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Datasheet for the decision of 16 February 2016

Case Number: T 0524/11 - 3.3.04

Application Number: 99955046.0

Publication Number: 1123313

IPC: C07K14/505, A61P7/06, C12N5/10, C12N15/12

Language of the proceedings: EN

Title of invention:
Methods and compositions for the prevention and treatment of anemia

Patent Proprietor:
Amgen Inc.

Opponent:
Sandoz AG

Headword:
Anemia treatment/AMGEN

Relevant legal provisions:
EPC Art. 54, 56, 84, 123(2), 123(3)
EPC R. 80

Keyword:
Main request - meets requirements of EPC (yes)

Decisions cited:
G 0002/08

Catchword:
-

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Case Number: T 0524/11 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 16 February 2016

Appellant: (Patent Proprietor)	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 (US)
Representative:	Vogelsang-Wenke, Heike Grünecker Patent- und Rechtsanwälte PartG mbB Leopoldstraße 4 80802 München (DE)
Respondent: (Opponent)	Sandoz AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Wichmann, Hendrik Wuesthoff & Wuesthoff Patentanwälte PartG mbB Schweigerstraße 2 81541 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 22 December 2010 revoking European patent No. 1123313 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	B. Claes
	M.-B. Tardo-Dino

Summary of Facts and Submissions

I. The appeal was lodged by the patent proprietor (hereinafter "appellant") against the decision of the opposition division to revoke European patent No. 1 123 313 entitled "*Methods and compositions for the prevention and treatment of anemia*" granted for European patent application 99955046.0, published as WO 2000/024893.

II. The sole independent claim 1 and dependent claims 5, 7, 13 and 14 of the patent as granted read:

"1. Use of a hyperglycosylated analog of erythropoietin for the preparation of a pharmaceutical composition for raising and maintaining hematocrit in a mammal, wherein the analog is to be administered less frequently than an equivalent molar amount of recombinant human erythropoietin to obtain a comparable target hematocrit, and wherein the analog comprises at least one additional glycosylation site compared to human erythropoietin at any one of positions 30 and 88 of the sequence of human erythropoietin such that the analog comprises at least one additional N-linked carbohydrate chain.

5. The use according to claim 1, wherein the hyperglycosylated analog of erythropoietin is to be administered about one time per month.

7. The use according to claim 1, wherein the target hematocrit is at least about 30%.

13. The use according to claim 1, wherein the analog is Asn30 Thr32 Val87 Asn88 Thr90 Epo.

14. The use according to claim 1, wherein the analog comprises two additional N-linked carbohydrate chains."

III. An opposition was filed requesting the revocation of the patent on the grounds for opposition pursuant to Article 100(a) EPC, in conjunction with Articles 54 and 56 EPC, and Article 100(b) EPC.

IV. The opposition division decided that, although the subject-matter of the claims of the patent as granted (main request) was novel, it lacked inventive step. The subject-matter of auxiliary requests 1 and 2 shared the same fate. A third auxiliary request was not admitted into the proceedings.

V. With the statement of grounds of appeal the appellant maintained the main request and submitted six auxiliary requests, further documents and arguments in support of its requests. Auxiliary requests 1 to 3 were identical to the auxiliary requests considered in the decision under appeal. Auxiliary requests 4 to 6 were new requests.

VI. In its reply to the appeal, the opponent (hereinafter "respondent") requested that the appeal be dismissed and provided further documents and arguments to the effect that the claimed subject-matter did not comply with the requirements of Articles 54 and 56 EPC and that the patent did not comply with the requirements of Article 83 EPC.

VII. In a communication pursuant to Article 15(1) RPBA which accompanied the summons to oral proceedings, the board *inter alia* expressed the preliminary opinion, in agreement with the decision under appeal, that the

subject-matter of the claims of the main request, although novel, lacked inventive step.

VIII. With a letter dated 15 January 2016, the appellant submitted new auxiliary requests 2 to 7, replacing previous auxiliary requests 2 to 6, as well as further arguments in support of the allowability of its requests.

The sole independent claim of auxiliary request 6 (consisting of four claims) read:

"1. Use of a hyperglycosylated analog of erythropoietin for the preparation of a pharmaceutical composition for raising and maintaining hematocrit in a mammal, wherein the analog is to be administered less frequently than an equivalent molar amount of recombinant human erythropoietin to obtain a comparable target hematocrit, wherein the target hematocrit is at least 30 %, and wherein the analog comprises two additional glycosylation sites compared to human erythropoietin at positions 30 and 88 of the sequence of human erythropoietin such that the analog comprises two additional N-linked carbohydrate chains to these sites, and wherein the analog is Asn30 Thr32 Val87 Asn88 Thr90 Epo, wherein the hyperglycosylated analog of erythropoietin is to be administered one time per month."

IX. With a letter likewise dated 15 January 2016, the respondent informed the board that it would not be attending the scheduled oral proceedings.

X. Oral proceedings took place on 16 February 2016 in the absence of the respondent. The appellant was heard in relation to the allowability of the requests pending

before the board. The appellant promoted auxiliary requests 6 and 7 (see section VIII), as filed with the letter of 15 January 2016, to become the new main request and the sole auxiliary request, respectively, and withdrew all previously filed requests, including the request for reimbursement of the appeal fee. At the end of the oral proceedings the chairwoman announced the decision of the board.

XI. The following documents are referred to in this decision:

D1: Egrie *et al.* (1997), Blood, Vol. 90, Abstract 243 and slides of the corresponding presentation as filed by the patent proprietor with a letter dated 26 May 2000.

D2: Egrie & Brown (2001), Nephrol. Dial. Transplant, Vol. 16 (Suppl.3), pages 3-13.

D3: EP-A-640 619

D13: Jadoul *et al.* (2004), Nephrol. Dial. Transplant, Vol. 19, pages 898-903.

XII. The appellant's arguments can be summarised as follows:

Inventive step

The administration frequency "one time per month" was a significant improvement over that of rHuEpo which was routinely administered three times per week, and amounted to more than "at least some degree of reduction" as referred to by the opposition division in the decision under appeal.

An administration once per month was even way beyond what was derivable from document D1 for the then described molecule "NESP" (see below), the only report in the prior art on a successful experiment regarding the lowering of the dosage frequency of Epo. Document D13 showed that the safety profile of "NESP" administered once per month was comparable to those obtained for a once per week dosing.

XIII. The respondent's arguments can be summarised as follows:

Inventive step

Document Dl, which represented the closest prior art, described an erythropoietin (Epo) analog designated "NESP" which contained two extra N-linked carbohydrates over rHuEpo. Document D1 disclosed that "NESP" could be administered once weekly or once every other week due to its longer half-life. The document thus disclosed all the features of claim 1, except that hyperglycosylation occurred at positions 30 and 88 of human Epo and that the analog is for administration one time per month.

Since document D2 demonstrated that the amino acid sequence of NESP differed from that of human Epo at five positions (*i.e.* Asn30, Thr32, Val87, Asn88 and Thr90), thereby providing two additional N-linked carbohydrate attachments at the residues at positions 30 and 88, the structural features of NESP were if not explicitly inherently disclosed in document Dl.

Document D3 disclosed hyperglycosylated Epo analogs containing additional N-glycosylation sites which were expected not to perturb the secondary structure or tertiary conformation required for biological activity. The document furthermore taught that an increase of the

number of carbohydrates, and thus sialic acids compounds per Epo molecule, might result in increased serum half-life and increased biological activity. Table 6 of document D3 disclosed *in vivo* data for a number of Epo analogs with additional N-glycosylation sites, including three Epo analogs having five, *i.e.* two additional, N-linked chains. One analog, designated "N47", comprised the following residues at the indicated positions Asn30 Thr32 Val87 Asn88 Thr90, *i.e.* was the analog underlying the patent in suit.

Document D3 disclosed that there was a direct relationship between the sialic acid content, clearance half-life and the ability to increase the hematocrit of treated mice, regardless of the strength of receptor binding.

In view of this guidance in document D3, the skilled person, starting from document Dl, was prompted to administer the Epo analog N47 less frequently than recombinant human Epo, thereby arriving at an analog encompassed by claim 1.

The feature "wherein the hyperglycosylated analog of erythropoietin is to be administered one time per month" was obvious to the skilled person since document D1 expressly taught a less frequent dosing than the conventional three times a week, *i.e.* a dosing of once weekly or once every other week, and in view of the fact that document D3 stated that the "*required dosage will be in amounts sufficient to raise the hematocrit of patients...*", which thus made clear that devising a dosage scheme for the analog was merely a matter of routine experimentation. This was confirmed by the patent in suit which stated that "*any adjustments in the dosing range being routine to one skilled in the art*".

Claim 1 referred to a target haematocrit which was "at least 30 %". This feature rendered the subject-matter of claim 1, by definition, not inventive over the whole range claimed because the range was open-ended. It was common technical knowledge that a treatment leading to a haematocrit exceeding 33% (or 36% at most) was to be avoided for medical reasons.

The subject-matter of claim 1 therefore lacked inventive step in view of the teachings of documents D1 and D3.

Sufficiency of disclosure

The invention was based on the (known) properties of the analog "N47" disclosed in document D3. Therefore an argument in favour of inventive step to the effect that, at the priority date, no molecules allowing the dosing regime of the claim had been disclosed would lead to a finding of insufficiency of disclosure for both the patent in suit and document D3. The same was true for an argument that the skilled person was unable to identify NESP as disclosed in document D1, or a molecule having the same properties, without inventive ingenuity.

XIV. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims of the main request (previous auxiliary request 6 as filed with the letter of 15 January 2016) or, alternatively, on the basis of auxiliary request 1 (previous auxiliary request 7 as filed with the letter of 15 January 2016).

The respondent requested in writing that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. The duly summoned respondent did not attend the oral proceedings, as announced in its letter of 15 January 2016. In accordance with Rule 115(2) EPC and Article 15(3) RPBA, the board decided to continue the proceedings.

Main request - claim 1

3. The subject-matter of claim 1 of the main request (see sections VIII and X) is a combination of the subject-matter of claims 1, 5, 7, 13 and 14 as granted (see section II). The request is identical to auxiliary request 6 filed by the appellant with its statement of grounds of appeal (see section VI), except that the wording "wherein the target hematocrit is at least 30 %" replaces the wording "wherein the target hematocrit is at least *about* 30 %" (italic emphasis added by the board).

Clarity, added matter and Rule 80 EPC

4. The board is satisfied that the amendments to the patent with the claims of the main request comply with the requirements of Article 84 EPC and Article 123(2) and (3) EPC and Rule 80 EPC and notes that the respondent has not argued otherwise.

Novelty

5. Claim 1 is for the use of an analog of erythropoietin (Epo), *i.e.* Asn30 Thr32 Val87 Asn88 Thr90 Epo, which comprises two additional N-linked carbohydrate chains at positions 30 and 88, for the preparation of a pharmaceutical composition for raising and maintaining the hematocrit, wherein the analog is to be administered one time per month.

6. The board is satisfied that none of the cited prior-art documents discloses an administration regimen for an analog of erythropoietin which is one time per month. The board notes, furthermore, that the Enlarged Board of Appeal in decision G 2/08 (OJ 2010, 456) has acknowledged that a dosage regimen which was not comprised in the state of the art can confer novelty on the subject-matter of a medical use claim. Accordingly, the board is satisfied that the subject-matter of claim 1 is novel. The board notes that the respondent has not disputed novelty.

Inventive step

Closest prior art

7. The board concurs with the respondent that the disclosure in document D1 represents the closest prior art for the purpose of the assessment of inventive step of the subject-matter of claim 1, *i.e.* the sole independent claim of the main request.

8. Document Dl describes an Epo analog designated "NESP" reportedly containing, as compared to recombinant human Epo (rHuEpo), in its amino acid sequence two new consensus N-linked carbohydrate sites at positions which

do not disrupt the tertiary structure or interfere with receptor binding, and therefore contains five N-linked oligosaccharide chains (see first and second paragraphs). Document D1 is silent on the exact position of the two extra N-linked glycosylation sites in the amino acid sequence. It discloses however that the "*consequences of the increased carbohydrate content are an approximate 3-fold increase in serum half-life of NESP and thereby an increase in its in vivo potency compared with rHuEPO. NESP is approximately 3.6 times as potent as rHuEPO in increasing the hematocrit in normal mice*" and that "*the longer half-life allows NESP* ***to be administered once weekly or once every other week,*** *whereas EPO is only marginally effective at these dosing frequencies. On a one time per week dosing schedule, NESP is 20-fold more efficacious than rHuEPO*" (for both see third paragraph). Document D1 continues that "[R]*ecently, a pharmacological study demonstrated that, consistent with the animal studies, NESP has a significantly longer serum half-life than rHuEPO in chronic renal failure patients. This increased serum half-life and biological activity may likely confer the clinical advantage of less frequent dosing*." (see fourth paragraph; emphasis added by the board).

9. In the context of the structure of the NEPS Epo analog the respondent has argued that since document D2, a post-published document from the same authors as document D1, demonstrated that the amino acid sequence of NESP differed from that of human Epo at five positions (*i.e.* Asn30, Thr32, Val87, Asn88 and Thr90), thereby providing two additional N-linked carbohydrate attachments at the residues at positions 30 and 88, the structural features of NESP were if not explicitly inherently disclosed in document Dl.

10. Article 56 EPC refers to "the state of the art" as the reference point for determining whether a person skilled in the art considers an invention obvious or not. The "state of the art" is thereby defined in Article 54(2) EPC comprising everything made available to the public *before the date of filing of the European patent application*. It is uncontested that document D2 was published after the date of filing of the patent application underlying the patent in suit. Furthermore, the board notes that the respondent has not argued that document D2 shows that the skilled person, when contemplating the disclosure in document D1, would immediately understand the structural details of NESP as disclosed in document D2. Consequently, the board judges that the disclosure in document D2 cannot be taken into account for the purpose of the assessment of inventive step.

The problem to be solved

11. The difference between the subject-matter of claim 1 and the disclosure in document D1 is thus *inter alia* that the claim defines the precise structural identity of an Epo analog and the technical effect that the analog can be administered in a regimen of one time per month, *i.e.* a regimen with intervals which are significantly longer than once a week or once every other week as disclosed in document D1. Accordingly, the problem to be solved by the invention forming the subject-matter of claim 1 is the provision of an Epo analog which can be administered in a regimen which is significantly longer than the administration regimen of once a week or once every other week.

Obviousness

12. It can be taken from point 8 above that document Dl describes an Epo analog designated "NESP", containing five N-linked oligosaccharide chains, that has, an increased serum half-life and *in vivo* potency as compared to rHuEPO and is approximately 3.6 times as potent as rHuEPO in increasing the hematocrit in normal mice. In this context document D1 discloses that the longer half-life allows NESP to be administered once weekly or once every other week. Document D1 furthermore discloses that, consistent with the animal studies, NESP has a significantly longer serum half-life than rHuEPO in chronic renal failure patients, *i.e.* human patients, which may likely confer "*the clinical advantage of less frequent dosing*".

13. The board notes therefore that document D1 does not contain a pointer for the skilled person to the effect that the NESP analog disclosed therein would be suitable for a dosage regimen which is significantly longer than the administration regimen of once a week or once every other week.

14. The board is satisfied that none of the other prior-art documents under consideration in the present appeal proceedings discloses, explicitly or implicitly, pointers to the possibility that certain Epo analogs allow a dosage regimen less frequent than once a week or once every other week, let alone one time per month as required by the subject-matter of claim 1. The board notes that the respondent has not argued so either.

15. When arguing that the subject-matter of claim 1 lacked inventive step, the respondent referred rather to document D3, which disclosed hyperglycosylated Epo

analogs having additional N-glycosylation at sites in the molecule which are expected not to perturb the secondary structure or tertiary conformation required for biological activity. Table 6 disclosed biological activity data for Epo analogs with additional glycosylation sites, including one analog, designated "N47", which was identical to the analog underlying the patent in suit. This analog had a substantially higher biological activity than human Epo. The document further disclosed a direct relationship between the sialic acid content, clearance half-life and the ability of Epo analogs to increase the hematocrit of treated mice, regardless of the strength of receptor binding. Document D3 stated that for a given analog the "*required dosage will be in amounts sufficient to raise the hematocrit of patients...*" The latter made it clear that dosing the analogs was merely a matter of routine experimentation for the skilled person. In view of this guidance in document D3, the skilled person, when starting from document Dl, was not only prompted to administer Epo analog N47 less frequently than human Epo but also in a dosage regimen of only one time per month.

16. The board notes that, independently of the question whether or not the skilled person would in an obvious manner identify compound "N47" as disclosed in document D3 to be identical or equivalent to the "NESP" analog as disclosed in document D1, document D3 suggests that hyperglycosylated Epo analogs can be administered *less frequently* than rHuEpo, a suggestion not going beyond the statements made in document D1 (see point 13 above). The board accordingly considers that the skilled person seeking to solve the technical problem and contemplating the state of the art would not have selected in an obvious manner the compound N47 as

disclosed in document D3 and administered the compound in a regime of one time per month.

17. In the context of inventive step the respondent has submitted the additional argument that, "*due to the open-ended range* [that the target haematocrit is "at least 30 %"] *the claim cannot be inventive over the whole range claimed, since treatment leading to a haematocrit exceeding 33% or 36% at most is to be avoided for medical reasons. If the hematocrit* [sic] *exceeds 40%, the dose should even be discontinued*".

18. The board notes in this context however that the feature "wherein the target haematocrit is at least 30%" is not the technical effect on which inventive step of the claimed subject-matter hinges (see point 16). Furthermore, the feature rather refers to a *minimum* and medically meaningful haematocrit to be obtained by the invention in the claim ("target") rather than to a haematocrit which is medically meaningless and hence should be avoided. Accordingly, the board is of the opinion that in the present case it is immaterial for the purpose of the assessment of obviousness whether or not the feature that the target haematocrit is at least 30%, is open-ended. Accordingly, the respondent's argument fails also in this respect.

19. In view of the above considerations the board judges that the subject-matter of claim 1 was not rendered obvious to the skilled person by the prior art and that consequently it involves an inventive step (Article 56 EPC). The same applies to the subject-matter of claims 2 to 4 of the main request which are dependent on claim 1.

Sufficiency of disclosure

20. The respondent has argued that the patent in suit lacked sufficiency of disclosure of the claimed invention if the assessment of inventive step were to be based on the fact that, at the priority date, no molecules allowing the dosing regime of the claim had been disclosed or that the skilled person was unable, without inventive ingenuity, to identify NESP as disclosed in document D1 or a molecule having the same properties.

21. The board notes that the assessment of inventive step above has neither relied on, nor makes reference to, those findings which the respondent considers a basis for a finding of lack of sufficiency of disclosure.

22. Accordingly, the board notes that no arguments have been brought forward that would persuade the board to come to a judgement that the invention as claimed is not sufficiently disclosed in the patent in suit.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of the claims of the main request (previous auxiliary request 6 as filed with the letter of 15 January 2016) and a description and figures to be adapted thereto.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated