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D E C I S I O N
of 4 August 1999

Case Number: T 0493/94 - 3.3.4

Application Number: 85109336.9

Publication Number: 0169566

IPC: C07K 15/00

Language of the proceedings: EN

Title of invention:
Novel CSF and method for obtaining the same

Patentee:
Chugai Seiyaku Kabushiki Kaisha

Opponent:
Hoechst Aktiengesellschaft
F. Hoffmann-La-Roche & Co. Aktiengesellschaft
Amgen Inc

Headword:
CSF/CHUGAI

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

Keyword:
"Added subject-matter (no)"
"Clarity (yes)"
"Sufficiency of disclosure (yes)"
"Novelty (yes)"
"Inventive step (yes)"

Decisions cited:
T 0794/94

Catchword:

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Case Number: T 0493/94 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 4 August 1999

Appellant I: (Opponent 01)
Hoechst Aktiengesellschaft
Brüningstrasse 50
65926 Frankfurt am Main (DE)

Representative:
Bösl, Raphael, Dr. rer. nat., Dipl.-Chem.
Patent- und Rechtsanwälte
Bardehle, Pagenberg, Dost, Altenburg,
Geissler, Isenbruck
Galileiplatz 1
81679 München (DE)

Other party: (Opponent 02)
F. Hoffmann-La Roche & Co.
Aktiengesellschaft
Grenzacherstrasse 124
4002 Basel (CH)

Representative:
Lederer, Franz, Dr.
Lederer, Keller & Riederer
Patentanwälte
Prinzregentenstrasse 16
80538 München (DE)

Other party: (Opponent 03)
Amgen Inc
1900 Oak Terrace Lane
Thousand Oaks
California 91320 (US)

Representative:
Armitage, Ian Michael
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP (GB)

Respondent: (Proprietor of the patent)
Chugai Seiyaku
Kabushiki Kaisha
5-1, 5-chome. Ukima
Kita-ku
Tokyo (JP)

Representative:
Jaenichen, Hans-Rainer Dr.
Vossius & Partner
Postfach 86 07 67
81634 München (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 5 April 1994 concerning maintenance of European patent No. 0 169 566 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: D. D. Harkness
S. C. Perryman

Summary of Facts and Submissions

I. The appeal lies from the interlocutory decision of the opposition division dated 5 April 1994 whereby the European Patent No. 0 169 566 (application No. 85 109 336.9), which had been opposed by three parties, was maintained in amended form on the basis of claims 1 to 10 for all designated contracting states except Austria (non-AT States) filed on 11 February 1993, claims 1 to 3 filed on 31 October 1991 for AT and an amended description. Claims 1 and 5 for the non-AT States read as follows:

"1. Human granulocyte colony stimulating factor (hG-CSF) having a specific activity of at least 3.94 x 10^7 U/mg and the ability of promoting the differentiation and proliferation of human bone marrow cells to neutrophilic granulocytes but not to eosinophils having the following physicochemical properties:

i) Molecular weight:

19,000 ± 1,000 as determined by sodium dodecylsulfatepolyacrylamide gel electrophoresis;

ii) Isoelectric point:

Having at least one of the three isoelectric points A, B and C, shown in Table 1:

[Table 1 reported]

iii) UV absorption:

Maximum absorption at 280 nm and minimum absorption at 250 nm;

iv) The N-terminal 21 amino acids are

[sequence recited]

wherein X represents a naturally occurring unidentified amino acid residue."

"5. The hG-CSF according to Claim 1, wherein the molecule is glycosylated."

Claims 2 to 4 concerned particular embodiments of the hG-CSF according to claim 1, claims 6 and 7 a method for preparing it, and claims 8 to 10 pharmaceutical compositions comprising it. Claims 1 to 3 for AT were correspondingly formulated as method claims.

II. The set of claims on the basis of which the opposition division maintained the patent differed from the claims as granted essentially in that:

- Claim 1 (for non-AT States and for AT) incorporated the "specific activity" feature of granted claim 6 (claim 3 for AT), it stated that the claimed G-CSF was "human", and it contained the feature "having the ability to promote differentiation and proliferation of human bone marrow cells to neutrophilic granulocytes but not to eosinophils" in place of the more general feature "has the ability to promote the differentiation and proliferation of human bone marrow cells to granulocytes";

- In process claim 6 (claim 1 for AT) (corresponding to granted claim 7 = claim 1 for AT), step 2 was more precisely defined by the introduction of operational parameters;

- Granted claim 9 (claim 5 for AT), which was directed to the deposited cell line I-315, was deleted.

III. Seventy-four documents were cited during the opposition proceedings. The opposition division considered that none of them affected the novelty of the claims as amended because no prior art product had the same pattern of biological activities as the product of claim 1 at issue. Moreover, none of the cited documents rendered obvious the claimed hG-CSF. The requirements of Articles 83 and 123 EPC were also considered to be satisfied.

IV. The appellants (opponents 01) lodged an appeal and filed with the statements of grounds of appeal a declaration by Dr Roger Camble.

V. The respondents (patent proprietors) replied to the submissions by the appellants and filed a further document.

VI. Further submissions were made by the appellants which were commented upon by the respondents.

VII. On 1 February 1999 the parties were summoned to oral proceedings. The appellants filed further submissions in reply to the comments by the respondents. The other parties (opponents 02 and 03) informed the board of

their intention not to attend oral proceedings.

VIII. The respondents made further submissions and filed a new document. These submissions were answered by the appellants who requested that the late-filed document not be admitted into the proceedings. Oral proceedings had to be rescheduled.

IX. Both the appellants and the respondents made further submissions. The appellants also filed new documents.

X. Oral proceedings took place on 4 August 1999. The respondents, also in view of the board's objections under Article 123(2) EPC to claim 1 of the set as maintained by the opposition division, filed finally amended claims (claims 1 to 10 for non-AT states and claims 1 to 3 for AT) as a sole request together with amended description pages. Claim 1 (non-AT states) read as follows:

"1. Human granulocyte colony stimulating factor (hG-CSF) having a specific activity of at least 3.94 x 10^7 U/mg in the human bone marrow cell assay, and the ability of promoting the differentiation and proliferation of human bone marrow cells to neutrophilic granulocytes but not to granulocyte-macrophages and not eosinophils in the human bone marrow cell assay at days 7, 10 and 14 of the incubation having the following physicochemical properties:

i) Molecular weight:

19,000 ± 1,000 as determined by sodium

dodecylsulfatepolyacrylamide gel electrophoresis;

ii) Isoelectric point:

Having at least one of the three isoelectric points A, B and C, shown in Table 1:

[Table 1 reported]

iii) UV absorption:
Maximum absorption at 280 nm and minimum absorption at 250 nm;

iv) The N-terminal 21 amino acids are

[sequence recited]

wherein X represents a naturally occurring unidentified amino acid residue."

The remaining claims 2 to 10 were identical to the claims as maintained by the opposition division. The corresponding amendments were introduced also in method claim 1 of the set of claims for AT.

XI. The following documents are referred to in the present decision:

(1) Poster presentation by Dr Karl Welte at the conference entitled "Modern Trends in Leukemia VI" in Wilsede, Germany on June 17-20, 1984: (a) copy of the poster; (b) abstract;

(2) Poster presentation by Dr Erich Platzer at the

conference entitled "Modern Trends in Leukemia VI" in Wilsede, Germany on June 17-20, 1984: (a) copy of the poster; (b) abstract;

(7) M. A. Vadas et al., J. Immunol., 2 February 1983, Vol. 130, pages 795 to 799;

(8) T. Okabe et al., J. Cell. Physiol., 1982, Vol. 110, pages 43 to 49;

(14) K. Welte et al., Proc. Natl. Acad. Sci. USA, March 1985, Vol. 82, pages 1526 to 1530;

(15) L. M. Souza et al., Science, 4 April 1986, Vol. 232, pages 61 to 65;

(16) D. Metcalf and N. A. Nicola, J. Cell. Physiol., 1983, Vol. 116, pages 198 to 206;

(17) N. A. Nicola et al., J. Biol. Chem., July 1983, Vol. 258, pages 9017 to 9023;

(19) S. Nagata et al., The EMBO J., 1986, Vol. 5, No. 3, pages 575 to 581;

(20) K. Welte et al., in "Leukemia: Recent Advances in Biology and Treatment", Proceedings of a UCLA Symposium held in Keystone, Colorado, US on Jan. 27-Feb. 2, 1985, 1985, R. P. Gale and D. W. Golde Eds., Alan R. Liss, New York (US), pages 339 to 347;

(27) M. Oh-eda et al., J. Biol. Chem., 1990, Vol. 265, pages 11432 to 11435;

(28) A. Strife et al., Blood, 1987, Vol. 69, No. 5, pages 1508 to 1523;

(29) WO-A-87/01132 (= EP-A-0 237 545);

(70) N. A. Nicola, Ann. Rev. Biochem., 1989, Vol. 58, pages 45 to 77.

XII. The appellants essentially submitted that:

(a) Claim 1 offended against Article 123(2) EPC because (i) the specific activity feature which according to the application as filed was a feature of the mixture of the three G-CSFs had now become also a feature of the individual species A, B and C; (ii) in consequence of the presence of a specific claim directed to glycosylated hG-CSF (claim 5), claim 1 encompassed also unglycosylated hG-CSF which was not disclosed in the application as filed.

(b) Claim 1 was not clear because: (i) it failed to state the concentration of the factor, which was known to have a bearing on the proliferative effect on different colonies (cf in particular, as an expert opinion, document (70), bottom paragraph of page 47 and Figure (1), and (ii) it referred in general terms to a test on human bone marrow cells which was known to be affected by a series of factors such as eg cell purity and cell density (cf second declaration by Dr K. Welte), none of which was disclosed in the patent specification.

(c) The embodiments referred to in items (i) and (ii)

of point (a) above were not disclosed in the patent specification (objection under Articles 84 and 83 EPC).

(d) The pluripoietin disclosed at the meeting in Wilsede (cf eg documents (1a) and (2a)) was the same product as that of claim 1. The two products had in common features such as the molecular weight, the isoelectric point, the specific activity. The N-terminal amino acid sequence was later shown to have been an inherent feature of the prior art product (cf eg documents (15) and (29)). Also the two methods of purification did not substantially differ. As for the pattern of activity which had now been introduced in claim 1, it was not a feature useful to establish any distinction over the known prior art product because: firstly, in the absence of a reference to the concentration of the factor and to a reliable test, the said feature had no clear technical meaning (cf item (b) supra), and, secondly, the stimulatory activity on "some" eosinophil progenitors reported for pluripoietin was merely a consequence of the assay conditions. When assayed on low-density, non-adherent bone marrow cells pluripoietin produced no eosinophils (cf. second declaration of Dr Welte and document (28)). Post-published evidence (cf documents (15), (28) and (29)) and the declaration of Dr Welte demonstrated that pluripoietin of document (1a), which was the same product referred to in document (14), was indeed hG-CSF falling within the scope of claim 1. Thus, the claim lacked novelty.

(e) At any rate, in view of the closest prior art as represented by the disclosure of pluripoietin at the Wilsede meeting (cf documents (1a,b), (2a,b)), there could not be an inventive contribution to the art by a product, such as that claimed, whose activity was unclearly defined and which had a specific activity lower (3.94×10^7 U/mg) than that of the known pluripoietin (1.5×10^8 U/mg).

XIII. The respondents argued that:

(a) The specific activity value referred to in the claim applied to each of the individual components or to any mixtures since the glycosylation status of hG-CSF was irrelevant for its biological activity as shown in the patent;

(b) Claim 5 was supported by the application as filed which disclosed glycosylated hG-CSF. Moreover, the reference to the possibility of producing it in a microorganism by a recombinant DNA method supported also unglycosylated embodiments. These could in any case be carried out by the skilled person without any difficulties as methods and means for deglycosylating a glycoprotein were well known in the art;

(c) The complete identity of pluripoietin disclosed at the Wilsede meeting (cf documents (1a,b), (2a,b)) with the claimed subject-matter had never been shown by the appellants. The respondents had demonstrated by way of the experimental reports of Dr Nomura (cf in particular the second experimental report) that, when working according

to the method described in document (1a), a product was obtained which differed in its pattern of activity from the hG-CSF of the patent in suit, and that only when the method according to the patent in suit was used could hG-CSF be isolated from the Welte's starting material. Contrary to the appellants' submissions, the two methods of purification were not identical. The purpose of the work described at the Wilsede meeting was the isolation of the human counterpart of murine interleukin-3, and the authors were satisfied that this had been achieved on the basis of the colony growth stimulation profiles. As confirmed also by the declaration of Dr Nicola, pluripoietin as disclosed in document (1a) or in the later corresponding publication (14) was not a purified hG-CSF, but a mixture of hG-CSF with other co-purified CSFs. The said product was not the same described in the later documents (15), (19), (29). Thus, novelty had to be acknowledged;

(d) The disclosure at the Wilsede meeting provided no incentive at all for the skilled person to attempt the isolation of hG-CSF from pluripoietin as the latter was not described as a mixture but as a product purified to homogeneity. On the other hand, the skilled person, when starting from the knowledge of prior art document (8) and faced with the problem of providing pure hG-CSF, had no reasonable expectation of success because, apart from the fact that the product described in document (8) was curiously accompanied by some inhibitory materials, the source cell line was not available. Nor was any strategy to overcome this

problem suggested by documents (16) or (17) both of which were concerned with murine G-CSF. Under these circumstances, the skilled person had to devise an inventive strategy in order to solve the technical problem, as done by the patent in suit.

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

The respondents requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims submitted at the oral proceedings on 4 August 1999 and pages 3, 4, 5, 12 and 13 of the description as submitted on 4 August 1999, page 6 as filed on 11 February 1993, page 7 as filed on 29 September 1990 and pages 8 to 11 as granted, and the drawings as granted.

Reasons for the Decision

Procedural matters

1. The appellants objected to the respondents repeatedly being given, during the initial phase of oral proceedings, the possibility to amend the claims on file in order to meet an Article 123(2) EPC objection which was raised by the board for the first time at oral proceedings.

It is established jurisprudence that the admission of additional late requests into the proceedings is a matter of discretion of the board concerned, in the light of the particular circumstances (cf eg T 794/94

of 17 September 1998, in particular point 2 of the reasons). There is normally no right to file an endless succession of new requests in substitution for requests found inadmissible or unallowable by the board (ibidem, point 2.1.4 of the reasons). However, the particular circumstances of the present case, especially the fact that amendments were in response to a formal objection never raised during the written phase, justified granting the respondents repeatedly the opportunity to amend claim 1 in order to find the most appropriate wording, as they had declared their willingness to fully meet the objection.

2. Other procedural matters raised by the appellants (cf Section VIII supra) need not be discussed here as they had no bearing upon the decision-making.

Article 123(2)(3) EPC

3. Claim 1 on file (for non-AT States and for AT) has been restricted in comparison to claim 1 as granted by further specifying the required pattern of biological activity. In this respect, the appellants had no objections under Article 123(3) EPC, nor does the board see any objection.

4. The feature "the ability of promoting the differentiation and proliferation of human bone marrow cells to neutrophilic granulocytes but not to granulocyte-macrophages and not eosinophils in the human bone marrow cell assay at days 7, 10 and 14 of the incubation" finds its basis on page 2, lines 2 to 8 and page 24, lines 5 to 13 of the application as filed.

The reference to the method for activity determination in connection with the specific activity is based on page 20, lines 18 to 20 of the application as filed. Both these amendments were not contested by the appellants under Article 123(2) EPC.

5. The objections raised by the appellants under Article 123(2) EPC are two-fold: (i) the attribution of the specific activity value also to the individual hG-CSF species with isoelectric points A, B and C, respectively; and (ii) the extension of the contents of the specification to unglycosylated hG-CSF.

6. As regards the objection under (i), the following is observed:

(a) It is true that the specific activity value of at least 3.94×10^7 U/mg was measured as being the specific activity of the hG-CSF preparation of Example 1, and that the specific activity of the hG-CSF of the three bands with isoelectric points A, B and C which were derived therefrom was neither directly determined, nor explicitly mentioned;

(b) However, the skilled person reading the application as filed would notice: firstly, that the isoelectrophoretic separation of the three components was carried out on the already purified material of Example 1, ie on material having a specific activity of at least 3.94×10^7 U/mg (cf page 13, line 18 to page 14, line 33 and Example 4); secondly, that the differences in the isoelectric points were attributed to differences

in the number of sialic acid residues (cf page 15, lines 10 to 13); and, thirdly, that removal of sialic acid residues by treatment with neuraminidase caused no injury to CSF (cf page 15, lines 9 to 10). On the whole, this information leads the skilled person to the logical conclusion that the further separation of the hG-CSF of Example 1, which has a specific activity of 3.94 x 10^7 U/mg or higher, into the individual hG-CSF components by preparative isoelectric electrophoresis as carried out in Example 4 results in fractions also having a specific activity of 3.94 x 10^7 U/mg or higher;

(c) The appellants remarked, with reference to prior art document (8)(cf abstract and page 46, right-hand column, lines 2 to 3) and to post-published document (27) as an expert opinion, that neuraminidase causes a decrease in activity and that thus the specific activity of the individual species A, B, and C cannot be assumed to remain the same. The board, however, observes that, as regards the effect of the neuraminidase treatment on hG-CSF, document (8) refers in the abstract to a "slight" decrease, on page 46 to a "partial loss" of activity and on page 47, left-hand column, line 37 to 39 to **no loss** of biological activity. This confirms what is stated in the patent in suit, ie that treatment with neuraminidase does not substantially damage the factor. As for later document (27), it refers to "deglycosylated" hG-CSF, ie to a CSF digested with additional enzymes, not only neuraminidase. Thus, neither document (8) nor document (27) can affect

the conclusion drawn in item (b) supra. In any case, what matters are the contents of the application as filed and what the skilled person would logically deduce therefrom. For the reasons given above, in the board's judgement, the contents of the application as filed provide a fair basis for the contested amendment.

In conclusion, the board sees no objection under Article 123(2) in respect of the amendment referred to under item (i) of point 5 supra.

7. As regards the objection under item (ii) of point 5 supra, it has to be observed that "unglycosylated" hG-CSF **is not** specifically claimed. Thus, the allowability of such a specific claim need not be considered because it is not part of the specification. The mere introduction of a dependent claim directed to "glycosylated" hG-CSF (claim 5) does not necessarily imply that the content of the application as filed has been extended to include specifically "unglycosylated" hG-CSF. The application as filed provides support, on the one hand, for a general claim, such as claim 1 at issue, directed to hG-CSF which **does not** refer to glycosylation as a specific feature (cf claims 1 and 2 as filed), and, on the other hand, for a claim, such as claim 5 at issue, specifically directed to glycosylated hG-CSF, this being explicitly disclosed (cf eg page 19, lines 28 to 30). For these reasons, no objection is seen by the board under Article 123(2) EPC.

Clarity (Article 84 EPC)

8. The appellants consider that claim 1 at issue (for non-

AT States and for AT) does not clearly define the subject-matter for which protection is sought. Their view is that, due to the absence from the claim of (i) a reference to a reliable way of testing, (ii) concentration data, and (iii) an upper limit for the specific activity, the skilled person is left in doubt as to the real meaning of the claim.

The board does not share the appellants' concerns for the following reasons:

(a) Apart from stating a number of physicochemical features, claim 1 requires that the hG-CSF possess "the ability of promoting the differentiation and proliferation of human bone marrow cells to neutrophilic granulocytes but not to granulocyte-macrophages and not eosinophils in the human bone marrow cell assay at days 7, 10 and 14 of the incubation". This is a feature which can be tested according to methods known in the art. The patent specification provides the necessary details in this respect on page 5, lines 1 to 35 and in Example 6. Analogous determinations are described in the prior art (cf eg documents (1a), (2a), (8)) so that no particular difficulties, other than possibly the usual variability of biological assay systems, are seen by the board in performing them;

(b) As for the lack of a reference to a given concentration of the factor in the claim, the board considers that no such reference is needed. The skilled person knows from the art (eg document (8), see in particular the passage bridging pages 48 and 49) that an hG-CSF preparation

typically stimulates in a selective manner neutrophilic granulocytes **at all dilutions** and that essentially no other colonies or a very low percentage of other colonies are found. Thus, the claim requirement is not unusual and, as in the prior art (cf documents (1a), (2a) and (8)), it can be routinely tested at serial dilutions of a sample. The fact that at higher concentrations of the factor additional stimulatory effects can possibly be observed (cf post-published document (70), page 47, last paragraph and Figure (1)) does not change this conclusion because it is the overall pattern of biological activity at the different dilutions which provides the skilled person with the information about the nature of the factor under determination.

(c) An upper limit for the specific activity would be unjustified as it is well known that in the course of a purification process the specific activity of a biologically active protein is normally increased by any further step. Thus, it is quite normal to refer to the lower limit in the same form as done in claim 1 at issue.

Sufficiency of disclosure (Article 83 EPC) and support by the description (Article 84 EPC)

10. In the appellants' view, a skilled person, having read the patent specification, is unable to perform without undue burden the three particular embodiments falling under the scope of claim 1, namely the hG-CSFs having a specific activity of at least 3.94×10^7 **and** any one of the stated isoelectric points. In their view, these

embodiments are not supported by the description in the patent specification.

11. The board does not share the appellants' view for the following reasons:

(a) The patent in suit provides in Example 1 a detailed disclosure of the experimental protocol for the isolation and purification of hG-CSF to a specific activity of at least 3.94 x 10^7 U/mg. In this respect all methods and means are described, the source cell line for the factor having been also made publicly available by way of deposition (C.N.C.M. Deposit No. I-315);

(b) Example 4 describes the preparative isoelectric electrophoresis for the separation of the said hG-CSF material into the individual components. For the reasons given in point 6, item (b) above, the board believes that the skilled person would logically expect them to have, as the starting material, a specific activity of at least 3.94 x 10^7 U/mg. This determination is a matter of routine for the skilled person;

(c) No particular difficulties or gaps in technical information are seen by the board which could prevent the skilled person from repeating the experimental protocols given without the need to apply inventive skill or undue effort. Nor were the appellants able to point to any such difficulties or gaps.

12. The appellants also object that the patent

specification does not provide a sufficient disclosure of "unglycosylated" hG-CSF which allegedly falls under the scope of claim 1.

13. Even assuming that "unglycosylated" hG-CSF does fall under the scope of the generally worded claim 1, as already observed above in point 7, it is not specifically claimed as such. Nor is there any experimental evidence here that methods routine at the priority date would not enable such unglycosylated hG-CSF to be made with the activity required by the claims. Thus a discussion on whether or not the description of the patent specification enables it is unnecessary for the purpose of either Articles 123(2) or 83 EPC. The fact that a claim covers subject-matter broader than specifically described embodiments is not in itself an objection.

Novelty (Article 54 EPC)

14. Claim 1 (non-AT states) is directed to an hG-CSF factor, which, when tested for its activity in a human bone marrow cell assay, at days 7, 10 and 14 of incubation promotes the differentiation and proliferation of neutrophilic granulocytes **but not** to granulocyte-macrophages and **not** to eosinophils. The factor is characterised by its molecular weight, isoelectric point, UV absorption, N-terminal amino acid sequence (21 residues) and specific activity. The patent specification describes the method of assay on page 5, lines 1 to 35 and shows that low-density, non-adherent cells were used.

15. At the Wilsede meeting the isolation and purification

of pluripoietin from the 5637 cell line was disclosed (cf documents (1a,b), (2a,b)). This factor was described as having characteristics that partly overlap with those of the factor of the patent in suit (molecular weight, specific activity, isoelectric point, stimulation of neutrophils), but also as having a series of biological activities which the latter does not display, namely stimulation of colony growth from human early erythroid and multipotential progenitors, monocyte and some eosinophil progenitors. The assay system used was a low density human marrow cell assay, it not being specified whether the cells were non-adherent cells. Document (14), which - as submitted by the appellants - constitutes the later publication of the results presented at the Wilsede meeting, indicates that the assay was performed on cells which were non-adherent on tissue culture dishes. Thus, the assay system was submitted to be comparable to the one used in the patent in suit.

16. Based on later evidence, especially document (28), and on the declaration of Dr Welte, the appellants submit that this pluripoietin (also called pluripotent CSF or ß-CSF) is identical to the claimed hG-CSF (cf Section XII, item (d)). The respondents dispute this in particular on the basis of the experimental reports of Dr Nomura (cf Section XIII, item (c)).

17. The teaching made available at the Wilsede meeting was that of the isolation and purification of a factor capable of stimulating in vitro colony growth formation from human early erythroid and multipotential progenitors, monocyte and neutrophil and some eosinophil progenitors. The name given to the factor

reflects these multiple biological activities and shows that the authors (and, thus, the public receiving the information) were convinced that a **pluripotent** factor had been made available in relatively pure and homogeneous form, **not** a factor specifically stimulating only colonies of neutrophilic granulocytes. The authors gave no indication that they suspected that the product of the fraction they had characterised and disclosed as homogeneous contained an hG-CSF **together** with one or more other co-purified human CSFs, nor would the public attending the meeting have understood this. In this sense, the contents of the poster presentation at Wilsede is substantially different from the subject-matter of claim 1 and this, in the board's judgement, must result in the novelty of claim 1 being acknowledged.

18. The board reached this conclusion based on the examination of the whole body of evidence available, and in particular based on the following documents and/or considerations:

- In the second experimental report, Dr Nomura repeated the work as described in document (1a) and confirmed in a human bone marrow cell assay the pattern of biological activities reported for pluripoietin, which differ from those required by claim 1 at issue. The criticism by the appellants that the said experimental report is invalid because Dr Nomura omitted a further preparative SDS-Page step is not considered justified because: firstly, Dr Nomura, followed the purification steps of the Table "Purification of human Pluripoietin CSF" which does not include such a

step, and, secondly, document (1a) does not report that such a step resulted in a product without eosinophil colony formation activity. The appellants have not provided experimental evidence contradicting the finding by Dr Nomura. The declaration of Dr Camble, which they filed in order to show that hG-CSF can be isolated from the cell line 5637 when working according to document (1a), refers inter alia to HPLC elution conditions different from those of document (1a) and is silent about the pattern of biological activities. Consequently it does not allow any conclusion to be drawn which could contradict the findings of Dr Nomura;

- In their declarations, Dr Nicola and Dr Metcalf (second declaration), known experts in this area of technology, both conclude that pluripoietin was **not** essentially a purified hG-CSF, but a mixture of hematopoietically active factors showing a profile of activity uncharacteristic of hG-CSF.

- Later document (15) describes prior art pluripoietin as a factor **encompassing** the activities of murine IL-3 and G-CSF (cf page 61, middle column). This confirms that pluripoietin was perceived by the experts in the field as a factor with multiple biological activities.

- Later publications by the same authors of document (1a) confirmed in assays on low density, non-adherent human bone marrow cells the broader pattern of activity of pluripoietin, in particular on eosinophil formation also after day 14 of

incubation (cf documents (14) and (20)).

- As regards later document (28), which in the appellants' view, shows that, when properly assayed (ie on low density, non-adherent bone marrow cells), pluripoietin produced no eosinophils and thus was identical to hG-CSF, its significance in the present discussion of the novelty issue is very much reduced inter alia by the fact that: firstly, the assay therein described is different from the ones used in the patent in suit and in the "pluripoietin" prior art as it involves a rigorous depletion of the so-called accessory cells by way of monoclonal antibodies and cloning at very low numbers to minimize the effects that non-colony-forming cells as well as large number of developing granulocyte-macrophages may have (cf page 1509 "Panning procedure" and page 1520, right-hand column, second paragraph); secondly, there is no certainty that the natural pluripoietin which is said to have been supplied by Dr Welte, who declared that it was from the same batch of material purified prior to May 1984 (cf second declaration of Dr Welte), was exactly the product whose features were disclosed at Wilsede in 1984 and not a product resulting from some further developments in the subsequent years, Dr Welte being also co-author of the work described in document (28) and thus having potentially access to "inside" information. In any case, the data reported in document (28) do not contradict Dr Nomura's experiments.

- While it is understandable that Dr Welte in his declarations, in tracing back the history of the work on pluripoietin and hG-CSF, comes to the conclusion that pluripoietin was hG-CSF, for the purpose of novelty it is decisive to establish the true value of the prior art divulgation at the Wilsede meeting for a skilled person, regardless of any "inside" or later information which may have become available at a subsequent date. As already stated (cf point 17 supra), at the Wilsede meeting the teaching made available was that of an apparently homogenous factor with multiple colony forming activities, which does not fall under the scope of claim 1 at issue, and of a method for purifying it which, as confirmed by Dr Nomura, could not lead the skilled person to a product having **all** the features of the product now claimed.

19. Product claim 1 (non-AT states) being acknowledged as novel, the subject-matter of the remaining claims for non-AT states and of the claims for AT is a fortiori novel as they concern either embodiments of claim 1 or a method of preparation of the factor of claim 1.

Inventive step (Article 56 EPC)

20. At the priority date (in 1984), colony stimulating factors (CSFs) were known chiefly as activities attributable to proteins. Certainly in relation to humans it was not yet known how many such proteins existed, what their full amino acid sequence was or what precise CSF activity or activities could be attributed to which protein. The problem solved by the

invention as now claimed can be stated as being the provision of a CSF that stimulated the differentiation and proliferation of human bone marrow cells to neutrophilic granulocytes but not to granulocyte-macrophages and eosinophils. This was a problem that the skilled person could have posed for himself or herself at the priority date.

21. In relation to the problem as above defined, the disclosures at the Wilsede meeting as evidenced by documents (1a,b) and (2a,b) cannot be taken as the closest prior art from which a skilled person would have started, because from them the skilled person would have got the impression that the "pluripoietin" had more activities that he or she was looking for. Nor, as the disclosures at Wilsede suggested that a single CSF was involved, would these disclosures have been selected as a starting point by someone looking for a CSF with activities different from those mentioned as there was no hint that the Wilsede material could be resolved into more than one CSF or purified to obtain a CSF with the desired properties.

22. In the board's view, the closest prior art is rather represented by document (8) which is concerned with the preparation and characterisation of an hG-CSF from a CSF-producing cell line called T3M-1. The factor, which is found in the conditioned medium of the cells, is reported to stimulate only granulocytic colony formation of human and mouse bone marrow cells, no eosinophil or macrophage CSF activities being found. No real purification of the factor is described as merely fractions from a gel filtration run are recovered and assayed on human bone marrow cells, the highest value

of specific activity measured being 4.900 U/mg. No chemical characterisation of the product is reported in the document. Gel filtration shows two peaks of activity, one at an apparent molecular weight of about 30,000, the other at an apparent molecular weight of 15,000. The document states that further studies are necessary to ascertain whether the two distinct peaks represent distinct molecular species or simply an association-dissociation phenomenon.

23. The underlying technical problem can be defined as the preparation of purified hG-CSF and its further characterisation. The solution proposed by the patent in suit is the product of claim 1 (non-AT states), its preparation method of claim 6 (non-AT states; cf claims 1 to 3 for AT) and the pharmaceutical compositions containing it (claims 8 to 10 for non-AT states).

24. The position of the appellants *tout court* that the said claims do not provide any type of contribution to the art having regard to the prior disclosure of pluripoietin which had also a better specific activity (cf Section XII, item (e) supra), cannot be accepted because, as discussed above under "Novelty", the claims at issue relate to novel subject-matter which as such constitutes the contribution to the art for which inventive step has to be assessed.

25. The key questions in respect of inventive step is what steps the skilled person, starting from document (8), would have considered taking and whether these would have led him or her with a reasonable expectation of success to the claimed-subject matter.

26. In the board's view, the obvious option for the skilled person would have been the isolation and chemical characterisation of the factor produced by the cell line of document (8). However, for this the skilled person would have been faced with the problem of obtaining the source cell line. As this cell line was not publicly available, the skilled person was left to his/her own resources to find or develop an alternative source. In this respect, other prior art documents concerned with hG-CSF (ß-CSF) like eg document (7), would not have provided any useful suggestions as the said documents referred to the factor prepared in non-purified form from human placental conditioned medium and to some uncertainties as to whether the same factor was responsible for the stimulation of the progenitor cells and for the activation of mature cells (cf loc.cit., page 798, left-hand column, last paragraph). Also the prior art documents concerned with the murine G-CSF (cf documents (16) and (17)) would not have suggested any suitable source of hG-CSF. The idea of using the 5637 cell line referred at the Wilsede meeting would also not have readily occurred to the skilled person as this cell line had been shown to be the source of a different factor, namely pluripoietin, with multiple biological activities. The latter was not what he or she was looking for.

27. Under these circumstances, the skilled person expected to have to establish a suitable cell line, before being able to prepare and purify hG-CSF therefrom. He or she knew that this was not simply a routine exercise as it required a considerable amount of experimentation and/or luck. Consequently, it was not possible for the skilled person to predict a successful conclusion

within acceptable time limits, and thus there was not a reasonable expectation of success. Nor is there any evidence before the board that contrary to this expectation, only routine work would have in fact been required starting from document (8).

28. For these reasons, the claimed subject-matter involves an inventive step and is allowable under Article 56 EPC.

The adaptation of the description

29. Of the amendments made to the description, the respondents objected only to the amendment made on page 13 where lines 5 to 6, which in the granted version read: "From the following results of experiments (1) to (5), the G-CSF of the present invention was found to have been purified to apparent homogeneity:...", have been changed to read "From the following results of experiments (1) to (5), the G-CSF of the present invention was found to have been substantially purified:...". In their view, the said amendment changes the interpretation to be given to product claim 1 and renders a distinction over the known pluripoietin impossible.

30. The board finds no basis for such an objection because the paragraph on page 13, lines 5 to 14 makes merely reference to results of experiments (1) to (5) demonstrating the substantial purity of the hG-CSF of the patent in suit which, as stated above under "Novelty", has been found to be distinctly different from the known pluripoietin. Whether in the description the said product is referred to by the label "substantially purified" (this was the wording used in

the application as filed) or as "purified to apparent homogeneity" makes no difference to what will be understood by the reader. In these circumstances the wording as originally filed is to be preferred."

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 claims submitted at the oral proceedings on 4 August 1999, with a description having pages 3, 4, 5, 12 and 13 as filed on 4 August 1999, page 6 as filed on 11 February 1993, page 7 as filed on 29 September 1990 and pages 8 to 11 as granted, and the drawings as granted.

The Registrar: The Chairman:

U. Bultmann L. Galligani