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# Datasheet for the decision of 6 December 2010

**Case Number:** T 0480/08 - 3.3.04

**Application Number:** 95943452.3

**Publication Number:** 0805822

**IPC:** C07K 14/505

**Language of the proceedings:** EN

**Title of invention:**
Spray dried erythropoietin

**Patentee:**
ORTHO PHARMACEUTICAL CORPORATION

**Opponent:**
F. Hoffmann-La Roche AG

**Headword:**
Spray dried EPO/ORTHO

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

**Keyword:**
"Main request and auxiliary requests 1-10 - added subject-matter (yes)"
"Auxiliary request 11 - added subject-matter (no), sufficiency of disclosure, novelty, inventive step - (yes)"

**Decisions cited:**
T 0823/96, T 0860/00

**Catchword:**
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Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** T 0480/08 - 3.3.04

# D E C I S I O N
**of the Technical Board of Appeal 3.3.04**
**of 6 December 2010**

**Appellant**: (Opponent)
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**Representative**:
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**Decision under appeal:**
**Decision of the Opposition Division of the European Patent Office posted 8 February 2008 rejecting the opposition filed against European patent No. 0805822 pursuant to Article 101(2) EPC.**

**Composition of the Board:**

**Chairman:** C. Rennie-Smith
**Members:** M. Wieser
R. Gramaglia

## Summary of Facts and Submissions

I. An appeal was lodged by the Opponent (Appellant) against the decision of the Opposition Division according to which the opposition against European patent No. 805 822 was rejected (Article 101(2) EPC).

II. The patent application as originally filed (published as WO 96/18 647) contained 14 claims. Claims 1 to 7 referred to a method for preparing spray dried recombinant human erythropoietin (rhEPO), claims 8 to 14 referred to dry rhEPO.

III. Claims 1 and 8 as originally filed read:

"1. A method for preparing spray dried rhEPO, comprising;

a) providing an aqueous solution of rhEPO having a concentration within the range of about 20 mg/ml to about 100 mg/ml;
b) atomizing said solution into a spray;
c) drying said spray with hot drying air in order to evaporate the water from the spray; and
d) separating the dried rhEPO from the drying air.

8. Dry rhEPO produced by the method of Claim 1."

IV. The patent as granted also contained 14 claims. Claims 1 to 3 and 8 to 11 thereof read:

"1. A method for preparing spray dried rhEPO, fragments, analogs or chemically synthesized derivatives thereof, comprising:

a) providing an aqueous solution of rhEPO, fragments, analogs or chemically synthesized derivatives thereof, having a concentration within the range of about 20 mg/ml to about 100 mg/ml;
b) atomizing said solution into a spray;
c) drying said spray with hot drying air in order to evaporate the water from the spray; and
d) separating the dried rhEPO, fragments, analogs or chemically synthesized derivatives thereof, from the drying air,

wherein said rhEPO fragments, analogs or chemically synthesized derivatives thereof, possess the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and to increase haemoglobin synthesis or iron uptake.

2. The method of Claim 1, wherein the aqueous solution of rhEPO, fragments, analogs or chemically synthesized derivatives thereof, contains no salts or other additives.

3. The method of Claim 1, wherein the aqueous solution is dialyzed to remove salts prior to step (b).

8. Dry rhEPO wherein the dry rhEPO comprises less than 2 percent aggregates after 6 months of storage at 5$^{o}$C.

9. The rhEPO of Claim 8 which is 100% EPO (w/w).

10. A spray-dried recombinant human erythropoietin (rhEPO) which has the following formulation:

| | |
|---|---|
| (a) rhEPO | 25%(w/w) |
| (b) Mannitol | 37.5%(w/w) |
| (c) Glycine | 37.5%(w/w) |

wherein the spray dried rhEPO has been obtained by the method of claim 1.

11. The rhEPO of Claim 10, which additionally contains a surfactant."

V. 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) and under Articles 100(b) and (c) EPC.

VI. The Opposition Division decided, inter alia, that claim 8 as granted did not violate the requirements of Article 123(2) EPC (see item (3) of the decision under appeal).

VII. The Opponent (Appellant) filed a notice of appeal dated 28 February 2008. The grounds of appeal were submitted with a letter dated 10 June 2008. The entire statement of grounds of appeal (pages 1 to 37) was concerned with claim 8 as granted and claim 9 dependent thereon. The only exception to this was a short passage, seven lines bridging pages 16 and 17 of the grounds for appeal, which dealt with granted claims 10 and 11.

VIII. The Patent Proprietor (Respondent) submitted its response in a letter dated 22 December 2008 with which it filed ten auxiliary requests, each differing from the claims as granted only with regard to the wording of claim 8.

The Appellant submitted two further letters in the written phase of this appeal, dated 18 September 2009 and 5 October 2010, respectively, which both, solely and exclusively, referred to claim 8 as granted and as contained in Respondent's auxiliary requests 1 to 10.

Finally, with its letter dated 6 October 2010, the Respondent filed auxiliary request 11, which contained 12 claims, corresponding to claims 1 to 7 and 10 to 14 as granted with claims 8 and 9 as granted being deleted.

IX. The Board expressed its preliminary opinion in a communication dated 15 April 2010. Oral proceedings were held on 6 December 2010.

The Appellant requested that the decision under appeal be set aside and that the patent be revoked.

The Respondent requested that the appeal be dismissed or, if not, that the decision under appeal be set aside and that the patent be maintained on the basis of one of auxiliary requests 1 to 10, all filed on 22 December 2008 or of auxiliary request 11 filed on 6 October 2010.

X. Claim 8 of each of Respondent's auxiliary requests 1 to 10 reads as follows:

*Auxiliary request 1*

"Dry rhEPO wherein the dry rhEPO is a stable rhEPO powder which comprises less than 2 percent aggregates after 6 months of storage at 5$^{o}$C."

*Auxiliary request 2*

"Dry rhEPO wherein the dry rhEPO comprises less than 2 percent aggregates after 6 months of storage at 5°C, wherein the aggregate content is determined by Western Blot."

*Auxiliary request 3*

"Dry rhEPO in the form of a composition comprising from 4% (w/w) to 100% (w/w) rhEPO, wherein the dry rhEPO comprises less than 2 percent aggregates after 6 months of storage at 5°C."

*Auxiliary request 4*

"Dry rhEPO in the form of a composition comprising from 4%(w/w) to 100%(w/w) rhEPO and from 3.0% to 5.0%(w/w) residual moisture, wherein the dry rhEPO comprises less than 2 percent aggregates after 6 months of storage at 5°C."

*Auxiliary request 5*

"Dry rhEPO obtainable by spray drying wherein the dry rhEPO comprises less than 2 percent aggregates after 6 months of storage at 5°C."

*Auxiliary request 6*

"Dry rhEPO, obtainable by spray drying according to the method of claim 1, wherein the dry rhEPO comprises less than 2 percent aggregates after 6 months of storage at 5°C."

*Auxiliary request 7*

"Dry rhEPO, obtainable by spray without the addition of stabilizers, wherein the dry rhEPO comprises less than 2 percent aggregates after 6 months of storage at 5°C."

*Auxiliary request 8*

"Dry rhEPO, obtainable by spray drying according to the method of claim 3, wherein the dry rhEPO comprises less than 2 percent aggregates after 6 months of storage at 5°C."

*Auxiliary request 9*

"Dry rhEPO, obtainable by spray drying according to the method of claim 2, wherein the dry rhEPO comprises less than 2 percent aggregates after 6 months of storage at 5°C."

*Auxiliary request 10*

"Dry rhEPO which maintains its biological activity over time, wherein the dry rhEPO comprises less than 2 percent aggregates after 6 months of storage at 5°C."

XI. The submissions made by the Appellant, as far as they are relevant to the present decision, may be summarised as follows:

The application as published disclosed two specific spray dried rhEPO formulations, designated as numbers III and IV, whose ingredients were shown in table I on

page 9. The stability data of these two formulations were given in tables 2 and 3 on page 11 where it was shown that they comprised less than 2% aggregates after 6 months of storage at 5°C (page 10, last paragraph).

Samples of lyophilized rhEPO stored under the same conditions were said to show more than 2% EPO aggregates and were therefore determined to be of poor stability (page 10, lines 23 to 25 and page 12, lines 20 to 22).

The application as published did not contain any information which could serve as a basis for a claim generally referring to dry rhEPO comprising less than 2% aggregates after 6 months of storage at 5°C, which claim was not restricted to the formulations number III and IV.

Samples III and IV referred to specific rhEPO formulations which were characterized by their rhEPO content and by containing specific amounts of different excipients or stabilizers, which had an influence on the stability of the end products. Therefore, the isolation of the specific feature "less than 2% aggregates after 6 months of storage at 5°C" from a set of features which had originally been disclosed in combination for the specific embodiments of samples number III and IV was not admissible under Article 123(2) EPC.

With regard to auxiliary request 11, the Appellant, at the oral proceedings, did not provide any arguments but referred to its written submissions only.

XII. The submissions made by the Respondent, as far as they are relevant to the present decision, may be summarised as follows:

The present invention provided stable rhEPO powder (page 5, line 1 of the application as published). According to lines 2 to 3 on page 5, "stable" meant that the rhEPO maintained its biological activity over time while its structure was maintained in the native state. Aggregates of rhEPO neither showed the biological activity nor the native structure of rhEPO. Accordingly, although the definition of "stable" on page 5 did not expressly refer to aggregates, it was plain that a formulation of rhEPO containing excessive quantities of aggregates was not "stable" within the meaning of the patent.

The acceptable level of aggregates was set out on page 10, lines 23 to 26 of the application as published, where it was said that "the 6 month lyophilized samples showed more than 2% EPO aggregates on SDS-PAGE after reconstitution" and "this indicates instability of the reconstituted rhEPO."

Although the samples referred to on page 10, lines 23 to 26 were lyophilized samples, it was plain that the acceptable level of aggregate formation applied to any rhEPO sample. It would be bizarre if a different level of aggregate formation were acceptable in, for example, a spray dried rhEPO sample. Indeed the "less than 2%" threshold was specifically disclosed in the final paragraph on page 10 in relation to spray dried rhEPO.

Accordingly, it was implicitly disclosed that the "stable" rhEPO referred to on page 5 of the application as published, contained "less than 2% aggregates after 6 months of storage at 5°C."

Considering the Appellant's argument, that the feature "less than 2% aggregates after 6 months of storage at 5°C" has been taken out of its original context and has been combined with others, it was noted that such "intermediate generalization", i.e. the extraction of an isolated feature from an originally disclosed combination and its use to delimit claimed subject-matter, was allowable under Article 123(2) EPC if that feature was not inextricably linked with other features of that combination. As this was presently the case, claim 8 met the requirements of Article 123(2) EPC.

## Reasons for the Decision

*Amendments - Article 123(2) EPC*

*Main request*

1. Claim 8 refers to a dry rhEPO formulation comprising less than 2% aggregates after 6 months of storage at 5°C. The claim is not restricted to spray dried rhEPO.

2. Page 1, lines 6 to 8 of the application as published reads: "**This invention** concerns a method for the preparation of spray dried erythropoietin and the dry erythropoietin powder produced thereby" (emphasis added by the Board; see also page 3, lines 15 to 16).

Page 5, lines 1 to 4 of the published application reads: "The **present invention** provides stable rhEPO powder. As used herein, "stable" means that rhEPO maintains its biological activity over time and its structure is maintained in its native state, i.e. it is not oxidized or otherwise degraded into another chemical species." (emphasis added by the Board).

3. Example 1, starting on page 5 of the application as published, describes "a process of spray drying used to produce amorphous rhEPO exclusively in solid form or in conjunction with inert, pharmaceutically acceptable excipients". Five concentrated aqueous solutions containing different amounts of rhEPO and different amounts of excipients such as mannitol, glycine and/or Tween$^{R}$ 80 were prepared, stored at 5$^{o}$C and finally spray dried (page 6, "Dialysis and concentration"; page 9, table 1). The final solid rhEPO content of the spray dried formulations was 4% (w/w) (numbers I and II), 25% (w/w) (numbers IV and V) and 100% (w/w) (number III) (page 9, last paragraph).

4. As a comparison, formulations I, II and II were also lyophilized according to the method described in comparative example 2 (starting on page 11 of the published application).

5. It was found that "the spray dried rhEPO of the present invention has advantages over lyophilized rhEPO" in terms of stability (page 10, lines 19 to 20 and page 12, last sentence to page 13, line 2). By using Western blot analysis, described on page 8, second paragraph, the content of aggregates in some of the spray dried formulations and in the lyophilized "comparative"

formulations was determined after 6 months of storage at 5°C. A high content of aggregates which did not have the biological activity of native rhEPO indicated instability. The data obtained from the lyophilized "comparative" formulations all showed more than 2% aggregates after 6 months of storage at 5°C. They were determined to have poor stability (page 10, lines 23 to 25, page 12, lines 20 to 24 and table 4). The data of stability tests of spray dried formulation numbers III and IV are shown in tables 2 and 3 on page 11. In both cases the samples, after 6 months of storage at 5°C, comprised less than 2% aggregates (page 10, lines 28 to 31).

6. The Respondent argued, that according to page 5, lines 2 to 5 of the published application, "stable" meant that the rhEPO maintained its biological activity. Aggregates were not biologically active. Therefore, a formulation containing elevated levels of aggregates was not "stable". The threshold by which it could be defined whether a dry rhEPO formulation was stable or not lay at 2%. It was clear from the disclosure on page 10, lines 23 to 30 and page 12, lines 20 to 22 of the published application that formulations which comprised less than 2% aggregates after 6 months of storage at 5°C were stable while formulations comprising more than 2% aggregates after storage were instable.

This argument, in the Respondent's opinion, serves to substantiate the view that the term "stable" when used in the patent in combination with a dry rhEPO formulation, like for instance on page 5, line 1, implicitly discloses that the formulation comprises less than 2% aggregates after 6 months of storage at 5°C.

If the Board followed this argument, claim 8 of the main request would meet the requirements of Article 123(2) EPC.

7. The decisive question to be answered under Article 123(2) EPC is whether there is a clear and unambiguous disclosure of the subject-matter of claim 8 in the application as published. Applying the established yardstick to be used in the framework of Article 123(2) EPC, such disclosure may be explicit or implicit. Implicit disclosure includes what any person skilled in the art would consider necessarily implied by the patent application as a whole (see T 860/00 of 28 September 2004, point 1.1). The term "implicit disclosure" relates to matter which is not explicitly mentioned in a document, but which is a clear and unambiguous consequence of what is explicitly mentioned and which therefore forms part of the disclosure content of this document (decision T 823/96 of 28 January 1997, point 4.5).

8. The application as published refers three times to an aggregate concentration of 2% after six months of storage at 5$^{o}$C (on page 10, lines 23 to 25 and lines 29 to 31 and on page 12, lines 20 to 22; see point (5) above).

9. It is established practice, that, when drafting an application, an Applicant has the right to choose the definitions of terms used therein and to have its own lexicography.

This is exactly what the Applicant, now Respondent, did in the present case. Immediately after stating that "the

present invention provides stable rhEPO powder" (page 5, line 1) a definition of the term "stable" is given. However, this definition does not disclose that "stable" means less than 2% aggregates after six months of storage at 5°C, rather it refers to the maintenance of the biological activity and of the native structure of rhEPO.

10. Neither the patent in suit, whether in the passage on page 5 referred to above or in any other passage, nor any of the cited prior art documents discloses that the term "stable" when used for defining a dry rhEPO formulation has the implicit meaning, in the sense of the established case law of the Boards of Appeal (see point (9) above), that the formulation comprises less than 2% aggregates after 6 months of storage at 5°C.

11. Accordingly, the disclosure on page 5, lines 1 to 4, when read in combination with the disclosure on pages 10 and 12 of the application as published does not form a basis for claim 8 of the main request.

In conclusion, the patent according to the main request, and in particular claim 8 thereof, has been amended in such a way that it contains subject-matter which extends beyond the content of the application as filed, contrary to the requirements of Article 123(2) EPC.

*Auxiliary requests 1 to 4*

12. Claim 8 of each of these auxiliary requests refers to dry rhEPO and is not restricted to spray dried formulations.

For the same reasons given in points (7) to (11) above with regard to claim 8 of the main request, claim 8 of each of auxiliary requests 1 to 4 also does not meet the requirements of Article 123(2) EPC.

*Auxiliary requests 5 and 6*

13. Claim 8 of auxiliary request 5 refers to dry rhEPO obtainable by spray drying; claim 8 of auxiliary request 6 refers to dry rhEPO obtainable by spray drying according to the method of claim 1 (see section (VIII) above).

14. The Respondent argued that the application as published on page 10, lines 28 to 31 and in tables 2 and 3 explicitly disclosed that spray dried formulations comprised less than 2% aggregates after six months of storage at 5°C. These formulations were prepared according to the method of example 1, which was the subject-matter of claim 1.

Although this feature was disclosed in combination with two specific embodiments of the application only, namely formulation numbers III and IV, the "intermediate generalization" of this feature, i.e. its extraction from an originally disclosed combination and its use to delimit claimed subject-matter, was allowable under Article 123(2) EPC, as this feature was not inextricably linked with other features of that combination.

15. The Boards of Appeal have, in a considerable number of decisions, already considered situations where an amendment concerns taking features out of their initial

context and combining them with others. The crucial issue to decide was under what conditions the resulting amendments fulfilled the requirements of Article 123(2) EPC (see Case Law of the Boards of Appeal of the EPO, 6th edition, 2010, chapter III.A.2).

The case law can be summarised by saying, that it was normally not permissible under Article 123(2) EPC to extract isolated features from a set of features originally disclosed for a specific, preferred embodiment. That kind of amendment would only be justified in the absence of any clear recognisable functional or structural relationship among these features.

16. Formulations number III and IV are two out of five spray dried examples disclosed in example 1 of the application as published underlying the patent in suit. As already mentioned in point (3) above, these five formulations are prepared from five concentrated aqueous solutions containing different amounts of rhEPO (from 4 to 100% (w/w)) and different amounts of the "excipients" mannitol, glycine and Tween® 80. They were stored at 5°C and finally spray dried according to a method falling within the scope of claim 1. That spray drying method is described in claim 1 in generic terms in the form of a fundamental technical description of the technique of spray drying (see section (III) above).

17. The influence of the "excipients" contained in the rhEPO formulations on their stability is the subject-matter of page 10, lines 10 to 14 of the published application, which read: "It was determined that Tween® 80 was not necessary to produce stable spray dried

rhEPO by comparing stability data on formulations I and II and formulations IV and V. Also, the 6 month stability data on pure rhEPO [i.e. formulation III] suggests that mannitol and/or glycine may not be necessary for producing stable spray dried rhEPO." (insert added by the Board).

On page 13, lines 2 to 5 of the application as published, cyclodextrins, glycine, mannitol and Tween® 80 are designated as being "excipients or stabilizers" and it is said that the present invention provides stable spray dried rhEPO which can be prepared without the addition of any of these substances.

18. The application as published discloses one single formulation not containing any "excipient", namely formulation number III, which contains 100% (w/w) rhEPO. The stability data for this formulation which prove that it comprises less than 2% aggregates after six months of storage at 5°C are shown in table III.

The only other formulation for which the application as published contains stability data showing the same effect, is formulation number IV, containing 25% (w/w) rhEPO and in addition considerable amounts of glycine and mannitol, but no Tween® 80.

The published application does not contain any stability data for formulations number I, II and IV. Thus, there are, for example, no data proving that formulations with a rhEPO content below 25% (w/w), either with or without "excipients", meet the stability criteria set out in claim 8.

19. In the light of the experimental design of example 1, and the statements on page 10, lines 10 to 14 and on page 13, lines 2 to 5 of the published application (see point (21) above), the Board is of the opinion that the stability of a spray dried formulation, defined by its content of aggregates after six months of storage at 5°C, is a technical feature of this formulation which has a clear recognisable functional or structural relationship with the rhEPO content and "excipient" (stabilizer) concentration of the aqueous solution before spray drying.

Therefore, the feature "less than 2% aggregates after six months of storage at 5°C" which is disclosed on page 10, lines 28 to 31 and in tables 2 and 3 of the application as published, for two spray dried formulations prepared from specific aqueous solutions having a defined rhEPO and "excipient" content, cannot be taken out of its initial context and generalized in a claim without violating the requirements of Article 123(2) EPC.

20. Neither is there a basis in the application as published for any kind of spray dried formulation having this feature, nor for any kind of formulation spray dried according to the method of claim 1, which formulations are different from formulations number III and IV.

Claim 8 of auxiliary request 5, as well as claim 8 of auxiliary request 6, do not meet the requirements of Article 123(2) EPC.

*Auxiliary requests 7 to 10*

21. In none of these auxiliary requests claim 8 is restricted to formulations III and IV.

For the same reasons given in points (20) to (24) above with regard to claim 8 of the fifth and sixth auxiliary requests, claim 8 of each of auxiliary requests 7 to 10 also does not meet the requirements of Article 123(2) EPC.

*Auxiliary request 11*

22. Claims 1 to 12 of this request correspond to claims 1 to 7 and 10 to 14 as granted (present main request). Claims 8 and 9 have been deleted.

23. At the oral proceedings before the Board the Appellant did not make any submissions with regard to the subject-matter of the claims of this request, but referred to its written submissions only.

Appellant's written submissions consist of three letters, dated 10 June 2008 (grounds of appeal), 18 September 2009 and 5 October 2010, respectively.

With the only exception of point (2.2) on pages 16 to 17 of the grounds of appeal, which deals with claims 10 and 11 as granted (claims 8 and 9 of auxiliary request 11), the three letters submitted by the Appellant refer solely and exclusively to claims 8 and 9 as granted, thus the two claims which are no longer contained in auxiliary request 11.

24. In item (2.2) of the grounds of appeal the Appellant objected that claims 10 and 11 as granted, contrary to claims 10 and 11 as originally filed, did not refer back to the method of claim 1 and did not therefore meet the requirements of Article 123(2) EPC.

The Board does not agree. Claim 10 as granted, which is identical to claim 8 of auxiliary request 11, refers to spray dried rhEPO defined by its rhEPO-, mannitol- and glycine-content which "has been obtained by the method of claim 1."

Thus, claim 8 and dependent claim 9 of auxiliary request 11 are clearly restricted to products obtained by the method of claim 1. Appellant's objection in this respect is without merit.

25. The Appellant did not put forward any other formal objections under Articles 84, 123(2) of 123(3) EPC with regard to the claims of auxiliary request 11. It did not contest sufficiency of disclosure (Article 83 EPC), novelty (Article 54 EPC) or the presence of an inventive step (Article 56 EPC).

The Board has no reason to raise any of these issues of its own motion.

26. Consequently, claims 1 to 12 of auxiliary request 11 are found to meet the requirements of the EPC.

## Order

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

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of claims 1 to 12 of auxiliary request 11 filed on 6 October 2010 and the description as granted.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith