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File No.: T 0893/90 - 3.3.2
Application No.: 86 305 733.7
Publication No.: 0 214 737
Classification: A61K 35/16
Title of invention: Method for controlling bleeding.

D E C I S I O N
of 22 July 1993

Applicant: Queen's University at Kingston
Proprietor of the patent: -
Opponent: -

Headword: Controlling bleeding/QUEEN'S UNIVERSITY KINGSTON

EPC: Art. 84, 54
R. 27,67

Keyword: "Clarity (yes) - functional feature"
"Novelty (yes) - second medical indication - particular group of patients"
Background art - missing citation"
"Substantial procedural violation (yes)" - Reimbursement of appeal fee (no)".

Headnote
Catchwords



Case Number: T 0893/90 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 22 July 1993

Appellant: Queen's University at Kingston
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Representative: Wood, Anthony Charles
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Decision under appeal: Decision of the Examining Division of the European Patent Office dated 2 July 1990 refusing European patent application No. 86 305 733.7 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: P.A.M. Lançon
Members: L. Galligani
S.C. Perryman

Summary of Facts and Submissions

- I. European patent application No. 86 305 733.7 published under No. 0 214 737 was refused by the Examining Division.

The decision was taken on the basis of Claims 1 and 2 as filed by letter dated 28 November 1989.

Claim 1 read as follows:

" A method of producing a pharmaceutical composition for controlling bleeding in non-hemophilic mammals characterized by forming a mixture of phospholipid vesicles and mammalian blood Factor Xa in a form suitable for administration, the phospholipid and Factor Xa being present in amounts and in proportions just sufficient to arrest bleeding, said mixture excluding other physiologically-active materials."

Dependent Claim 2 specified that the phospholipid vesicles are a mixture of phosphatidylcholine and phosphatidylserine (PCPS).

- II. The Examining Division refused the application under Article 97(1) EPC on the grounds that the subject-matter of Claims 1 and 2 lacked novelty within the meaning of Article 54 EPC, having regard to the following documents:

- (1) EP-A-0 129 998;
- (2) THE REGULATION OF COAGULATION, Proceedings of the International Workshop on Regulation of Coagulation, The University of Oklahoma, Norman, USA, September 4-8, K.G. Mann and F.B. Taylor Eds., Elsevier/North Holland, New York, 1979, pages 145 to 159.

Moreover, the Examining Division considered that Claim 1 lacked clarity under Article 84 EPC because its subject-matter was defined by the result to be achieved ("just sufficient to arrest bleeding").

The main reason given for the decision was that, since the intended use of the pharmaceutical composition was not a technical feature of the method claimed, the latter was not novel having regard to document (1) which disclosed the same composition for use in the treatment of haemophilia in mammals. In addition, also document (2) - known to the applicant from a parallel case - which disclosed a composition comprising a phospholipid and Factor Xa and its activity in the clotting process, affected the novelty of the claimed subject-matter.

III. The Appellant lodged an appeal against this decision and paid the appeal fee.

IV. The Appellant's arguments are essentially that:

- a) While document (1) is concerned with a composition for the treatment of bleeding in haemophiliacs the present application is concerned with a composition for the treatment of non-haemophiliacs. These are mutually exclusive conditions.
- b) Although the phenomena involved in the halting of bleeding are not completely understood, persistent bleeding in haemophiliacs is the result of the absence of one or more factors *inter alia* Factor VIII:C. The composition of (1) compensates for the absence of Factor VIII:C. On the other hand, Factor VIII:C is present in the blood of non-haemophiliacs. This demonstrates that the effect of the two compositions is different in the two health conditions.

- c) The statement of purpose is a technical feature which assists in defining the invention. Document (1) and the present application concern two different specific combinations for two different specific purposes. The lack of novelty objection is therefore unjustified.
- d) As for document (2), it discloses a ratio of Factor Xa to phospholipid which is determined *in vitro*. This is at least an order of magnitude different from that described in the present application. Moreover, the *in vitro* effect disclosed in (2), most likely a thrombotic effect, is completely different from the haemostatic effect claimed for the present composition. Therefore, the composition of document (2) is not the same composition claimed in the present application.
- e) As for the lack of clarity objection, it is unjustified because the functional limitation as used in Claim 1 is necessary in order to identify the compositions which arrest bleeding. The verification by the tests or procedures specified in the description is well within the competence of the skilled person to whom the description is addressed.
- f) As the Appellant has not been given the opportunity to comment on document (2) in connection with the present application before refusal, a substantial procedural violation occurred. Although the Appellant was aware of the document, it could not foresee that it would be so misinterpreted by the Examining Division. Thus, the appeal fee should be reimbursed (see decisions T 18/81 OJ EPO, 1985, 166 and T 30/81 of 17 March 1982, not published in the OJ EPO).

- V. The Appellant requests the setting aside of the appealed decision and the grant of a patent on the basis of Claims 1 and 2. In addition, the Appellant requests the reimbursement of the Appeal fee under Rule 67 EPC on the basis that there was a substantial procedural violation.

Reasons for the Decision

1. The appeal is admissible.
2. The only issues to be decided in this appeal are the clarity of Claim 1 and the novelty of Claims 1 and 2.
3. *Clarity (Article 84 EPC)*

The feature "being present in amounts and proportions just sufficient to arrest bleeding" is indeed a functional feature which defines a technical result. However, said feature constitutes also a testable criterion which has to be satisfied by the claimed pharmaceutical composition. Its testing might appear *prima facie* bothersome, but it is nothing out of the ordinary for the field of medicines and involves only routine trials. Thus, the adopted functional language is allowable and in line with the EPO case law (see in particular T 68/85, OJ EPO 1987, 228).

The claimed subject-matter is clearly enough defined to meet the requirements of Article 84 EPC without a limitation of Claim 1 by introduction of a reference to specific amounts and/or proportions of the components.

4. *Novelty (Article 54 EPC)*
 - 4.1 The present claims are formulated as method claims, namely as a method of producing a pharmaceutical composition for controlling bleeding in non-hemophilic mammals characterized by admixing the two components in

functionally defined amounts and proportions. In their formulation the said claims do not substantially differ from use claims, i.e. from claims directed to the use of the mixture of the two components in functionally defined amounts and proportions for the stated purpose, namely for producing a pharmaceutical composition for controlling bleeding in non-hemophilic mammals (see Decision G 05/83, OJ EPO 1985, 64, item 11). In this respect, it is also observed that, according to Claim 1, the mixture excludes other physiologically-active materials; thus, the said mixture is well-defined in terms of its components.

- 4.2 The present claims are thus in accordance with established EPO case law that claims are allowable directed to the use of a substance or composition for the manufacture of a medicament for a specified new and inventive therapeutic application, even if the process of manufacture as such does not differ from known processes using the same active ingredient(s) ("second medical indication", cf. G 5/83, *loc.cit.*).

As stated in decision T 19/86 (OJ EPO 1989, 24, see paragraph 8) the question of whether a new therapeutic use is in accordance with decision G 5/83 should not be answered exclusively on the basis of the ailment to be cured but also on the basis of the subject or patient to be treated.

- 4.3 The claims in the present application are directed to a pharmaceutical composition for "controlling bleeding in non-hemophilic mammals" whereas cited prior art document (1) relates to the same pharmaceutical compositions for "controlling hemophilic bleeding in hemophilic mammals".

Non-hemophilic mammals differ from hemophilic mammals in their blood coagulation process, as this latter group lacks at least one essential blood-clotting factor, namely

Factor VIII:C. Despite the superficial similarity in the phrasing of the intended pharmaceutical use, the present application and document (1) are thus directed to quite distinct applications: the present application being directed to modifying the normal stoppage of bleeding of normal mammals, whereas document (1) is concerned with curing the defective stoppage of bleeding in hemophilic mammals. On this basis, novelty can be acknowledged for Claims 1 and 2 of the present application, provided that the use of said pharmaceutical composition for controlling bleeding in non-hemophilic mammals is not incidentally disclosed in (1).

4.4 With respect to this latter question, it is observed that, although document (1) is concerned with an invention relating to the control of hemophilic bleeding in hemophilic mammals, it also describes in Examples 1 and 2 the infusion of a PCPS/Xa composition (40 units/0.05 units per kg body weight respectively) in **normal** (non-hemophilic) mammals **before** induction of bleeding. The conclusion drawn in the said Examples is that "...bleeding became abnormal immediately after the infusion of PCPS/Xa at this dosage suggesting that the relative excess of PCPS had favoured the anticoagulant effect of activated Protein C...." (see page 10, lines 10-17). Bleeding was then stopped in these Examples 1 and 2 by cautery with silver nitrate application. No mention is made in (1) of any possibility of controlling bleeding in **normal** mammals by means of a PCPS/Xa composition in amounts and proportions just sufficient to arrest bleeding.

4.5 The present application shows in Examples 8 to 10 that the infusion of PCPS/Xa in a **normal** dog immediately **after** induction of bleeding causes its abrupt arrest. The dose used is 4.0 Units/0.2 Units per Kg of body weight (Ex.8-9) and 40 Units/0.05 Units (Ex.10).

It is true that Example 6 of (1) shows that an infusion of a PCPS/Xa composition (4.0 Units/0.2 Units per Kg of body weight) to a hemophilic dog, which had been bleeding for 15 minutes after severance of a nail, caused the bleeding to stop abruptly, and that this is the same dosage which in Examples 8 and 9 of the present application are shown to stop bleeding abruptly in a non-hemophilic dog. However, whether or not a skilled person in this art would extrapolate from what is described in Example 6 of (1) to the invention now claimed is a question that can only be considered in relation to inventive step under Article 56 EPC, **and not** in relation to novelty under Article 54 EPC. This is because Example 6 does not state that the same abrupt stoppage of bleeding would occur in a non-hemophilic animal, and in view of the differences between hemophilic and non-hemophilic animals as regards the stoppage of bleeding, an example relating to abrupt stoppage of bleeding in a hemophilic dog cannot be relied on as a publication of something that will occur irrespective of whether the animal is hemophilic or not.

4.6 Therefore, since the functional technical feature of use for controlling bleeding in non-hemophilic mammals, which characterizes present Claims 1 and 2, is not made available to the public by document (1), the said claims can be regarded as novel under Article 54 EPC *vis-à-vis* (1).

4.7 Document (2), which in the opinion of the Examining Division also affects the novelty of the present claims, deals mainly with the participation of Factor Va in prothrombinase. Table II shows the reaction rates of various combinations of components - *inter alia* the combination Factor Xa/PCPS - of the prothrombinase complex. It is shown that the said combination has *in vitro* the same activity as Factor Xa alone. Nothing is said in (2) with respect to a possible use *in vivo* of the

said combination for controlling bleeding in non-hemophilic mammals. Thus, document (2) does not affect the novelty of the present claims under Article 54 EPC.

5. *Further matters*

5.1 *Rule 27 EPC*

5.1.1 According to Rule 27 (b) EPC the description should indicate the background art which, as far as known by the applicant, can be regarded as useful for understanding the invention and cite the documents reflecting such art. According to Rule 27 (c) the description should disclose the invention, as claimed, in such terms that the technical problem (even if not expressly stated as such) and its solution can be understood and state any advantageous effects of the invention with reference to the background art.

5.1.2 The text of the present application corresponds largely word for word to that of document (1). In fact the present US priority application is a continuation-in-part of Ser. No. 508 213 of 27 June 1983, which is the priority application of (1). However, no reference whatsoever is made in the present application to document (1). This is contrary to the requirements of Rule 27 EPC as outlined in section 5.1.1 above. This deficiency could be cured during the further prosecution of the case (see section 6 below).

5.2 *Reimbursement of appeal fee (Rule 67 EPC)*

Document (2) was introduced for the first time into the proceedings by the Appellant (see letter dated 28 November 1989) in order to show that, when measuring the effect on prothrombinase activity *in vitro*, the combination Factor Xa/PCPS has the same activity as Factor Xa alone. The document deals mainly with the participation of Factor Va

in prothrombinase. Table II shows the reaction rates of various combinations of components - *inter alia* the combination Factor Xa/PCPS - of the prothrombinase complex. The point made by the Appellant was that the skilled person would not have considered said combination as a candidate for the therapeutic use as hemostatic *in vivo*.

In its decision to refuse the present application the Examining Division relied also on document (2) to deny novelty (see item 1.7 of the contested decision). However, prior to the refusal, the Appellant was not given an opportunity to put forward comments. In doing so, the Examining Division neglected Article 113 (1) EPC (see also Guidelines for Examination in the EPO, Part C, VI-7.7, second paragraph). However, in the circumstances of the present case, the Board considers that though this amounts to a substantial procedural violation, the requirement of Rule 67 for reimbursement, namely that such reimbursement be equitable by reason of a substantial procedural violation, is not met because the contested decision on lack of novelty was based primarily on document (1) (see item 3 in the said decision where reference is made to paragraphs 1.1 to 1.6). Even if the passages in the decision relating to document (2) are left out of account, the decision under appeal would have been fully reasoned, and an appeal, including payment of the appeal fee, would have been required to reverse it. The procedural violation as regards the reliance on document (2) was thus not sufficiently closely linked to the need to pay an appeal fee for it to be equitable for the appeal fee to be reimbursed. The request for reimbursement must thus be refused.

6. The question of the inventiveness of the claimed subject-matter has been only marginally discussed during the Examination proceedings with respect to a broader set of claims.

In order to ensure that the Appellant has the opportunity of having the question decided by the Examining Division, so that the possibility of a further appeal remains open, the Board considers it appropriate to make use of the power granted to it under Article 111(1) EPC to remit the case to the Examining Division for further prosecution.

Order

For these reasons, it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the Examining Division for further prosecution.
3. The request for reimbursement of the appeal fee is refused.

The Registrar:

The Chairman:

P.Martorana

P.A.M.Lançon