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D E C I S I O N
of 21 April 1997

Case Number: T 0749/94 - 3.3.4

Application Number: 86900400.2

Publication Number: 0209539

IPC: C07K 7/10

Language of the proceedings: EN

Title of invention:
Homogeneous Erythropoietin

Patentee:
Genetics Institute, Inc.

Opponent:
Janssen-Cilag GmbH
Kirin-Amgen Inc.

Headword:
Erythropoietin/GENETICS INSTITUTE

Relevant legal provisions:
EPC Art. 123(2), 84, 52(1), 57

Keyword:
"Not susceptible of industrial application - new ground of opposition not considered"
"Main request - added subject-matter (yes)"
"First, second and third auxiliary requests - clarity (no)"

Decisions cited:
G 0001/95, G 0007/95, T 0260/85, T 0412/93, J 0004/85

Catchword:
To assess whether the requirements of Article 123(2) are fulfilled it may be necessary if the application as filed does not contain an expressis verbis disclosure of the amendment introduced into the claim to examine in a first step whether the subject-matter of the amended claim fulfils the requirements of Article 84 EPC.

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Case Number: T 0749/94 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 21 April 1997

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 19 August 1994 concerning maintenance of European patent No. 0 209 539 amended form.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
J. Saisset
L. Galligani
S. C. Perryman

Summary of Facts and Submissions

I. European patent No. 0 209 539 (application No. 86 900 400.2) relating to "Homogeneous erythropoietin" was granted on international application PCT/US85/02358 filed on 27 November 1985 (published as WO 86/04068) claiming priority from US application 690,853 of 11 January 1985, for ten Contracting States with three claims and two claims for AT.

Claim 1 was directed to a process for purifying erythropoietin (Epo) of natural origin. Claims 2 and 3 read:

"2. Homogeneous erythropoietin, characterized by:
a) movement as a single peak on a reverse phase-HPLC;
b) a molecular weight of about 34,000 daltons on SDS-PAGE; and
c) a specific activity of about 160,000 IU per absorbance at 280 nm.

"3. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogeneous erythropoietin of claim 2 in a pharmaceutically acceptable vehicle.

The two claims for AT corresponded to claims 1 and 2 for the other non AT Contracting States.

II. Amongst the more than one hundred documents which were filed and referred to by the parties during opposition and appeal proceedings, the following are considered by the Board in the present decision:

(1) Miyake et al., J.Biol.Chem., Vol.252, pages 5558 to 5564, (1977),

(4) EP-A-0 148 605,

(7) Declaration of Dr.Eugene Goldwasser dated 28 January 1993,

(16) Sasaki et al., J.Biol.Chem., Vol.262, pages 12059 to 12076, (1987),

(19) Goldwasser et al., Endocrinology, Vol.97, pages 315 to 323, (1975),

(25) Krumvieh in 20th Congress on Cytokines, Develop.biol.Standard, Vol.69, pages 1 to 22, (1987),

(31) Egrie at al., Immunobiology, Vol.172, pages 213 to 224, (1986),

(38-1) Excerpts from Volume 1.3 of Chugai Pharmaceutical Co. Ltd.'s FDA Notice of Claimed Investigational Exemption for a New Drug (District Court's Exhibit PX812)

(56) WO 86/03520,

(68) Storring et al., J.Endocrinology, Vol. 134, pages 459 to 484, (1992),

(69) Imai et al., J.Biochem., Vol.107, pages 352 to 359, (1990),

(92) Shimizu et al., Expt.Cell Biol., Vol.54, pages 225 to 233, (1986).

III. Notices of opposition were filed against the European patent by two parties. Revocation of the patent was requested on the grounds of Articles 100(a) EPC (lack of novelty and inventive step), Article 100(b)EPC (insufficient disclosure) and 100(c) EPC (extension beyond the content of the application as filed).

IV. On 19 August 1994, the Opposition Division issued an interlocutory decision within the meaning of Article 106(3) EPC whereby the patent was maintained in an amended form on the basis of an auxiliary request for the non-AT States which contained one claim reading as follows:

"A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of homogeneous erythropoietin characterized by:

(a) movement as a single peak on a reverse phase-HPLC;

(b) a molecular weight of about 34,000 daltons on SDS-PAGE; and

(c) a specific activity of about 160,000 IU per absorbance at 280 nm

in a pharmaceutically acceptable vehicle."

The Opposition Division considered that the amended claim was clear (Article 84 EPC) as the skilled person would not take its wording literally but would understand (c) as being "a specific activity of 160,000 International in vivo EPO Units per absorbance Unit at 280 manometers, the error range of the activity being about +/- 20 to 30%" (see decision of the Opposition Division, page 23, paragraph 1.4.4).

The invention of this claim was found sufficiently disclosed, even if understood as comprising both uEpo (Epo derived from urine) and rEpo (Epo derived by recombinant DNA technology), because one example had been provided how to prepare the claimed Epo and the Opponents had failed to show that by following this example the claimed Epo could not be obtained.

Novelty was acknowledged over documents (1),(4) and (56).

The closest prior art document was identified as document (1). The underlying technical problem was to be seen as the provision of a new and repeatable method of obtaining an Epo preparation with the defined specific activity, the product being for the intended use in a pharmaceutical.

The provided solution was a process which could not have been derived in a straightforward manner from the state of the art and was, thus, inventive. The pharmaceutical preparation itself derived inventive step from the inventive step of said process.

V. Both Opponents (Appellants I and II) lodged an appeal against the decision of the Opposition Division, paying the appeal fee at the same time. Statements of grounds of appeal were submitted.

VI. The Respondent (patentee) filed a reply.

VII. In a letter dated 15 April 1996 in reply to the Respondent's submissions, Appellant I argued for the first time that the invention did not fulfil the requirement of Article 52(1) EPC that a patent shall only be granted for an invention which is susceptible of industrial application. It was obvious that the minimal quantities of uEpo available after extreme labourious purification from the urine of patients suffering from aplastic anemia (which urine itself was not a commercially available source) would never allow the industrial manufacture of a pharmaceutical composition (cf. decision T 412/93 of 21 November 1994, point 148).

VIII. The Board issued a communication pursuant to Article 11(2) of the rules of procedure of the Boards of appeal, setting out the Board's provisional position.

IX. In reply thereto, the Respondent and both Appellants filed further submissions.

X. Oral proceedings were held on 5 and 6 February 1997. At these proceedings, the Respondent submitted three auxiliary requests consisting of a single claim each. For auxiliary request I, the claim was the same as the claim upheld by the Opposition Division except for feature (c) which read (emphasis by the Board):

(c) a specific activity of **about but at least** 160,000 IU per absorbance at 280 nm in a pharmaceutically acceptable vehicle.

For auxiliary request II, the single claim was the same except for feature (c) which read:

(c) a specific activity of 160,000 IU per absorbance at 280 nm.

For auxiliary request III, the single claim was again the same except for feature (c) which read (emphasis by the Board):

(c) a specific activity **in vitro** of 160,000 IU per absorbance at 280 nm.

After a short discussion on allowability the first and second auxiliary requests were refused because the Board considered them prima facie unallowable.

XI. At the end of oral proceedings, the Chairwoman gave the following decision:

1. The decision under appeal is set aside.

2. The main request and the first and second auxiliary requests are refused.

3. The Board closes the debate on the third auxiliary request on the issues regarding Article 123, Article 84, Article 83 and novelty over D56.

4. The proceedings before the Board will be continued in writing either by issuing by the 21 April 1997 the final decision on the third auxiliary request on the basis of the submissions made so far or by issuing a communication setting out a time limit for further submissions by the parties on the remaining issues.

XII. The arguments submitted by the Appellants in writing and during oral proceedings can be summarized as follows:

Main request; *Article 123(2)EPC*

Four lines of arguments existed why the requirements of Article 123(2) were not fulfilled:

- Firstly, the claimed specific activity of **about** 160,000 IU (i.e possibly below 160,000 IU) was never disclosed in the original application which only mentioned a specific activity of **at least** 160,000 IU (i.e. of 160,000 IU and above).

- Secondly, the value of about 160,000 IU could not implicitly be derived from the facts that the Epo coming out of the hydroxylapatite column had a specific activity of 83,000 IU and had been made twice as pure (i.e. allegedly of about 160,000 IU) after HP-RPLC, as obtaining a two fold purification did not mean that the purified sample contained twice as much Epo protein but rather that it contained twice as little contaminants.

- Thirdly, in the patent specification, the specific activity of Epo was measured in vitro. On the other hand, the claim being addressed to a pharmaceutical preparation of Epo, the specific activity had to be understood as measured in vivo. The likelihood of the in vivo and in vitro measurements of specific activity being the same depended on the amount of sialidases originally present in the sample and remaining throughout purification. There was no evidence that the sialidases had been destroyed by the method disclosed in the patent in suit (heat treatment 5' at 80°C). In fact, document (92) showed that after such a heat treatment, 20% of sialidases remained present in the sample. Therefore, the application as filed did not disclose the claimed pharmaceutical preparation with an (in vivo) specific activity of about 160,000 IU.

- Fourthly, the Respondent had attempted to justify the value of about 160,000 IU by reference to the priority document. The case law of the EPO (T 260/85 OJ EPO 1989,105) was clear that "For the purpose of Article 123(2) EPC, the content of the application as filed does not include any priority documents, even if they were filed on the same day

as the European patent application". Whichever specific activity was disclosed in the priority document was thus irrelevant.

Auxiliary request 3; Articles 123(3) and 84 EPC

- The change to an in vitro specific activity amounted to an enormous broadening of the claim since it now covered Epo with an in vitro specific activity of 160,000 IU and any in vivo specific activity from 0 to 160,000 IU.

  The value of 160,000 IU was unclear per se if only because no information had been provided on which in vitro assay had been used.

- There was no support for the claim in the description because only an in vivo activity made sense in the context of a pharmaceutical preparation. Thus, only if there had been a clear indication in the specification that the assay to be carried out on the therapeutic substance was an in vitro assay, could there have been support for the claim.

XIII. The Respondent replied as follows:

Main request; Article 123(2) EPC

The amendment "about 160,000 IU" was fairly based on the application as filed on the basis of the foregoing considerations:

- Firstly, the disclosure of a specific activity of **about** 160,000 IU was to be understood as the

disclosure of a specific activity of 160,000 IU because the uncertainties linked to any biological means of measurement made this latter figure intrinsically unprecise.

- Secondly, a basis for the figure of 160,000 IU could be found on pages 8 and 9 of the application as filed where it was disclosed that the Epo coming out of the hydroxylapatite column had a specific activity of 83,000 IU and that it was twice as pure after the RP-HPLC column. These data could not but mean that after RP-HPLC, the Epo had a specific activity of 83 000 IU x 2. Thus, the original application disclosed, albeit indirectly, an Epo with a specific activity of about 160,000 IU.

- Thirdly, it was generally accepted by scientific experts (including those of both parties) that the specificity of pharmaceutical compositions had to be understood in terms of in vivo units. In document (1) (Miyake), the same specific activities were obtained in vivo and in vitro for the Epo coming out of the hydroxylapatite column. As the present patent made use of a "Miyake type" procedure to purify the Epo, it necessarily meant that the specific activity of 83,000 IU determined in vitro for the Epo coming out of the hydroxyapatite column had to be the same in vivo. And since the Epo coming from the RP-HPLC column was twice as pure as that resulting from the hydroxylapatite column it must have a specific activity of about 160,000 in vivo IU.

  Documents (7), (31), (69) also showed that the same values for the specific activity of Epo could be obtained in vitro and in vivo. On the other hand, document (68) which disclosed Epo specific

activities determined in many different laboratories by many different methods, was not suited to assess whether the purification process of "Miyake" was carried out in such a manner that in vivo and vitro measurements of specific activity would give the same results.

- Fourthly, it was stated in decision J 4/85 (Headnote II) (OJ EPO 1986,205) that "the priority document was an important element in establishing the applicant's intention and must be taken into consideration even if it was not filed with the European patent". The priority document of the patent in suit disclosed an Epo with a specific activity of preferably 160,000 IU. It was, thus, to be understood that the original specification intended to disclose an Epo with a specific activity of about 160,000 IU.

Auxiliary request 3; Articles 123(2)(3) and 84 EPC

- Support for the claim was found in the original patent specification which disclosed the specific activity of the Epo as being **at least** 160,000 IU and the assays used to determine the specific activity as being in vitro. The "at least" feature evidently included a specific activity of 160,000 IU straight.

- There was no unclearness and no extension of the protection conferred because the person skilled in the art would know that the disclosed in vitro specific activity of 160,000 units had to be the same in vivo. So the claim was also directed to a pharmaceutical preparation with an in vivo activity of 160,000 units.

XIV. The Appellants requested that the decision under appeal be set aside and that the European patent No. 0 209 539 be revoked.

XV. The Respondent requested as main request that the appeal be dismissed and that the patent be maintained as upheld by the Opposition Division, or as auxiliary request that the decision under appeal be set aside and that the patent be maintained on the basis of the first or second or third auxiliary request submitted at the oral proceedings on 5 February 1997.

XVI. The decision on the third auxiliary request was communicated to the parties in writing by telefax on 21 April 1997.

Reasons for the Decision

Susceptible of industrial application (Articles 52(1) and 57 EPC)

1. In the course of appeal proceedings, Appellant I argued (see point VII above) that the invention lacked industrial application. In view of the Decisions of the Enlarged Board of Appeal G 1/95 (OJ EPO 1996, 615) and G 7/95 (OJ EPO 1996, 626), the present Board considers that this argumentation is based on a new ground of opposition and decides not to pursue the matter any further.

Article 123(2) EPC; main request

2. The now claimed Epo is said to have a specific activity of **about 160,000 IU** per absorbance at 280 nm. The application as filed discloses an Epo with a specific activity of **at least** 160,000 IU (page 3, line 23) or **at**

least 120,000 IU (page 3, line 22). A specific activity of about 160,000 IU clearly includes specific activities below the value of 160,000 IU whereas a specific activity of at least 160,000 IU excludes such values. Both figures cannot thus have the same meaning. A specific activity of at least 120,000 IU comprises any specific activity of 120,000 IU and above, without any limit. This is yet again in contrast with a specific activity of about 160,000 IU which covers any values around 160,000 IU, within a certain limit. Accordingly, the initial disclosure of a specific activity of at least 160,000 IU or at least 120,000 IU does not amount to an unambiguous disclosure of the now claimed specific activity.

3. The originally filed application (page 8, line 20 and Figure 1) also discloses that the Epo coming from the hydroxylapatite column (penultimate step in the purification procedure) has a specific activity of 83,000 IU and that a further RP-HPLC purification step carried out on this Epo enables the recovery of 50% Epo and 50% impurities. There is no evidence that the specific activity of this last Epo was ever tested but the Respondent submitted that the person skilled in the art would understand from the purification data (Figure 1) that the Epo initially loaded on the RP-RPLC column had to be 50% pure and that, therefore, after purification on RP-HPLC, it must have had twice the initial specific activity of 83,000 IU, i.e. a specific activity of about 160,000 IU.

4. In the Board's view, the conclusion drawn by the Respondent could only be reached if evidence existed that no contaminating proteins had remained in the column. This evidence is not forthcoming. The situation is further confused by the fact that the patent specification also describes the Epo eluted from the RP-HPLC column as about twice as pure as the Epo eluted

from the hydroxylapatite column (page 9, line 30). This statement seems to imply that half of the amount of impurities present in the Epo preparation after the hydroxylapatite column purification step has been separated from the Epo during the RP-HPLC purification step. This, of course cannot mean that the Epo coming out of the RP-HPLC column would have twice its initial specific activity. Thus, the Board does not consider that the specification of the application as filed constitutes unambiguous and straightforward evidence for the recovery of an Epo with a specific activity of about 160,000 IU.

5. The Respondent has also drawn the Board's attention to the priority document which discloses an Epo with a specific activity of 160,000 IU straight. In his view, this indicated that an Epo with a specific activity of about 160,000 IU was intended since the inherent variability of biological assays made both figures indistinguishable. The Board, however, sees no reasons to depart from the well established case law of the EPO (T 260/85, supra)) that "For the purpose of Article 123(2) EPC, the content of the application as filed does not include any priority documents..." and, therefore, does not consider that the disclosure of a specific activity of 160,000 IU in the priority document should be taken into account.

6. There is no basis in the application as filed for a specific activity of about 160,000 IU per absorbance unit. The main request is rejected as the requirements of Article 123(2) are not fulfilled.

First auxiliary request

Articles 123(2) and 84 EPC.

7. This request contains an amended claim and, thus, it is necessary to check that the requirements of Articles 123(2)(3) and 84 EPC are fulfilled.

8. Feature (c) of the claim of auxiliary request 1 reads (emphasis added):

"a specific activity of **about but at least** 160,000 IU per absorbance at 280 nm"

9. There is no expressis verbis disclosure in the application as filed of this specific activity (see point 3, supra). Thus, a substantive analysis of the technical teaching of the application as filed is required to determine whether or not the subject-matter of the claim can be derived from said application in a direct and unambiguous way. This analysis can only be performed if it is clear what the claim means. Thus, before assessing compliance with Article 123(2) EPC, the Board investigates whether the claim is clear.

10. All parties argued before the Board that only an in vivo specific activity made sense for a pharmaceutical, and that, therefore, part (c) of the claim had to be relating to a specific activity determined by in vivo assays.

11. The description as originally filed does not refer to the production of a pharmaceutical composition but rather to making homogeneous Epo. The quantification of Epo is said to be carried out by in vitro assays

(page 9, lines 13 to 16). The commentary to Table 2 provides the statement that "only this RP-HPLC fraction of about 34,000 MW showed any significant biological activity in vitro".

12. The claim does not specify the type of assays used to determine the specific activity. Thus, there is an internal inconsistency in that although it would be understood that the specific activity ought to have been measured in vivo, it could be taken from the patent application that it was measured in vitro.

13. Many documents (i.e. documents (16), (19), (25), (38-1)) have been filed where the relationship between in vivo and in vitro specific activities is discussed. From these documents it can be concluded that the in vivo and in vitro specific activities of an Epo extracted from a urine sample will **never** be the same unless specific steps are taken to eliminate the sialidases enzymes at the beginning of the purification procedure. It is, thus, the Board's view that expressing the specific activity of Epo in terms of units per absorbance at 280 nm without specifying the assay used to obtain this value is not clear within the meaning of Article 84 EPC, which serves the purpose of giving guidance to the competitors to know what they can do without infringing the claim.

14. The Respondent has submitted that the in vivo specific activity would within the limits of experimental error be the same as the in vitro activity. Yet the patent specification does not provide any evidence that the sialidases would have been entirely eliminated by the procedure disclosed in the patent specification. None of the cited documents where the in vivo and in vitro specific activities were found to be identical describes the exact same procedure. If taken at its face value, document (92) would imply that 20% of the

sialidases should have remained in the sample which would mean that the in vivo and in vitro activities could not be the same.

15. The patent specification does not provide any evidence that the purification process was conducted in such a way that the in vivo and in vitro activities would be identical. The Board believes that the reciting of the specific activities as in the claim of auxiliary request 1, i.e. without specifying the nature of the assay does not help resolve the internal inconsistency of said claim (see point 12, supra).

16. The first auxiliary request is rejected for lack of clarity (Article 84 EPC).

Second auxiliary request

Articles 123(2) and 84 EPC

17. Feature (c) of the claim of auxiliary request II reads:

"a specific activity of 160,000 IU per absorbance at 280nm".

There again, there is no expressis verbis disclosure of such an activity in the application as originally filed (see point 3, supra). The reasoning with regard to Article 84 EPC is the same as presented in points 11 to 16 with regard to auxiliary request I and leads to the same conclusion that the request must be rejected for lack of clarity.

Third auxiliary request

Article 123(2) EPC

18. Feature (c) of the claim of this auxiliary request reads:

(c) a specific activity **in vitro** of 160,000 IU per absorbance at 280 nm.

References in the original description to specific activities of homogeneous Epo are to specific activities measured in vitro (page 9, lines 13 to 16). The specific activity of homogeneous Epo was given as at least 160,000 IU (page 3, lines 23 to 25). To the Board, this means that the originally disclosed homogeneous Epo had an in vitro specific activity of at least 160,000 IU. Accordingly, the originally disclosed pharmaceutical composition comprising the homogeneous Epo is understood as having an in vitro specific activity of 160,000 IU and above. Thus, the subject-matter of the claim of the third auxiliary request was already disclosed in the application as filed and the requirements of Article 123(2) are fulfilled.

Article 123(3) EPC

19. Restricting the claimed pharmaceutical composition to a preparation having a specific activity of 160.000 IU implies that the claim covers any such preparations irrespective of their in vivo specific activity. The Board has doubts whether it was also the case for claim 3 as granted which, by virtue of its dependency on claim 2 relates to a pharmaceutical composition containing an Epo obtained by the specific process given in the patent specification i.e. which could possibly always retain the same specific correlation between its in vivo and in vitro specific activity.

However, in view of its findings with regard to Article 84 EPC, the Board need not reach a decision on this particular point.

Article 84 EPC

20. The question to be dealt with at this point is whether specifying that the measurement of the specific activity has been carried out in vitro is sufficient for an unambiguous characterisation of the claimed product, so that the scope of the claim is clear.

21. Document (68) is of relevance in this context as it compares the specific activities of human urinary Epo (Table 4, EPO-A, EPO-B) measured by no less than six different in vitro bioassays. The authors find that four of the assays including the 3H-thymidine (MSC) assay give essentially the same result (Table 4, last line). The CFUe and the receptor assays are not put in the same category as they do not provide a measurement of the specific activity of Epo on the same scale as the other four assays. For a given preparation, the CFUe assay leads to values of specific activity which may be up to four times higher. It would therefore appear that the significance of any in vitro specific activity very much depends on the assay used.

22. The patent specification indicates that the Epo is quantified by either the 3H-thymidine assay or the CFUe assay. Following the principle that the claims should be read in the light of the description, the Board is prepared to accept that the claim refers to a specific activity of 160,000 IU as measured by one of these two assays. Yet, as already mentioned above, both the 3H-

thymidine and the CFUe assays give results which are not in any way comparable. Thus, the conclusion must be reached that it is impossible to figure out which Epo is actually being claimed.

23. At this point, the Board would like to remark that it is customary if not compulsory, when scientific features are defined by numbers, to mention the assay which led to these numbers. This is even illustrated by the claim itself since feature (b) which specifies the molecular weight of Epo as being 34,000 daltons also mentions that this molecular weight was arrived at by SDS-gel electrophoresis.

24. The claim is unclear. The third auxiliary request is rejected as it does not fulfil the requirements of Article 84 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar:

D. Spigarelli

The Chairwoman:

U. Kinkeldey