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D E C I S I O N
of 19 May 1998

Case Number: T 0879/94 - 3.3.4

Application Number: 86113671.1

Publication Number: 0217404

IPC: C12P 21/02

Language of the proceedings: EN

Title of invention:

Pharmaceutical composition containing a human granulocyte colony stimulating factor for the treatment of leukopenia

Patentee:

Chugai Seiyaku Kabushiki Kaisha

Opponent:

Boehringer Mannheim GmbH Patentabteilung

Headword:

Human G-CSF/CHUGAI

Relevant legal provisions:

EPC Art. 54, 56

Keyword:

"Novelty (yes)"

"Inventive step (yes)"

Decisions cited:

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Catchword:

-

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Case Number: T 0879/94 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 19 May 1998

Respondent:
(Opponent)

Boehringer Mannheim GmbH
Patentabteilung
Sandhofer Strasse 116
68298 Mannheim (DE)

Representative:

Huber, Bernhard, Dipl.-Chem.
Patentanwälte
H. Weickmann, Dr. K. Fincke
F.A. Weickmann, B. Huber
Dr. H. Liska, Dr. J. Prechtel, Dr. B. Böhm
Postfach 36 08 20
81635 München (DE)

Appellant:
(Proprietor of the patent)

Chugai Seiyaku
Kabushiki Kaisha
5-1, 5-chome, Ukima
Kita-ku
Tokyo (JP)

Representative:

VOSSIUS & PARTNER
Postfach 86 07 67
81634 München (DE)

Decision under appeal:

Interlocutory decision of the Opposition Division
of the European Patent Office posted 7 September
1994 concerning maintenance of European patent
No. 0 217 404 in amended form.

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
S. C. Perryman

Summary of Facts and Submissions

I. The appellants (patentees) lodged an appeal against the interlocutory decision of the opposition division issued on 7 September 1994 whereby the European patent No. 0 217 404, which had been opposed by one party under Article 100(a) EPC, was maintained in amended form on the basis of claims 1 to 4 filed on 14 April 1994, these being the sixth auxiliary request then on file (cf Section III infra).

II. Claim 1 as granted for all designated Contracting States except Austria and Spain (non-AT, non-ES States) was as follows:

"A leukopenia treating agent containing a human granulocyte colony stimulating factor as an effective ingredient."

Claim 1 as granted for AT, ES was as follows:

"A method for preparing leukopenia treating agent which comprises combining a human granulocyte colony stimulating factor as effective ingredient with a pharmaceutically acceptable carrier or excipient and optionally a stabilizer and/or anti-adsorption agent."

The commonly used abbreviation for granulocyte colony stimulating factor is G-CSF.

III. Claim 1 for the non-AT, non-ES States on the basis of which the patent was maintained by the opposition division read as follows:

"Use ^{of} a human G-CSF for the preparation of a pharmaceutical composition for the treatment of leukopenias that require increasing the number of

neutrophiles having a fully matured form, wherein said G-CSF is produced from a transformant containing a recombinant vector harboring a gene encoding it and is represented by the amino sequence shown below:

(Met)_n [amino acid sequence given]
(provided that n is 0 or 1)"

Dependent claims 2 to 4 related to embodiments of the use according to claim 1.

The corresponding claims 1 to 4 for AT, ES were drafted in terms of a method for the preparation of a pharmaceutical composition.

The opposition division considered that of all the claim requests then on file only the said claims of the sixth auxiliary request satisfied the EPC requirements.

In the decision, reference was made in particular to the following documents:

- (1) EP-B-0 169 566, which is the granted version of the published European patent application EP-A-0 169 566;
- (2) Proc.Natl.Acad.Sci. USA, Vol. 82, March 1985, pages 1526 to 1530;
- (3) Exp. Hematol., Vol. 9, April 1981, pages 332 to 345;
- (4) Acta Haematol. Jap., Vol. 47, 1984, pages 1714 to 1721;

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(6) EP-B-0 237 545, which is the granted version of the published international patent application WO-A-87/01132;

(8) Nature, Vol. 314, 1985, pages 625 to 628.

IV. With the statement of grounds of appeal, the appellants filed an auxiliary claim request and introduced into the proceedings three further documents.

V. With their reply, the respondents requested the dismissal of the appeal and submitted one additional document.

VI. The appellants by letter of 16 April 1998 filed a new auxiliary request and introduced four additional documents into the proceedings.

VII. The respondents by letter of 28 April 1998 stated that they withdrew their request for dismissal of the appeal and for oral proceedings, and that they would not be represented at the oral proceedings.

VIII. Oral proceedings took place on 19 May 1998. As a sole claim request during oral proceedings claims 1 to 10 were filed in the two versions for the non-AT, non-ES States and for AT, ES.

Claim 1 for the non-AT, non-ES States read as follows:

"Use of a human G-CSF for the preparation of a pharmaceutical composition for the treatment of neutropenia by increasing the number of neutrophils having a fully matured form."

Dependent claims 2 to 10 related to specific embodiments of the use according to claim 1.

Claim 1 for AT, ES read as follows:

"A method for the preparation of a pharmaceutical composition for the treatment of neutropenia by increasing the number of neutrophils having a fully matured form, comprising combining human G-CSF with a pharmaceutically acceptable carrier or excipient and optionally a stabilizer and/or an anti-adsorption agent."

Dependent claims 2 to 10 related to specific embodiments of the method according to claim 1.

A description fully adapted to the said claims was also submitted.

- IX. The appellants essentially maintained that the subject-matter of the sole claim request on file was novel over that disclosed in document (1). This document contained only some in vitro data on bone marrow cells from healthy donors. These data demonstrated the ability of human G-CSF to promote the differentiation of precursor stem cells to granulocytes and did not suggest using G-CSF for the preparation of a composition for the treatment of neutropenia. Moreover, they argued that none of the cited prior art documents, alone or in combination, rendered obvious for a skilled person the claimed use of G-CSF in the preparation of a pharmaceutical composition for the treatment of neutropenia. In particular, both documents (4) and (8), which were referred to by the board, demonstrated that the knowledge in the art about the G-CSF as molecular entity was not yet complete and its therapeutic usefulness was still under study. Thus, an inventive step had to be recognised.

- X. The appellants requested that the decision under appeal be set aside and the patent be maintained on the basis of the claims and the description submitted at the oral proceedings on 19 May 1998.

Reasons for the Decision

The formal requirements (Articles 123(2)(3) and 84 EPC)

1. The extent of protection conferred by the claims at issue is narrower than that conferred by the claims as granted since the claims are now limited to the use of human G-CSF for the preparation of a composition for the treatment of neutropenia, the latter medical condition being one type of leukopenia. Thus, there is no objection under Article 123(3) EPC.
2. The application as filed explicitly describes the use of human G-CSF in the preparation of a pharmaceutical composition for the treatment of neutropenia by increasing the number of neutrophils having a fully matured form (cf eg paragraph bridging pages 2 and 3; page 4, lines 27 to 37). Thus, the subject-matter of the claims at issue does not extend beyond the contents of the application as filed. Consequently, no objection under Article 123(2) EPC is seen by the board.
3. The claims at issue satisfy also the clarity requirements of Article 84 EPC.

Novelty (Article 54 EPC)

4. In the decision under appeal documents (1) and (6), which are both prior art under Article 54(3)(4) EPC, were discussed in respect of the novelty issue.

5. Document (1) (references being to the text of the published patent application) deals with the isolation of a human G-CSF identical to the one described in the patent in suit. This document also suggests G-CSF as a potential curative agent for leukopenia (cf page 1, lines 12 and 13) as well as for serious infections (cf page 25, lines 1 to 9). The effect of the factor on the proliferation and differentiation of neutrophiles is emphasized (cf page 7, lines 2 to 8 as well as page 25 lines 8 to 9). On page 24, lines 10 to 13, it is reported that at days 7, 10 and 14 of the incubation of human bone marrow cells, the colonies formed by using G-CSF were entirely composed of chloroacetate esterase positive neutrophiles, no other colony type being found.

6. In the board's judgement, although document (1) points to the effect of human G-CSF on the proliferation and differentiation of bone marrow cells to neutrophiles (this being in fact the characteristic biological activity of this factor) and suggests a "potential" clinical use in the treatment of leukopenia, its whole contents do not convey to the skilled person the specific suggestion of using human G-CSF in the preparation of a pharmaceutical composition for the treatment of neutropenia. This is because:

(a) firstly, the clinical use of human G-CSF for the treatment of leukopenia is qualified only as "potential", ie as a possibility worth investigating;

(b) secondly, the said prudent suggestion is made in respect of leukopenia, not of neutropenia. As confirmed on page 3, lines 35 to 48 of the patent in suit, leukopenia is a term used in the art in respect of a medical condition in which a generalized reduction in the number of leukocytes,

ie of the while blood cells (eg neutrophiles, basophiles, eosinophiles, monocytes), is observed. Leukopenia, although encompassing inter alia neutropenia, cannot be equated thereto. The term neutropenia refers to a particular leukopenic condition in which a decrease in the number of **neutrophilic** leukocytes is observed. In this respect, it is a distinct medical condition which can be recognised by a doctor on the basis of diagnostic tests.

Thus, while document (1) refers to a potential use of G-CSF in a **general** therapeutic application (leukopenia), present claim 1 refers - in the terms of a second medical use claim - to a **specific** therapeutic application (neutropenia). The fact that, as recognized in the patent in suit (see page 3, lines 38 to 39), on a clinical basis most cases of leukopenia are due to a decrease in the number of neutrophiles, does not allow the conclusion that the novelty of the specific clinical application is affected by the disclosure in document (1) of the suggestion for a more general clinical application. Consequently, since in assessing novelty any inventive-step elements have to be left out of consideration, document (1) does not take away the novelty of the present claims.

7. As regards document (6) (references being to the text of the published patent application), it refers even more generally to the clinical use of pluripotent G-CSF in the treatment of hematopoietic deficits arising from chemotherapy or from radiation therapy and in bone marrow transplantation (see page 8, lines 7 to 12), neither leukopenia nor neutropenia being mentioned. Thus, this document does not take away the novelty of the present claims.

8. None of the remaining documents affects the novelty of the claimed subject-matter.

Inventive step (Article 56 EPC)

9. In the board's view, the closest prior art is represented by document (4) which describes the purification of a human urine colony stimulating factor (CSF-HU) and its use by way of intravenous infusions in treating leukocytopenic patients. As reported, the latter treatment produced an early rise in the absolute neutrophile counts. The document also reports that in leukocytopenic mice, daily injections of CSF-HU stimulated the restorative granulocyte production. Although the exact nature of the isolated CSF-HU is not described, from the profile of activity reported in the document the skilled person would have considered it to be a mixture of different human colony stimulating factors, human granulocyte/macrophage-CSF (GM-CSF) and macrophage-CSF (M-CSF) being predominant. Document (4) does not make reference to human G-CSF. Nevertheless it is seen as the most appropriate starting point for a discussion of inventive step in the present case because it deals with the treatment of a leukocytopenic condition.
10. In the light of document (4), the problem to be solved was the finding of a pharmaceutical composition for treating neutropenia, ie a specific leukocytopenic condition characterized by a decrease in the number of neutrophilic leukocytes.
11. As a solution thereto, the claims on file propose the use of human G-CSF. The patent specification, relying on animal models, shows that indeed human G-CSF is active in increasing the number of neutrophiles, these having a fully matured form (cf eg Example 14).

12. The relevant question is whether the skilled person, starting from the teaching of document (4), would have readily derived from any other prior art document(s) an hint or suggestion in respect of the use of human G-CSF in the treatment of neutropenia.

13. At the priority date of the patent in suit (1985), some information about the human G-CSF was already available, its possible clinical use was yet unidentified (cf documents (8) to (10)). For example, document (8) reported the identification of human G-CSF and its activity in inducing differentiation of cells from a human promyelocytic leukaemia cells line with formation of colonies of neutrophils. The conclusion drawn in this study was that human G-CSF merited further study as regards its possible therapeutic usefulness (see page 628, left column, second paragraph).

14. In the board's judgement, the skilled person, faced with the stated technical problem, starting from the teaching of document (4), would not have readily come to the idea of using human G-CSF for preparing a pharmaceutical composition for the treatment of neutropenia because, firstly, in the art only preliminary information was available in respect of the factor itself (cf documents (8) to (10)) and, secondly, its possible clinical application was still a matter of speculation (cf document (8)). From document (4) itself, the skilled person would have only inferred that colony stimulating factors were possible candidates for a clinical application in the treatment of leukocytopenic conditions. This, however, was not enough to direct to the skilled person's attention specifically to human G-CSF as an agent for the treatment of neutropenia.

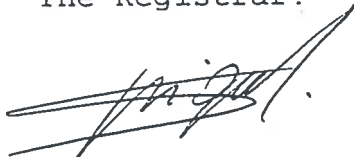
15. For these reasons, in the board's judgement the subject-matter of the claims presently at issue involve an inventive step and consequently the appellants' request is allowable.

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 description and claims as submitted at the oral proceedings on 19 May 1998 and the Figures as published in the patent as granted.

The Registrar:



D. Spigarelli

The Chairperson:



L. Galligani

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