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**Datasheet for the decision
of 13 January 2010**

Case Number: T 0847/07 - 3.3.04

Application Number: 94915722.6

Publication Number: 0710114

IPC: A61K 38/37

Language of the proceedings: EN

Title of invention:

A coagulation factor VIII formulation

Patentee:

Biovitrum AB

Opponent:

CSL Behring GmbH

Headword:

Factor VIII formulation/BIOVITRUM

Relevant legal provisions:

EPC Art. 54, 56

Keyword:

"Main request: novelty (no)"

"Auxiliary request: novelty, inventive step (yes)"

Decisions cited:

T 0198/84, T 0017/85, T 0026/85, T 0279/89, T 0666/89,
T 1599/06

Catchword:

-



Case Number: T 0847/07 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 13 January 2010

Appellant: CSL Behring GmbH
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 29 March 2007
rejecting the opposition filed against European
patent No. 0710114 pursuant to Article 102(2)
EPC 1973.

Composition of the Board:

Chair: U. Kinkeldey
Members: G. Alt
R. Moufang

Summary of facts and submissions

I. The appeal lies against the decision of the opposition division to reject the opposition against European patent No. 0 710 114. The patent has the title "A coagulation factor VIII formulation". The patent application was filed on 31 March 1994. The patent claims the priority from the Swedish application No. 9302308 filed on 5 July 1993.

II. The patent was granted with 11 claims.

Claim 1 as granted read:

"1. A pharmaceutical formulation suitable for subcutaneous, intramuscular or intradermal administration, comprising highly purified recombinant coagulation factor VIII in a concentration of at least 1000 IU/ml."

III. The opposition filed against the grant of the patent requested revocation of the patent based on Article 100(a) EPC on the grounds of lack of novelty and lack of inventive step, Article 100(b) EPC on the ground of insufficiency of disclosure and Article 100(c) EPC on the ground of added matter vis-à-vis the application as filed.

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

D1 WO 93/24137

D2 WO 93/07890

D3 EP-B-0 506 757

D4 New England Journal of Medicine, 1966, vol. 275,
no. 10, pages 547-548, Pool J. et al.

D7 WO 94/07510

D8 British Journal of Haematology, 1992, vol. 81,
pages 610-613

D11 US 5,565,427

D12 EP-A-0 508 194

V. In its reasons to reject the opposition the opposition division concluded that the subject-matter of the claims of the main request, i.e. the claims as granted, fulfilled the requirements of Articles 123(2) and 83 EPC. Moreover, the subject-matter was held to be novel over the disclosure in either of documents D5 and D7. With regard to document D7 it was in particular stated that for considering factor VIII preparations having concentrations of at least 1 000 IU/ml from the disclosure in document D7, the skilled person had to make a selection from the ranges disclosed in that document.

The opposition division acknowledged that the claimed subject-matter involved an inventive step. It held that the skilled person would not have combined the teachings of documents D3, relating to the production of a human factor VIII deletion derivative by recombinant techniques, and document D4, describing the

ineffective intramuscular application of factor VIII, and therefore would not have arrived at the claimed subject-matter in an obvious way.

- VI. In response to the statement of the grounds of appeal the respondent (i.e. the patent proprietor) filed three auxiliary requests essentially corresponding to the three auxiliary requests filed during opposition proceedings.
- VII. With a submission dated 14 December 2009, the appellant filed document D11, a US patent.
- VIII. Oral proceedings took place on 13 January 2010.

At the oral proceedings the appellant filed document D12, the European patent application corresponding to document D11.

The respondent filed a new first auxiliary request. It contained nine claims. Claim 1, the sole independent claim, read:

"1. A pharmaceutical formulation which has a volume of 0.1 to 2 ml and is suitable for subcutaneous, intramuscular or intradermal administration, comprising highly purified recombinant coagulation factor VIII in a concentration of at least 1000 IU/ml."

In the context of the assessment of the relevance of document D1 the board informed the parties of its provisional view that the feature in some of the claims of the requests that the concentration of factor VIII

was at least 1 000 IU/ml was not derivable from the priority document.

IX. At the end of the oral proceedings the board announced its decision.

X. The appellant's arguments may be summarised as follows:

Admission of document D12

The information content of document D12 was essentially identical with that of document D11 which had been submitted earlier in the proceedings. Thus, since the respondent in fact knew the contents of document D12, it should be admitted into the procedure.

Main request

Novelty

The disclosure in any of documents D5, D7 and D12 anticipated the subject-matter of claim 1.

In particular, document D7 disclosed pharmaceutical formulations containing highly purified recombinant factor VIII with a concentration of factor VIII ranging from 10 to 100 000 IU/ml, preferably from 50 to 10 000 IU/ml (page 5, lines 25 to 26, claim 4). Thus, document D7 disclosed preparations having a factor VIII concentration of at least 1 000 IU/ml and therefore anticipated the subject-matter of claim 1.

Auxiliary request

Novelty

Document D7 disclosed preparations with the claimed factor VIII concentrations (see main request). Moreover, it was disclosed on page 9, lines 4 and 5 that the volume of the preparation could be adapted by dilution. Thus, the skilled person would derive from document D7 that the preparations disclosed in the document could have any volume. Therefore, the skilled person would implicitly derive from document D7 pharmaceutical formulations with a factor VIII concentration of 1 000 IU/ml and having a volume of 0.1 to 2 ml. Hence, the disclosure in document D7 also destroyed the novelty of the subject-matter of claim 1 of the auxiliary request.

Inventive step

Document D12, the closest prior art document, disclosed all features of claim 1 except the volume at which the formulation was to be applied.

At the priority date of the patent there was a need for factor VIII formulations that could be administered via a more convenient route than the standard route which was the intravenous administration. The skilled person would have considered any of the subcutaneous, intramuscular or intradermal routes as more convenient compared with intravenous injection. The skilled person also knew that small injection volumes were a prerequisite for the application of a medicament by any of these routes. Document D12 on page 3, lines 22 to 23

suggested to provide highly concentrated factor VIII preparations in a small volume. Both document D2, a patent application, and document D8, the related scientific publication, disclosed that subcutaneous injection of a highly concentrated factor IX preparation resulted in successful delivery of the factor into the bloodstream. Thus, the subject-matter of claim 1 was obvious in view of document D12 in combination with either of documents D2 or D8.

The subject-matter of claim 1 was also obvious in view of a combination of document D12 with document D4. Document D4 disclosed that the concentration of factor VIII in the circulation was too low and thus the activity of the factor ineffective after intramuscular injection of a factor VIII concentrate obtained from plasma. It was however an obvious measure to increase the concentration of factor VIII in order to ensure its effective delivery to the bloodstream.

XI. The respondent's arguments may be summarised as follows:

Admission of document D12

Document D12 should not be admitted into the procedure since its disclosure was not relevant to any of the claimed subject-matter.

Main request

Novelty

The claimed concentration range of at least 1 000 IU/ml was narrow with respect to the ranges disclosed in

document D7, i.e. 10 to 100 000 IU/ml, preferably 50 to 10 000 IU/ml. Moreover, it was far removed from the concentrations in the specific examples of document D7. Thus, the skilled person would not seriously contemplate working in the claimed range. Furthermore, the claimed subject-matter related to a new technical teaching, namely that, at the claimed concentration, administration of factor VIII by the subcutaneous, intramuscular or intradermal route was possible. Hence, the subject-matter of claim 1 was also novel with regard to the disclosure in document D7.

Auxiliary request

Novelty

Document D7 did not disclose a formulation having a volume of 0.1 to 2 ml and comprising factor VIII in a concentration of at least 1 000 IU/ml. Therefore the subject-matter of claim 1 was novel over the disclosure in document D7.

Inventive step

The skilled person would not have derived the suggestion from document D12 to apply factor VIII at the small volume indicated in claim 1.

Document D1 disclosed the subcutaneous administration of a factor VIII preparation. However, factor VIII was used for the treatment of disorders different from haemophilia A which did not necessitate delivery of the factor to the bloodstream.

Document D4 disclosed that only insufficient amounts of factor VIII were found in the bloodstream after intramuscular injection of a factor VIII concentrate obtained from plasma. Thus, this disclosure would have dissuaded the skilled person from using the intramuscular or a similar route for the use of factor VIII in the treatment of haemophilia A.

Factor IX was a protein completely different from factor VIII. Hence, the successful subcutaneous application of factor IX disclosed in either of documents D2 or D8 would not have given the skilled person any expectation that the same route would work for factor VIII.

Reasons for the Decision

Admission of document D12

1. Document D12, a European patent application, was filed at the oral proceedings. It is prior art pursuant to Article 54(2) EPC. The respondent has requested that document D12 not be admitted into the proceedings on the grounds that its content is not relevant to any of the claimed subject-matter.
2. According to Article 114(2) EPC the non-admission of late-filed material is at the discretion of the board. In exercising this discretion the parties' right to be heard and to a fair conduct of the proceedings is to be taken into account, as well as the public's interest in a speedy outcome of the proceedings and the existence of valid patents. Criteria considered by the boards

have thus been, inter alia, the complexity of the new material, its relevance, the point in time during the proceedings and the reason for its filing.

3. Document D12 was indeed filed at a very late point in time during the proceedings, i.e. at the oral proceedings. On the other hand, document D12 is rather short - 2 1/2 pages of description and examples, 12 claims and no figures. Moreover, the contents of document D12 were already known to the respondent (and the board) via document D11, the corresponding post-published US patent which had been submitted in the written proceedings with a letter dated 14 December 2009, i.e. one month before the oral proceedings. Finally, document D12 relates to preparations with a high concentration of factor VIII and is therefore relevant with regard to the claimed subject-matter.
4. Thus, despite its late filing, the respondent could be expected to be in a position to deal adequately with the document at the oral proceedings. The board therefore decided to admit document D12 into the proceedings.

Main request (claims as granted)

Article 100(b) and (c) EPC

5. At the oral proceedings before the opposition division the appellant withdrew the objections under Article 100(b) and (c) EPC to the main request before it (see the minutes of the oral proceedings, point 1.3). The main request before the opposition division was the

same as the present main request, i.e. the claims as granted. In the decision under appeal the opposition division held that this request fulfilled the requirements of Article 100(b) and (c) EPC. The appellant has not recurred to these objections in the appeal proceedings.

The board has no reason to deviate from the opposition division's view on these issues.

Novelty

Interpretation of claim 1 with regard to the feature "suitable for subcutaneous, intramuscular or intradermal administration"

6. Claim 1 relates to "[a] pharmaceutical formulation suitable for subcutaneous, intramuscular or intradermal administration, comprising highly purified recombinant coagulation factor VIII in a concentration of at least 1000 IU/ml".

7. The mention of the grant of the patent in suit was published in European Patent Bulletin 2003/09 of 26 February 2003. Therefore according to Article 1 point 3 of the decision of the Administrative Council of 28 June 2001 on the transitional provisions under Article 7 of the Act revising the European Patent Convention of 29 November 2000 (OJ EPO 2007, Special edition No. 1, p. 197), the revised Article 54(5) EPC, which provides for a notional novelty of a known medicament for a specific novel use, does not apply to the present claims since the patent in suit had already been granted when EPC 2000 entered into force on 13 December 2007.

8. The board considers that under the applicable provisions of EPC 1973 claim 1 has to be construed as relating to formulations that may be used for **any** form of administration as long as they are also suitable for subcutaneous, intramuscular or intradermal administration.

In the board's view the term "suitable for subcutaneous, intramuscular or intradermal administration" does however limit the meaning of the claim in so far as it excludes preparations which are not suitable for these forms of administration, such as preparations containing potentially toxic constituents or inactive factor VIII.

International application D7

9. Document D7 is an international patent application published under the PCT. International application D7 (hereinafter "application D7" or "application") has entered the European phase. All states designated by the patent in suit are also designated by the application and the national fee pursuant to Article 158(2) EPC 1973 and Rule 106 EPC 1973, including all designation fees, has been paid.
10. Application D7 was filed on 1 October 1993 and published on 14 April 1994. It claims priority from three Swedish applications, i.e. SE 9202878-6 filed on 2 October 1992, SE 9301580-8 filed on 7 May 1993 and SE 9302006-3 filed on 11 June 1993.

The appellant did not contest the validity of the three priorities claimed by application D7. The board is also satisfied that the relevant disclosure in the application (see points 12 to 15 below) is contained in all the three priority applications. Thus, application D7 validly enjoys the right of priority from each of the three Swedish applications as far as the relevant subject-matter is concerned.

11. The priority application for the patent was filed on 5 July 1993. The patent application pertaining to the patent in suit was filed on 31 March 1994.

Since the priority dates of application D7 are prior to the priority date of the patent in suit and since application D7 was published after the priority and the filing date of the patent in suit, the relevant information disclosed in that document is prior art pursuant to Articles 54(3) and 89 EPC.

12. Application D7 discloses factor VIII preparations containing highly purified recombinant factor VIII and at least a non-ionic surfactant as a stabiliser (claims 1 and 2) for the treatment of haemophilia A by injection (page 1, lines 14 to 27, and page 5, lines 7 to 13). In the specific compositions of the examples, histidine, mannitol and sodium chloride, inter alia, are further constituents.
13. Before the priority date of the patent in suit the common way of administering factor VIII to haemophilia A patients was by intravenous injection. Given the absence of any specific disclosure in application D7, the board is convinced that the skilled person would

have considered that the application only relates to this common route of administration, i.e. the intravenous application of factor VIII.

14. In response to a question from the board at the oral proceedings, the respondent acknowledged that the preparations disclosed in application D7 would be suitable for subcutaneous, intramuscular or intradermal administration.
15. Moreover, application D7 discloses that the amount of factor VIII in the preparation is from 10 to 100 000 IU/ml, preferably from 50 to 10 000 IU/ml (page 5, lines 25 and 26; claim 4).

Thus, the claimed range, i.e. "at least 1 000 IU/ml", is not explicitly disclosed in application D7. However, the general range disclosed in the application overlaps the claimed range of a factor VIII concentration from 1 000 IU/ml to 100 000 IU/ml. Furthermore, the preferred range disclosed in this application also overlaps, namely from 1 000 IU/ml to 10 000 IU/ml.

16. According to the case law a sub-range selected from a larger range of the prior art is considered as a selection and therefore as novel if each of the following three criteria are satisfied (T 198/84, OJ EPO 1985, 209; T 279/89 of 3 July 1991; Guidelines for Examination in the European Patent Office, C.IV 9.8):

(a) The selected sub-range is narrow compared with the known range.

(b) The selected sub-range is sufficiently far removed from any specific examples disclosed in the prior art and from the endpoints of the known range.

(c) The selected range is not an arbitrary specimen of the prior art, but another invention, i.e. a new technical teaching.

17. According to decision T 17/85 (OJ EPO 1986, 406), point 7.5 of the reasons, these criteria can also be applied when considering novelty in the context of overlapping ranges.
18. In the present case the part of the known range overlapping with the claimed range is larger than its non-overlapping part, i.e. there is an overlap between 1 000 IU/ml and 10 000 and 100 000 IU/ml, and a non-overlap between 10 IU/ml and 50 IU/ml and less than 1 000 IU/ml. Thus, regarding the whole range known from application D7, the overlap of the claimed range with the known range is not narrow.
19. Since, according to the case law, each of the three above cited criteria must be fulfilled for considering an invention as a selection from a larger range and therefore as novel, the finding that criterion (a) above (point 16) is not fulfilled is alone a sufficient reason for denying novelty for the claimed range.
20. The board notes however that in addition neither criterion (b) nor criterion (c) is fulfilled in the present case. As to criterion (b) the factor VIII preparation in the examples of application D7 has a concentration of around 100 IU/ml (examples 1 and 11),

125 IU/ml (example 12), 200 IU/ml (example 10) and 300 IU/ml (example 2) (see below). Given the magnitude of the claimed range, i.e. the lower value is defined as "at least 1000 IU/ml", but that there is no limit at the upper end, the board considers that the specific examples in application D7 are not far removed from the lower value of the claimed range.

Finally, given that the subject-matter of the claims is not limited to the use of the formulation for only subcutaneous, intramuscular or intradermal administration (see points 7 and 8 above), the claimed subject-matter is not considered as reflecting that the selection is non-arbitrary. Consequently, criterion (c) above is not fulfilled either.

21. The board's finding that the claimed range is not novel is in line with a further principle for the evaluation of the novelty of overlapping ranges applied for example in decisions T 26/85 (OJ EPO 1990, 22) and T 666/89 (OJ EPO 1993, 495). According to these decisions the question to be asked is whether or not a person skilled in the art would, in the light of all the technical facts at his disposal, seriously contemplate applying the technical teaching of the prior art document in the range of overlap. Provided the information in the prior art document in combination with the skilled person's common general knowledge is sufficient to enable him/her to practise the technical teaching, and if it can reasonably be assumed that he/she would do so, then the claim in question will lack novelty.

22. In the general description and the claims, application D7 discloses pharmaceutical preparations having a concentration of factor VIII between 10 and 100 000 IU/ml, preferably 50 to 10 000 IU/ml. The application repeatedly refers to preparations with a high concentration of factor VIII and also points out that super-pure preparations are on the market (page 2, lines 16 to 17, page 5, lines 6 to 7 and lines 20 to 21; claim 2). Thus, there is no evidence that the skilled person would see any obstacles to preparing the highly concentrated preparations disclosed in application D7. Consequently, the board is convinced that the skilled person would not consider the disclosure in application D7 to be limited to a range of concentrations suggested by the values in the examples, i.e. below 1 000 IU/ml (see point 20 above), but rather would seriously contemplate applying the technical teaching of the prior art document in the range of overlap, and that therefore the claimed range is not new.

23. Hence, application D7 discloses subject-matter anticipating the subject-matter of claim 1 of the main request. Therefore, the subject-matter of this claim does not fulfil the requirements of Article 54(1) and (3) EPC.

Auxiliary request

Admission of the auxiliary request

24. The auxiliary request was filed at the oral proceedings as a reaction to the board's finding of lack of novelty of claim 1 of the main request over application D7. The

auxiliary request differs from the main request in that the additional feature of claim 4 as granted, i.e. that the formulation has a volume of 0.1 to 2 ml, has been introduced into claim 1, in a corresponding renumbering of the claims and in the omission of granted claim 10. The claims of the auxiliary request correspond to claims 1 to 9 of a request filed with a written submission as "3rd auxiliary request" in February 2008. Given that the new feature had been announced as a fall back position as early as February 2008 and that the claims do not suffer from formal deficiencies (see point 26 below), the board considers that the appellant could deal appropriately with the request, although it was only submitted at the oral proceedings.

The appellant had not requested that the auxiliary request not be admitted.

Thus, the board decided to admit the auxiliary request into the proceedings.

Articles 123(2), 123(3) and 84 EPC

25. The feature in claim 1 "which has a volume of 0.1 to 2 ml" has a basis in claim 4 as filed and therefore the amendment does not add matter over that disclosed in the application as filed. The additional feature restricts the claim to a specific range of volumes. Therefore, the amendment does not extend the protection conferred beyond that of the claims as granted. Moreover, the expression is in itself clear and does not create any lack of clarity in the context of the claims.

The requirements of Articles 123(2), 123(3) and 84 EPC are fulfilled.

Article 83 EPC

26. The patent discloses how to prepare a formulation containing the claimed concentration of factor VIII (see paragraphs [0030] to [0036]) and that subcutaneous administration of such a factor VIII preparation in a volume of the claimed range results in delivery of active factor VIII into the circulation (see examples 1 and 3; see also point 46.1 below).

The appellant has not raised any objection.

The requirements of Article 83 EPC are fulfilled.

Novelty

Interpretation of claim 1 with regard to the meaning of the term "pharmaceutical formulation"

27. Claim 1 relates to a pharmaceutical formulation which comprises factor VIII in a concentration of at least 1 000 IU/ml in a volume of 0.1 to 2 ml.
28. The board considers that the claims have to be interpreted as relating to formulations ready for administration, given the feature in the claim that the formulation is "**suitable** for subcutaneous, intramuscular or intradermal application" and in the light of the relevant examples 1 and 3 disclosing preparations which when applied subcutaneously have a

concentration of 1 060 IU/ml and 1 130 IU/ml respectively.

International application D7

29. The only document cited against the novelty of the subject-matter of claim 1 of the auxiliary request is the international patent application published as document D7. It has been established above that application D7 discloses preparations suitable for subcutaneous, intramuscular or intradermal application and containing factor VIII in a concentration encompassing a range of 1 000 IU/ml to 100 000 IU/ml, and is thus novelty-destroying for the subject-matter of claim 1 of the main request (see points 12 to 23 above).

Claims 1 of the main and the auxiliary requests differ in that the latter additionally refers to the feature "which has a volume of 0.1 to 2 ml". A first issue is therefore whether or not this feature is derivable from application D7.

30. The appellant refers to page 9, lines 4 to 8, where it says: "The VIII:C activity and the concentration of the inactive components were adjusted by diluting with an appropriate buffer. The solution was then sterile filtered (0,22µm), dispensed and freeze-dried." The respondent argues that the disclosure of the possibility of adjusting the concentration by dilution with an appropriate buffer implies that the solution to be used has any suitable volume, i.e. including a volume between 0.1 and 2 ml as claimed.

31. The board is not convinced. Firstly, the cited passage refers to an adjustment of the concentration in the preparation before freeze-drying and thus does not refer to the volume of a ready-for-use formulation. Secondly, according to established case law of the boards of appeal a general disclosure does not take away the novelty of a specific one (Case Law of the Boards of Appeal, 5th edition 2006, I.C.3.2.6, last paragraph, last sentence). Thus, the general disclosure that a factor VIII formulation may have any volume cannot be considered as the disclosure of the specific volumes between 0.1 and 2 ml.
32. Application D7 has twelve examples disclosing the preparation of formulations for injection containing factor VIII and some other constituents. A given amount of a preparation containing factor VIII, i.e. 2 ml (see examples 1, 2, 3, 4, 9, 12) or 2.2 ml (see examples 5, 7, 8, 10, 11) is lyophilised and thereafter reconstituted in order to obtain the preparation for administration.
33. According to example 2, 2 ml of a preparation of factor VIII having 300 IU/ml is lyophilised. Thus, assuming in the appellant's favour that no factor VIII activity is lost during lyophilisation (which is the - rather unrealistic - best-case scenario), the activity of factor VIII in the dried material is at best 600 IU. This material is dissolved in 2 ml of sterile water, resulting in a concentration of factor VIII of 300 IU/ml.
34. Thus, the volume of the ready-for-use formulation according to example 2 of application D7, i.e. 2 ml, is

within the claimed range of volumes, i.e. 0.1 to 2 ml, but with a concentration of factor VIII which is considerably lower than the claimed one. The question arises whether or not the skilled person would have combined the disclosure in example 2 of a small administration volume with the general disclosure in application D7 of highly concentrated preparations of factor VIII and thus would have derived from the application the disclosure of a formulation with 1 000 IU/ml or more in a volume of 2 ml.

35. All the further relevant examples in application D7 (examples 1, 3 to 5, 7 to 12) disclose the reconstitution of the lyophilised material with either 5 ml (examples 1, 3 to 5, 7 to 11) or 4 ml (example 12) of sterile water.
36. The board has concluded in point 13 above that application D7 relates to administration by intravenous injection. Volumes of 4 to 5 ml are in the range of volumes that the skilled person would have expected for intravenous application (see point 49 below).

Therefore, given that example 2 in application D7 is the sole example disclosing an injection volume of 2 ml and that this volume would appear rather unusual to the skilled person in the context of intravenous administration, he/she would, in the board's view, have considered that example 2 relates to a specific formulation and therefore that its features cannot be separated.

Hence, the skilled person would not have combined the disclosure in example 2 of a small administration

volume with the general disclosure in application D7 of highly concentrated preparations of factor VIII and would therefore not have derived from this application the disclosure of the combination of a high concentration of factor VIII, in particular 1 000 IU/ml or more, with an injection volume of 2 ml.

37. Hence, the subject-matter of claim 1 is not unambiguously disclosed in application D7. This finding also applies to claims 2 to 9 which are all dependent on claim 1.

38. The requirements of Article 54 EPC are fulfilled.

Inventive step

Closest prior art

39. Document D12 is referred to by the appellant as the closest prior art document. It relates to a process for the production of stabilised preparations containing highly concentrated factor VIII. In particular, preparations with an activity per volume of at least 200 IU/ml are disclosed (page 3, lines 20 to 21). Such preparations may be used as medicaments for the treatment of haemophilia A (page 2, lines 5 and 6; claims 1 and 9). It is not specified in the document at which volume and by which route the stabilised, highly concentrated factor VIII is to be administered.

40. For the reasons given in relation to international application D7 (see point 13 above), the board is convinced that the skilled person would also have considered that document D12 concerns the common route

of administration for factor VIII, i.e. intravenous administration.

Problem to be solved and solution

41. Haemophilia A is an inherited disorder characterised by a greatly decreased level or the absence of functional blood clotting factor VIII. Patients suffering from haemophilia A need constant administration of factor VIII. Intravenous application is disadvantageous for these patients because it must be mandatorily carried out by medical staff. Moreover, repeated intravenous injections may lead to fibrosis of the vein at the site of injection. It is also a problem when veins are small, for example in babies (see for example document D2, page 1, line 31 to page 2, line 2).
42. Subcutaneous, intramuscular or intradermal administration of medicaments is advantageous by comparison with intravenous application, inter alia because the injections can be carried by the patient him/herself.
43. Thus, in view of the known factor VIII preparations for intravenous application such as that disclosed in document D12, and given that the term "suitable for subcutaneous, intramuscular or intradermal administration" does not limit the claim to these administration routes (see points 7 and 8 above), the problem to be solved by the patent is to provide a formulation for the treatment of haemophilia A which overcomes the disadvantage of the known factor VIII preparations that are suitable for intravenous administration only.

44. This problem is solved according to claim 1 by a formulation which is applied to the patient in a volume of 0.1 to 2 ml.

Evidence in the patent that the problem is solved

45. Due to their small volume the claimed formulations are suitable not only for intravenous, but also for subcutaneous, intramuscular or intradermal administration.

- 45.1 The patent in suit discloses in examples 1 and 3 the subcutaneous application of a factor VIII preparation according to claim 1 to mice and cynomolgous monkeys. Active factor VIII was found in the bloodstream after administration. On the basis of this evidence the board is satisfied that the claimed invention indeed solves the problem underlying the patent.

Obviousness

46. Generally, the skilled person was aware of both the disadvantage of the intravenous application route in the treatment of haemophilia A (see point 41 above) and of the advantages in general offered by the subcutaneous, intramuscular or intradermal route. Therefore, in the board's view, the provision of factor VIII formulations which are applicable by these advantageous routes certainly was an obvious desideratum for the skilled person. In fact, intramuscular application of factor VIII for the treatment of haemophilic patients was tried as early as 1945 (see document D4, second paragraph).

47. However, merely wishing to provide claimed subject-matter is not sufficient to make a claim obvious. According to established case law, it must be shown that the skilled person in the light of the problem to be solved would have arrived at the claimed subject-matter due to promptings in the prior art (Case Law of the Boards of Appeal of the EPO, 5th edition 2006, I.D. 5.).
48. In the present case, documents D1, D2, D4, D8 and the closest prior art document D12 are the most relevant ones among the cited documents for the assessment of the obviousness of the claimed subject-matter.

Document D12

49. Document D12 discloses factor VIII preparations for intravenous administration (see point 40 above). Typical volumes for intravenous injection range from 5-10 ml (see introductory part of the patent in suit, page 2, lines 55 to 56) up to 50 ml or more (see document D8, first paragraph).
50. Since, as already stated above, claim 1 does not exclude formulations for intravenous administration, the first question arising in view of document D12 is whether or not the skilled person would have had an incentive in view of the prior art to reduce the injection volume of factor VIII formulations for intravenous administration. However, there is no document in the proceedings which is relevant for the assessment of inventive step and from which the skilled person would have derived such an incentive.

51. As regards document D12 itself, it discloses that preparations with volume activities of at least 200 IU/ml allow convenient use ("problemlose Handhabung") due to the possibility of applying small volumes (page 3, lines 22 to 23). It is not explicitly specified in document D12 what is meant by a "small" volume.
52. As stated above in point 49, typical volumes for intravenous injection range from 5-10 ml up to 50 ml or more. Therefore, in the board's view, in the context of document D12 which relates to formulations for intravenous injection, the skilled person would have understood the term "small" to describe volumes that may be conveniently applied intravenously, i.e. which are at least within the range of volumes normally used for intravenous injection. Since the volumes specified in claim 1 of between 0.1 to 2 ml fall outside this range, the person skilled in the art would not understand the term "small" in document D12 as referring to these volumes.
53. Consequently, the document would not have given the skilled person any motivation to modify the preparations disclosed in that document so as to arrive at the claimed preparations.

Document D12 in combination with document D4

54. Document D4 reports the intramuscular injection of factor VIII concentrates obtained from cryoprecipitates of human plasma. The level of factor VIII circulating in the bloodstream after the injection was determined. It was found that it was 5% of what would have been

recovered after intravenous administration (page 548, left-hand column, second paragraph). These findings suggest that the "intramuscular route for this preparation has very little promise" (page 548, left-hand column, second paragraph, last sentence). In the "Summary" on page 548 it is stated that "[c]ryoprecipitate factor VIII concentrate was ineffective in producing significant circulating factor VIII levels after intramuscular injection, ...".

55. Thus, document D4 teaches that factor VIII preparations from cryoprecipitates of human plasma as described in the document are not suitable for intramuscular application.

56. Document D4 indicates two reasons for the ineffective delivery of factor VIII from the disclosed cryoprecipitate into the bloodstream after administration via the intramuscular route (page 548, first paragraph of "Discussion").

Factor VIII might (a) remain at the muscular site, being unable to cross the vascular barrier due to its high molecular weight which is reported to be between 180 000 and more than 200 000, or (b) be readily inactivated.

57. In the board's view, although the authors of document D4 had limited their conclusions to the preparation used by them (see point 54 above), it is doubtful whether the skilled person having the highly purified preparations of document D12 at his/her disposal would be prompted at all by the disclosure in document D4 to administer factor VIII intramuscularly.

58. However, even if he/she had contemplated doing so in the light of document D4: firstly, the skilled person would not have expected a linear relationship between the concentration of factor VIII in the injected preparation and the subsequent availability of the factor in the blood on the basis of his/her common knowledge regarding the generally high degree of unpredictability of the properties of a protein under specific circumstances.
59. Secondly, in view of document D4 the skilled person would attempt to modify the highly purified preparations of document D12 so as to take account of the reasons given in document D4 for the ineffective delivery (see point 56 above), i.e. he/she would for example have provided a preparation with a more stable factor VIII or with a smaller, but equally active derivative.
60. Thus, for these reasons the skilled person would not have considered in the light of the disclosure in document D4 that an increase in the concentration of factor VIII per volume unit would necessarily change its bioavailability after intramuscular administration. Hence, even the combination of the disclosures in documents D12 and D4 does not make the claimed subject-matter obvious.

Document D12 in combination with documents D8 or D2

61. Document D8 relates to the treatment of patients suffering from haemophilia B. Haemophilia B, like haemophilia A, is an inherited bleeding disorder. It is

caused by a defect in blood clotting factor IX. The usual treatment for haemophilia B consisted in the intravenous administration of factor IX.

62. Document D8 discloses in the introduction that factor IX had been administered intravenously to haemophilia B patients in volumes of 50 ml or more due to the low purity of the preparations, that highly purified factor IX preparations have become available and that therefore a therapeutic dose of 1 000 to 2 000 IU could be administered in <1-2 ml (page 610, first paragraph), i.e. in a volume suitable for subcutaneous administration.

Document D8 demonstrates with model animal experiments, i.e. in mice, that effective levels of factor IX in the circulation are achieved after subcutaneous administration.

63. Thus, document D8 teaches that effective subcutaneous administration was achieved by increasing the concentration of factor IX in the injected dose.

64. Given that highly pure, i.e. highly concentrated preparations of factor VIII were known (see document D12), the question arises whether or not the skilled person would have been prompted by the teaching in document D8 to apply the highly concentrated factor VIII preparations via the subcutaneous route.

65. In the board's opinion this would not have been so. Document D8 does not contain an explicit hint that the results obtained with factor IX could be obtained with the subcutaneous administration of factor VIII. While

the "Summary" states that "[m]ore generally, our studies emphasise that the subcutaneous route of injection should be useful for other therapeutic proteins, including other clotting factors, which have to be delivered to the blood stream", this is done only subject to the condition mentioned in the following half-sentence, i.e. "as long as their half-life is at least a few hours allowing time for transport into the general circulation". Neither document D8 nor any other of the available documents reports that factor VIII in a highly purified factor VIII preparation would be sufficiently stable.

66. Thus, on the basis of the prior art cited in the proceedings the availability of factor IX in the bloodstream after subcutaneous administration would not have prompted the skilled person to carry out the same approach with factor VIII. Additionally, the skilled person knew that the stability of a protein depends largely on its primary structure which, as the skilled person also knows, is completely different between factor VIII and factor IX. Therefore, the mere fact that both proteins take part in the blood clotting cascade would not lead the skilled person to assume that the stability properties of the two coagulation factors are similar, particularly since it was also known that both have different functions in the overall blood clotting pathway.

67. Document D2 has also been adduced by the appellant. It is the patent application corresponding to the scientific publication D8. As far as the teaching relevant in the present context is concerned the information content of this document does not exceed

that of document D8. Thus, the skilled person would draw the same conclusions from document D2 as from document D8.

68. The board has considered whether or not the skilled person faced with the disclosure in document D8 would be in a "try and see" situation. The board in decision T 1599/06 of 13 September 2007, point 20.2 comes to the conclusion that the "try and see" approach has been applied in the assessment of inventive step in situations where, in view of the prior art, the skilled person had clearly envisaged a group of compounds or a compound and then could determine by routine tests whether or not such compound(s) had the desired effect.
69. It follows however from the observations above that highly purified factor VIII had not been identified as a candidate for an administration route other than the intravenous one, i.e. it was never envisaged for injection volumes in the range of 0.1 to 2 ml. Consequently, applying the rationale of the decisions which have used the "try and see" approach as summarised by the board in decision T 1599/06, the board concludes that in the present case the skilled person is not in a "try and see" situation in the light of the disclosure in document D8.
70. Finally, in the board's view, it is questionable whether the skilled person would adopt a "try and see" attitude at all in cases such as the present one where extensive in vivo animal and ultimately human testing would be necessary in order to determine whether or not a compound has a certain property.

Document D12 in combination with document D1

71. The opposition division held document D1 to be prior art pursuant to Article 54(3) EPC and therefore did not consider it in the evaluation of inventive step. Claims 1 of the request before the opposition division and of the present request recite the feature that the formulation "comprises highly purified recombinant coagulation factor VIII in a concentration of at least 1000 IU/ml".

However, the board has doubts as to whether this feature is derivable from the priority document of the patent in suit. Consequently, those claims which relate to subject-matter characterised by that feature might not be entitled to the claimed priority date. Thus, because the publication date of document D1, i.e. 9 December 1993, is before the filing date of the patent, i.e. 31 March 1994, document D1 would be prior art pursuant to Article 54(2) EPC for this subject-matter.

72. The board informed the parties of its preliminary view on the validity of the priority of the patent in suit at the oral proceedings. This issue was however left open in view of the board's finding that none of the claimed subject-matter is obvious in view of the disclosure in document D1 (see below).

73. Document D1 discloses pharmaceutical compositions containing factor VIII for subcutaneous, intradermal or topical administration in the treatment of **inflammation** disorders such as skin inflammation, inflammation of the joints affected by arthritis and intestinal

inflammation conditions such as colitis in the **non-haemophilic** body (page 1, first paragraph and claim 1).

When administered subcutaneously or intradermally, the injection volume is 0.1 ml (see the examples).

In the general part, document D1 discloses the total dose to be injected into the patient (page 2, lines 19 to 25), but does not indicate the concentration of factor VIII per volume unit. The relevant examples disclose subcutaneous or intradermal injection into rats of factor VIII preparations at concentrations which are far below the range claimed in the patent in suit of "at least 1000 IU/ml". For instance, in example 1 the maximum dose delivered is 15 IU/kg (page 4, line 32). Since the laboratory rats have a maximum weight of 200 g (page 4, line 16) and the injected volume is 0.1 ml/rat (page 4, line 31), the deduced concentration in the preparation is at best 30 IU/ml. By similar calculations the concentration of factor VIII in the injected preparations according to the other examples may be determined to be 55 IU/ml (example 2; page 5, line 29 and 31); 6.2 IU/ml (example 4; page 7, lines 9, 13 and 17); 247 IU/ml, 123.5 IU/ml or 24.7 IU/ml (example 5; "Group A").

74. Given this disclosure in document D1, the question is whether or not the person skilled in the art would have arrived at the claimed invention by combining the feature of the administration of high concentrations of factor VIII as disclosed in document D12 with the administration of a volume of 0.1 ml as disclosed in D1.

75. However, the board is not convinced that the skilled person would have taken account of the teaching in document D1 at all. Document D1 discloses factor VIII for the treatment of inflammation disorders in non-haemophilic patients. For the therapeutic activity of factor VIII in this context, transport of the factor to the blood stream is not necessary. This is, however, the crux after subcutaneous, intramuscular or intradermal administration in the treatment of haemophilia A with factor VIII (see for example point 56 above).
76. If the skilled person had considered a combination of the teaching of document D12 - highly concentrated factor VIII preparations - with that of document D1, in particular the examples (see point 73 above), he/she would have arrived at the conclusion that the concentration of factor VIII should be less than 1 000 IU/ml for successful subcutaneous or intradermal administration.
77. Thus, the combination of the disclosure in document D12 with that in document D1 would not have motivated the skilled person to provide the claimed formulation.
78. Thus, in summary, the subject-matter of claim 1 and also of the dependent claims 2 to 9 is not obvious in view of document D12 alone or in combination with either of documents D1, D2, D4 or D8. The requirements of Article 56 EPC are fulfilled.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance with the order to maintain the patent in amended form on the basis of the following documents:
 - claims: 1 to 9 of the first auxiliary request filed at the oral proceedings;
 - description: pages 2 and 3 filed at the oral proceedings, pages 4 to 9 of the published patent specification.

The Registrar:

The Chair:

P. Cremona

U. Kinkeldey