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Datasheet for the decision of 6 November 2013

Case Number: T 0103/09 - 3.3.04

Application Number: 01943331.7

Publication Number: 1311285

IPC: A61K38/18, A61K9/08, A61K47/02, A61K47/18

Language of the proceedings: EN

Title of invention:
Liquid pharmaceutical composition containing an erythropoietin derivative

Patent Proprietor:
F. Hoffmann-La Roche AG

Opponents:
Sandoz AG
Neose Technologies, Inc.
BioGeneriX AG

Headword:
Stable liquid human EPO at room temperature/F. Hoffmann-La Roche AG

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2)
RPBA Art. 13(3)

Keyword:
Amendments - added subject-matter (yes)
Late-filed auxiliary requests - admitted (yes)
Claims - clarity - auxiliary request (yes)
Novelty - auxiliary request (yes)
Sufficiency of disclosure - auxiliary request (yes)
Inventive step - auxiliary request (yes)

Decisions cited:
G 0010/91, G 0001/03

Catchword:

Europäisches Patentamt
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Office européen des brevets

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Case Number: T 0103/09 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 6 November 2013

Appellant: (Patent Proprietor)	F. Hoffmann-La Roche AG Grenzacherstrasse 124 4070 Basel (CH)
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Party as of right: (Opponent 3)	BioGeneriX AG High-Tech-Park Neckarau, Janderstrasse 3 68199 Mannheim (DE)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 4 November 2008 concerning maintenance of the European Patent No. 1311285 in amended form.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: M. Montrone
R. Morawetz

Summary of Facts and Submissions

I. The appeals were lodged by the patent proprietor (hereinafter "appellant-patentee") and by the opponent 1 (hereinafter "appellant-opponent") against the interlocutory decision of the opposition division to maintain European patent EP 1311285 entitled "Liquid Pharmaceutical Composition Containing an Erythropoietin Derivative" in amended form, which was granted for European patent application 01943331.7.

II. The patent was opposed under Article 100(a) EPC on the ground of lack of novelty (Article 54 EPC) and inventive step (Article 56 EPC), under Article 100(b) EPC and under Article 100(c) EPC.

III. The opposition division held that:
the main request, based on claims 1 to 44 and 46 to 51 as granted and an amended claim 45 filed on 3 August 2006, contained added matter relating to the subject-matter of claims 34 and 46 and that the subject-matter of claim 1 was not novel. Moreover, the subject-matter of claim 1 of auxiliary request 1 (AR1) filed on 3 August 2006 was not considered to be inventive because it did not solve the problem over the whole scope claimed. The patent was maintained on the basis of auxiliary request 2 (AR2) filed during oral proceedings on 7 October 2008.

IV. The appellant-patentee requested in its statement of grounds of appeal of 11 March 2009 that the decision under appeal be set aside and that the patent be maintained on the basis of the same requests as before the opposition division. Oral proceedings were requested should the board not contemplate maintaining the patent on the basis of the main request.

V. The appellant-opponent requested in its statement of grounds of appeal dated 12 March 2009 that the decision under appeal be set aside and that the patent be revoked in its entirety. Oral proceedings were requested on an auxiliary basis.

VI. The opponent 3 (respondent 1 to the proprietor's appeal and party as of right to the opponent's 1 appeal - hereinafter “respondent 1”) requested in its letter dated 22 July 2009 that the appeal of the appellant-patentee be dismissed.

VII. The appellant-opponent filed a reply to the appellant-patentee's statement of grounds of appeal on 29 September 2009.

VIII. The appellant-patentee filed a reply to the appellant-opponent's statement of grounds of appeal on 22 December 2009.

IX. The board sent out a summons dated 2 July 2013 to oral proceedings on 6 November 2013.

X. The appellant-patentee filed in addition auxiliary requests 3 to 7 with its letter dated 4 October 2013.

XI. Respondent 1 filed further arguments supporting its case on 4 October 2013.

XII. The opponent 2 (hereinafter "respondent 2") announced on 10 October 2013 that it would not attend the oral proceedings on 6 November 2013.

XIII. The board informed the parties of its preliminary view in its communication dated 11 October 2013.

XIV. With its letter dated 25 October 2013 the appellant-patentee replaced its main request of 11 March 2009 by a new main request (corresponding to auxiliary request 1 filed on 3 August 2006), and filed a new first auxiliary request and new auxiliary requests 8 to 14. It also requested that document (D32) filed by appellant-opponent on 29 September 2009 (see section XVII, below) be not admitted into the proceedings.

Claims 1, 31, 43 and 46 of the main request read as follows:

"1. A liquid pharmaceutical composition comprising a pegylated human erythropoietin protein, a multiple charged inorganic anion in a pharmaceutically acceptable buffer suitable to keep the solution pH in the range from 5.5 to 7.0, and optionally one or more pharmaceutically acceptable excipients, said liquid composition being stable at room temperature, wherein the anion is a sulfate anion.

31. The composition of claims 1 to 30, comprising 10 mM sodium phosphate, 40 mM sodium sulfate, 3% (w/v) mannitol, 1 mM methionine, pH 6.2.

43. The composition of claim 41 comprising 10 mM sodium phosphate, 40 mM sodium sulfate, 3% (w/v) mannitol, 1 mM methionine, pH 6.2.

46. A process for preparing a composition according to any of claims 1 to 45, comprising mixing a pegylated human erythropoietin protein with a solution comprising a multiple charged anion and optionally one or more pharmaceutically acceptable excipients and adjusting the pH to 5.5 to 7.0 using a pharmaceutically

acceptable buffer, wherein the anion is a sulfate anion."

Claims 1 and 44 of the auxiliary request 1 read as follows:

"1. A liquid pharmaceutical composition comprising a pegylated human erythropoietin protein, a multiple charged inorganic anion in a pharmaceutically acceptable buffer suitable to keep the solution pH in the range from 5.5 to 7.0, and optionally one or more pharmaceutically acceptable excipients, said liquid composition being stable at room temperature, wherein the anion is a sulfate anion.

44. A process for preparing a composition according to any of claims 1 to 43, comprising mixing a pegylated human erythropoietin protein with a solution comprising a multiple charged anion and optionally one or more pharmaceutically acceptable excipients and adjusting the pH to 5.5 to 7.0 using a pharmaceutically acceptable buffer, wherein the anion is a sulfate anion."

XV. The respondent 1 announced on 4 November 2013 that it would not attend the oral proceedings on 6 November 2013.

XVI. Oral proceedings before the board were held on 6 November 2013.

XVII. The documents referred to in the present decision are:
D5: WO9805363
D9: EP0539167
D11: WO9428024
D15: US5354934

D26: Timasheff & Arakawa, "Stabilization of protein structure by solvents", Chapter 14, Protein Structure - A Practical Approach, T.E. Creighton (ed.), 1990, pg. 331-345
D27: Wang, Y-C.J., et al., J. Parenteral Sci. & Tech., 1988, pg. S4-S26
D28: US5716644
D29: US5817343
D30: A. Wiseman, "Stabilization of Enzymes", Chapter 6, Topics in Enzyme and Fermentation Biotechnology 2, 1978, pg. 280-303
D31: Declaration by Dr. A. Papadimitriou
D32: WO9012874

XVIII. The appellant-patentee'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 "liquid composition being stable at room temperature" of claim 1 of the main request was provided by the disclosure on page 2, line 28 to page 3, line 5 and on page 3, lines 15 to 26 of the application as filed.
- A basis for the back references in claims 31 and 43 to all previous claims was provided by "formulation C" of example 11 on page 42, lines 13 to 18 of the application as filed.
- The subject-matter of claim 46 was based on the disclosure of page 23, lines 20 to 23 and claim 56 of the application as filed.

Auxiliary request 1

Admissibility

- The subject-matter of auxiliary request 1 only differed from the subject-matter of the main request by deleting claims 31 and 43 which were found not to comply with the requirements of the Article 123(2) EPC. It was therefore admissible.

Amendments, Clarity (Articles 123(2), 84 EPC)

- The amendments carried out (deletion of claims 31 and 43) did not extend beyond the content of the application as filed and were moreover clear. They were thus in compliance with the requirements of Article 123(2) and 84 EPC.

Novelty

- The liquid pharmaceutical composition of present claim 1, the process of claim 44, the use of claim 45 and the device of claim 46 were not known from the prior art. The subject-matter of claims 1 to 46 was thus novel (Article 54 EPC).

Sufficiency of disclosure

- The requirements of Article 83 EPC were met for the stable liquid pharmaceutical composition according to present claim 1 in view of the provision of several working examples which related to liquid pegylated erythropoietin (EPO) compositions containing different concentrations of sulfate in the application as filed. These compositions were found to be stable at room

temperature over a period of 6 months (see figures 3, 6, 9 and 10, examples 10 and 13). In addition, the application as filed provided a clear guidance for identifying further EPO derivatives falling within the scope of claim 1 in view of the provision of different methods which could be used to assess with a reasonable effort the stability of the EPO within a certain defined pH range.

Inventive Step

- Documents (D5) or (D15) represented the closest prior art. The objective technical problem to be solved was the provision of a stable liquid EPO formulation at room temperature. The problem was considered to be solved in view of the provision of several working examples in the patent in suit. The use of sulfate for the stabilisation of liquid EPO at room temperature was not known from the available prior art documents, avoided the formation of EPO aggregates and was thus considered to be non-obvious for the skilled person.

XIX. The appellant-opponent'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 feature "liquid composition being stable at room temperature" of claim 1 had no basis in the application as filed. In particular, stability of EPO was not defined *per se*, but there was a

definition of the term "unstable" in the application as filed which related to protein degradation comprising physical and chemical changes. In this context protein modifications by oxidation were explicitly mentioned (see page 2, line 33 to page 3, line 5). This disclosure related to table 4 on page 42 of the application as filed, which indicated an oxidation percentage of 13.38% of methionine54 after 6 months storage of EPO at 25°C. This high percentage of oxidation would not be regarded as insignificant thereby extending the content of the application as filed, contrary to the requirements of Article 123(2) EPC.

- Further objections were raised against the back references in claims 34 and 46 to previous claims.
- Another objection was raised against the subject-matter of claim 46.

Auxiliary request 1

Admissibility

- No admissibility objections were raised.

Amendments, Clarity (Articles 123(2), 84 EPC)

- *No further objections of added matter (Article 123(2) EPC) were raised. No objections of lack of clarity were raised either (Article 84 EPC).*

Novelty

- *No objections of lack of novelty (Article 54 EPC) were raised.*

Sufficiency of disclosure

- An objection under lack of sufficiency (Article 83 EPC) was raised against the subject-matter of claim 1 because the feature "stable at room temperature" comprised non-working embodiments due to the undefined upper concentration limit of sulfate. Document (D31) disclosed that pegylated EPO was rendered unstable in the presence of 1 molar ammonium sulfate (see document (D31), page 1).

Inventive Step

- Either document (D5) or (D15) represented the closest prior art. The objective technical problem to be solved was the provision of a stable liquid EPO formulation at room temperature. The problem was not solved over the whole scope of the claim because concentrations of 1 molar ammonium sulfate resulted in a degradation of EPO in liquid solution (see document (D31), page 1). Moreover, the use of sulfate for stabilising liquid EPO formulations was obvious for the person skilled in the art in the light of the teaching of documents (D26), (D27) or (D30) wherein sulfate was preferably used to stabilise protein solutions.

XX. Respondent's 1 arguments, as far as they are relevant for the present decision, may be summarised as follows:

Main request

Amendments (Article 123(2) EPC)

- Objections were raised against the back references in claims 34 and 46 to previous claims of added matter (Article 123(2) EPC).

Auxiliary request 1

Admissibility

- No admissibility objections were raised.

Amendments, Clarity (Articles 123(2), 84 EPC)

- No objections of added matter (Article 123(2) EPC) or lack of clarity (Article 84 EPC) were raised.

Novelty

- No written objections of lack of novelty (Article 54 EPC) were raised.

Sufficiency of disclosure

- The subject-matter of claim 1 was objected to because the technical effect, namely stability, was not achieved over the whole scope claimed. In particular, the application as filed provided only EPO compositions containing sulfate which were found to be stable at a pH of 6.2. But this disclosure could not be extrapolated across the

whole scope of the claim defining the pH range as 5.5 to 7.0.

Inventive Step

- The problem, namely the provision of a stable liquid EPO formulation at room temperature of present claim 1, was not solved over the whole scope of the claim because concentrations of 1 molar ammonium sulfate resulted in a degradation of EPO in liquid solution (see document (D31), page 1). Moreover, the use of sulfate for stabilising liquid EPO formulations was obvious for the skilled person in the light of the teaching of document (D26), wherein natrium and magnesium sulfate were described as the natural choice for protein stabilisation (see document D26, page 342, table 3).

XXI. The appellant-patentee requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request filed on 25 October 2013 (which was previously auxiliary request 1 filed on 3 August 2006) or that the decision under appeal be set aside and that the patent be maintained on the basis of its auxiliary request 1, also filed on 25 October 2013, or to dismiss appellant-opponent's appeal (and thus maintain the patent on the basis of its auxiliary request 2 filed on 7 October 2008 which is the request allowed by the Opposition Division), or that the decision under appeal be set aside and that the patent be maintained on the basis of one of its auxiliary requests 3 to 7 filed with its letter of 4 October 2013, or of one of its auxiliary requests 8 to 14 filed with its letter of 25 October 2013. The appellant-opponent requested that the decision under appeal be

set aside and that the European patent No. 1311285 be revoked. The respondent 1 requested that the appeal of the appellant-patentee be dismissed.

Reasons for the Decision

1. The appeals are admissible

Main Request - claims 1, 31, 43, 46 - added matter

2. Article 123(2) EPC provides that a European patent application or a European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed.

3. It is an accepted principle of the established case law of the Boards of Appeal that, in order to determine whether or not an amendment violates Article 123(2) EPC, it has to be established whether the amendment results in the introduction of technical information into the description and/or the claims which a skilled person would not have objectively and unambiguously derived from the application as filed, when account is taken of matter which is implicit to a person skilled in the art in what has been expressly mentioned (see Case Law of the Boards of Appeal of the EPO, 6th Edition, 2010, III.A.7).

4. The appellant-opponent submitted that the subject-matter of claim 1 - in particular with regard to the amended feature "stable at room temperature" - was not supported by the content of the application as filed and thus extended beyond the disclosure of the application. It argued that the application as filed neither provided an explicit disclosure for this

feature nor a definition of its meaning. Instead it provided a definition for the meaning of "unstable" which indicated that oxidation constituted a form of protein degradation (see page 2, line 33 to page 3, line 5 of the application as filed). This passage in combination with an observed oxidation rate of 13.38% for pegylated EPO at 25 °C in the presence of sulfate as disclosed for formulation B in table 4 (see page 42 of the application as filed) thus amounted to a clear contradiction to the feature "stable at room temperature" of claim 1 which consequently extended the scope beyond the content of the application as filed.

5. It was not disputed by the appellant-patentee that the application as filed did not contain an explicit disclosure of the feature "stable at room temperature" of claim 1.

6. It submitted that the passages on page 2, line 28 to page 3, line 5 and page 3, lines 15 to 26 of the application as filed provided an implicit basis for the contested feature. These passages read as follows:

"- all presently commercially available erythropoietin compositions are **unstable** at elevated temperatures, i.e. above refrigerator temperature which is usually between 2 and 8 °C. Therefore, they have to be stored in a refrigerator (2-8 °C) and cannot be stored at room temperature (around 20 °C). This leads to increased costs, caused by storage and shipment at low temperature and also causes inconvenience in handling of the drug product. **Unstable** in this context means that storage at elevated temperatures, e.g. 25 °C for a prolonged period of time (i.e. several months, or more than 6 months) leads to degradation of the protein. **Degradation** in this context describes physical changes

(e.g. aggregation or denaturation) and chemical changes (e.g. oxidation or modification of chemical bonds in general) of the protein molecule which are known to occur preferably at elevated temperatures (above 8 °C)."

"The problem underlying the present invention is therefore to provide a composition which is able to minimize or suppress the above mentioned disadvantages.

The problem is solved, according to the present invention, by providing a pharmaceutical composition comprising an erythropoietin protein, a multiple charged inorganic anion in a buffer solution of pH of about 5.5 to about 7.0, and optionally one or more pharmaceutically acceptable excipients. It has been surprisingly found that **formulating an erythropoietin** in this composition **improves its stability** at temperatures above refrigerator temperature (2-8 °C), **especially at room temperature** (i.e. below 25 °C) and even at higher temperatures, e.g. 40 °C. **This means that the composition can be stored without cooling for a prolonged period of time, without loosing significant amounts of activity and without significant degradation.**" (Emphases added by the board).

7. The board is satisfied that these passages support a stable erythropoietin (EPO) at room temperature as referred to in claim 1 in view of the general disclosure that it can be stored without cooling for a prolonged period of time without loosing significant amounts of activity and without significant degradation. In its essence this disclosure constitutes the definition of how a skilled person understands the feature "stable protein" because he or she is aware

that protein stability is not an absolute property but has to be seen within the limits as defined above.

This finding of the board is further confirmed by the experimental data provided in the application as filed showing a liquid pegylated human EPO in the presence of sulfate anions which is thermally stable over a period of six months at 25 °C without any detectable aggregation/denaturation (see table 3 on page 41, formulations "B", "D" or "E" and example 14 on page 43) by keeping 100% of its biological activity (see example 13 on page 43). A slightly increased methionine54 oxidation rate of 13.38% at 50 µg/ml despite the presence of sulfate (see table 4, page 42, formulation "B") is not rendering the pegylated EPO "unstable", since it neither affects its thermal stability nor its activity (see table 3 and example 13) nor results in any detectable protein aggregation (see table 3, page 41 and example 14 on page 43).

Hence the skilled person would consider it as insignificant in line with the definition given on page 3, lines 24 to 26 of the application as filed. Consequently, the feature "stable at room temperature" of present claim 1 does not add any new technical information and is made within the limits of what a skilled person would derive directly and unambiguously, by using his or her common general knowledge and seen objectively at the date of filing, from the whole of the disclosure of the application as filed.

8. A further objection was raised by the appellant-opponent and respondent 1 against the back references in claims 31 and 43 to previous claims resulting in an intermediate generalisation of the claimed subject-matter beyond the content of the application as filed.

9. It was undisputed between the parties that "formulation C" of example 11 in the application as filed is the only basis for this contested subject-matter.

10. The board observes that the title of example 11 reads "**Optimized** formulations suppress oxidation of methionine54 in EPO protein, methionine as an anti-oxidant" (emphasis added by the board). The skilled person reading the term "optimized" or the term "superior to other formulations" (see page 42, lines 16 and 17) would immediately understand that the anti-oxidative effect of methionine in this particular composition depends on all its ingredients disclosing a strong functional relationship between them. In this context also the indication that this formulation "is the preferred formulation of the invention" (see page 42, line 15) does not provide a basis for a generalisation but rather on the contrary specifically discloses the single most optimal composition for stabilising pegylated EPO against oxidative stress.

Moreover, the board notes that there are no other passages in the application as filed indicating that the superior anti-oxidative effect of "formulation C" is independent from the particular pH, the anions, the polyol or the salt concentration used - or is moreover preserved in the presence of further ingredients. On the contrary, figure 6 of the application as filed shows a strong dependency on the transition temperature (meaning stability) of the EPO protein on the pH, anion, polyol and salt concentration used. Consequently, it appears to the board that the superior effect of "formulation C" is closely linked to this particular "optimised" composition which cannot be extrapolated to all other compositions falling under the general scope of claims 1 to 30 or 1 to 41, which

for example includes $CaCl_2$ (see claim 18 of the patent as granted) or additional non-ionic detergents (see claim 19 of the patent as granted).

Hence the back references in claims 31 and 43 to previous claims result in an unallowable intermediate generalisation which extends beyond the content of the application as filed, contrary to the requirements of Article 123(2) EPC.

11. In its letter dated 29 September 2009 the appellant-opponent raised a further objection under Article 123(2) EPC against the subject-matter of independent claim 49 as granted which is now claim 46 of the main request (see point 4.3, page 7). This objection has not been raised in its notice of opposition dated 14 December 2005 nor by any of the other opponents (here respondents 1 and 2) under Article 100(c) EPC during the first instance proceedings. It therefore constitutes a new ground which can only be considered by the board with the approval of the proprietor (here appellant-patentee, see decision G 10/91, OJ EPO 1993, 420, Headnote). The substantive objection of the appellant-opponent was that the term "adjusting" extended the scope of the claim by allowing a different order in which the pH "adjustment" steps are carried out and that the adjustment was not restricted to the use of the buffer but extended to any acid or base which was suitable in adjusting the pH to its claimed range.

12. The appellant-patentee agreed to admit this ground into the present appeal proceedings and indicated as a basis for the contested subject-matter claim 46, page 23, lines 20 to 23 and claim 56 of the application as filed.

13. Original claim 56 reads:

"A process for preparing a composition according to any of claims 1-54, comprising mixing a erythropoietin protein with a solution comprising a multiple, negatively charged anion and optionally one or more pharmaceutically acceptable excipients."

14. The board is satisfied that this claim in combination with original claims 1, 26 and 34 referring to "human pegylated erythropoietin" and "a buffer suitable to keep the composition in the claimed pH range" supports the claimed process wherein the pH is adjusted to a range of 5.5 to 7.0 by using a pharmaceutically acceptable buffer. The skilled person is aware of the fact that the use of a buffer to keep a solution within a certain predefined pH range requires adjustments. The board, in this context, cannot accept the argument of the appellant-opponent that this would introduce a new order of process steps. First, the contested claim itself does not refer to any specific order. Second, the suitability of keeping the solution in a predefined pH range as originally claimed implies necessarily that adjustments can be carried out at any time and thus in any order. Moreover, the board notes that the claim requires that the pH adjustment is performed by using the buffer which excludes any isolated adjustment steps by other means such as e.g. the addition of an acid.

15. In view of the above considerations of point 10 the board concludes that, although the objections of added matter relating to claims 1 and 49 of the main request are not sustained, the subject-matter of claims 31 and 43 extends beyond the content of the application as filed contrary to the requirements of Article 123(2) EPC.

Auxiliary request 1 - admissibility

16. The auxiliary request 1 differs from the main request in that claims 31 and 43 have been deleted.

17. The appellant-opponent did not object to the admissibility of the present request.

18. The board notes that the amendment is a direct reaction to the board's finding expressed in point 15 above and can be reasonably dealt with by the appellant-opponent and the board. Hence, the board exercises its discretion and admits the request into the appeal proceedings (Article 13(3) RPBA).

Auxiliary request 1 - added matter, clarity

19. Neither the appellant-opponent nor either of the respondents raised objections under Article 123(2) EPC or clarity (Article 84 EPC) against the subject-matter of the remaining claims.

20. In view of the amendments carried out the board is satisfied that the request meets the requirements of Articles 123(2) and 84 EPC.

Auxiliary request 1 - novelty

21. Neither the appellant-opponent nor either of the respondents raised a novelty objection against the subject-matter of any of the claims of the present request.

22. The board in view of the available prior art documents has no reason to come to a different conclusion. The

subject-matter of the claims thus meets the requirements of Article 54 EPC.

Auxiliary request 1 - sufficiency of disclosure

23. The opposition division decided that claim 1 of auxiliary request 1 before them, which is identical to claim 1 of this auxiliary request, lacked an inventive step. This finding was mainly based on the post-published document (D31) which disclosed that in the presence of 1 molar ammonium sulfate the pegylated human EPO showed a severe loss of protein stability due to a dramatic increase in its hydrodynamic parameters (see document (D31), page 1). As a consequence thereof, the opposition division decided that the problem posed had not been convincingly solved over the whole scope of the claim (see point 4.2 of the decision of the opposition division dated 4 November 2008). This view was shared by the appellant-opponent and respondent 1.

24. The board observes that the feature "stable at room temperature" of claim 1 is to be seen as a result or a technical effect. According to decision G 1/03 (OJ EPO 2004, page 413, point 2.5.2 of the Reasons) "...If a claim comprises non-working embodiments, this may have different consequences, depending on the circumstances.....(i)f an effect is expressed in a claim, there is a lack of sufficient disclosure. Otherwise, i.e. if the effect is not expressed in a claim but is part of the problem to be solved, there is a problem of inventive step ...". In the present case, claim 1 contains such an effect and thus, in line with the criteria set out in the decision G 1/03 (supra), the issue raised in the decision under appeal with respect to Article 56 EPC is, in principle, an issue which is to be addressed under Article 83 EPC. In

addition, the board notes that Article 83 EPC is within the legal framework of the present appeal proceedings since it was raised as a separate ground in the notice of opposition by the opponents (see e.g. notice of opposition of appellant-opponent, dated 14 December 2005, points 2 and 6).

25. The board is satisfied that the requirements of Article 83 EPC are met for the subject-matter of claim 1 for the following reasons. The application as filed does contain several working examples disclosing that the liquid pegylated EPO composition is stable at room temperature over a period of 6 months in the presence of 30, 40, 120 or 140 mM sulfate (see figures 6, 9 and 10, examples 10 and 13). In addition, the use of sulfate as a separate excipient does not exceed a concentration of 63 mM and the application teaches an upper limit of 200 mM sulfate, if used as inorganic anion according to the composition of claim 1 (see page 6, line 19 and page 7, lines 13 to 15 of the application as filed).

26. Hence the application as filed provides a certain number of exemplary alternative compositions falling within the scope of claim 1 rendering it thus clearly reproducible. In addition, it defines criteria for finding appropriate further alternatives by indicating a certain pH range (pH 5.5 to 7.0) and requiring that the composition has to be stable at room temperature which means that it can be stored for a prolonged period of time (i.e. several months) without loosing significant amounts of activity and without a significant degradation. The board notes that the application as filed provides different methods to assess the thermal stability of the human pegylated EPO and its activity (see examples 8, 10, 11 and 13). Hence

the board is satisfied that in the present situation the skilled person can with reasonable efforts test if the claimed composition is still stable at increased sulfate concentrations within the defined pH range and thus has all the relevant information at hand to find further suitable alternatives over the whole scope claimed. In these circumstances the existence of a single non-working embodiment as disclosed in document (D31) is of no harm for the requirements of sufficiency according to established case law (see decision G 1/03, supra, point 2.5.2 of the Reasons).

27. A further objection was raised by the appellant-opponent against the pH range of "5.5 to 7.0" of claim 1 since the application itself allegedly indicated only a suitable pH range of 6.0 to 6.5, if sulfate was used as an inorganic anion (see page 39, lines 10 to 13 of the application as filed).

28. The board cannot concur with the argumentation of the appellant-opponent for the following reasons. The cited passage on page 39 of the application as filed does not disclose that sulfate is in fact unsuitable if used at a pH higher than 6.5 or lower than 6.0 since it compares its suitability against phosphate with reference to figure 6. In this context, it indicates explicitly that sulfate is also suitable at a low pH whereas phosphate in comparison is less suitable at pH 6.2 than at pH 7.5. Consequently, the skilled person reading this passage would rather be taught that phosphate is not suitable at a low pH whereas sulfate is equally suitable at a low and at a higher pH, such as 7.5. This finding is further supported by the data in figure 5 which disclose that sulfate and phosphate have an equally high stabilising effect on liquid pegylated EPO at pH 7.5. Furthermore, the experimental

data of figure 3 disclose that pegylated EPO faces a strong denaturation only at a pH lower than 5.5. These data are obtained without the presence of sulfate since it solely served to assess the mere pH effect on the thermal stability of pegylated EPO (see example 8). However, in view of the data presented in figures 3 and 6, the board is of the opinion that it is credible that the addition of sulfate stabilises the pegylated EPO at a pH of 5.5. In addition, the board notes that neither the appellant-opponent nor any of the respondents have presented any data to the contrary.

29. The board further notes that respondent 1 in its letter dated 4 October 2013 raised additional arguments against the subject-matter of claim 1 with regard to the non solved problem of the composition over the whole scope claimed (see points 2.5 and 2.6). While these objections have been raised under the heading of "inventive step", the board considers them to be rather an issue of sufficiency for the reasons outlined above (see point 24). Respondent 1 pointed out that the contested patent only provided data for a composition according to claim 1 showing a stabilising effect for sulfate at a pH of 6.2 (see formulation "D" of table 3 and column 8 of figure 6). However, the contested patent explicitly stated that a pH of below 6.5 or even 6.2 by itself already stabilised pegylated EPO without adding additional sulfate (see example 9 and figure 7 and 8 of the patent in suit). This rendered its isolated stabilising effect on pegylated EPO questionable, in particular since any control of a pegylated EPO composition at pH 6.2 without sulfate was lacking in the patent in suit.

30. The board cannot agree with this argumentation of the respondent 1 since column 4 and column 7 of figure 6

disclose a pegylated EPO composition at pH 6.2 without sulfate which is - however - in comparison to formulations containing sulfate less stable (see columns 5 and 8 of figure 6). This clearly shows that a low pH by itself only inadequately stabilises liquid pegylated EPO. Moreover, as already mentioned above (see point 28) the application as filed discloses evidence for a stabilising effect of sulfate also at the higher pH of 7.5.

31. In view of the above considerations the board holds that the subject-matter of the present claims is sufficiently disclosed and thus in compliance with the requirements of Article 83 EPC.

Auxiliary request 1 - inventive step

32. Claim 1 relates to a liquid pharmaceutical composition comprising a pegylated human EPO protein, a multiple charged inorganic anion in a pharmaceutically acceptable buffer suitable to keep the solution pH in the range from 5.5 to 7.0, and optionally one or more pharmaceutically acceptable excipients, said liquid composition being stable at room temperature, wherein the anion is a sulfate anion.

Closest prior art

33. For assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the Boards of Appeal apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art. This is generally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most technical

features in common, i.e. requiring the minimum of structural modifications.

34. Both appellants proposed either document (D5) or (D15) as closest prior art. The board considers document (D5) to qualify as closest prior art since it discloses explicitly a liquid pegylated EPO formulation in a phosphate buffer (with phosphate as an inorganic anion) having a longer *in vivo* biological activity than its native non-pegylated form (see page 2, line 5; page 24, lines 15 to 26; page 32, lines 3 to 22). This extended activity seems rather to depend on its higher *in vivo* hydrolysis resistance (see document (D11), page 3, lines 1 to 4, lines 10 to 13 and lines 34 to 38) than on its increased overall stability. Nevertheless, it seems to belong to the common general knowledge at the relevant date that the pegylation of proteins in general results *inter alia* in an increased shelf-live by improving protein stability (see document (D9), page 1, lines 37 to 41). Nevertheless, the board observes that the purpose or aim of document (D5) is silent on any shelf-live stability in particular at room temperature. Document (D15) however, neither uses inorganic anions in its EPO formulations nor mentions any stability issues either *in vivo* or with respect to its storage at room temperature. Consequently, in the board's opinion it does not qualify as the closest prior art in view of the criteria as set out above (see point 33).

The objective technical problem to be solved

35. The formulation of document (D5) essentially differs from the subject-matter of claim 1 in that it uses phosphate as an inorganic anion whereas claim 1 relates to the use of sulfate. Moreover, it is silent on

storage stability. The present invention discloses that only the presence of sulfate anions at room temperature results in stable liquid pegylated EPO formulations that do not show any aggregation. The board sees the objective technical problem to be solved by the present invention as the provision of a stable liquid pegylated EPO formulation at room temperature.

Solution

36. In the board's view the above formulated problem is credibly solved by the subject-matter of claim 1 for the reasons given above in points 25 to 30.

Obviousness

37. Document (D5) provides a liquid pharmaceutical pegylated EPO formulation in a phosphate buffer showing *in vivo* an extended biological activity most probably due to an increased *in vivo* hydrolysis resistance (see point 34, above). The board observes that there is no prior art available which relates explicitly to a stable liquid pegylated EPO at room temperature. In addition, there is no prior art available which discloses a stabilising effect of sulfate anions on liquid EPO either in pegylated or in its native form.

38. For this reason alone the board is satisfied that the prior art does not render the claimed subject-matter obvious to the skilled person.

39. Moreover, even if the skilled person would take the teaching of documents (D26), (D27) or (D30) into account as stated by the appellant-opponent or respondent 1, the board observes that the claimed sulfate was only one of many potential stabilisers the

skilled person could have used but would not have used in view of the lack of any pointers (see document (D26), table 1; document (D27), page S9, column 2, second para., tables I to V; document (D30), page 283, first paragraph). In addition, the teaching of documents (D28) or (D29) does not provide any motivation for the skilled person to select sulfate as a stabiliser because these documents neither refer to a liquid EPO formulation nor use any pegylated EPO. On the contrary, these two documents disclose solid and immobilised EPO particles in a sustained release composition which is mixed with ammonium sulfate to produce aggregation-stabilised EPO particles before lyophilisation (see document (D28), column 11, line 10 to col. 12, line 16; document (D29), column 8, line 55 to column 9, line 27). Consequently, in view of the fundamental difference between the teaching of these two documents and the subject-matter of claim 1, the skilled person when looking for a solution to the problem mentioned above would not have taken their disclosure into account.

40. Consequently, none of the available prior art documents can be interpreted as containing a clear pointer for the skilled person to arrive at the claimed invention. Hence, the board concludes that the subject-matter of claim 1 involves an inventive step (Article 56 EPC).

41. The subject-matter of claims 2 to 43 depends on the subject-matter of claim 1 and is therefore inventive as well. The subject-matter of claims 44, 43 and 46 is considered to be inventive for the same reasons as outlined above for the subject-matter of claim 1.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The case is remitted to the department of first instance with the order to maintain the patent on the basis of the auxiliary request 1 filed on 25 October 2013 and the description and figures to be adapted thereto.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith

Decision electronically authenticated