue" and the "green" or "red" is not significant. As a side remark the board further notes that the data of the A4F chromatography are based on a single experiment for each of the three hGH exposure conditions tested. This renders the statistical significance of the observed difference even more questionable. For all these reasons, the arguments of the appellants must fail.

28. In view of these observations, the board regards the formation of benzyl alcohol aggregates to be equally plausible in the formation of the alleged hGH aggregates under the experimental conditions of document (D27).

29. Moreover, the board observes that all hGH formulations of document (D27) are opalescent and contain fine particles even if manufactured under the most stabilising conditions according to present claim 1 (see number "i" and "ii" in the table at the bottom of page 4 of document (D27). Hence, the hGH formulations as analysed seem *prima facie* to suffer from a general incompatibility between the different ingredients irrespective of whether or not the hGH has been exposed to excipients above or below the factor of 2x their final concentration during the formulation process. In this respect, the board remarks that it was undisputed by the parties that the used preservative benzyl alcohol has a known destabilising effect on the hGH. This observation casts further doubts on the suitability of the data disclosed in document (D27) to render a stabilising effect by the claimed process step at least plausible.

30. In summary, neither the data of example 3/figure 4 of the patent in suit nor the data of document (D27) provide evidence that the exposure of hGH to concentrations of buffer/Pluronic polyols exceeding 2x of their final concentration induces structural changes on hGH thereby resulting in a decreased stability. Consequently, the board considers the structural overlaps between the hGH proteins prepared according to the method of the patent in suit and the ones known from the art (see documents (D5), page 23, lines 33 to 37; (D7), example IV, table 3; and (D8), page 11, lines 2 to 5) to be so considerable that there can be no question of a significantly different and therefore new product. In view of these arguments, the board does not need to examine further the relevance of the additional supplementary experimental data of documents (D28) and

(D29) provided by the respondent since the data provided by the appellants do not disclose an effect for the claimed process step on the hGH stability.

31. The subject-matter of claim 7 is therefore not novel, contrary to the requirements of Article 54 EPC.

*Auxiliary request 2 - claim 7 - novelty*

32. The subject-matter of claim 7 of auxiliary request 2 is identical to the subject-matter of claim 7 of auxiliary request 1 except for the use of Pluronic F-68 instead of Pluronic polyols in general. However, it was undisputed by the parties that "Pluronic F-68" is identical to "Poloxamer 188" as used in documents (D5), (D7) and (D8) (see document (D5), page 23, line 36); (D7), table 3; (D8), page 11, line 4;). Accordingly, the reasons outlined above for the subject-matter of claim 7 of auxiliary request 1 apply *mutatis mutandis* to the subject-matter of claim 7 of this request.

*Auxiliary requests A; B; C; A1; B1; B2; C1 - admissibility*

33. Auxiliary requests A, B, C, A1, B1, B2 and C1 were filed one month before the oral proceedings in reply to the response of the respondent dated 23 August 2010. They were thus clearly late filed and are an amendment to the appellant's case. Admissibility of these requests thus depends on the board's discretion (Article 13(1) RPBA).

34. The board considers however that, in view of its finding in the substance of the matter (see further), these procedural issues can be left unanswered as they have or would have no bearing on the outcome of the present decision.

*Auxiliary requests A; B; C; A1; B1; B2; C1 - claim 7 - novelty*

35. The board observes that the subject-matter of claim 7 of auxiliary requests A and A1 is identical to the subject-matter of claim 7 of auxiliary requests 1 and 2 see sections IV and VIII, above). Accordingly, the reasons outlined above apply *mutatis mutandis* to the subject-matter of claim 7 of the present requests A and A1.

36. Moreover, the subject-matter of claim 7 of auxiliary requests B, B1, B2, C and C1 differs from auxiliary request 1, 2, A and A1 only insofar as the product claim is converted into a first medical use claim according to Article 54(4) EPC (see section VIII, above). However, the disclosure of documents (D5), (D7) and (D8) already relates to stable liquid hGH formulations for a pharmaceutical use (see documents (D5), page 23, lines 33 to 38; (D7), example IV, table 3; claim 1; and (D8), page 11, lines 2 to 6). Hence, the mere conversion of the claim into a first medical use claim is not sufficient to render it novel over the cited prior art documents. In addition, this conversion has no bearing on the process feature of claim 7. Consequently, the same arguments as outlined above for the subject-matter of claim 7 of auxiliary requests 1, 2, A and A1 apply *mutatis mutandis* to the subject-matter of claim 7 of the present requests B, B1, B2, C and C1.

**Order**

**For these reasons it is decided that:**

The appeal is dismissed

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith

Decision electronically authenticated