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**D E C I S I O N**  
**of 15 February 2005**

**Case Number:** T 0656/03 - 3.3.8

**Application Number:** 91901327.6

**Publication Number:** 0506757

**IPC:** C12N 15/12

**Language of the proceedings:** EN

**Title of invention:**

A recombinant human factor VIII derivative

**Patentee:**

BIOVITRUM AB

**Opponent:**

Chiron Corporation

**Headword:**

Factor VIII/BIOVITRUM

**Relevant legal provisions:**

EPC Art. 54, 56

**Keyword:**

"Main request: novelty (yes); inventive step (no)"

"First auxiliary request: novelty (yes); inventive step (yes)"

**Decisions cited:**

G 0009/92, T 0750/94, T 1208/97, T 0314/99

**Catchword:**

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Case Number: T 0656/03 - 3.3.8

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.8  
of 15 February 2005

**Appellant:** BIOVITRUM AB  
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**Decision under appeal:** Interlocutory decision of the Opposition  
Division of the European Patent Office posted  
4 April 2003 concerning maintenance of European  
patent No. 0506757 in amended form.

**Composition of the Board:**

**Chairman:** L. Galligani  
**Members:** T. J. H. Mennessier  
M. B. Günzel

## Summary of Facts and Submissions

- I. The patent proprietor (appellant) lodged an appeal against the interlocutory decision of the opposition division dated 4 April 2003, whereby the European patent No. 0 506 757 was maintained on the basis of the third auxiliary request (claims 1 to 4) filed on 23 January 2003. The patent had been granted on European application No. 91 901 327.6 which originated from an international application published as WO 91/09122 (to be referred to in the present decision as the application as filed).
- II. The patent had been opposed by one opponent on the grounds that (i), as set forth in Article 100(a) EPC, the invention was not new and did not involve an inventive step and (ii), as set forth in Article 100(b) EPC, that the invention was not sufficiently disclosed.
- III. The opponent also filed an appeal that by decision T 656/03 of 23 June 2004 was rejected by this board as inadmissible.
- IV. The opposition division had refused a main request as well as the first and second auxiliary requests. The main request had been found to lack novelty (see Article 54 EPC) over document D6 (see section X, *infra*) and the second auxiliary request, as regards claims 1 and 2, to contain added matter (see Article 123(2) EPC).
- V. The statement of grounds of appeal was filed on 12 August 2003. The appellant filed therewith a main request as well as three auxiliary requests, the main request being identical to the main request refused by

the opposition division and the third auxiliary request being identical to the request allowed by the opposition division. The respondent (opponent) did not file any observations in reply to this statement of grounds of appeal.

- VI. The Board issued a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal in which provisional and non-binding opinions were expressed. Neither of the parties filed observations in reply to this communication.
- VII. Oral proceedings took place on 15 February 2005 at which the appellant filed a new first auxiliary request to replace all those on file. The oral proceedings were not attended by the respondent as announced in its letter of 17 January 2005.
- VIII. **The main request** consisted of 5 claims of which claim 1 read:

Claim 1 read:

"1. A DNA sequence coding for a biologically active recombinant human factor VIII derivative composed of two polypeptide chains of 90 kDa and 80 kDa molecular weight, respectively, said DNA sequence being capable of expressing, in an appropriate host cell, said derivative for secretion from said cell, and comprising a first DNA segment coding for the 90kDa chain of human factor VIII and a second DNA segment coding for the 80 kDa chain of human factor VIII, said segments being interconnected by a linker DNA segment coding for a linker peptide of at least 7 and up to 20 amino acid

residues of the B domain of human factor VIII, at least 4 of said amino acid residues originating from the C-terminal of said domain and at least 2 amino acid residues originating from the N-terminal of said domain."

IX. **The first auxiliary request** consisted of 5 claims.

Claims 1 to 4 exactly corresponded to claims 1 to 4 of the second auxiliary request as refused by the opposition division.

Claim 1 read:

"1. A DNA sequence coding for a biologically active recombinant human factor VIII derivative composed of two polypeptide chains of 90 kDa and 80 kDa molecular weight, respectively, said DNA sequence being capable of expressing, in an appropriate host cell, said derivative for secretion from said cell, and comprising a first DNA segment coding for the 90kDa chain of human factor VIII and a second DNA segment coding for the 80 kDa chain of human factor VIII, said segments being interconnected by a linker DNA segment coding for a linker peptide of 14 amino acid residues of the B domain of human factor VIII, wherein said linker DNA codes for 12 amino acid residues originating from the C-terminal and 2 amino acid residues from the N-terminal of the B domain of human factor VIII."

While claim 2 was directed to a particular embodiment of claim 1, the subject-matter of claims 3 and 4 concerned, respectively, an expression vector comprising the DNA sequence according to claims 1 or 2

and a host cell transformed with such an expression vector.

Claim 5 was independent. It was directed to a process for the manufacture of a biologically active recombinant human factor VIII and was formulated with exactly the same wording as that of independent claim 4 of the third auxiliary request of 23 January 2003 on the basis of which the patent had been maintained by the opposition division.

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

(D1) John J. Toole et al., Proc. Natl. Acad. Sci. USA, Vol. 83, August 1986, Pages 5939 to 5942

(D4) Dan L. Eaton et al., Biochemistry, Vol. 25, No. 26, 30 December 1986, Pages 8343 to 8347

(D6) R. C. Hoeben et al., Thrombosis and Haemostasis, Vol. 62, No. 1, 19 August 1989, Page 209, Abstract No. 636

(D8) Nava Sarver et al., DNA, Vol. 6, No. 6, 1987, Pages 553 to 564

(D14) WO 88/00831 (published on 11 February 1988)

(D24) Peter Lind et al., Eur. J. Biochem., Vol. 232, 1995, Pages 19 to 27

(D28) Document submitted by the appellant with its letter of 22 November 2002 providing a schematic

representation of prior art relating to  
recombinant B-domain deleted factor VIII

(D25o) Rob C. Hoeben et al., J. Biol. Chem., Vol. 265,  
No. 13, 5 May 1990, Pages 7318 to 7323

(D32o) Declaration of Professor R. C. Hoeben dated  
15 November 2002

(A) Letter of the British Library Document Supply  
Centre dated 13 January 2003 filed with the  
respondent's letter of 15 January 2003

(B) Letter of the British Library dated 20 January  
2003 submitted by the appellant at the oral  
proceedings held before the opposition division  
on 23 January 2003 (see exhibit II of the  
decision under appeal)

(C) Scheme showing structure and processing of full-  
length factor VIII, submitted by the appellant at  
the oral proceedings before the opposition  
division and attached to the decision under  
appeal as Annex VI

XI. The submissions made by the appellant (patent  
proprietor), insofar as they are relevant to the  
present decision, may be summarised as follows:

Main request

Novelty over document D6 (claim 1)

The date printed in the top left corner of the cover sheet of document D6 was 19 August 1989. Under normal circumstances, a scientific journal was published on or around the date printed on its cover sheet. However, this was only the case for periodicals that were published at regular intervals. The issue of "Thrombosis and Haemostasis" of document D6 was a special edition. It had been printed exclusively in connection with the XII<sup>th</sup> Congress of the International Society on Thrombosis and Haemostasis which took place from August 19 to August 25, 1989 in Tokyo, Japan. In the bottom left corner on the second page of document D6, it was indicated that this special issue of the journal was printed in Tokyo, Japan and not - as usual - by the publishing house F. K. Schattauer, in Stuttgart, Germany. Therefore, the date of 19 August 1989 was not the date of publication of this special issue but a direct reference to the conference which indeed started on that date. In fact, as it was known among scientists, special issues of journals that contained papers, lectures or posters presented at a conference were often published some time after the conference took place, since the papers, posters and lecture manuscripts had to be gathered at the conference first and then edited, so that they were ready for publication only a few months later. Actually, in view of the evidence obtained at the British Library with respect to the further dates relating to the receipt (13 November 1989) and processing (14 December 1989) of document D6, this scenario seemed very plausible. It could not safely be assumed that the abstract itself was distributed at the conference. The overall picture made it just as probable that this did not occur and the printed



abstract became available when the special edition of "Thrombosis and Haemostasis" became available to the public by other means, for example, availability in the British Library.

The British Library did not have the afore-mentioned conference abstracts available until after the priority date, as might be taken from document B. Even assuming that document D6 was catalogued on 14 December 1989, it would not have been made available to a member of the public until at least the next working day. Thus, on the balance of probabilities, it had not been established that the abstract of document D6 had been made available to the public before the priority date (15 December 1989). Decisions T 750/94 (OJ EPO 1998, 32) and T 314/99 of 21 June 2001 were referred to.

Document D6 did not satisfy the "clear and unambiguous" disclosure standard. It was a short abstract, containing vague and obscure information. Case law suggested that abstracts were inherently unreliable and that their disclosure should be verified by checking the full document whenever possible. In this respect, Figure 1 of document D250, which was published after the priority date, showed that in the construction of document D6 an artificial linker of 5 amino acids was added. Assuming that the numbering system used was based on the mature sequence, this would have led to a complete linker (made of the remaining amino acid residues of the B domain and the artificial linker) longer than indicated in claim 1. There were two potential deletions that could be made, since there were two numbering systems available, based on either the precursor or the mature sequence. Unlike all of the

other cited prior art documents, document D6 did not specify which numbering system was to be used. This missing information led to the fact that document D6 was ambiguous. The post-published full document, D250, taught that the deletion was between the codons for amino acid residues 746 and 1638 and referred to Figure 1, which showed the deletion of the mature 2332 amino acid sequence. However, document D250 was not relevant for assessing how the skilled person would have interpreted document D6 at its publication date. Moreover, the factor VIII clone referred to in the abstract in question was not available to the public at the priority date.

Furthermore, the term "codons" as used in document D6 rendered the whole disclosure indefinite because the numbers used in connection therewith designated amino acid residues rather than nucleotide codons.

Inventive step (claim 1)

Not document D6 but document D14 was the closest state of the art. Document D14 disclosed the "RE" DNA sequence which had a deletion of all of the nucleotides coding for the B-domain and, like the patent in suit, it dealt with the technical problem of the provision of a recombinant DNA sequence encoding a primary translation product which could be properly processed in the cells so as to allow the secretion of a biologically active factor VIII protein. Nevertheless, post-published experiments as reported in document D24 showed that not a cDNA sequence encoding the primary translation product with the RE deletion of document D14 (see rVIII RE polypeptide on Figure 2 of document

24) but the cDNA sequence encoding the primary translation product rVIII SQ (see Figure 2), was properly and correctly processed allowing that a protein with factor VIII activity, the preferred biologically active human factor VIII:SQ protein of the patent in suit, be obtained which consisted of two non-covalently associated polypeptide chains of 80-kDa and 90-kDa. In addition, as shown by document C, the DNA sequences described in the state of art, in particular those of documents D1, D4 and D8, having a deletion of part of the nucleotides coding for the B-domain could not be properly processed. Therefore, the skilled person would not have found in any of these documents the necessary guidance to modify the DNA sequence of document D14 encoding the rVIII RE polypeptide and, thereby, arrive at a DNA sequence according to claim 1.

First auxiliary request

The DNA sequence of claim 1 was inventive over the state of the art including document D6.

- XII. The respondent did not make any substantive submissions in the present appeal proceedings.
  
- XIII. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed on 12 August 2003 or the first auxiliary request filed during the oral proceedings, ie the claims and the description pages filed during the oral proceedings and Figures 1 to 6 as granted.

## Reasons for the Decision

### *Main request*

#### Article 54 EPC

1. Novelty of the subject-matter of claim 1 has been challenged on the basis of document D6 only. The appellant argues that document D6 neither belongs to the state of the art according to Article 54(2) EPC nor provides an enabling disclosure.
2. Document D6 is an abstract published in an issue of "Thrombosis and Haemostasis", the journal of the International Society on Thrombosis and Haemostasis. This issue which is identified as No. 1 of volume 62 exclusively reports on what was presented at the XII<sup>th</sup> Congress of the afore-mentioned society which was held from 19 to 25 August 1989 in Tokyo, Japan. This specific content which is in the form of a compilation of abstracts makes it special as well as the fact that it was printed not in Germany, as usual for other issues, but in Japan.
3. The question to be answered is whether that issue of "Thrombosis and Haemostasis" had been made available to the public before the date of priority claimed for the patent in suit, ie **15 December 1989**. If so, then document D6 would be part of the state of the art as defined in Article 54(2) EPC.
4. The cover sheet of the journal issue bears the nominal date of **19 August 1989**. As indicated in decision T 750/94 (point 6 of the Reasons; see supra), such a

nominal date may have nothing to do with the publication date in the sense of Article 54(2) EPC and, for example, could simply refer to the date on which the contents of the issue were finalised within the publishers' office. The appellant regards it only as the date of beginning of the conference.

5. Three other dates have to be considered, namely the dates of **30 October 1989** (referred to in document A), **13 November 1989** (printed on a sticker affixed on the cover sheet of the original document of which document D6 on file is a copy) and **14 December 1989** (stamped on the same cover sheet).

5.1 According to document A, the date of **30 October 1989** is the date on which a first copy of the journal issue had been received at the British Library Document Supply Centre (BLDSC), while the date of **13 November 1989** is the date on which a second copy of the journal issue was received at the BLDSC and the date of **14 December 1989** is the date on which that second copy was passed to cataloguing and from which it would have been made available for public use.

5.2 According to document B issued by a service of the British Library other than the BLDSC, the BLDSC was not in a position to verify that the second copy with the sticker and the stamp was catalogued on **14 December 1989** and, moreover, if it had been catalogued on that date, nevertheless, it would have been kept in the cataloguing area until the next working day and then sent to the relevant storage area.

6. From the above comments, what may be regarded as certain is the fact that a copy of the journal issue in question had been received by a subscriber library on **30 October 1989** which necessarily implies that by that date the issue had been sent out to all subscribers and, moreover, that the journal issue would have been made available, eg on demand, to any member of the public, including private readers and institutions such as public libraries. There would have been no reason to delay further the distribution of the journal issue which was expected by the attendees of the Congress and those used to read "Thrombosis and Haemostasis", which at the priority date was a periodical published every two months.
  
7. It is to be noted that the situation in the present appeal differs considerably from the situation in decision T 750/04 (see supra) where the Board had to decide whether the particular issue of a journal which had been printed with the date of **12** October 1985 had been made available to the public on the same date, the priority date at issue being **13** October 1985!
  
8. Also decision T 314/99 (see supra), which is referred to by the appellant, relates to a very different situation, as the Board had to decide when a dissertation prepared by a student, of which the members of the public could not have been aware before its publication, had been made publicly available by the Chemistry Department of the University.
  
9. Therefore, it is the Board's judgment that on the balance of probabilities it may be considered that the issue No. 1 of volume 62 of "Thrombosis and

Haemostasis" had been made available to the members of the public at least as from **30 October 1989**. Thus, document D6 is part of the state of the art as defined in Article 54(2) EPC.

10. Document D6 describes that with the view of facilitating the introduction of transcriptionally active factor VIII genes into the genome of somatic cells of hemophiliacs, a recombinant retrovirus was constructed that encoded the human factor VIII (F8) protein. For the construction, almost the entire region coding for the B-domain was deleted from a factor VIII clone, the deleted sequence being delimited by codons 747 and 1637. Upon infection with the recombinant retrovirus, Balb/c 3T3 cells were shown to secrete a fully active factor VIII protein.
11. Taking the disclosure of document D6 at its face value, the skilled person would have understood that only part of the B-domain had been deleted and that, consequently, the deleted region was delimited by the amino acid residues 747 and 1637 as counted using the numbering system based on the mature protein. This would have been in line with the prior art knowledge, as reflected in document D1 (see page 5939), that the B-domain was essentially delimited by amino acid residues 740 and 1649.
  - 11.1 The appellant argues that one cannot exclude that the numbering system based on the precursor, ie the mature protein plus the signal peptide, had been used, with the consequence that not only part of the B domain but also part of the A2 domain would have been deleted. This assumption finds no realistic basis in document D6

- which only indicates that "almost the entire region coding for the B-domain [...] has been deleted".
- 11.2 The appellant also argues that the particular factor VIII clone referred to in document D6 had not been made available to the public at the priority date. The remark is not relevant, in that, as there is no pointer in the abstract indicating that a special factor VIII clone was used, the skilled person would have understood that what was required was a clone encoding the human factor VIII as known from the state of the art (see for example Figure 1 of document D1).
- 11.3 As for the further appellant's remark that the term "codons" as used in document D6 renders the whole disclosure unclear because the numbers used in connection therewith designated amino acid residues rather than nucleotide codons, there can be no doubt that the skilled person, a person with a practical, pragmatic approach (see decision T 1208/97 of 3 November 2000) would have understood that codons had been referred to which coded for amino acids 747 to 1637 (see point 12 of the declaration of Prof. R. C. Hoeben (document D320)).
12. Nevertheless, what is not explained in document D6 is the way the remaining codons coding for amino acids 746 and 1638 of the B-domain were linked. The skilled person would not have been in a position to determine whether the codons had been linked in such a way that in the encoded factor VIII the amino acids 746 and 1638 were either linked directly or linked by a short amino acid sequence as described later in document D250 (see Figure 1 on page 7320), thereby providing a linker of



17 amino acids (in the case of a direct link) or more, eg 22 amino acids (17+5) as described later in document D250, ie possibly outside the scope of claim 1, wherein a linker of at least 7 and up to 20 amino acids is referred to. Document D6 lacks a clear and unambiguous disclosure in this respect. For that reason, it is the Board's judgment that, strictly speaking, claim 1 is new over document D6.

Article 56 EPC

13. The DNA sequence of claim 1, while coding for a **biologically active** human factor VIII derivative composed of two polypeptide chains of 90 kDa and 80 kDa (as delimited by amino acids 1 to 740 and 1649 to 2332, respectively; see page 2, lines 43 to 49 in the patent specification), encodes a primary translation product (see page 4, lines 14 and 15 in the patent specification) consisting of said 90 kDa and 80 kDa chains interconnected by a linker of at least 7 and up to 20 amino acid residues of the B-domain.
  
14. Before the priority date, there had been a series of investigations leading to the preparation of DNA sequences encoding **biologically active** human factor VIII derivatives comprising a first DNA segment coding for the 90 kDa chain and a second DNA segment coding for the 80 kDa chain, each as defined above, said segments being **interconnected by a linker DNA segment coding for a linker peptide consisting of residues of the B-domain**.
  
15. Thus, as schematically illustrated in document D28, which summarises the background art, DNA sequences had

been described in the prior art encoding a primary translation product having a linker of **143 amino acids** ( $\Delta$ FVIII ( $\Delta$ 797-1562) polypeptide; see document D4), **95 amino acids** ( $\Delta$ FVIII ( $\Delta$ 747-1560) polypeptide; see document D8), **90 amino acids** (QD polypeptide; see document D14) or **29 amino acids** (LA polypeptide; see document D1). Said DNA sequences had been reported to direct the synthesis of **biologically active** factor VIII (see: in document D1, the last sentence of the abstract on page 5939 reading "These constructs directed the synthesis of biologically active factor VIII"; in document D4, the sentence starting with the terms "When this variant" at the top of the left-hand column on page 8344; in document D8, in the abstract on page 553, the sentence starting with the terms "We demonstrate" and, in the left-hand column on page 562, the sentence reading "Both recombinant vectors directed expression of biologically active FVIII as measured in *in vitro* assays."; and in document D14, Example G on pages 27 and 28).

16. Not document D14, as argued by the appellant, but document D1 is to be regarded as the closest state of the art, the reason therefor being that document D1 describes a DNA sequence which encodes a primary translation product with a deletion of the B-domain such that it contains the shortest linker in the state of the art (with namely 29 amino acids). This is more structurally related to the DNA sequence of claim 1 than the DNA sequence of document D14 which encodes the QD polypeptide.
  
17. In view of document D1, the technical problem to be solved by the invention may be regarded as the

- provision of alternative DNA sequences encoding a primary translation product, from which a biologically active factor VIII protein is derivable, lacking a large part of the B-domain, the solution to said problem being a DNA sequence according to claim 1.
18. The question to be answered is whether a person skilled in the art would have found an incentive in the state of the art to prepare a DNA sequence encoding a primary translation product having a B-domain linker with a reduced length compared to the B-domain linker referred to in document D1.
  19. As noted above (see point 15), there was a trend in the state of the art to prepare DNA sequences encoding a primary translation product having a large deletion of the B-domain. Indeed, it had been acknowledged (see eg in document D8 the last sentence of the discussion on page 562) that the fact that an extensive deletion in the B-domain did not impede its biological activity and yet increased its expression level relative to full-length factor VIII suggested its use for economical production of recombinant factor VIII.
  20. As argued by the appellant (see point 11 of the declaration of Prof R. C. Hoeben (document D320)), the authors of document D6 were looking for a factor VIII clone as short as possible to be packed in a recombinant retrovirus for directing in infected cells the expression of a fully active factor VIII protein. Their proposal was a DNA sequence encoding a primary translation product, from which a biologically active factor VIII protein was derivable, lacking 791 amino acids of the B-domain with a linker peptide comprising

6 amino acids originating from the N-terminal part of said domain (amino acids 741 to 746) and 11 amino acids originating from the C-terminal part thereof (amino acids 1638 to 1648). Even if the document fails to mention how amino acids 746 and 1638 were linked, at most the skilled person would have envisaged a direct link or a link through the use of a short peptide, ie in any case the preparation of a DNA sequence encoding a primary translation product with a linker having in total at least 17 amino acids and most probably less than 29 amino acids.

21. Thus, document D6 would have provided the skilled person with a clear incentive to prepare a DNA sequence encoding a primary translation product for a human factor VIII derivative having a linker as short as possible with a minimum of 17 amino acids corresponding to a portion of the B domain. Consequently, the solution proposed in claim 1 of this request is regarded as obvious for the skilled person.
22. Therefore, claim 1 does not involve an inventive step. Consequently, the main request does not meet the requirements of Article 56 EPC and is not allowable.

*First auxiliary request*

23. As the patent proprietor is the sole appellant against the interlocutory decision under appeal, the Board may not challenge claim 5 which corresponds exactly to claim 4 of the third auxiliary request accepted by the opposition division (prohibition of *reformatio in peius*; see decision G 9/92 OJ EPO 1994, 875). Therefore, only claims 1 to 4 of the first auxiliary request will be

assessed as to their compliance with the requirements of the EPC.

Articles 123(3) EPC

24. Claim 1 of the first auxiliary request (see Section IX, supra) is directed to a particular embodiment of claim 1 of the main request, the linker peptide being restrictively limited to a sequence of 14 amino acid residues, 12 of them originating from the C-terminal of the B domain of human factor VIII and 2 of them originating from the N-terminal of the same. Claim 1 corresponds to claim 4 as granted. Claim 2 is directed to a particular embodiment of claim 1. Claims 3 and 4 correspond to claims 5 and 6 as granted, respectively, with a back-reference to claims 1 and 2.

25. Therefore, there has been no extension of the protection conferred by the patent as granted. Thus, the requirements of Article 123(3) EPC are met.

Article 123(2) EPC

26. A support for claim 1 is found in the application as filed (see page 6, lines 18 to 22 as well as claim 6). The DNA sequence of claim 2 is the preferred one of the application as filed (see in particular Figure 1). Claims 3 and 4 have also an appropriate support therein (see page 6, lines 23 to 29 as well as claims 7 and 8).

27. Therefore, claim 1 does not contain subject-matter which extends beyond the content of the application as filed. Thus, the requirements of Article 123(2) EPC are met.

Article 84 EPC

28. The amendments contained in claims 1 to 4 which were not already in the claims as granted and, therefore, are open to an objection under Article 84 EPC are allowable under that article.

Article 54 EPC

29. Claim 1 of the first auxiliary request is new as no prior art document describes a DNA sequence encoding a factor VIII with a linker of 14 amino acid residues (cf also point 12, supra). As claim 2 is a dependent claim and as claims 3 and 4 contain a back-reference to claims 1 and 2, the auxiliary request as a whole meets the requirements of Article 54 EPC.

Article 56 EPC

30. For the assessment of whether the subject-matter of claim 1 involves an inventive step, document D1 (see point 16, supra) is to be considered in the same way as for the main request to represent the closest state of the art.
31. In view of document D1, the technical problem to be solved by the invention is also the provision of an alternative DNA sequence encoding a primary translation product, from which a biologically active factor VIII protein is derivable, lacking a large part of the B-domain. The solution to said problem is the particular DNA sequence according to claim 1, comprising a linker DNA segment which encodes **a linker**

- peptide of 14 amino acids, 12** of them originating from the **C-terminal** of the B-domain of human factor VIII and **2** of them originating from the **N-terminal** of the same.
32. The question to be answered is whether for such subject-matter the same conclusions reached for the main request apply or whether for this particular subject-matter an inventive step can be acknowledged.
33. In claim 1 at issue not only the length of the linker (14 amino acids) is below the minimal length (17 amino acids) that the skilled person would have readily derived from document D6 (see point 21, supra) but the linker is also structurally precisely defined as being 12 amino acids from the C-terminal of the B-domain and 2 from the N-terminal of the same. The patent specification shows convincingly that this precise tailoring of the linker results in a correct and efficient processing of factor VIII. It is shown that the preferred biologically active recombinant human factor VIII:SQ protein derived from the primary translation product encoded by a DNA sequence according to claim 1 is recovered upon secretion from the transformed cells **essentially** in the form of two polypeptide chains, one of 90 kDa and the other one of 80 kDa (see page 8, lines 13 to 29, and Figure 4, in which two distinct bands are shown which correspond one to the 90 kDa chain and the other to the 80 kDa chain while additionally only a **weak** band at 170 kDa assumed to represent uncleaved primary translation product is also observed). With reference to document C, the appellant submitted that the DNA sequences of the prior art also comprising a first DNA segment coding for the 90 kDa chain and a second DNA segment coding for the

80 kDa chain said segments being interconnected by a linker DNA segment coding for a linker peptide consisting of amino acid residues of the B domain (see point 15, supra), gave rise to a primary translation product which **could not be correctly and efficiently *in vivo* processed.**

34. In view also of this evidence, the Board considers that the proposal of a linker of a length below the range readily derivable from documents D1 and D6 (17 to 29 amino acids) was not obvious for the skilled person, this also when the further prior art documents D4, D8 and D14 are taken into consideration.

35. For these reasons, it is found that the subject-matter of claim 1 involves an inventive step. As claim 2 is dependent on claim 1 and as the subject-matter of claims 3 and 4 is defined with a back-reference to claims 1 and 2, the same conclusion applies to claims 1 to 4. Thus, the first auxiliary as a whole meets the requirements of Article 56 EPC.

*Amendments to the description*

36. The appellant has proposed amendments to the description. The Board considers that these amendments result in an appropriate adaptation of the description to the claims of the first auxiliary request and are in compliance with the requirements of Article 123(2) 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 with the following documents: claims and description pages submitted during the oral proceedings, Figures 1 to 6 as granted.

The Registrar:

The Chairman:

A. Wolinski

L. Galligani