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D E C I S I O N
of 4 January 2005

Case Number: T 0157/03 - 3.3.4

Application Number: 93902779.3

Publication Number: 0624095

IPC: A61K 38/45

Language of the proceedings: EN

Title of invention:

Methods and compositions for reducing blood loss

Patentee:

ZYMOGENETICS, INC.

Opponents:

01 Baxter Aktiengesellschaft

02 Aventis Behring GmbH

Headword:

Reducing blood loss/ZYMOGENETICS

Relevant legal provisions:

EPC Art. 54, 56, 83, 114(2)

Keyword:

"Admissibility of late filed documents (no)"

"Sufficiency of disclosure (yes)"

"Novelty (yes)"

"Inventive step (yes)"

Decisions cited:

G 0005/83, T 0002/81, T 0071/86, T 0375/91, T 0994/95,

T 0342/98, T 0120/00, T 0792/00

Catchword:

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Case Number: T 0157/03 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 4 January 2005

Appellant: ZYMOGENETICS, INC.
(Proprietor of the patent) 4225 Roosevelt Way, N.E.
Seattle, WA 98105 (US)

Representative: MacLean, Martin Robert
Mathys & Squire
100 Gray's Inn Road
London WC1X 8AL (GB)

Respondent I: Baxter Aktiengesellschaft
(Opponent 01) Industriestrasse 67
AT-1221 Wien (AT)

Representative: Alge, Daniel, Mag. Dr. rer.nat.
Sonn & Partner Patentanwälte
Riemergasse 14
AT-1010 wien (AT)

Respondent II: Aventis Behring GmbH
(Opponent 02) Emil-von-Behring-Strasse 76
D-35041 Marburg (DE)

Representative: Pfeil, Hugo, Dr.
Aventis Behring GmbH
Postfach 12 30
D-35002 Marburg (DE)

Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 22 November 2002
revoking European patent No. 0624095 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairwoman: U. Kinkeldey
Members: M. Wieser
G. E. Weiss

Summary of Facts and Submissions

I. The appeal was lodged by the Patent Proprietors (Appellants) against the decision of the Opposition Division, whereby the European Patent No. 624 095 was revoked according to Article 102(1) EPC.

II. The patent has been granted with claims 1 to 11. Claims 1, 5 and 6 thereof read as follows:

"1. The use of factor XIII for the production of a pharmaceutical composition for the reduction of perioperative blood loss in a patient undergoing surgery.

5. Use according to any of claims 1 to 4, wherein factor XIII is administrable at a dose of 0.1 - 1.00 mg per kg of patient weight.

6. Use according to any of claims 1 to 4, wherein factor XIII is administrable at a dose of 0.15 - 0.4 mg per kg of patient weight."

III. The patent had been opposed by Opponents 01 and 02 (Respondents I and II) under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC). Article 100(b) EPC on the ground of lack of sufficient disclosure (Article 83 EPC) had been raised by Respondent I as a new ground of opposition after expiry of the nine month opposition period (Article 99(1) EPC). The Opposition Division in application of Article 114(1) EPC decided to allow the introduction into the proceedings of this new ground.

IV. The Opposition Division decided that the subject-matter of claim 1 of the main request before them, namely the claims as granted, was anticipated by the disclosure in document

(1) Gebrauchsinformation der Firma Behringwerke zu Fibrogammin^R HS, 1986

contrary to the requirements of Article 54 EPC.

V. Moreover the Opposition Division decided that claim 1 of auxiliary requests I and II before them did not involve an inventive step (Article 56 EPC) in the light of the disclosure in documents

(2) EP-B-0 268 772

(21) US-A-3 931 399.

These claims read as follows:

Auxiliary request I

"The use of factor XIII for the production of a pharmaceutical composition for the reduction of perioperative blood loss in a normal patient undergoing surgery, wherein said reduction in perioperative blood loss is a reduction in blood loss during surgery and/or reduced post-surgical drainage, and wherein said normal patient is one not suffering from inborn or other pre-operative bleeding disorders".

Auxiliary request II

"The use of recombinant factor XIII a₂ dimer for the production of a pharmaceutical composition for the reduction of perioperative blood loss in a normal patient undergoing surgery, wherein said reduction in perioperative blood loss is reduced post-surgical drainage, and wherein said normal patient is one not suffering from inborn or other pre-operative bleeding disorders".

- VI. The Board expressed their preliminary opinion in a communication dated 9 July 2004, where it was *inter alia* pointed out that the introduction of experimental data at a very late stage of the proceedings did not seem to be compatible with the principle of fair and equal treatment of the parties. The communication was annexed to summons to attend oral proceedings on 4 January 2005.

- VII. The Appellants filed final written submissions on 3 November 2004. These submissions included additional evidence in the form of new documents (A1) to (A7). Documents (A1) and (A4) were excerpts from textbooks. Document (A2) was the curriculum of Dr.Rojkjaer, Appellants' technical expert. Documents (A3) and (A5) to (A7) disclosed experimental data.

- VIII. The Board dispatched a further communication on 23 December 2004, informing the parties that it was of the preliminary opinion that the results of clinical trials filed by the Appellants on 3 November 2004 could not be taken into account.

IX. Oral proceedings took place on 4 January 2005 in the absence of Respondents I and II, who had informed the Board in letters dated 21 and 23 December 2004 that they will not attend.

At the oral proceedings the Appellants filed a new, single main request. Claim 1 thereof read:

"Use of Factor XIII for the production of a pharmaceutical composition for the reduction of perioperative blood loss in a normal patient undergoing surgery, wherein said normal patient is one not suffering from inborn or other pre-operative bleeding disorders, and wherein the Factor XIII is administered at a dose of 0.15 - 1.00 mg per kg of patient weight."

Dependent claims 2 to 9 referred to preferred embodiments of the use according to claim 1.

X. The Appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 9 filed at the oral proceedings.

The Respondents I requested that the appeal be dismissed.

The Respondents II did not file any request.

XI. Besides those mentioned in sections (IV) and (V) above, the following documents are referred to in this decision:

(6) Ann. Thorac. Surg., vol.51, 1991, pages 936 to 941

(11) Zbl. Chirurgie, vol.10, 1980, pages 642 to 651

(23) Thorac. Cardiovasc. Surg., vol.46, 1998, pages 263
to 267

(24) Roche Lexikon Medizin, 4th Ed., 1998, page 1299

XII. The submissions made by the Appellants as far as they are relevant to the present decision may be summarized as follows:

Article 83 EPC

The perioperative time period was the period shortly before, during and shortly after a surgical procedure has taken place. It was distinct from the unlimited post-operative time period.

Document (23) provided evidence that normal patients, treated with Factor XIII during the recovery phase of the perioperative period showed significantly lower blood loss, measured in drain volumes, than patients of a control group.

Documents (A3) and (A5) to (A7) provided evidence that Factor XIII reduced blood loss of patients during surgery. These documents showed simple, not complex experimental data and should be allowed into the proceedings despite their late filing.

Article 54 EPC

Claim 1, containing the exact dosage to be administered to a patient, was novel over the cited prior art documents.

The invention was not concerned with Factor XIII replacement or partial replacement therapy, but rather with the maintenance of supranormal (i.e. greater than 100%) Factor XIII levels in patients undergoing surgery.

Reduction in blood loss and wound healing were two different therapeutic indications, as acknowledged by the Opposition Division.

Article 56 EPC

Document (6), disclosing the reduction of intra- and post-operative blood loss by the proteinase inhibitor aprotinin, was considered to represent the closest state of the art for the assessment of an inventive step (Article 56 EPC). The problem to be solved by the present invention was seen in the provision of an alternative to aprotinin administration. The claimed solution could not be derived in an obvious way from the disclosure in the cited prior art documents.

XIII. The submissions made by Respondents I as far as they are relevant to the present decision may be summarized as follows:

Article 83 EPC

Different opinions existed in the art as to when the perioperative period ended. It followed therefrom that this period could not be regarded as a period with concrete and defined limits. A precise delimitation between the perioperative and the postoperative period was not possible.

Document (23), disclosing the administration of Factor XIII concentrate to patients after surgery, could impossibly support the reduction of blood loss during surgery. Since, in this respect, the actual effect of Factor XIII was unproven, the requirements of Article 83 EPC were not fulfilled.

Experimental data submitted by the Appellants two months before the date scheduled for oral proceedings were filed much too late to be considered according to the general decision practice of the Boards of Appeal of the EPO.

Article 54 EPC

Even when assuming that the process of wound healing was different from reduction of perioperative blood loss, it had to be borne in mind that the reduction of blood loss during surgery made up one of the necessary prerequisites of wound healing.

Article 56 EPC

Neither of documents (2) or (21) was restricted to the administration of Factor XIII to patients suffering

from inborn or other pre-operative bleeding disorders. The solution to the problem underlying the invention according to claim 1, namely the provision of means for reducing perioperative blood loss in normal patients undergoing surgery, was obvious in the light of the disclosure in this prior art documents.

The definition of an administration dose in "mg per kg of patient weight" was completely useless for the man skilled in the art, unless combined with the information for a specific activity of the Factor XIII preparation in units Factor XIII per dose, which were not contained in the patent in suit. Preparations containing only a low amount of Factor XIII might not have fulfilled the object of claim 1.

XIV. Respondents II did not file any submissions.

Reasons for the Decision

Late filed documents (A1) to (A7) - Article 114(2) EPC

1. Documents (A1) to (A7) were filed by the Appellants on 3 November 2004, two months before the oral proceedings.

Document (A1) is an excerpt from a textbook corresponding to the disclosure in document (1).

Document (A2) is the curriculum vitae of Appellants' technical expert Dr.Rojkjaer. Document (A4) is an excerpt from a textbook whose disclosure is considered to belong to the general knowledge of a skilled person in the field of haematology.

Documents (A3) and (A5) to (A7) disclose experimental data already announced by the Appellants in a letter dated 1 April 2003, which have been submitted in response to an objection because lack of evidence with regard to the embodiment of the invention referring to the reduction of blood loss during surgery.

2. The Board, having examined the relevance of documents (A1), (A2) and (A4), has found that they are not relevant for the outcome of the present case and exercises its discretion to disregard these late filed documents (cf decision T 71/86 of 19 January 1988; point (3)).

With regard to documents (A3) and (A5) to (A7) the facts of the present case are comparable to those in decisions T 375/91 (17 November 1995; point (3.2)), T 342/98 (20 November 2001; point (2)) and T 120/00 (18 February 2003; point (3)). These decisions have in common that experimental data submitted about one or two months prior to the oral proceedings before the Board of Appeal were not allowed into the proceedings under Article 114(2) EPC as having been late-filed. The reason invoked was that the handling of such data was more cumbersome and time-consuming than that of scientific publications, since most of the time they call for counter-experiments.

Documents (A3) and (A5) to (A7) contain Thromboelastography (TEG) data providing a means for assessing the efficiency of blood clotting which, according to the Appellants is integral to reducing blood loss during surgery. Although the data filed by the Appellants are in vitro data, a skilled person

trying to control, repeat or verify these data could do this only with a considerable expenditure of time and work.

In accordance with the established case law of the Boards of Appeal, the present Board finds that it is not compatible with the principle of fair and equal treatment of the parties to place the Respondents in such a situation shortly before the oral proceedings.

3. Therefore, the Board decides under Article 114(2) EPC not to allow documents (A1) to (A7) annexed to Appellants' submission of 3 November 2004 into the proceedings.

Amendments and Clarity - Articles 123(2), 123(3) and 84 EPC

4. Claim 1 of Appellants' only request is based on claims 1, 8 and 9 and on page 3, lines 3 to 4 of the description as originally filed.
5. The dose of administration of "0.15 to 1.00 mg per kg of patient weight" is based on a combination of the lower limit of the range indicated in originally filed claim 9 (claim 6 as granted; 0.15 to 0.4) and the upper limit of the range given in originally filed claim 8 (claim 5 as granted; 0.1 to 1.0). The disclosure of a quantitative range of values together with an included preferred narrower range also directly discloses the two possible part-ranges lying within the overall range on either side of the narrower range (cf decision T 2/81, OJ EPO 1982, 394; point (3)).

Dependent claims 2 to 9 correspond to claims 2, 12, 13, 9, 6, 10, 11 and 14 as originally filed.

6. By defining the patient to be treated as being a normal patient not suffering from inborn or other pre-operative bleeding disorders, and by indicating the exact dose to be administered, the protection conferred by the claims has been restricted when compared to the claims as granted.

Consequently, claims 1 to 9 of Appellants' only request meet the requirements of Articles 123(2) and 123(3) EPC.

7. The amendments to the claims do not give rise to an objection under Article 84 EPC.

Sufficiency of disclosure - Article 83 EPC

8. According to Article 83 EPC and the relevant, established case law of the Boards of Appeal, the invention must be disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art over the entire scope of the claim without undue difficulty.

Claim 1 is in the form allowed by the Enlarged Board of Appeal in the decision G 5/83 (OJ EPO 1985, 064) for a second or further medical use of a substance.

The patent does not contain experimental data showing that the effect of the claimed medical use is achieved, namely the reduction of perioperative blood loss in a normal patient undergoing surgery.

9. In the absence of any tangible proof in the patent specification that the claimed concept can be put into practice, post-published documents may be used as evidence whether the invention was indeed reproducible without undue burden at the relevant filing date (cf decision T 994/95 of 18 February 1999; point 8).

10. Document (23), published after the filing date of the patent in suit, investigates the effects of Factor XIII on bleeding in coronary surgery. In detail the aim of the pilot study published in document (23) was to investigate the Factor XIII level in patients, who were not designated as suffering from inborn or other pre-operative bleeding disorders, before and after extracorporeal circulation, and to answer the question, whether postoperative application of commercially available Factor XIII can reduce the amount of blood loss and - as a consequence - the need for blood transfusions (page 263, right column, second paragraph). Factor XIII levels of a control group were measured preoperatively and postoperatively immediately after the arrival at the intensive care unit (ICU). 2500 units Factor XIII were administered to the patients of the "Factor XIII group" after taking the postoperative blood sample (page 264, left column, first paragraph and paragraph bridging pages 264 and 265). The perioperative course of Factor XIII plasma levels of both groups were monitored (Fig.2). Blood loss, measured in drain volumes, noted in the morning of the first and second postoperative day (page 264, right column, first full paragraph), was significantly lower in the "Factor XIII group" than in the control group (Fig.3).

11. Claim 1 refers to "the reduction of **perioperative** blood loss in a normal patient undergoing surgery" (emphasis added by the Board).

The technical term "perioperative", used in claim 1, seems to be commonly used in the medical field. However, there exists no clear and precise, unique definition of this term. While it is undisputed that the periods immediately before and during surgery form part of the perioperative period, there seems to be no consensus, neither between the parties nor in the relevant prior art documents, as to when the perioperative period ends and the postoperative period starts.

Document (24), a textbook, defines the perioperative period as the period before, during and **shortly** after a surgical intervention. Document (6), saying that the intraoperative blood loss accounts for two thirds, the postoperative blood loss for one third of the total perioperative blood loss, measures drainage volumes in the first 18 post-surgical hours (page 938, right column and Table 3). According to document (23) the first two postoperative days form part of the perioperative period. In detail, laboratory parameters were taken until the patients discharge from the ICU, which was between 32 and 44 hours postoperatively (document (23), page 264, right column, first full paragraph).

12. The Board concludes that the perioperative time period consists of the time during surgery and of short, not precisely defined, periods directly before and after

surgery. Thus, it overlaps to some extent with the postoperative time period. A generally accepted definition, stating when exactly the perioperative time period ends and the postoperative time period starts, cannot be identified by the Board.

For these reasons the Board considers the disclosure in document (23) to be relevant for the present case as it is considered to refer to a study performed on patients during the perioperative phase.

13. In further supporting their case for insufficiency of disclosure, Respondents I argued that the definition of an administration dose in "mg per kg patient weight", as contained in claim 1, is meaningless to a skilled person unless combined with information as to the specific activity of the Factor XIII preparation. Thus, many preparations when administered according to claim 1 would not fulfil the object of the claim.

The Board does not agree but rather is convinced of the submission put forward by the Appellants in the oral proceedings. According to them one unit Factor XIII corresponds to the Factor XIII activity of 1 ml plasma of a normal donor (document (1), footnote on page 1). The average concentration of Factor XIII in the plasma of humans is known to the skilled person in the field of haematology and lies at 10 µg per ml. Accordingly 10 µg Factor XIII are equivalent to 1 unit Factor XIII. A dose of 0.15 to 1.00 mg Factor XIII per kg of patient weight thus corresponds to 15 to 100 units Factor XIII per kg patient weight. For a patient with 70 kg this amounts to between 1050 and 7000 units. The dose

administered according to document (23), namely 2500 units per patient, lies within this range.

14. In the light of this situation, the Board accepts the disclosure in post-published document (23) as evidence showing that the invention, namely the use of Factor XIII according to claim 1 for reducing perioperative blood loss in a normal patient undergoing surgery, was indeed reproducible without undue burden at the relevant filing date.
15. Since document (23) refers to administration of Factor XIII concentrate after surgery, Respondents I argue that the experiments disclosed cannot support the reduction of blood loss during surgery, encompassed by the wording of claim 1, so that in this respect, the effect of Factor XIII is unproven and the requirements of Article 83 EPC were not fulfilled.
16. Document (11) is considered to be a basis for a prevailing technical opinion pointing in a direction directly opposite to the patent in suit. The document reports the results of clinical trials wherein it was found that the intraoperative blood loss of a group of patients, who preoperatively received Factor XIII, was higher than blood loss of a control group (page 646 to 647, Fig. 6a).

Document (11), on page 646, discloses the calculation of an administration dose for Factor XIII, which differs from the one specified in present claim 1.

17. The present situation differs from a situation where an invention going against prevailing technical opinion did not provide the skilled person with a real guidance to perform the claimed subject-matter but offered only an outline of a research program (cf decision T 792/00 of 2 July 2002; point (24) of the reasons).

Contrary to this, present claim 1 contains a technical feature, namely the administration dose of 0.15 - 1.00 mg per kg of patient weight, which is not disclosed in document (11), the basis for the prevailing technical opinion. The realization of the additional technical feature, namely the administration of Factor XIII to a normal patient in the dose indicated in claim 1, has been shown in document (23) to give rise to the desired effect, the reduction of perioperative blood loss.

18. The objection of lack of sufficiency of disclosure presupposes that there are serious doubts, substantiated by verifiable facts (cf decision T 19/90, OJ EPO 1990, 476; point (3.3) of the reasons).

The Board is satisfied that the invention was indeed reproducible without undue burden at the relevant filing date (point (13) above). In the lack of evidence to the contrary, the Board has no reason to doubt that the invention is capable of execution over the entire scope of the claim without undue difficulty.

Accordingly, the requirements of Article 83 EPC are met.

Novelty - Article 54 EPC

19. Document (1) discloses the administration of Factor XIII to patients with congenital Factor XIII deficiency immediately before and on the five days following surgery. It mentions the administration of Factor XIII to normal patients for the promotion of wound healing and healing of bone fractures. The administration dose of claim 1 is not disclosed.

"Wound healing" is a process mediated by many steps, including, but not consisting of, stabilisation of blood clots, and is a therapeutic application distinguishable from "reduction of blood loss" (cf point (7) of the reasons for the decision under appeal).

20. Document (2) is concerned with the production of Factor XIII by recombinant DNA technology. In the last paragraph on page 3, the document refers to current treatment practices for patients having Factor XIII deficiencies generally involving replacement therapy. The document goes on to report of different new uses of Factor XIII. Page 4, lines 4 to 5 read: "... and has been suggested for use in antifibrinolytic therapy for the prevention of postoperative bleeding ...". This passage is not restricted to the treatment of Factor XIII deficient patients. No indication of a dose of administration is given.

21. Document (21) refers to a process for isolating Factor XIII from human placentae. Column 4, lines 9 to 16 thereof reads: "The factor XIII obtained according to the present invention can be used to treat any factor-

XIII deficiency symptoms, for example the inherited lack thereof and any haemorrhagic syndromes resulting therefrom, bleeding and disturbances in the healing of wounds, as well as any transitory lack of factor XIII, for example after an operation and a retard healing of wounds resulting therefrom." The document does not mention the dose to be administered.

22. The other cited prior art documents are more remote from the claimed subject-matter. Therefore, the subject-matter of claims 1 to 9, which is not disclosed in the cited prior art documents, is novel within the meaning of Article 54 EPC.

Inventive step - Article 56 EPC

23. In accordance with the problem and solution approach, the Boards of Appeal in their case law have developed certain criteria for identifying the closest prior art providing the best starting point for assessing inventive step. It has been repeatedly pointed out that this should be a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (cf Case Law of the Boards of Appeal of the European Patent Office, 4th Edition 2001, chapter I.D.3).

24. The Appellants consider document (6) as being the closest state of the art, which refers to the reduction of intra- and postoperative blood loss in normal patients undergoing cardiopulmonary surgery by

administration of the proteinase inhibitor aprotinin (see summary on page 936).

25. The Board is of the opinion that documents (6) and (2) (or likewise document (21)) disclose subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention, namely the reduction of perioperative blood loss in a normal patient undergoing surgery. However, since the disclosure in documents (2) and (21), when compared with document (6), has the most relevant technical feature in common with the claimed invention, namely the use of Factor XIII, they are considered to represent the closest prior art.
26. The problem underlying the present invention in the light of the disclosure in this state of the art is seen in the provision of improved methods and compositions for reducing perioperative blood loss in normal patients undergoing surgery (compare column 1, lines 41 to 43 of the patent in suit).
27. Documents (2) and (21) themselves refer to the postoperative administration of Factor XIII to normal patients only very shortly and in a rather speculative way ("... has been suggested ...", document (2); "... can be used for ...", document (21)). They do not disclose any data concerning the dose of administration.

Document (1), when referring to the reduction of perioperative blood loss, is restricted to treatment of Factor XIII-deficient patients undergoing a replacement or partial replacement therapy. Contrary to this the subject-matter of claim 1 results in an achievement of

supranormal Factor XIII levels in normal patients not suffering from inborn or other pre-operative bleeding disorders.

Document (6) is solely concerned with the administration of aprotinin and does not mention Factor XIII. Document (11) which describes a technical effect opposite to the one being the goal of the present invention applies different administration doses (see point (16) above).

28. The documents representing the closest prior art, documents (2) and (21), provide nothing more than a suggestion to use Factor XIII for the purpose as claimed in the patent in suit. The skilled person, being aware of this suggestion and confronted with the problem to be solved, as formulated in point (26) above, cannot find information in the cited prior art documents that would encourage him to arrive at the use according to claim 1, wherein factor XIII is administered to patients in need thereof in the specifically indicated administration dose, in an obvious way.

As a consequence, the use according to claim 1, and claims 2 to 9 dependent thereon cannot be derived in an obvious way from the disclosure in the cited prior art documents, either if taken alone or in any combination.

29. Respondents' I further argument, namely that claim 1 lacks an inventive step as it covers the administration of preparations having only low Factor XIII activity which might not fulfil the claimed object, as a result of the allegedly meaningless definition of the

administration dose in "mg per kg patient weight", must fail. As has been shown in point (13) above the administration dose given in claim 1 is not meaningless to a skilled person, who would understand that a dose of 0.15 to 1.00 mg Factor XIII per kg of patient weight corresponds to 15 to 100 units Factor XIII per kg patient weight.

The Board arrives at the conclusion that the subject-matter of claims 1 to 9 involves an inventive step and meets the requirements of Article 56 EPC.

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 as amended in the following version:
 - claims 1 to 9 filed at the oral proceedings
 - description pages 2 to 4 filed at the oral proceedings.

The Registrar:

The Chairwoman:

P. Cremona

U. Kinkeldey