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D E C I S I O N
of 26 June 2003

Case Number: T 0787/00 - 3.3.4

Application Number: 90311193.8

Publication Number: 0428267

IPC: C07K 14/00

Language of the proceedings: EN

Title of invention:
Erythropoietin isoforms

Patentee:
Kirin-Amgen, Inc.

Opponent:
Gruppo Lepetit S.p.A.

Headword:
Erythropoietin/KIRIN-AMGEN

Relevant legal provisions:
EPC Art. 52(4), 54, 56, 83, 114, 123(2)(3)

Keyword:
"Admissibility of late-filed documents/amended claims into the proceedings - (yes)"
"Extension of subject-matter (no)"
"Extension of protection - (no)"
"Sufficiency of disclosure - (yes)"
"Method of treatment - (no)"
"Novelty - (yes)"
"Inventive step - (yes)"

Decisions cited:
-

Catchword:
-

Case Number: T 0787/00 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 26 June 2003

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 22 May 2000 concerning maintenance of European patent No. 0428267 in amended form.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: A. L. L. Marie
V. Di Cerbo

Summary of Facts and Submissions

I. European patent EP-0 428 267 with the title "Erythropoietin isoforms" was granted on the basis of a set of 29 claims for the contracting states AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL and SE, of which claims 1, 8, 9, 14 and 20 to 25 read:

"1. An isolated biologically active erythropoietin isoform having a single isoelectric point and having a specific number of sialic acids per erythropoietin molecule, said number being selected from the group consisting of 1 to 14."

"8. A pharmaceutical composition comprising a therapeutically effective amount of said erythropoietin isoform of Claim 1 and a pharmaceutically acceptable diluent, adjuvant or carrier."

"9. A composition consisting essentially of two or three erythropoietin isoforms according to Claim 1."

"14. Erythropoietin consisting essentially of biologically active erythropoietin molecules having an identical number of sialic acids per molecule, said number being selected from the group consisting of 1 to 14."

"20. A pharmaceutical composition comprising a therapeutically effective amount of erythropoietin of Claim 14 and a pharmaceutically acceptable diluent, adjuvant or carrier."

"21. A method of preparing an erythropoietin isoform according to Claim 1 comprising the steps of: subjecting a purified erythropoietin to preparative isoelectric focusing, and eluting a single isoform from the gel."

"22. A method of preparing a mixture of erythropoietin isoforms having a predetermined number of sialic acids per molecule, said number being greater than 11, comprising subjecting material containing erythropoietin to ion exchange chromatography."

"23. A method of preparing a mixture of erythropoietin isoforms having a predetermined number of sialic acids per molecule, said number being greater than 11, comprising subjecting a material containing erythropoietin to chromatofocusing."

"24. The composition according to Claim 9 for use in a method of increasing haematocrit levels in mammals."

"25. A method for obtaining an erythropoietin composition having a predetermined number of sialic acids per molecule comprising preparing a mixture of two or more erythropoietin isoforms according to claim 1."

Dependent claims 2 to 7 and 15 to 19 related to further embodiments of the isoforms of claim 1 and the erythropoietin (Epo) of claim 14, respectively. Dependent claims 10 to 13 further characterized the

composition of claim 9 as did claims 26 to 29 for claim 25.

Claims 1 to 24 for the contracting states ES and GR corresponded to claims 1 to 8 and 14 to 29 and were formulated as method claims.

II. Oppositions were filed on the grounds of Article 100(a)(b)(c) EPC for lack of novelty (Article 54 EPC) and inventive step (Article 56 EPC), insufficiency of disclosure (Article 83 EPC) and added subject-matter (Article 123(2) EPC).

III. The opposition division maintained the patent pursuant to Article 102(3) EPC on the basis of the claims of the auxiliary request which only differed from the claims as granted by the addition at the end of claim 25 of the words "*..., by mixing said isoforms.*".

IV. The following documents are mentioned in this decision:

(2) W.A. Lukowsky and R.H. Painter, Canadian Journal of Biochemistry, 1972, Vol. 50, No. 8, pages 909 to 917
(3) R.N. Shelton et al., Biochemical Medicine, 1975, Vol. 12, pages 45 to 54
(4) J.E. Fuhr et al., Biochemical and Biophysical Research Communications, 1981, Vol. 98, No. 4, pages 930 to 935
(5) US 4,667,016
(7) T. Miyake et al., Journal of Biological Chemistry, 1977, Vol. 252, No. 15, pages 5558 to 5564
(11) H. Sasaki et al., Journal of Biological Chemistry, 1987, Vol. 262, No. 25, pages 12059 to 12076

(12) M. Takeuchi et al., Journal of Biological Chemistry, 1988, Vol. 263, No. 8, pages 3657 to 3663

(14) US 4,703,008

(16) "Versuchsbericht zur Nachbearbeitung der Publikation von Miyake et al. (1977) J. Biol. Chem., 252, 5558-5564"

(31) T.W. Strickland et al., Abstract and Poster at the Keystone Symposium on Glycobiology, March 1992 (Exhibit B filed by the patentee on 7 October 1999)

(33) P.L. Storring and R.E. Gaines Das, Journal of Endocrinology, 1992, Vol. 134, pages 459 to 484

(34a) Data on "Sulfated oligosaccharides of human Epo from C127 cells" submitted by appellant II with the grounds of appeal

(34b) Data on "desialylated rEpo" submitted by appellant II with the grounds of appeal

(36) P. Hermentin and R. Witzel, Pharm. Pharmacol. Comm., 1999, Vol. 5, pages 33 to 43

(37) P.L. Storring in "Molecular and Cellular Aspects of Erythropoietin and Electrophoresis", NATO ASI Series, I.N. Rich editor, Berlin, Springer Verlag, 1987, Vol. H8, pages 429 to 438

(40) M. Dorado et al., 1972, Biochemical Medicine, Vol. 6, pages 238 to 245

(41) Declaration of Dr Conradt dated 4 December 2001

(42) Declaration of Professor Dr Leatherbarrow dated 26 March 2003

(44) Declaration of Professor Dr Flitsch dated 4 April 2003

(45) Declaration of Professor Dr Walker

(46) Declaration of Dr Pierce

(47) Declaration of Dr Nimtz with a letter to Dr R. Williams dated 3 April 2002

(48) M. Nimtz et al., FEBS Letters, 1995, Vol. 365, pages 203 to 208

V. Appeals were filed against the decision of the opposition division by the patentee (appellant I), opponent 1 (appellant II) and opponent 2 (appellant III). The latter withdrew his opposition on 4 July 2001.

VI. Oral proceedings were held on 26 June 2003, at the outset of which a new main request for the contracting states AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, and SE was filed which consisted of a set of 25 claims. Claims 1 to 24 were identical to the corresponding granted claims and claim 25 as granted was amended by the introduction of the subject-matter of granted claims 26 to 29, so as to read:

"25. A method for obtaining an erythropoietin composition having a predetermined number of sialic acids per molecule comprising preparing a mixture of two or more erythropoietin isoforms according to claim 1, wherein said mixture consists essentially of at least two isoforms having less than 12 sialic acids per molecule, or wherein said mixture consists essentially of erythropoietin isoforms having 9, 10 and 11 sialic acids per molecule, or wherein said mixture consists essentially of at least two isoforms having greater than 11 sialic acids per molecule, or wherein said mixture consists essentially of

erythropoietin isoforms having 13 and 14 sialic acids per molecule."

The claims for the contracting states ES and GR were accordingly amended as well as the numbering and dependency of claims 22 to 24 as granted.

VII. The arguments submitted in writing and during the oral proceedings by appellant I can be summarized as follows:

Article 114(2) EPC

- amended claim 25 was clear and addressed objections of the opposition division and appellant II and no time-limit for submissions had been set by the Board.

Article 123(2)(3) EPC

- the amendment of claim 25 of the new main request had a basis in the application as published (page 5, lines 49 to 57) and did not result in an extension of the scope of protection, since the term "*consisting essentially*" was already present in claims 26 to 28 as granted.

- as far as the subject-matter of claim 24 was concerned, the application as published not only embraced, as preferred embodiment, pharmaceutical compositions (page 7, lines 4 to 13), but also compositions in general, not intended for a pharmaceutical use (page 5, line 49 to page 6, line 1).

Article 52(4) EPC

- claim 24 was not a claim to a method of treatment, but a proper first medical indication claim in that it clearly and unambiguously stated "*for use in a method of increasing hematocrit levels*".

Article 83 EPC

- Examples 1 to 5 of the patent in suit provided a routine method for the isolation of erythropoietin (Epo) isoforms or mixtures thereof and the determination of their sialic acid content and biological activity.

- the presence of 2% sulfated carbohydrates as described in document (31) had no consequence on the migration of Epo isoforms in isoelectric focusing (IEF).

- it was always possible to isolate from a cell population cells producing a high sulfatation or phosphorylation or to select culture conditions leading to such high sulfatation and phosphorylation as in documents (41) and (47). The question, however, was how representative of the technical reality this was. Furthermore, documents (45) and (46) showed that the skilled person was able to find conditions to separate Epo isoforms even in presence of high sulfatation or phosphorylation. Furthermore, the results obtained in the patent in suit were satisfactorily explained by a variation in the sialic acid content, so that there was no need to speculate on other reasons for the presence of isoforms.

- the subject-matter of claims 8 and 20 was enabling, although neither Table 2, nor Figures 2A to 2C gave an indication on the biological activity, the precondition for being therapeutically efficient as the claims required, of Epo isoforms with a sialic acid content less than 5, since document (14) showed that even asialo-Epo produced in *E. coli* still had 1% biological activity. The skilled person would have assumed the activity of Epo isoforms with 1 to 4 sialic acid residues to lie between that of asialo-Epo and of the isoform with 5 sialic acids.

- claim 22 was not restricted to the use of ion exchange chromatography, since the term "*comprising*" allowed the use of other methods or the re-mixing of the isolated Epo isoforms.

Article 54 EPC

- none of the documents (2) to (5) and (40) described an "isolated" Epo isoform having, as required by claim 1, a single pI and a specific number of sialic acids and, consequently, methods and compositions related to such isoforms. Indeed, in document (40) the starting material was highly impure. There was no indication in Figure 4 on the separation of the proteins on the isoelectric focusing (IEF) gel, since only Epo activity had been determined. It was thus not possible to know whether the Epo activity peaks obtained did correspond to isolated isoforms or a mixture thereof as in the claims of the main request. Furthermore, document (40) was not concerned with the sialic acid content of the fractions obtained.

Document (3) did not disclose the method of claims 21 to 23, since no purified Epo solution was used as a starting material and since isoforms were not described. Epo isoforms were not described in document (5).

- document (16) was no *bona fide* repetition of document (7), which was silent about isoforms, and could therefore not be novelty-destroying for the subject-matter of claims 9 and 22. Indeed, recombinant Epo (rEpo) was used instead of human urinary Epo (uEpo) and a mixture of Epo isoforms obtained after elution of the DEAE-Agarose column with a buffer containing 30mM $CaCl_2$ was shown in Figure 1, whereas in document (7) the fraction was eluted with 17 mM$CaCl_2$.

Article 56 EPC

- if any one of the documents (2) to (5) was considered as the closest prior art, the technical problem to be solved was the provision of a less heterogenous Epo preparation suitable for increasing haematocrit. The solution given in the claims of the patent in suit was the preparation of isoforms differing in their sialic acid content. To arrive at this solution in the patent in suit, the inventors discovered that variation in sialic acid content of Epo gave rise to distinct isoelectric species, referred to as Epo isoforms. As a consequence, it was the inventors who disclosed for the first time the relationship between isoforms and *in vivo* biological activity.

- at the priority date of the patent in suit, there was no incentive for the skilled person to make further

investigation on the purification of Epo, since document (5), which was silent on isoforms, disclosed a biologically active Epo product satisfactorily used in therapy.

- document (3) did not disclose the separation of the Epo isoforms and the dependence of the *in vivo* biological activity to the content of sialic acid and thus gave no incentive for further research in this direction.

- in documents (2) and (4) no isolated isoforms were disclosed and purified Epo was not used as a starting material. In document (2), it was even suggested that the use of purified Epo as a starting material resulted in a failure and it was concluded from the migration of asialo-Epo in IEF as a three component entity that Epo microheterogeneity would not be explained by variations in sialic acid content.

- in Figure 4 of document (40) the pattern obtained when subjecting an Epo preparation to IEF was shown. However, an impure Epo preparation was used and only the repartition of the Epo activity on the IEF gel was given in Figure 4. There was no determination of the specific activity of the various Epo activity peaks, which could have given an idea of the degree of purification obtained. The pattern of the separation of the proteins along the IEF gel was also not indicated, so that there was no evidence for a substantially pure Epo preparation which could have motivated the skilled person to further fractionate said preparation. Furthermore, there was in document (40) no indication whether the various regions of Epo activity seen on the

IEF gel differed from each other by their content in sialic acid. Therefore, there was no basis to consider document (40) as the closest prior art or to combine it with other documents.

- in document (37) an Epo standard for biological assays was looked for and the problem of variability of Epo preparations depending upon the sources of Epo and the methods of purification was addressed, but it was not suggested to prepare isoforms or that such isoforms could be of any therapeutical benefit. In document (33) the Epo standards which were developed after those of document (37) did not relate to Epo isoforms. Document (37) was thus neither the closest prior art, nor a document to be combined with other prior art documents.

- the authors of document (11) were concerned with the elucidation of the carbohydrate structure of Epo, but did not teach that the number of sialic acids was between 1 and 14. Accordingly, document (11), when combined with documents (2) to (4) and/or (40), did not suggest to expect Epo isoforms with a sialic acid content ranging from 1 to 14. Furthermore, there was in document (11) no appreciation of the relationship between sialic acid content and *in vivo* activity.

VIII. The arguments submitted in writing (by appellant II and appellant III) or during the oral proceedings (by appellant II) can be summarized as follows:

Article 114(2) EPC

- the submission of the new main request at the outset of the oral proceedings amounted to a breach of

fairness, since it could have been done with the statement of grounds of appeal, took the parties by surprise and increased the complexity of the matter to be decided on, because, although claim 25 was a method claim, the amendments concerned the product obtained by this method.

Article 123(2)(3) EPC

- the amendment made to claims 25 to 29 as granted resulted in the disappearance of the "nested relationship" which existed before among these claims and thus increased the importance of the expression "*consists essentially of*", which, because of its imprecise nature, introduced a degree of uncertainty in the scope of amended claim 25. For instance, claim 27 as granted was dependent on claim 26 and hence did not embrace an isoform with 12 sialic acid residues per molecule; however, due to the disappearance of this dependency and the imprecise character of the expression "*consisting essentially of*", such an isoform was encompassed by amended claim 25.

- there was no basis in the application as filed for the non-pharmaceutical composition of claim 24 as granted which referred back to a composition according to claim 9, containing two or three Epo isoforms, since the application as filed, even on page 7, lines 4 to 13, on which appellant I and the opposition division relied, referred to pharmaceutical compositions.

Article 52(4) EPC

- claim 24 was neither an acceptable first medical indication claim, since it did not simply refer to the claimed compositions being "*for use as a pharmaceutical*", nor an acceptable second medical indication claim and had to be considered as a method of medical treatment excluded from patentability under Article 52(4) EPC.

Article 83 EPC

- apart from claims 2, 7 and 18, the claims cover every kind of Epo of every origin, such as urinary Epo (uEpo).

- 100% pure Epo isoforms free from contamination by other Epo isoforms or unrelated proteins as claimed in claim 14 were not described in the patent in suit.

- documents (12), (31), (33), (34a,b) and (36) showed that rEpo and uEpo, depending on the culture conditions or the host cell (cf. also document (41)), contained sulfate and/or phosphate groups in an amount susceptible to hinder the separation pattern of the Epo isoforms using methods based on the net charge, but the patent in suit did not enable the skilled person to separate from each other Epo isoforms with the same net charge but differing by their sialic acid and sulfate/phosphate contents.

- in document (2) the Epo microheterogeneity was related not only to the sialic acid content, but also

to the amide content and the polymorphism, which the patent was silent about.

- the patent in suit did not show whether all the possible mixtures of Epo isoforms covered by claim 22 could be obtained using any ion exchange chromatography method. For instance, Example 4 disclosed the use of an anion exchanger, but Figure 3, relating to the separation obtained with an anion exchanger, did not show on lanes 2 to 6 a mixture of only two isoforms with a sialic acid content greater than 11 as embraced by claim 22. Furthermore, the patent in suit was silent on the use of a cation exchanger.

- there was no evidence that Epo isoforms with 1 to 14 sialic acids as required by claims 1 or 14 could be isolated. The patent in suit only showed isoforms with 5 to 14 sialic acids (Figures 2A to 2C) and even document (33), published about three years after the priority date of the patent in suit, did not show 14 isoforms in Figure 4.

- claim 20 was directed to a pharmaceutical composition with a therapeutically effective amount of Epo of claim 14, i.e. having an identical number of sialic acids per molecule, said number ranging from 1 to 14. However, the patent in suit was silent about isoforms with a sialic acid content of 1 to 4. Table 2 and Figure 2A to 2C showed that the biological activity decreased as the sialic acid content decreased. An extrapolation of these results made doubtful whether the object of claim 20 could be achieved using Epo isoforms having 1 to 4 sialic acids per molecule.

Article 54 EPC

- because of the unclear term "*isolated*", the subject-matter of claim 1, which had to embrace the erythropoietin of claim 14, had to be defined as meaning "*having undergone some process of isolation wherein the process does not promise 100% chemical purity and thus the complete absence of anything*". It did not properly and clearly exclude naturally occurring Epo isoforms as they exist in complex mixtures, which could include other Epo isoforms or unrelated proteins.

- document (5) disclosed a rEpo preparation in a projected pharmaceutical formulation (column 5, lines 50 to 56), which was the starting material of the patent in suit and considered in the patent in suit (page 4, lines 28 and 29; Figure 1, far left and right lanes) as containing six isoforms with a sialic acid content ranging from 9 to 14. Having regard to the definition of the term "*isolated*" mentioned above, document (5) thus anticipated claims 1 to 13 and 24 of the main request. It also anticipated claim 20 directed to a pharmaceutical composition comprising a therapeutically effective amount of Epo of claim 14, if claim 14 was interpreted as also embracing mixtures of the Epo isoforms of claim 1.

- document (5) also anticipated method claim 25, since the term "*preparing a mixture*" was entirely unspecific, so that claim 25 was not limited to any particular method of preparation of Epo. The term "*predetermined*" was to be understood by the skilled person aware of the variability of the glycosylation patterns in nature as

meaning "*as determined by nature*". On the other hand, appellant I had neither discovered the heterogeneity of Epo, nor the existence of a number of sialylated isoforms, nor the correlation between loss of sialic acids and loss of *in vivo* activity. An additional characterisation of a known compound did not represent patentable matter and, furthermore, there was no technical contribution in selecting an isoform composition.

- a crude Epo preparation was resolved in document (2) (Figure 1) in about 30 fractions in IEF. This was about twice as much as the number of possible isoforms, so that there were on the IEF gel isolated Epo isoforms. Furthermore, fractions were pooled and their Epo activity determined. Therefore, document (2) also anticipated claims 1 to 14, 24 and 25 of the main request.

- the IEF pattern obtained with crude Epo preparations was also shown in Figure 1 of document (3). Epo activity was found in all the 60 fractions. The number of fractions being greater than the number of isoforms, there were isolated isoforms on this IEF gel which were subsequently pooled (Table 1). Therefore, also document (3) anticipated claims 1, 9 to 13, 15 to 17, 21 and 25 of the main request.

- in document (4) the Epo IEF pattern was shown using a pH gradient from 3.5 to 9.5 to result in 30 fractions arranged in four areas, the first of which (fractions 4 to 7) contained all the Epo activity, i.e. all the Epo isoforms either in single form or as a mixture. Document (4) anticipated claim 25 of the main request,

since it provided the skilled person with a method for preparing a mixture of two or more Epo isoforms.

- document (40) disclosed in Figure 4 the activity pattern obtained by submitting a purified Epo to IEF. Several activity peaks were seen, for instance at fractions 8, 11 and 18. Document (42), which made a theoretical calculation of the pI variation in relation to the sialic acid content (assuming that all the sialic acids were exposed and accessible), showed that the resolution power of IEF was sufficient to isolate at least the peak on the right part of Figure 4 corresponding to the fractions having a high pI (i.e. the poorly sialylated isoforms). These fractions either corresponded to a single isoform or to a mixture of isoforms. Document (40) anticipated claims 1, 8 to 11, 14, 20, 21 and 25 of the main request.

- in document (7) a seven-step purification of human uEpo was disclosed which included various ion-exchange chromatography columns. Document (16), an attempt to reproduce the teaching of document (7), showed in Figure 1, lanes 6 and 10 that the fraction eluted from the DEAE-Agarose column with 30 mM $CaCl_2$, when examined in IEF, contained three isoforms having a mean sialic acid content (Table 1) ranging between 12.6 and 12.8. Therefore, document (7), as repeated in document (16), anticipated claim 22 of the main request.

Article 56 EPC

- the general relationship between the sialic acid content and the *in vivo* biological activity was already disclosed in the prior art, for instance in

document (2). The contribution of the patent in suit was not the discovery of this relationship, but only its quantification.

- the problem to be solved after the disclosure of document (40) on the electrophoretic and electrofocusing behaviour of Epo was defined on page 245 (lines 3 to 4) of this document as the provision of additional information. In 1989, the priority date of the patent in suit, it was obvious to use rEpo and IEF, so that the skilled person would straightforwardly have come to the solutions defined by the subject-matter of the claims of the patent in suit.

- alternatively, document (5) disclosed the preparation of Epo isoforms with 9 to 14 sialic acid residues per molecule for pharmaceutical preparations and could also be considered as the closest prior art. The technical problem to be solved was a better characterisation of the microheterogeneity in order to obtain a more standardized product and the solution was to use the method of choice at that time, i.e. IEF.

- another alternative closest prior art was document (2), showing the relationship between sialic acid content and Epo activity *in vivo,* in view of which the problem to be solved was to further investigate this relationship. Again, IEF was the method of choice and led to the subject-matter of the claims of the main request.

- if document (11), showing that the heterogeneity was due to the carbohydrate moiety of Epo and suggesting up to fourteen isoforms differing from each other by their

sialic acid content, was considered as the closest prior art, then the technical problem to be solved was the provision of a highly active and homogenous Epo characterised by its carbohydrate structure and the obvious solution to this problem was to use IEF as described in documents (2) or (3).

- in document (37) a standard for the assay of Epo (page 431, third and fourth paragraphs and page 435, third full paragraph) was looked for and Epo was said to exist in a number of different biologically active forms, as demonstrated by IEF (page 433, first paragraph), which were expected to be due, by analogy with other glycoproteins, to the source of the specimen, the physiological state of the subject or the purification procedure. The problem to be solved was to separate these different forms and IEF was the method of choice, as shown by documents (42), (44).

IX. Appellant I requested that the decision under appeal be set aside and that the patent be maintained on the basis of the new main request filed during the oral proceedings.

X. Appellant II requested that the decision under appeal be set aside and that the European patent No. 0 428 267 be revoked.

Reasons for the Decision

Article 114 EPC

Late-filed documents

1. Both appellants I and II have filed documents after the submission of their grounds of appeal or answers thereto. These documents have to be considered as late-filed. Neither appellant I nor appellant II objected to the introduction of the late-filed documents of the adverse party into the proceedings. Document (40) is *per se prima facie* relevant for novelty and/or inventive step; the other documents filed by appellant II as well as all the documents filed by appellant I give an answer to arguments submitted by the adverse party and highlight documents or arguments already present on file, from which they should not be dissociated, as they contribute to their relevance. Since their introduction into the proceedings does not increase the degree of procedural complexity, the Board decides to allow these documents into the proceedings pursuant to Article 114(2) EPC.

Main request

Late-filed amendments to claim 25 as granted

2. At the outset of the oral proceedings, appellant I submitted a new set of claims corresponding to the claims as granted, except for claim 25 which was amended in such a way as to incorporate the subject-matter of claims 26 to 29 as granted.

3. It is not a totally unusual practice to submit amended claims during oral proceedings before the Boards of appeal in order to overcome objections raised by the adverse party or the Board. In the present case, claim 25 in its granted form had already been objected to under Article 54 EPC not only during the opposition proceedings, but also in appellant II's letter of 18 June 2001 and, as amended before the opposition division, under Article 56 EPC in appellant II's letter of 7 April 2003, so that an amendment to claim 25 was to be expected. Furthermore, the amendment to claim 25 as granted by introduction of the alternatives mentioned in claims 26 to 29 as granted, does not *prima facie* result in an increase of the complexity of the technical or legal issues. In the Board's view, this amendment is not a breach of the duty of fairness, since it cannot have taken appellant II by surprise. Therefore, it is allowed into the proceedings pursuant to Article 114(2) EPC.

Article 123(2)(3) EPC

4. The application as filed discloses both compositions containing two or more Epo isoforms which are not restricted to a pharmaceutical use (page 5, lines 49 to 57) and pharmaceutical compositions containing a specific isoform or a mixture of isoforms (page 7, lines 4 to 6) and hence offers a basis for the subject-matter of claim 24 relating to Epo compositions for use in a method of increasing hematocrit levels in mammals which are not defined as pharmaceutical compositions.

5. The subject-matter of amended claim 25 can be found in the application as filed which describes on page 12,

line 17 to page 13, line 19 compositions comprising two or more Epo isoforms and on page 13, lines 19 to 29 methods for preparing these compositions.

6. Appellant II argued that the expression "*consisting essentially*" had an increased importance due to the disappearance of the "nested relationship" following the amendment of claims 25 to 29 as granted and, because of its imprecise character, resulted in an extension of the scope of protection. This expression was only mentioned in dependent claims 26 to 29 as granted, but the overall scope of protection defined by claims 25 to 29 as granted was *de facto* determined by claim 25, which was more broadly formulated than claims 26 to 29 and embraced any kind of mixtures of two or more Epo isoforms, whereas claims 26 to 29 as granted only concerned sub-groups of these mixtures. The subject-matter of claim 25 as granted is still present in amended claim 25 and is still determinant for the overall scope of protection, which has thus not been changed by the amendment.

7. Therefore, the amended claims meet the requirements of Article 123(2)(3) EPC.

Article 52(4) EPC

8. Claim 24 is formulated as a product claim "*for use in a method of increasing the hematocrit levels in mammals*" and is a purpose-limited product claim in agreement with the form of a first medical indication claim defined in Decision G 5/83 (cf. *supra* section VII) and, as argued by appellant I, exemplified in Guidelines,

Part C, Chapter IV, 4.2. Therefore, claim 24 does not contravene the requirements of Article 52(4) EPC.

Article 83 EPC

9. For the purpose of considering whether a European patent does disclose the invention in a manner sufficiently clear and complete to be carried out by a person skilled in the art (Article 100(b) and Article 83 EPC), the Board has to be satisfied firstly that the patent specification puts the skilled person in possession of at least one way of performing the claimed invention and, secondly, that the skilled person can put the invention into practice over the whole scope of the claims.

10. As far as the absence of a disclosure of the preparation of Epo isoforms with 1 to 4 sialic acid residues per molecule and of their therapeutical use is concerned, it has to be noted that the rationale behind the separation method described in the patent in suit, which makes use of a difference in the net charge of the various isoforms, is applicable whatever the degree of sialylation is. Therefore, in the absence of evidence to the contrary, the Board considers that this method could also separate isoforms with 1 to 4 sialic acid residues per molecule, provided these isoforms are present in the mixture tested. Table 2 and Figure 2A to 2C of the patent in suit show that before reaching a plateau with isoforms 11 to 13 (or even 14, when Epo activity is measured by RIA), the biological activity of the isoforms increases proportionally with the content of sialic acid residues. Table 2 and Figures 2A to 2C begin with isoform 5. However, their

extrapolation leads the skilled person to conclude that isoforms 1 to 4 have a biological activity lying between that of isoform 5 and asialo-Epo, which is shown in document (14)(column 33, lines 40 to 51) to still possess up to one percent of the *in vivo* activity of sialylated human urinary standard Epo. Since the therapeutical use of Epo is related to its *in vivo* biological activity, it thus seems plausible that isoforms 1 to 4 can be used as therapeuticals. In this context, it has to be kept in mind that the notion of "*therapeutically effective amount*" as mentioned in claim 20 depends on the route of administration used and the purpose the skilled person wants to reach (patent in suit, page 6, lines 5 to 19), so that a less active preparation may nevertheless be advantageous for some applications.

11. Considering the alleged absence in the patent in suit of any disclosure of the production of a mixture of isoforms as defined in claim 22, it has to be considered that claim 22 mentions the word "*comprising*" which does not exclude the use, beside ion exchange chromatography, of other techniques, such as IEF or even re-mixing of separated Epo isoforms. Furthermore, the various Epo isoforms differ from each other by the content in sialic acid residues, i.e. by their net charge. The net charge is the factor used in ion (cation or anion) exchange chromatography to separate molecules from each other. There is thus no theoretical reason why the method of claim 22 could not lead to a mixture of isoforms having a predetermined number of sialic acids per molecule, said number being greater than 11. Appellant II has not provided evidence to the contrary although the burden of proof lies with him.

12. The objections concerning the absence of a disclosure of a 100% pure Epo isoform and of a teaching enabling the skilled person to routinely isolate and identify Epo isoforms with 1 to 14 sialic acid residues per molecule are nullified by the disclosure of Table 1, Figures 1, 3 and 4 and the Examples 1 to 5, which show that the teaching of the patent in suit leads to isolated biologically active Epo isoforms, which are well individualized on analytical IEF gel and, at least according to the criterion of IEF, are homogenous, i.e. free of contamination by other Epo isoforms or unrelated proteins. Example 1 provides the skilled person with a reliable method for the isolation of Epo isoforms and Example 2 and Table 1 with a way to identify the isolated Epo isoforms by determining their sialic acid content. The Board is convinced, also in view of Figure 10 of document (36), cited as an expert opinion, that IEF is well able to separate all the Epo isoforms with 1 to 14 sialic acids, provided said Epo isoforms are present in the tested sample. The Board is, therefore, satisfied that the patent in suit puts the skilled person in possession of at least one way to perform the invention over the whole scope of the claims.

13. Since the separation of the Epo isoforms can well be explained, according to Table 1 and Figures 1, 3 and 4, by their sialic acid content, the Board agrees with appellant I that there is no need to consider the hypothetical and speculative sources of microheterogeneity mentioned in document (2)(page 915, left and right columns).

14. Appellant II argued that the patent in suit does not address the problem of high sulfate and phosphate group concentration in Epo as disclosed in documents (41), (36) or (47) or of the other sources of microheterogeneity mentioned in document (2), so that there is some area of unreliability and uncertainty in the patent in suit. Documents (48), (31) and (36) show that Epo can be sulfated and quantify said sulfatation. Document (31) is an abstract and mentions that in rEpo obtained by transfection of CHO cells with human Epo gene sulfated oligosaccharides may represent up to 3% of the total rEpo oligosaccharides. Poster sheets are annexed to this abstract, sheet 12 of which ("F*igures VIII-XI: Chromatography of asialo oligosaccharide alditols*") states that rEpo obtained from CHO cells may contain one sulfate group. Further, said sheet also states that uEpo may contain up to three anionic groups. Document (48) indicates the presence of 2% phosphate groups. A concentration in phosphate or sulfate groups of 2 or 3% represents, in the Board's opinion, a negligible amount and it seems doubtful whether this could have any influence on the IEF separation. Post-published document (36) reports in Table 4 the presence in rEpo obtained by expression in C127 mouse fibroblast cells of about 30% sulfated oligosaccharides which would result in a modification of the IEF pattern (Figure 10). Experimental data (documents (41) and (47)) show a finding similar to that of document (36).

Post-published document (33)(page 459, paragraph bridging the left and right columns and page 476, right column, heading "*Basis for the differences between Epo preparations*") relates differences in the biological properties of uEpo and rEpo to their glycosylation

state due to differences in the type or physiological state of the cells expressing rEpo, in the subsequent metabolic or degradative modifications of these Epos and in the purification procedures, but is silent about sialylation. Document (12) highlights differences in the oligosaccharide composition of uEpo and rEpo and speculates on the influence of said differences on the biological properties (page 3660, left column) and on the presence of sulfate groups (page 3658, left column), but does not quantify the amount of sulfate groups present on the oligosaccharides of Epo. Documents (34a) and (34b) are experimental evidence obtained under conditions which are not precisely defined, so that they have to be considered with caution.

15. The question to be answered in this context is three-fold:

(a) was the skilled person at the priority date of the patent in suit able to note that the Epo isoforms obtained contained sulfate or phosphate groups?

(b) did the skilled person at the priority date of the patent in suit know remedies?

(c) is the occurrence of large amounts of sulfate or phosphate susceptible to modify the IEF pattern a common or a rare phenomenon?

16. The skilled person was enabled by the methods described in Examples 1 and 2 of the patent in suit to isolate Epo isoforms and determine their sialic acid content. The skilled person was able to determine whether the

Epo isoforms obtained contained sulfate or phosphate groups by running in IEF the sample Epo against an Epo standard known to be deprived of sulfate and/or phosphate groups and determining afterwards its sialic acid content. By doing so, the skilled person could determine whether the migration of the sample Epo was in line with its sialic acid content. In case of a negative answer, the skilled person could have determined the phosphate or sulfate content by routine methods.

17. Document (45)(page 5, paragraph 16) shows that remedies were known.

18. Finally, appellant II has not shown that the presence of sulfate and phosphate groups in an amount which can negatively influence the IEF pattern is a common phenomenon. Indeed, among all the documents cited in the present case, the only independent and reliable source for the presence of such an amount of phosphate or sulfate groups is post-published document (36) and, even in this case, only the use of the C127 cells leads to the presence of a degree of sulfatation which could negatively interfere with the IEF pattern. On the contrary, the use of BHK and CHO cells (the latter being the cells used in the patent in suit and mentioned in claim 7) does not result in such an amount of sulfate or phosphate groups (Table 4). This is confirmed by post-published document (48)(abstract and page 206, left column, second sentence), in which the use of BHK cells leads to a negligible 2 to 4% phosphate content and document (31) (abstract) which shows the presence of only 3% of sulfated groups when using CHO cells.

19. The Board is thus of the opinion that at the priority date of the patent in suit the skilled person was able to determine whether an excessive amount of phosphate or sulfate groups was present in the Epo isoforms, knew remedies, if such a situation nevertheless happened, and was provided by the patent in suit with guidance for an extrapolation over the examples described therein. Thus, if an occasional failure had occurred, the skilled person would have been able to perform the invention with only few additional routine experiments.

20. Therefore, the patent in suit meets the requirements of Article 83 EPC.

Article 54 EPC

21. Appellant II interpreted the term "isolated" as used in claim 1 as meaning that Epo had "undergone some process of isolation wherein the process does not promise 100% chemical purity and thus the complete absence of anything". In this interpretation, claim 1 does not exclude naturally occurring Epo isoforms as they exist in complex mixtures which could include other Epo isoforms or unrelated proteins and therefore would not be novel.

22. This interpretation leads to a rather unclear definition of the Epo in claim 1, which could accordingly contain anything in an undetermined amount and is in the Board's view not adequate, since claim 1 defines without ambiguity the claimed substance, which has to fulfil the following conditions:

- it is an Epo isoform
- it has a single pI
- it contains a specific number of sialic acid groups ranging from one to fourteen.

This definition excludes the presence of molecules other than Epo isoform. Thus, contrary to appellant II's interpretation, the subject-matter of claim 1 of the patent in suit is an Epo isoform which, according to the sensitive homogeneity criterion of IEF, is not contaminated by other Epo isoforms or non-related proteins (Figures 1 and 3 of the patent in suit).

23. Document (5), which is silent on isoforms, is shown in the patent in suit (page 4, lines 28 to 35) to disclose an Epo preparation containing 6 isoforms with 9 to 14 sialic acids per molecule. However, the word "***predominantly***" is used in the patent in suit to characterize the presence of these isoforms in the product obtained from the process of document (5). This implies the presence of other undetermined substances and there is in the patent in suit no evidence that these substances may not be contaminants structurally unrelated to Epo. It is further stated in the patent in suit (page 4, lines 9 to 15) that the purification method of document (5) may be modified as using a Q-Sepharose chromatography instead of the DEAE-Agarose chromatography. The following sentence (page 4, lines 15 to 17) concerns the performance of this Q-Sepharose chromatography and is followed by a sentence (page 4, lines 17 to 18) in which the degree of purity

of the material obtained is assessed by the presence of a single band in SDS electrophoresis. However, this sentence, because of the use of the word "***material***" in the singular form and because of its position just after the sentence concerning the Q-Sepharose chromatography, can only concern Epo obtained using the modified process. In other words, there is no information in document (5) and in the patent in suit on the true and exact structure of the substance obtained by the process of document (5). Therefore, there is no evidence that the obtaining of a mixture of Epo isoforms as defined in the claims of the main request is the inevitable result of the process disclosed in document (5). Therefore, document (5) is not novelty-destroying for the subject-matter of the claims of the main request.

24. Document (2) describes the performance of IEF on step I Epo, i.e. a crude preparation of Epo, and *in vivo* Epo activity is assessed in Figure 1 to the part of the IEF pattern corresponding to the lower pH (pH 3.5 to 4.0, page 914, right column). However, there is no indication that an Epo isoform or a mixture thereof as defined in the claims of the patent in suit is obtained, since the molecular nature of the Epo active material has not been determined and the fractions exhibiting Epo activity have not been shown to be free from unrelated proteins.

25. Document (3) also describes the performance of IEF on poorly purified human uEpo and step I sheep Epo using a pH range from 1.45 to 12.50. The pattern obtained is shown in Figure 1 and Epo activity is found in ***all*** the fractions obtained, the concentration in Epo being

maximum in the fractions between pH 4.13 and 4.72 (Table 1). Again, no structural analysis of the product obtained has been carried out which could allow determination of the molecular nature of the Epo active substance obtained in each fractions of Figure 1 and its contamination by unrelated molecules, especially in view of the poor purity of the starting material and of the extremely low Epo specific activity of the fractions (Table 1, last column) which is indicative of a high degree of contamination.

26. In Figure 1 of document (4) the IEF pattern obtained with step III Epo in a pH gradient ranging from 3.5 to 9.5 is shown: a smear appears in the acidic half of the pattern. The first sentence under the heading "*Results*" (page 931) indicates that more than 25 protein bands are detected after staining. This is much more than the 14 isoforms claimed and indicative of a contamination by other proteins. Moreover, no attempt is made in document (4) to determine the molecular nature of the product obtained.

27. Document (7) discloses the seven-step purification of human uEpo resulting in two Epo fractions with a minimum biological activity of 70,400 units/mg of protein (page 5563, right column, second paragraph) in a 21% overall yield (Table V) and which are homogenous in gel electrophoresis (Figures 7 to 9). The presence of these two fractions is speculatively explained by some kind of microheterogeneity due to sialic acid residues or amide groups (page 5563, right column, fourth paragraph). Thus, document (7) *per se* does not disclose an Epo isoform as defined in the present claims. Document (16) is an experimental report, the

purpose of which is to show that the process of document (7) leads to a mixture of isoforms (Figure 1) encompassed by the claims of the main request. However, document (16) is not a *bona fide* attempt to reproduce the teaching of document (7), since in document (16), instead of human uEpo, two rEpo preparations are used: an undefined "HA-Eluat" and the end-product of an equally undefined "BM-Herstellungprozeß". The latter preparation, as an "end-product", must definitely be different from the sample submitted to DEAE-Agarose chromatography in document (7) which, according to its specific activity mentioned in Table V, only contains about 1.3% Epo and is hence highly impure. The nature of the "HA-Eluat" is not defined in document (16), but, since its IEF pattern on Figure 1 (lanes 5 and 6) is almost the same as that of the end-product (lanes 9 and 10), it can be assumed to be a preparation far more pure than that chromatographed on DEAE-Agarose in document (7). Therefore, document (16) fails to show that the process of document (7) leads to a product falling within the scope of the present claims.

28. Document (40) describes the performance of IEF on an Epo preparation with a specific activity of 500 to 2300 units/mg of protein. In view of the specific activity of a pure Epo preparation (cf. supra point 27), Epo only represents a few percent of the total proteins of the starting material loaded on the IEF gel. In Figure 4 five Epo activity peaks are identified, but the protein separation over the IEF pattern is not shown, so that it is not possible to know which molecular entities each fraction contains and how (im)pure they are. Therefore, document (4) cannot be

considered as disclosing Epo isoforms and related methods as in the claims of the main request.

29. As a consequence, the Board is of the opinion that none of documents (2) to (5), (7)(in combination with document (16)) and document (40) disclose Epo isoforms and related methods as claimed in the claims of the main request, which thus meet the requirements of Article 54 EPC.

Article 56 EPC

30. The claims under consideration relate to isolate isoforms of Epo characterized by a single isoelectric point and a specific number of sialic acids per molecule, said number ranging from 1 to 14. Several documents have been cited as possible closest prior art and their disclosure is summarized below (or completed, if they have already been analysed in the context of novelty (cf. *supra* points 23 to 28)).

31. Document (2) is an attempt to characterize the Epo molecule by submitting crude preparations to IEF. In Figure 1, several fractions exhibiting *in vivo* Epo activity can be seen in the more acidic part of the IEF pattern. Document (2) concludes that Epo is heterogenous with respect to charge (page 915, left column) and speculates on the reason of said microheterogeneity as being differences in amide or in the carbohydrate content or as being the result of polymorphism. Of particular interest is the conclusion in document (2) (page 915, right column) that, since the microheterogeneity even persists in fully desialylated Epo, which invariably focuses as three

components (page 912, right column and Figure 3), variation in the sialic acid content cannot be the reason for said microheterogeneity, although it is shown in Figure 4 that Epo *in vivo* activity is destroyed by removal of the sialic acid residues.

32. In document (3), the disclosure of which has already been summarized above (cf. *supra* point 25), it is stated on page 51 (second paragraph) that Epo heterogeneity cannot be explained by a difference in the sialic acid content, as long as purified Epo, which would enable the skilled person to calculate the Epo sialic acid content, is not available. Furthermore, document (3) also proposes, as an explanation for the microheterogeneity, the action of deaminases or the influence of the first steps of the purification procedure (page 51).

33. In document (4), as already mentioned above (cf. *supra* point 26), the problem of Epo heterogeneity in relation to the sialic acid content is not addressed.

34. In document (40) a crude Epo preparation is separated on IEF gel (Figure 4) into few peaks of activity and it is speculated in the paragraph bridging pages 243 and 244 that said Epo activity could be related to a family of molecules differing from each other in their migration behaviour in IEF or electrophoresis. Besides minor differences in shape and sizes, this difference of migration behaviour is explained by variation of the charge of these different Epo forms. In document (40) it is concluded that such behaviour has already been seen with other glycoproteins and that studies are in progress in order to obtain additional information

(page 245, last sentence). Document (40) is silent about the presence and function of sialic acid.

35. In document (5), the disclosure of which was already defined above (cf. *supra* point 23), the purification of rEpo expressed in CHO cells (column 4, lines 33 to 37) using reverse phase, ion exchange chromatography (column 5, lines 19 to 49) and gel filtration (column 5, lines 49 to 56) is described, but there is no information on isoforms.

36. In document (37) a standard for the assay of Epo is looked for, which should consist in a purified hormone, free from non-hormone contaminants (page 431, second full paragraph). Problems related in general to glycoprotein hormones are mentioned on page 433: appearance of different biologically active molecular forms in IEF depending on the physiological state of the subject, the source of the specimen or the purification procedure used. This heterogeneity is said on page 433 (lines 14 to 17) to pose a problem for the standardization. However, document (37) is silent about the involvement of sialic acid in the microheterogeneity.

37. In document (11), a study of the carbohydrate structure of Epo, a comparison is made between rEpo and natural uEpo. The purpose of this study is mentioned on page 12059 (right column, last paragraph of the introduction) and lies in the fact that asialo-Epo being *in vivo* biologically inactive, the determination of the "*proper glycosylation*" was desired. The teaching of document (11) is that rEpo and uEpo have carbohydrate structures which are indistinguishable

from each other, except for a difference in degree of sialylation (page 12072, left column, last paragraph), and consist in three N-linked oligosaccharides and one O-linked oligosaccharide (page 12071, right column, first paragraph under heading "*Discussion*"). The former can be mono-, di-, tri- or tetrasialylated (page 12069, heading "*Fractionation of intact N-linked saccharides by TSK-DEAE ion exchange chromatography*"), whereas the latter is mono-, or disialylated (abstract, second paragraph) and, although it is not *expressis verbis* indicated in document (11), it can be deduced that Epo may theoretically contain up to 14 sialic acid residues. This is in agreement with the values mentioned in Table I, which shows the sialic acid content of uEpo and various preparations of rEpo, for each of which a ***precise number*** of sialic acid residues lying between 9.7 and 11.8 is assigned, which is not said to be a mean value due to the presence in each preparation of various Epo isoforms in different concentrations. In document (11) there is no suggestion of a possible microheterogeneity ***within*** a Epo preparation, but only ***among*** different Epo preparations. In line with this teaching a technical problem is formulated on page 12072 (left column, penultimate sentence): the comparison of the carbohydrate structure with Epo produced in ***other*** mammalian cells. In document (11) there is no comment on the respective *in vivo* biological activity of the various Epo preparations of Table I and, basically, there is no pointer to a possible correlation between sialic acid content and *in vivo* biological activity. In fact, it is suggested by Table I, showing different Epo preparations with different sialic acid contents, but without any indication of a difference of the *in vivo* activity,

that these preparations have the same activity, which hence speaks for an independency of the biological activity from the sialic acid content. This implies that the "*proper glycosylation*" must be a minimum number of sialic acid residues, above which every Epo isoform has the same *in vivo* biological activity. Thus, in document (11) the microheterogeneity ***within*** Epo preparations and its influence on the *in vivo* biological activity is not addressed.

38. The above analysis of the disclosure of the documents cited by appellant II as being detrimental to the inventive step of the subject-matter of the claims of the main request reveals a confusing situation as to what might have been the reason for the heterogeneity of the many Epo preparations, be it from natural sources or produced via recombinant DNA techniques. The Board sees the technical problem to be solved in the definitive explanation of the heterogeneity of Epo. The solution defined in the claims of the main request lies in the provision of fourteen distinct and defined Epo isoforms differing from each other by their sialic acid content.

39. As outlined above, there were many proposals, some of them dating more than 10 years before the priority date of the patent in suit (for instance, documents (2), (3), (7) and (40)), for explaining the reason for Epo heterogeneity. Thus, the skilled person faced with these various proposals had to decide which one might be promising for further investigation. It seems remarkable that only shortly before the priority date of the patent in suit, in 1987, it was still desirable to establish standards for the assay of Epo, as shown

in document (37), which mentions on page 429, that "*...erythropoietin has until now been something of a Cinderella*". The Board is convinced that the "sialic acid track" was at the priority date of the patent in suit at best one of several routes that the skilled person could have followed. When considering the teaching of the above mentioned documents (cf. *supra* points 31 to 37), even mentioning the possible relevance of sialic acid in the context of heterogeneity, the Board comes to the conclusion that the authors of these documents did not further carry on in the direction of the involvement of sialic acid and, even in the case of document (2), *expressis verbis* indicated that sialic acid is not involved in the microheterogeneity of Epo (page 915, right column) and hence taught away from following this route. Thus, the Board is convinced that the solution given in the claims under consideration was not obvious for the average skilled person and far away from routine work and is thus patentable under the provisions of Article 56 EPC. This conclusion also accordingly applies to the set of claims for the contracting states ES and GR.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the main request filed at the oral proceedings.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey