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Datasheet for the decision of 28 August 2018

Case Number: T 0872/13 - 3.3.01

Application Number: 05766825.3

Publication Number: 1745141

IPC: C12P21/00, C07K14/745, C12N9/64

Language of the proceedings: EN

Title of invention:
O-LINKED GLYCOFORMS OF FACTOR VII AND METHOD TO MANUFACTURE THEM

Patent Proprietor:
Novo Nordisk Health Care AG

Opponent:
Strawman Limited

Headword:
Factor VII Glycoforms/NOVO NORDISK

Relevant legal provisions:
RPBA Art. 15(3), 12(4), 13
EPC R. 115(2)
EPC Art. 54(2), 100(a), 123(2), 123(3), 84, 83, 56

Keyword:
Oral proceedings - held in absence of appellant
Acceleration of proceedings - (no)
Late-filed evidence - submitted with the statement of grounds of appeal or reply thereto: admitted - submitted at a late stage of appeal proceedings and complex: not admitted
Novelty - implicit disclosure (yes/no)
Amendments - allowable (yes)
Claims - clarity after amendment (yes)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

Decisions cited:
T 0793/93, T 1616/09, T 1329/04, G 0002/10, G 0003/89, G 0011/91

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Chambres de recours

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Case Number: T 0872/13 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 28 August 2018

Appellant: (Patent Proprietor)	Novo Nordisk Health Care AG Andreasstrasse 15 8050 Zürich (CH)
Representative:	J A Kemp 14 South Square Gray's Inn London WC1R 5JJ (GB)
Appellant: (Opponent)	Strawman Limited Orchard Lea Horns Lane Combe, Witney Oxfordshire OX29 8NH (GB)
Representative:	Almond-Martin, Carol Ernest Gutmann - Yves Plasseraud S.A.S. 88, Boulevard des Belges 69452 Lyon Cedex 06 (FR)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 14 December 2012 concerning the maintenance of European patent No. 1745141 in amended form**

Composition of the Board:

Chairman	A. Lindner
Members:	T. Sommerfeld
	M. Blasi

Summary of Facts and Submissions

I. European patent No. 1745141 is based on application 05766825.3, which was filed as an international application and published as WO 2005/111225. The patent is entitled "O-linked glycoforms of Factor VII and method to manufacture them" and was granted with 26 claims.

Claim 1 as granted reads as follows:

"1. A preparation of a Factor VII polypeptide containing a Cys-X1-Ser/Thr-X2-Pro-Cys motif and wherein said serine/threonine forms part of a Glc-O-Ser/Thr covalent bond, wherein the preparation contains a serine/threonine-linked glycosylation pattern that is at least 80% uniform."

Independent claim 21 as granted reads as follows:

"21. A method for making a preparation as described in claims 1-7, wherein the serine/threonine-linked glycan is Xyl-Xyl-Glc-; the method comprising the steps of:

(a) obtaining a preparation of a Factor VII polypeptide containing a Cys-X1-Ser/Thr-X2-Pro-Cys motif and wherein said serine/threonine forms part of a Glc-O-Ser/Thr covalent bond; e.g., from an engineered cell (cell culture) or by isolating the glycoprotein from a natural source;

(b) contacting the preparation obtained in step (a) with UDP-D-xylose:β-D-glucoside α-1,3-D-xylosyl-transferase and an activated xylosyl donor under conditions appropriate for transferring a xylose residue from the xylose donor moiety to the acceptor moiety, thereby producing the glycopeptide having an altered glycosylation pattern;

(c) contacting the preparation obtained in step (b) with UDP-D-xylose:α-D-xyloside α-1,3-xylosyltransferase and an activated xylosyl donor under conditions appropriate for transferring a xylose residue from the xylose donor moiety to the acceptor moiety, thereby producing the glycopeptide having an altered glycosylation pattern."

II. Opposition was filed against the granted patent, the opponent requesting revocation of the patent in its entirety on the grounds of lack of novelty and inventive step (Articles 54(2) and 56 EPC and Article 100(a) EPC), insufficiency of disclosure (Article 100(b) EPC) and added subject-matter (Article 100(c) EPC).

III. By an interlocutory decision announced at oral proceedings on 4 September 2012, the opposition division decided that the patent could be maintained in amended form on the basis of the second auxiliary request filed during the oral proceedings (Articles 101(3)(a) and 106(2) EPC).

IV. The patent proprietor lodged an appeal against that decision. With the statement of the grounds of appeal, the appellant-patent proprietor requested that the appealed decision be set aside and that the patent be maintained as granted (main request) or, alternatively, according to the set of claims of the first auxiliary request which had been decided upon by the opposition division.

V. The opponent also lodged an appeal against the decision of the opposition division. With the statement of the grounds of appeal, the appellant-opponent requested that the decision be set aside and the patent revoked

in its entirety. It also requested accelerated processing of the appeal and submitted new documents D19 to D23.

VI. Both appellants replied to each other's statements of grounds of appeal with letters dated 9 September 2013.

VII. With its reply, the appellant-patent proprietor submitted sets of claims of auxiliary requests 1 to 15, two amended versions of the description, and a new document D24. It also requested that documents D19 to D23 not be admitted into the proceedings and that the opponent's new objections under Article 123(2) and (3) and Article 84 EPC not be admitted either.

The **main request** corresponds to the patent as granted.

Claim 1 of **auxiliary request 1** differs from claim 1 of the main request by the following amendments:

"1. A pharmaceutical composition comprising:
(a) a preparation of a Factor VII polypeptide containing a Cys-X1-Ser~~/Thr~~-X2-Pro-Cys motif and wherein said serine~~/threonine~~ is located at position Ser52 of human wild type Factor VII or at the serine residue corresponding to Ser52 of human wild type Factor VII when the sequences are aligned, wherein said serine residue forms part of a Glc-O-Ser~~/Thr~~ covalent bond, wherein ~~the preparation contains a serine/threonine-linked glycosylation pattern that is at least 80% uniform~~ at least 85% of said serine residues in the preparation are glycosylated with Xyl-Xyl-Glc; and
(b) a pharmaceutically acceptable carrier."

Claim 1 of **auxiliary request 2** differs from claim 1 of the main request by the following amendments:

"1. A preparation of a Factor VII polypeptide containing a Cys-X1-Ser~~/Thr~~-X2-Pro-Cys motif and wherein said serine~~/threonine~~ is located at position Ser52 of human wild type Factor VII or at the serine residue corresponding to Ser52 of human wild type Factor VII when the sequences are aligned, wherein said serine residue forms part of a Glc-O-Ser~~/Thr~~ covalent bond, wherein ~~the preparation contains a serine/threonine-linked glycosylation pattern that is at least 80% uniform~~ at least 85% of said serine residues in the preparation are glycosylated with Xyl-Xyl-Glc for use in the treatment of a bleeding disorder."

Auxiliary request 3 comprises 6 claims, claims 1 and 3 differing from claims 1 and 21 of the main request, respectively, by the following amendments:

"1. A pharmaceutical composition comprising:

(a) a preparation of a human Factor VII polypeptide containing a Cys-X1-Ser~~/Thr~~-X2-Pro-Cys motif and wherein said serine~~/threonine~~ is located at position Ser52 and forms part of a Glc-O-Ser~~/Thr~~ covalent bond, wherein ~~the preparation contains a serine/threonine-linked glycosylation pattern that is at least 80% uniform~~ at least 85% of said serine residues in the preparation are glycosylated with Xyl-Xyl-Glc; and

(b) a pharmaceutically acceptable carrier."

"~~21~~3. A method for making a preparation as described in claims 1-~~7~~2, wherein the serine~~/threonine~~-linked glycan is Xyl-Xyl-Glc-; the method comprising the steps of:

(a) obtaining a preparation of a human Factor VII polypeptide containing a Cys-X1-Ser~~/Thr~~-X2-Pro-Cys motif and wherein said serine~~/threonine~~ is located at position 52 and forms part of a Glc-O-Ser~~/Thr~~ covalent

bond; e.g., from an engineered cell (cell culture) or by isolating the glycoprotein from a natural source;
(b) ...;
(c) ...."

VIII. With its reply, the appellant-opponent submitted a new document designated D24 (now D25).

IX. With a communication dated 1 April 2014, the board informed the parties that it did not intend to accelerate the appeal proceedings.

X. A number of submissions from both parties followed, with new documents D26 to D29 and D31 submitted by the appellant-patent proprietor and D30 by the appellant-opponent.

XI. By letter of 16 March 2017, the appellant-opponent submitted a second request for acceleration of the appeal proceedings. In reply, the board informed the parties in a communication dated 12 April 2017 that the appeal proceedings would not be accelerated.

XII. Summons for oral proceedings before the board were issued, scheduling oral proceedings for 28 August 2018.

XIII. With a letter dated 27 June 2018, the appellant-opponent announced that nobody would attend the oral proceedings on its behalf.

XIV. With a letter dated 27 July 2018, the appellant-patent proprietor submitted amended pages of the description and requested that its technical expert be allowed to make submissions at the oral proceedings.

XV. The following documents are cited in this decision:

D1 Björn S. et al. 1991, J. Biol. Chem. 266(17), 11051-11057
D2 WO 02/29025
D4 Grebenau R.C. et al. 1992, Molecular Immunol. 29(6), 751-758
D6 WO 03/031464
D7 Jurlander B. et al. 2001, Seminars in Thrombosis & Hemostasis 27(4), 373-383
D8 WO 2004/000366
D9 Iino M. et al. 1998, Arch. Biochem. Biophys. 352(2), 182-192
D12 Declaration of Niels K. Klausen
D17 Iwanaga S. et al. 1990, Proceedings of the International Scientific Symposium on Fibrogen, Thrombosis, Coagulation, and Fibrinolysis, held August 30-September 1, 1989, in Taipei, Taiwan; Plenum Press, New York, pages 121-131
D18 Second declaration of Niels K. Klausen
D19 WO 2004/000347
D20 Hase S. et al. 1988, J. Biochem. 104, 867-868
D21 Nishimura H. et al. 1989, J. Biol. Chem. 264(34), 20320-20325
D22 Declaration of Prof. N. L. Kelleher
D23 Fenaille F. et al. 2008, Glycoconj. J. 25,827-842
D24 Declaration of Anders D. Nielsen
D25 Declaration of J. Krarup
D26 Presentation by Daniel E. Rasmussen & J. Krarup, 2007 HIC-RPC Conference, Interlaken, Switzerland
D27 Second declaration of J. Krarup
D28 Internal memo with supporting data relating to D12, 1 September 2007; English translation D28A
D29 Summary report of experimental data of D12; English translation D29A
D30 Declaration by Dr. M. Condina
D31 Third declaration of N. K. Klausen

XVI. The submissions of the appellant-patent proprietor, in so far as they are relevant to the present decision, may be summarised as follows:

Request for accelerated proceedings

The opponent had not provided any specific reasons why acceleration would be justified in this case.

Admission of documents

Documents D19 to D23 could have been filed earlier, since the amendments in question, namely the medical uses, were already in the proceedings before the opposition division. Document D25 was late-filed too. As to document D30, the reasons given for its late filing were not convincing; moreover, as explained in D31, its data were inconclusive and not *prima facie* relevant and raised complex issues.

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

The objections under Article 123(2) and (3) EPC, concerning auxiliary requests 1 to 3, and the objection under Article 84, directed to auxiliary request 2, were all late-filed. They should not be admitted into the proceedings because the opponent had not raised these objections during the opposition proceedings, although they would be likewise applicable to all the auxiliary requests considered during the opposition oral proceedings. The basis for the disputed features was found in the combination of claims 1, 2, 3 and 6 as filed, as well as on page 2 of the application as filed, Factor VII being the preferred glycoprotein (pages 8 to 13 of the application) and the Ser52

residue being the most important O-glycosylation site in this context. As to Article 123(3) EPC, the opponent's line of argument was based on a new interpretation of the feature that found no support in the application as filed. The passage on page 4, lines 24 to 34, made it clear that a substantially uniform serine/threonine-linked glycosylation pattern meant a pattern in which substantially all polypeptides had the same glycan at a particular serine/threonine position. As to the objection under Article 84 EPC, the opponent's arguments appeared to be directed to Articles 83 or 56 EPC rather than Article 84 EPC.

Article 83 EPC

The opponent had failed to provide serious doubts, supported by verifiable facts, to demonstrate that the skilled reader of the patent could not produce a preparation of Factor VII according to the claims. Methods for providing such preparations were disclosed in the patent, either involving purification (page 10, in particular paragraphs [0075] to [0076]), or involving modification of glycosylation patterns (pages 8 to 10; granted claims 8 to 26; Example 6, in particular in paragraphs [0140] to [0141]).

Article 54 EPC

D17 disclosed very early work on Factor VII glycosylation and described the trisaccharide glycoform as being new (abstract, last five lines; title). Moreover, it studied human Factor VII rather than bovine (page 122, first full paragraph; page 123, middle paragraph towards the end and last paragraph). The conclusions drawn in relation to the bovine glycoproteins were made on account of earlier work

(D20: reference 4 in D17) and only reflected the fact that the authors did not know if there were other glycoforms because better separation methods were not available at that time. The authors themselves accepted that their knowledge might not be complete (page 127, first line, statement starting with "As yet, ..."). This was also supported by the fact that D17 had not identified all Serine 52-glycoforms of human Factor VII, as evidenced by D1 (e.g. abstract), published one year later and showing that there were three rather than two such glycoforms. It was also apparent from the figure on page 122 of D17, representing the structure of bovine Factor VII, that the authors did not know that Serine 60 was also glycosylated, as shown some years later (2001) in D7 (page 376); but even D7 still only indicated fucose as glycan for Serine 60 (page 377, right-hand column, lines 1 and 2), which again was incomplete information as apparent from the patent which disclosed a further glycan. While it was the opponent's burden to prove lack of novelty, no disclosure had been retrieved clarifying the glycan structure of bovine Factor VII. Therefore, there was no unambiguous disclosure in D17 of the claimed subject-matter, i.e. of a preparation with at least 85% homogeneity of the trisaccharide structure, and hence D17 did not meet the standards required for a lack of novelty objection.

As to D19, this document did not make any reference to D17 and only referred to bovine Factor VII at the bottom of page 5. There was no inevitable disclosure, "beyond reasonable doubt", as required by T 793/93 (catchword). It was not beyond reasonable doubt that the reference to bovine Factor VII in D19 was a reference to a product which fell within D17's disclosure. Moreover, D19 disclosed formulations of

Factor VII but they were not all meant for pharmaceutical uses: page 25, line 23, disclosed that they "may also be reconstituted for other purposes". In fact, it would not make sense to have pharmaceutical compositions of bovine Factor VII for use in humans, and thus the skilled person would understand the reference to bovine Factor VII as being meant for other purposes and not for pharmaceutical compositions. There was no disclosure of medical uses with bovine Factor VII, page 15, line 8 ff., explicitly referring to human Factor VII.

As to document D6, this was a large document that related to remodelling peptides by altering their glycosylation. Figure 1, which listed the peptides to which the method could be applied, extended for 29 pages with two columns of peptides listed on each of those pages, Factor VII being just one among many proteins. The opponent's objections were based on a combination of many different passages in D6, some relating to Factor VII and some not mentioning Factor VII at all. There was no direct and unambiguous disclosure of compositions wherein at least 85% of the Factor VII molecules had Xyl-Xyl-Glc at position Ser52.

Article 56 EPC

The patent had shown that preparations with different O-glycosylation had different levels of specific activity (Example 8), and the data were further supported by additional data in D12 and D24. The data in the patent made it plausible that preparations with higher content of Xyl-Xyl-Glc-Ser52 would have higher specific activity, plausibility being all that T 1329/04 required. Starting from D7, which disclosed recombinant activated Factor VII (rFVIIa), the problem

to be solved was to produce a Factor VII formulation having a different activity (main request) or an increased activity (auxiliary requests). It would not have been obvious to make changes to the glycosylation of a Factor VII preparation starting from D7 because the skilled person would not expect it to make a difference to the activity of the polypeptide (D7, abstract), even if combining with D1. The initial suggestion in D1 that glycosylation could have an impact in activity (abstract, second paragraph; page 11054, right-hand column, first full paragraph) was contradicted later: paragraph bridging pages 11053 and 11054.

Description amendments

The amendment done on page 40, lines 22 to 23, should be allowed as the correction of an obvious error. Example 7 listed assays that could be carried out, including tryptic peptide mapping. This particular assay was then carried out in Example 8 and the results shown in Figures 7A and 7B. It was evident that there were two disclosures that disagreed with each other, and the question was which one was the wrong one. There were only two possibilities: either that there was a single typographical error on page 40; or else that there were multiple errors, in Figures 7A and B and respective legends on page 3, and on page 41, lines 23 to 25 and lines 27 to 28. Moreover, page 40 provided just the assay description without any data to support it, while Example 8 actually showed data and described the order of elution; the skilled person would consider it highly likely that the correct statement was the one relating to the data. Additionally, the data of Example 8 were corroborated by the mass analysis carried out in the two fractions (Figures 7 and 8), showing that the

dominant peak of fraction 15 was heavier than fraction 10, therefore suggesting that the first one had to contain the trisaccharide and the second one the disaccharide.

XVII. The arguments of the appellant-opponent, in so far as they are relevant to the present decision, may be summarised as follows:

Request for accelerated proceedings

The patent was causing uncertainty and hampering investment and development decisions by interested parties (first request for acceleration presented with the statement of grounds of appeal). The real party of interest behind the opponent Strawman Limited was CSL Limited, which was developing a recombinant Factor VII-albumin fusion protein and therefore needed certainty to continue its development activities in view of the large sums involved. Any decision of CSL Limited as a potential licensee under the patent depended on the outcome of the appeal proceedings, and thus the request for accelerated proceedings should be granted as falling within one of the examples given in the Notice from the Vice-President DG3 of 17 March 2008 (OJ EPO 2008, 220; second request for acceleration of the appeal proceedings).

Admission of documents

Documents D19 to D23 were all filed in response to requests filed at, or arguments made during, the oral proceedings before the opposition division. Document D25 was filed as a direct response to the appeal of the patent proprietor, was highly relevant for the question of sufficiency, contradicting the position taken by the

appellant-patent proprietor, and was known to the patent proprietor since it was a declaration by one of its employees made in the course of another proceedings. As to document D30, although late-filed, it should be admitted because it was not complex and *prima facie* relevant for inventive step. It could not have been filed earlier because the methods used had only become available to the appellant-opponent since the appeal proceedings.

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

The combination of features "at least 85%" and "Ser52 residues being glycosylated with Xyl-Xyl-Glc" in the auxiliary requests was not disclosed in the application as filed. The first feature was disclosed in the application as filed on page 2, line 20, and in claim 2, but in both cases it related to a "substantially uniform serine/threonine glycosylation pattern" which was not necessarily at Ser52 or even necessarily in relation to Factor VII. The second feature was disclosed on page 4, lines 26 to 28; at the beginning of the following paragraph, the word "substantially" was used specifically in relation to Factor VII's Serine 52, but the list of percentages given did not include 85%.

As to Article 123(3) EPC, the replacement of the feature "glycosylation pattern that is at least 80% uniform" in the granted claims by the feature "at least 85% of said serine residues" broadened the scope of protection in view of the fact that Ser60 was also glycosylated and could be glycosylated with either fucose or a tetrasaccharide (D8, page 16, line 12). Hence six families of different serine/threonine O-glycosylation were possible in plasma (four in

recombinant forms, which did not have the Xyl-Glc-Ser52 form).

Moreover, auxiliary request 2 lacked clarity, because it was not clear how inactivated Factor VII variants (also encompassed in the claim according to the patent's definition of "Factor VII polypeptide" in paragraphs [0038] and [0043]) could be used in the treatment of a bleeding disorder.

Article 83 EPC

It was not apparent how a preparation as claimed could be obtained following the teachings of the patent. The only exemplified Factor VII preparations whose activity was given in the patent were those of Table 1 of Example 8; however, there was no indication of whether any of these preparations were within the claims or not. Example 9, on the other hand, did not report an experiment that had been carried out, but rather merely told the skilled person to "repeat Example 8, but on a larger scale". The deficiencies of Example 8, however, could not be resolved by simply scaling it up, as was apparent from D12 and D18; D12 had not followed Example 8 but instead had had to develop new conditions to achieve success. Moreover, it was evident from D25, a declaration by an employee of the patent proprietor, that there was an undue burden to use hydrophobic interaction chromatography (HIC) to separate the glycoforms.

Article 54 EPC

Document D17 disclosed bovine Factor VII preparations and explicitly taught that "all the bovine [Factor VII] peptides contained 1 mol of Glc and 2 mol of Xyl" (page

131 of D17, "Conclusion"). This was also supported by documents D20 and D21.

Document D19 disclosed pharmaceutical compositions comprising Factor VII and explicitly disclosed bovine Factor VII and treatment of bleeding disorders.

Document D6 disclosed remodelling of glycopeptides and explicitly of human Factor VII. Pharmaceutical compositions and use in treatment of bleeding disorders were also disclosed. Additionally, it was apparent that no mixtures were produced but rather individual glycoforms, among which the claimed glycoform was one of only five listed alternatives (the preferred subgenus of Glc-(Xyl)n of Figure 30, where n was 0-4). Moreover, the opposition division's interpretation of "substantially uniform glycoform" (pages 116 and 117 of D6) was incorrect, and there was no suggestion that each of the remodelled Factor VIIa molecules in Figure 30A was anything other than homogeneous.

Article 56 EPC

The technical problem was not plausibly solved in the application because Example 8 did not provide evidence that a preparation falling within the claim had indeed a better specific activity; post-published data such as those of D12 could not therefore be taken into consideration (T 1329/04). Moreover, inactive polypeptides were encompassed (paragraph [0043]), which obviously did not solve the problem, and many more different glycoforms also existed, adding to the variability of the glycoforms families. There was no evidence in the patent supporting its statement that "the Xyl-Xyl-Glc-O-Ser52 glycoform was responsible for the improved activity" or for the conclusion that there

was a correlation between Xyl-Xyl-Glc-O-Ser52 and activity. The mass analysis data of Figures 8A and B even contradicted the patentee's position because the mass difference could not be attributed to two Xyl residues (D22). Even if the problem could be considered solved, then the solution was obvious in view of D1, cited in D7, teaching the importance of the Serine 52 glycosylation for Factor VII activity. The argument that the skilled person might not have been able to predict which of the two glycoforms was responsible for greater activity was irrelevant in this case, for it corresponded to a "try-and-see" situation.

Description amendments

It was evident that there was a discrepancy in the description as filed, since the text before the amendment was in contradiction with Figures 7A and B and their legends on page 3. However, it was not obvious where the error was and how it should be corrected. There was no evidence that the labelling of Figures 7A and B was correct. Even if one correction was more likely than the other, it was the patentee's burden to satisfy the board beyond reasonable doubt that its resolution of the obvious contradiction was obviously correct. Hence, the amendment done to the description, allegedly to correct the error, constituted added subject-matter.

XVIII. The appellant-patent proprietor's final requests were as follows:

- The appellant-patent proprietor requested that the decision of the opposition division be set aside and that the patent be maintained as granted (main request) or, alternatively, that the patent be

maintained in amended form on the basis of the claims of auxiliary requests 1 or 2 filed with its letter dated 9 September 2013, or further alternatively, on the basis of auxiliary request 3 comprising claims 1 to 6 filed with letter dated 9 September 2013, description pages 2, 2a, 3 to 13 submitted at the oral proceedings, pages 14 to 20 and drawings 1 to 8b of the patent specification.

- It also requested that documents D25 and D30 not be admitted into the proceedings or, alternatively, if D30 was admitted, that documents D31, D31a, D31b and D31c, submitted by letter of 27 July 2018, be admitted.

The appellant-opponent requested in writing that the decision of the opposition division be set aside and the patent revoked in its entirety.

Reasons for the Decision

1. The appeals are admissible.

2. The appellant-opponent had been duly summoned but decided not to attend the oral proceedings. In accordance with Rule 115(2) EPC, the board decided to continue the proceedings in the appellant-opponent's absence.

Moreover, as stipulated by Article 15(3) RPBA, the board is not obliged to delay any step in the proceedings, including its decision, by reason only of

the absence at the oral proceedings of any party duly summoned. In line with this provision, the appellant-opponent was treated as relying on its written case.

3. Request for accelerated processing of appeal proceedings

3.1 Parties with a legitimate interest may ask the boards of appeal to deal with their appeals rapidly, and the boards can speed up an appeal as far as the procedural regulations allow (see Notice from the Vice-President Directorate-General 3 dated 17 March 2008 concerning accelerated processing before the Boards of Appeal, "Notice", OJ EPO 2008, 220, first paragraph).

3.2 With regard to the appellant-opponent's first request for accelerated processing of the appeal proceedings, the board could not accede to this request since the reason provided by the appellant-opponent that the patent was "causing uncertainty and hampering investment and development decisions by interested parties" was a general statement and not particularly related to a party to the proceedings.

3.3 As to the appellant-opponent's second request for acceleration, the board noted that the party requesting acceleration, the appellant-opponent, had not argued that it had itself a legitimate interest in the proceedings being dealt with rapidly. The interests on which the request for acceleration were based concerned the company CSL Limited. This company was however not a party to the present appeal proceedings and the board saw no reason why the interests of this third party should be attributed to the appellant-opponent.

3.4 Moreover, the reference to the second example of the Notice concerning accelerated processing did not apply in the present circumstances. The wording of the second example suggests that it relates to a situation in which the party requesting acceleration is the patent proprietor and not an opponent. In any case, however, no documents were presented to the board to support the contention that the decision of a potential licensee of the patent in suit hinged upon the outcome of the present appeal proceedings.

3.5 Therefore, on the basis of the submissions of the appellant-opponent, the board could not establish that the appellant-opponent had a legitimate interest in the case being dealt with rapidly. Hence, the board decided not to accelerate the present appeal proceedings.

4. Admission of documents

4.1 According to the established case law of the boards of appeal, the function of the appeal proceedings is to give a judicial decision upon the correctness of a separate earlier decision taken by a department of first instance. It derives directly from its review character and judicial nature that the appeal proceedings can, in principle, only be based on the reasons already submitted before the department of first instance. Nevertheless, parties, in their efforts to make a full statement of the grounds of why the revision of the contested decision is requested often rely on additional evidence. Yet, it is at the board's discretion, taking into account the particular circumstances of the case and the parties' arguments, to admit it into the proceedings or not.

Documents D19 to D23

4.2 These documents were all filed by the appellant-opponent with its statement of grounds of appeal. Their admission is thus governed by Article 12(4) RPBA.

4.3 According to the appellant-opponent, D19, which is a patent application from the appellant-patent proprietor, was filed "in response to the Patentee's claim requests filed at the oral proceedings, which for the first time were limited to a medical use of a preparation of a FVII polypeptide having an at least 85% uniform glycosylation pattern"; D19 was submitted to show that bovine Factor VII had been disclosed for treating bleeding disorders. D20 and D21 were filed in response to the argument by the patent proprietor at the oral proceedings that the disclosure of uniformly O-glycosylated bovine Factor VII in D17 was not reliable. D22 and D23 were filed in response to the argument by the patent proprietor at the oral proceedings that "the 295 Da mass difference (...) in Figures 8a and 8b of the patent was within 'analytical variation' (i.e. experimental error) of the 264 Da difference that would be expected from the mass difference between a Xyl-Xyl-Glc-glycostructure and a Glc-glycostructure".

4.4 The appellant-patent proprietor requested that D19 to D23 not be admitted into the proceedings, essentially arguing that these documents, and in particular D19, could have been filed earlier because they were filed not in reaction to the new amendments made at the oral proceedings but rather in reaction to the medical use feature that had already been inserted into claims filed in reply to the notice of opposition (auxiliary requests 4 to 6 filed in June 2011).

4.5 The board notes that, in fact, during the opposition proceedings the appellant-opponent had reacted to the medical use claims filed in June 2011 in its reply of 27 October 2011 by stating that "FVII is and was at the Priority Date well known for this purpose" (section 7, page 25 of the submissions), without however referring to any document. In the subsequent summons to oral proceedings, the opposition division considered all requests on file to lack sufficiency of disclosure and, while further considering that claim 1 of the main request (when disregarding the feature "at least 80% uniformity") lacked novelty over D1, D5 and D6, did not examine the auxiliary requests further. In the reply to the summons, the appellant-opponent agreed with the opposition division's view on lack of sufficiency of disclosure and raised a new novelty objection, but did not discuss the auxiliary requests further. It was only at the oral proceedings that the appellant-patent proprietor overcame the objection under Article 83 EPC by restricting the claimed subject-matter to the particular embodiment. Only then did a further discussion of novelty and inventive step of the newly claimed embodiment become necessary.

4.6 As to documents D20 and D21, the board considers that, contrary to the appellant-patent proprietor's argument that neither of them provides evidence about the reliability of the data in D17, both documents in fact support D17's conclusions regarding the proportion of the Xyl-Xyl-Glc glycan in bovine Factor VII preparations and are therefore *prima facie* relevant.

4.7 D22 is a new declaration relating to the examples of the patent, and D23 is a document referred to in D22; the issues discussed in D22 are the same issues that

were discussed throughout the proceedings before the opposition division but which were decided negatively for the appellant-opponent. The submission of these documents is thus a legitimate attempt to revert the decision of the opposition division.

4.8 The board is therefore convinced by the appellant-opponent's arguments that documents D19 to D23 were filed as a reaction to the decision of the opposition division. Hence, the board saw no reason to disregard these documents under Article 12(4) RPBA.

Document D24

4.9 This document was filed by the appellant-patent proprietor with its reply to the appellant-opponent's statement of grounds of appeal and in reaction to documents D22 and D23. There were no objections from the appellant-opponent as to its admission and the board also has none. D24 was thus taken into account in these proceedings under Article 12(4) RPBA.

Documents D25 to D29

4.10 Document D25 was filed by the appellant-opponent with its reply to the appellant-patent proprietor's statement of grounds of appeal. Objections to its admission were raised by the appellant-patent proprietor for the first time at the oral proceedings before the board.

4.11 The board notes that this document was also filed at an early stage of the appeal proceedings and that it does not introduce new, complex issues but rather provides further evidence to support arguments under Article 83 EPC that were already in the proceedings.

The board therefore considers it to be a legitimate reaction to the decision under appeal.

4.12 The board thus decided not to exclude D25 from the appeal proceedings under Article 12(4) RPBA. Likewise, documents D26 to 29, filed later by the appellant-patent proprietor as a reaction to D25, were also admitted into the proceedings pursuant to Article 13(1) RPBA).

Documents D30 and D31

4.13 Document D30 was filed by the appellant-opponent with a much later submission, namely a letter of 23 December 2016, allegedly to prove that the specific activity of a recombinant Factor VII-albumin fusion (rVIIa-FP) was not significantly correlated to the degree of uniformity of O-linked glycosylation at Ser52.

4.14 According to Article 13 RPBA, any amendment to a party's case after it has filed its grounds of appeal or reply may be admitted and considered at the board's discretion, such discretion being exercised in view of, *inter alia*, the complexity of the new subject-matter submitted, the current state of the proceedings and the need for procedural economy.

4.15 The board agrees with the appellant-patent proprietor that the data presented in the very late submission D30 do not enable straightforward conclusions. The document consists of complex subject-matter filed at a rather late stage of the proceedings, and whose admission would run against the need for procedural economy.

4.16 Accordingly, the board decided not to admit D30 into the proceedings pursuant to Article 13(1) RPBA.

4.17 Since D30 was not admitted into the proceedings, there was no reason to admit D31 either, since this document was filed by the appellant-patent proprietor solely as a reaction to document D30.

5. Main request - Novelty

5.1 Claim 1 of the main request is directed to a preparation of a Factor VII polypeptide containing a Cys-X1-Ser/Thr-X2-Pro-Cys motif and wherein said serine/threonine forms part of a Glc-O-Ser/Thr covalent bond, wherein the preparation contains a serine/threonine-linked glycosylation pattern that is at least 80% uniform. An example of a polypeptide preparation falling within this definition is the one defined in claim 1 of auxiliary request 1, namely: a preparation of a Factor VII polypeptide containing a Cys-X1-Ser-X2-Pro-Cys motif and wherein said serine is located at position Ser52 of human wild type Factor VII or at the serine residue corresponding to Ser52 of human wild type Factor VII when the sequences are aligned, wherein said serine residue forms part of a Glc-O-Ser covalent bond, wherein at least 85% of said serine residues in the preparation are glycosylated with Xyl-Xyl-Glc.

5.2 Document D17 discloses a preparation of bovine Factor VII, wherein the polypeptide contains a Cys-X1-Ser-X2-Pro-Cys motif and wherein said serine is located at position Ser52 of human wild type Factor VII (Figures 1 and 2 of D17). On page 125, second paragraph of the section "Component sugar analysis of isolated pentapeptides", it is stated that pentapeptides (from the region around Ser52, as apparent from Table 2 on

the same page) derived from human Factor VII contained Xyl:Glc at a molar ratio of 1:1 or 2:1, "indicating the existence of either an *O*-linked disaccharide or trisaccharide chain in these pentapeptides". It then goes on to describe that "In contrast, the molar ratio of Xyl:Glc in bZ-GP was 2 to 1, similar to that observed for bovine factors VII and IX (4)". The document cited as reference (4) in this passage is document D20 in the proceedings; it discloses the presence of a trisaccharide sugar chain in bovine coagulation factors VII and IX (title) and teaches that "(Xyl_2)Glc is linked through glucose to (...) Ser-52 of factor VII" (page 868, left-hand column, lines 9 to 11). Page 131 of D17 ("Conclusion", lines 5 to 6) then states that "all the bovine [Factor VII] peptides contained 1 mol of Glc and 2 mol of Xyl".

5.3 It follows that a preparation comprising a polypeptide as defined above (section 5.1) is disclosed in document D17. Moreover, the above-cited passages from pages 125 and 131 of D17 indicate that bovine Factor VII was present solely in the form of a trisaccharide-containing glycoform, in contrast to human Factor VII, which was present both as disaccharide- and trisaccharide-containing glycoforms. This is also supported by further statements in D17, such as "no microheterogeneity was so far observed for the sugar chains corresponding to the pentapeptides derived from bovine factors VII and IX" (page 125, last sentence) and "As yet, a pentapeptide linked with a disaccharide chain has not been found in those vitamin K-dependent proteins of bovine origin" (page 127, first two lines). Hence, although D17 does not explicitly disclose that "at least 85% of said serine residues in the preparation are glycosylated with Xyl-Xyl-Glc", i.e. that at least 85% of the polypeptides of the

preparation show this glycosylation pattern, the board concludes that this feature is implicit in the teaching of D17. Accordingly, document D17 is novelty-destroying for the subject-matter of claim 1 of the main request.

5.4 The appellant-patent proprietor essentially argued that there was no direct and unambiguous disclosure in D17 of a Factor VII preparation comprising at least 85% of the specific Ser52-glycoform. At the time of D17, the authors had not identified other glycoforms at that location but that did not mean that they did not exist. In fact, as regards human Factor VII, D17 identified only two different forms of Factor VII (a disaccharide Xyl-Glc chain and the trisaccharide Xyl-Xyl-Glc), while D1, which was published a year later and referred to the same experiments of D17, disclosed that three rather than two different carbohydrate forms were found in both plasma and recombinant human Factor VII (abstract) and that all three were present in approximately equal amounts. That D17's knowledge concerning Factor VII's glycosylation patterns was incomplete was further evidenced by the bovine Factor VII structure depicted on page 122, wherein only Serine 52 and not Serine 60 was indicated as glycosylation residue.

5.5 The board agrees that D17 is an early document and that its teachings may be incomplete in relation to some aspects. However, there is no evidence on file that D17's conclusions as regards bovine Factor VII glycosylation at Serine 52 have ever been contested or shown to be incorrect. While the existence of further glycoforms of human Factor VII is well-documented in both D17 and D1, the same is not true for bovine Factor VII preparation; on the contrary, D17, D20 and D21 (page 20321, right-hand column, third full paragraph)

all teach that the Xyl-Xyl-Glc trisaccharide-comprising glycoform is the only glycoform for bovine Factor VII. Hence, it has to be concluded that the preparation of bovine Factor VII disclosed in D17 (and in D20 and D21) is homogeneous in terms of glycoforms present, i.e. it consists of glycoforms which all have Xyl-Xyl-Glc at Serine 52.

5.6 The main request is thus not allowable for lack of novelty (Articles 100(a) and 54(2) EPC).

6. Auxiliary request 1

6.1 Added subject-matter, extension of scope

6.1.1 The appellant-patent proprietor requested that the objections under Article 123(2) and (3) EPC, raised by the appellant-opponent only during appeal, not be admitted into the proceedings. The board however notes that auxiliary request 1 was only filed at the oral proceedings before the opposition division, and in particular the objected combination of features of "at least 85%" and "Xyl-Xyl-Glc at position Ser52" had not been present in previous claims. Hence, it was only at the oral proceedings before the opposition division that the opponent was confronted with this amendment, and it is thus understandable that it might not have been in a position then to raise the objections. Accordingly, the objections under Article 123(2) and (3) EPC against claim 1 of the auxiliary request 1, first raised with the statement of the grounds of appeal in relation to auxiliary request 2 but equally applicable to auxiliary request 1 (as substantiated by the appellant-opponent with its letter of reply to the appellant-patent proprietor's grounds of appeal), are

taken into account in the appeal proceedings pursuant to Article 12(4) RPBA.

6.1.2 The claims as originally filed were directed to a "preparation of a glycoprotein containing a Cys-Xl-Ser/Thr-X2-Pro-Cys motif and wherein said serine/threonine forms part of a Glc-O-Ser/Thr covalent bond, wherein the preparation contains a substantially uniform serine/threonine-linked glycosylation pattern" (claim 1), "wherein the glycosylation pattern is at least 80% uniform, preferably at least 85%, at least 90%, at least 95%, or at least 98% uniform" (claim 2), "wherein the serine/threonine-linked glycan is Xyl-Xyl-Glc-" (claim 3), "wherein the glycoprotein is selected from the group of: Factor VII polypeptides, Factor VII-related polypeptides, Factor IX polypeptides, Factor X polypeptides, Factor XII polypeptides, and protein Z polypeptides" (claim 6). Hence, the claims as originally filed provide explicit disclosure for a preparation of a Factor VII polypeptide containing a Cys-Xl-Ser/Thr-X2-Pro-Cys motif and with a serine/threonine glycosylation pattern which is at least 85% uniform, wherein the serine/threonine-linked glycan is Xyl-Xyl-Glc-. In the case of Factor VII, the Cys-Xl-Ser/Thr-X2-Pro-Cys motif is in fact a Cys-Xl-Ser-X2-Pro-Cys motif at serine residue 52; hence also these features of claim 1 of the auxiliary request are implicitly disclosed in the claims as originally filed. The point is then whether "serine/threonine-linked glycosylation pattern [which] is (...) at least 85% uniform" (as in claim 2 as originally filed) "wherein the serine/threonine-linked glycan is Xyl-Xyl-Glc-" (claim 3 as originally filed) can be considered equivalent or not to "at least 85% of said serine residues in the preparation are glycosylated with Xyl-Xyl-Glc" (claim 1 of auxiliary request 1). The board

considers that this is the case in view of the teaching of page 4, lines 23 to 34, of the application as filed, wherein the glycosylation pattern is defined as "the percentage of acceptor moieties, i.e., serine or threonine residues, that are glycosylated by the glycan of interest", meaning that a "serine/threonine-linked glycosylation pattern which is at least 85% uniform, wherein the serine/threonine-linked glycan is Xyl-Xyl-Glc-" (claims 2 and 3 as originally filed) is identical to "at least 85% of said serine residues in the preparation are glycosylated with Xyl-Xyl-Glc" (claim 1 of auxiliary request 1). As to the further feature "pharmaceutical compositions comprising ... a pharmaceutically acceptable carrier", this feature is disclosed, e.g. on page 28, second paragraph, of the application as filed, in the context of "preparations comprising Factor VII and Factor VII-related polypeptides according to the invention".

6.1.3 The set of claims of auxiliary request 1 thus fulfils the requirements of Article 123(2) EPC.

6.1.4 As to Article 123(3) EPC, the appellant-opponent essentially argued that the feature "at least 85% of said serine residues..." renders claim 1 broader than the feature present in granted claim 1 "...glycosylation pattern that is at least 80% uniform", in view of the fact that Ser60 is also glycosylated and may be glycosylated with either fucose or a tetrasaccharide (D8, page 16, line 12). Hence, six families of different serine/threonine O-glycosylation are possible in plasma (four in recombinant forms, which do not have the Xyl-Glc-Ser52 form).

6.1.5 The board disagrees with the appellant-opponent's interpretation of granted claim 1. According to the

definition given in the patent application on page 4, lines 23 to 34, the term glycosylation pattern refers to the percentage of acceptor moieties, i.e. serine or threonine residues, that are glycosylated by the glycan of interest. The next paragraph, starting on line 35 and extending to page 5, then further explains that the term "substantially" (in the context of "substantially uniform glycsosylation pattern" as in line 24) "is intended to mean that at least about 80%, such as at least about 90%, at least about 95%, or at least about 98% of the serine/threonine residues in the glycoprotein is glycosylated with a predetermined, specific glycan or glycan of interest". Following this interpretation, it is apparent that granted claim 1, by virtue of the requirement that the preparation contains a "serine/threonine linked glycosylation pattern that is at least 80% uniform", encompassed preparations wherein at least 80% of the serine/threonine residues in the glycoprotein are glycosylated with a predetermined, specific glycan or glycan of interest. Since, as argued by the appellant-opponent, both Serine 52 and Serine 60 are glycosylated in Factor VII, and the glycan is either Glc- or Xyl-Glc or Xyl-Xyl-Glc for Serine 52 and either Fuc- or a tetrasaccharide for Serine 60, it follows that granted claim 1 was limited to preparations wherein at least 80% of the Factor VII molecules were glycoforms comprising either the glycans Glc- or Xyl-Glc or Xyl-Xyl-Glc at Serine 52, or comprising either the glycans Fuc- or a tetrasaccharide at Serine 60 (application, page 40, lines 9 to 11). Contrary thereto, claim 1 of auxiliary request 1 only encompasses such preparations wherein at least 85% of the Factor VII molecules are glycoforms comprising the Xyl-Xyl-Glc glycan at Serine 52. Hence, the ambit of claim 1 of auxiliary request 1 is narrower than that of

granted claim 1. The set of claims of auxiliary request 1 therefore fulfils Article 123(3) EPC.

6.2 Novelty

6.2.1 Claim 1 of auxiliary request 1 is directed to a pharmaceutical preparation comprising a Factor VII polypeptide, defined as above, and a pharmaceutically acceptable carrier. As discussed above in relation to the main request, a Factor VII preparation comprising at least 85% of the Xyl-Xyl-Glc-Ser52 glycoform was disclosed in D17. However, the board does not agree with the conclusions of the opposition division that D17 also discloses pharmaceutical preparations comprising said Factor VII preparation; the enzymatic digestion described on page 122 (under "Results"), while taking place in an aqueous environment, is not a pharmaceutical preparation. A pharmaceutical preparation should be both stable and acceptable to a patient (in the sense that the preparation itself is not toxic). Clearly, the solution where the enzymatic digestion takes place is not a stable solution but rather one where the active agent is modified. Hence, claim 1 of auxiliary request 1 is novel over D17.

6.2.2 Document D19 discloses Factor VII preparations which can be from different sources, including bovine (page 5, lines 32 to 37), for preparing medicaments, such as pharmaceutical compositions with pharmaceutically acceptable carriers (page 26, first paragraph). For the reasons discussed above in relation to the main request, bovine Factor VII preparations are preparations within the meaning of claim 1, as evidenced in D17 and apparent from D20 and D21. Accordingly, document D19 anticipates the subject-matter of claim 1 of auxiliary request 1.

6.2.3 The appellant-patent proprietor essentially argued that D19 mentioned bovine Factor VII just once, on page 5, line 36, in the context of explaining the meaning of "Factor VII polypeptide" (page 5, line 28 to page 9, line 30). Consequently, nothing would direct the skilled reader towards bovine Factor VII in preference to other forms of Factor VII, particularly in the context of pharmaceutical preparations. D19 was not exclusively directed to pharmaceutical preparations and medical uses but rather disclosed other uses for Factor VII preparations (e.g. page 25, line 23); the skilled person would therefore immediately understand that bovine Factor VII was meant for these other uses. Moreover, D19 did not make any reference to D17, and it was not inevitable that the bovine Factor VII preparations of D19 would be identical to those of D17 (T 793/93).

6.2.4 The board notes that while reference to bovine is indeed only made once in D19, the whole disclosure of D19 is directed to Factor VII in general, which is explicitly stated to include bovine Factor VII as an equally suitable alternative to all other forms listed. Moreover, the board disagrees that D19 contemplates uses other than medical uses for the Factor VII preparations. In fact, the whole disclosure of D19 is about providing stable Factor VII preparations for administration to patients. The passage mentioned by the appellant-patent proprietor as referring to other uses in fact still discusses pharmaceutical uses; it is part of a sentence that reads "They may also be reconstituted for other purposes, e.g. for reformulation into other pharmaceutical compositions" (page 25, lines 23 and 24). Finally, the board considers that the glycosylation pattern

disclosed in D17 for bovine Factor VII is implicit to D19's bovine Factor VII preparations. It is clear from D17, and corroborated by D20 and D21, that bovine Factor VII has the given pattern of glycosylation and, in the absence of evidence to the contrary, this is considered inherent to all bovine Factor VII preparations.

7. Auxiliary request 2

7.1 Added subject-matter, extension of protection, clarity

7.1.1 The same objections under Article 123(2) and (3) EPC as discussed above for auxiliary request 1 were also raised by the appellant-opponent for auxiliary request 2 and, for the reasons discussed above, were admitted into the proceedings. For the same reasons, the objection under Article 84 EPC, raised for the first time by the appellant-opponent in its statement of grounds of appeal, was also admitted.

7.1.2 Claim 1 of auxiliary request 2 differs from claim 1 of auxiliary request 1 in that it is not directed to pharmaceutical compositions but to a medical use, namely "for use in the treatment of a bleeding disorder". Treatment of bleeding disorders with the compositions of the invention is explicitly disclosed on page 27, lines 30 to 32. Hence, the set of claims of auxiliary request 2 complies with Article 123(2) EPC.

7.1.3 Moreover, the restriction to the medical use renders the claims of auxiliary request 2 narrower than the granted claims, which were directed to preparations. Accordingly, the set of claims of auxiliary request 2 also complies with Article 123(3) EPC.

7.1.4 As regards clarity, the objection raised by the appellant-opponent is essentially based on the patent's definition of "Factor VII polypeptide" as including Factor VII-related peptides which, according to the further definition in paragraph [0038], also include such polypeptides with disrupted bioactivity (further explained in paragraph [0043]). It is thus not clear how such largely inactivated Factor VII variants could be used in the treatment of a bleeding disorder.

7.1.5 The board notes that claim 1 of auxiliary request 2 clearly identifies the preparation to be used as medicament and the therapeutic indication. Hence, the board fails to see any lack of clarity in the claims of auxiliary request 2. The fact that inactivated polypeptides are also encompassed as medicament in a claim directed to medical uses may give rise to objections under Article 83 EPC rather than under Article 84 EPC. However, in view of the conclusions reached under novelty (see below), Article 83 EPC was not discussed for auxiliary request 2.

7.2 Novelty

7.2.1 Claim 1 of auxiliary request 2 is in the form of a second medical use claim, wherein the therapeutic composition is a preparation defined as in claim 1 of auxiliary request 1, while the therapeutic indication is bleeding disorder. The use of medicaments comprising Factor VII for the treatment of a number of well-known bleeding disorders is explicitly disclosed in D19 (page 26, lines 25 to 27). D19 is thus also novelty-destroying for the subject-matter of claim 1 of auxiliary request 2.

8. Auxiliary request 3

8.1 Added subject-matter, extension of scope

8.1.1 Claim 1 of auxiliary request 3 differs from claim 1 of auxiliary request 1 in that it is directed to preparations of human Factor VII. The basis for this amendment can be found, *inter alia*, in claim 7 as originally filed. Moreover, the present claims are now restricted to human Factor VII and are thus narrower than the granted claims. Accordingly, the requirements of Article 123(2) and (3) EPC are fulfilled.

8.2 Sufficiency of disclosure

8.2.1 According to Article 83 EPC, a European patent application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. For claims directed to pharmaceutical compositions it is generally sufficient that the application provides information which allows the skilled person to produce the composition, and that there are no substantiated doubts that it could indeed be used in therapy (see also T 1616/09, Catchword and Reasons, 6.).

8.2.2 In the present case, a pharmaceutical composition is claimed which is defined as comprising a preparation of a human Factor VII polypeptide wherein at least 85% of the serine 52 residues are glycosylated with Xyl-Xyl-Glc (for the exact wording see section VII). The patent application teaches on page 17, line 5 to page 24, line 19 a number of methods to produce glycoprotein preparations having a predetermined pattern of O-linked oligosaccharides, and in particular to increase the percentage of the Xyl-Xyl-Glc-Ser52 glycoform of human

Factor VII preparations. In Example 8, the patent application discloses purification of recombinant Factor VII preparations using HIC and shows that a fraction could be obtained with a higher percentage of the Xyl-Xyl-Glc-Ser52 glycoform. Although the percentages achieved are not indicated in the patent application, the board fails to see any reason why the desired percentage should not be attainable using the methods disclosed in the patent application, adapted to any particular circumstances, if needed, by routine modifications. Hence, the board is convinced that the requirements of Article 83 EPC are fulfilled for the claims of auxiliary request 3.

8.2.3 The appellant-opponent essentially argued that there was no evidence either in the patent application or in the post-published data of D12 that such a preparation could be obtained by the methods described in the patent application, D18 confirming that the experiments performed in D12 were not a direct repeat of the experiments of Example 8. Moreover, the appellant-patent proprietor had itself argued, on the basis of D25, that Factor VII preparations behaved differently under HIC depending on the activation status and on the source of the preparation and that therefore an inventive skill was needed to provide preparations with a purified glycoform.

8.2.4 The board notes that although Example 8 is the only example of an assay that was indeed performed, the patent application discusses a number of other methods that could be used for the purpose of obtaining a preparation with the desired pattern of glycosylation. Even if the method of Example 8 may not have attained the claimed pattern of glycosylation, the skilled person would be in a position, following the teachings

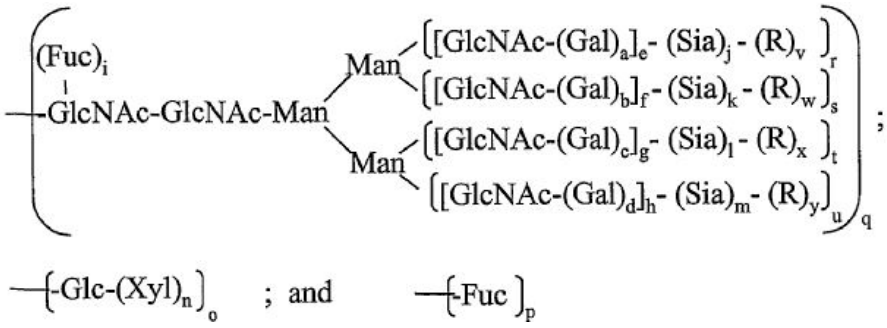
of the patent application and using common general knowledge, to modify said method in order to obtain the desired result: this is what was successfully done in D12. As to the arguments based on D25, the board notes that it is not surprising that Factor VII preparations obtained from different recombinant systems or in different activation status behave differently under HIC. After all, it was well known that different recombinant systems produce different patterns of glycosylation, as stated in the patent (paragraph [0005]) and confirmed in document D27. However, there is no evidence that an undue burden would be required to adapt the conditions of the HIC method or any other purification method in order to obtain the desired result. The appellant-opponent has described a number of possible difficulties that the skilled person might encounter, but has not presented any serious doubts, supported by verifiable facts, to demonstrate that a preparation as claimed could not be obtained following the teachings of the invention complemented by common general knowledge. In the absence thereof, the board has no reason to doubt that the patent application enablingly discloses such preparations.

8.3 Novelty

8.3.1 Neither of documents D17 and D19 discloses preparations of human Factor VII comprising at least 85% of glycoforms with the Xyl-Xyl-Glc glycan at Serine 52. As is apparent from D17, both glycoforms with Xyl-Glc and Xyl-Xyl-Glc are present in the human preparation; D1, moreover, discloses the presence of a third glycoform (with a Glc glycan) in human Factor VII preparations and teaches that all three glycoforms are present in "approximately equal amounts" (abstract). Accordingly,

claim 1 of auxiliary request 3 is novel over D17 and D19.

8.3.2 In its statement of grounds of appeal, the appellant-opponent had also maintained its objection for lack of novelty of claim 1 of auxiliary request 2 over document D6. Document D6 is a patent application of almost 1 000 pages which discloses remodelling and glycoconjugation of peptides. Human Factor VII is listed among a large number of possible peptides, e.g. in claim 11 and on page 16, line 17. Claim 166 is directed to "A Factor VIIa peptide conjugate formed by the method of claim 158"; claim 158 is directed to "A method of forming a conjugate between a Factor VIIa peptide and a modifying group, wherein said modifying group is covalently attached to said Factor VIIa peptide through an intact glycosyl linking group, said Factor VIIa peptide comprising a glycosyl residue having a formula which is a member selected from:



wherein a, b, c, d, i, o, p, q, r, s, t, and u, are members independently selected from 0 and 1; e, f, g, h and n are members independently selected from the integers from 0 to 6; j, k, 1 and m are members independently selected from the integers from 0 to 20; v, w, x and y are 0; and R is a modifying group, a mannose, an oligomannose, SialylLewis^{x} or SialylLewis^{a};

said method comprising: (a) contacting said Factor VIIa peptide with a glycosyltransferase and a modified glycosyl donor, comprising a glycosyl moiety which is a substrate for said glycosyltransferase covalently bound to said modifying group, under conditions appropriate for the formation of said intact glycosyl linking group". A schematic representation of the method is depicted in Figures 30A to 30D, wherein Figure 30A depicts Factor VII and VIIa peptides, and Figures 30B to 30D are diagrams of contemplated remodelling steps based on the type of cell the peptide is expressed in and the desired remodelled glycan structure. In Figure 30A it is indicated that the $[Glc-(Xyl)_n]_o$ modification is linked to the residue marked with the letter B, which is Serine 52, while the other modifications listed are linked to residues 145 and 322 (A) and 60 (C). As to the modification $[Glc-(Xyl)_n]_o$ to Serine 52, it is thus indicated that it is either present or not (o=0 or 1) and the number of xylose molecules varies between 0 and 6 (n=0 to 6). It is not apparent, nor is it stated anywhere in the document, that by following the procedure disclosed e.g. in claim 158 and schematised in Figures 30B to 30D, the skilled person would inevitably end up with a preparation comprising at least 85% of the Xyl-Xyl-Glc-Ser52 glycoform. Rather, it is likely that the enzymatic reactions performed, which involve the addition of glycosyl groups, would lead to preparations comprising mixtures of glycoforms corresponding to the $[Glc-(Xyl)_n]_o$ formula. There is no disclosure in the whole document of a Factor VII glycopeptide containing exclusively or predominantly the Xyl-Xyl-Glc-Ser52, let alone of pharmaceutical compositions comprising such a glycopeptide. Hence, claim 1 of auxiliary request 3 is also novel over D6.

8.3.3 The appellant-opponent essentially argued that D6 disclosed remodelling of the glycan structures to produce individual glycoforms and not mixtures of glycoforms, as would be apparent from the language of claims 166 and 158, and of page 137, lines 25 to 26, and that the interpretation of the term "substantially uniform glycoform" by the opposition division was incorrect. The board however notes that clam 158 refers to "a member selected from" a group which comprises a huge number of alternatives, as is apparent from the values that each of the letters a to x may have. As to the term "substantially uniform glycoform" on pages 116 to 117, its interpretation is similar to the one given in the patent, except that it refers to the glycosylating enzyme rather than to the glycan: "'Substantially uniform glycoform' or a 'substantially uniform glycosylation pattern', when referring to a glycopeptide species, refers to the percentage of acceptor moieties that are glycosylated by the glycosyltransferase of interest" (page 116, lines 24 to 26). On page 117, lines 3 to 6, it is further explained that "The term 'substantially' in the above definitions of 'substantially uniform' generally means at least about 40%, at least about 70%, at least about 80%, or more preferably at least about 90%, and still more preferably at least about 95% of the acceptor moieties for a particular glycosyltransferase are glycosylated", thus a definition that clearly encompasses preparations far away from the alleged 100% uniformity. Moreover, contrary to the arguments of the appellant-opponent, these passages refer to glycopeptides in general and thus also include Factor VII. Also the passage on page 137, lines 25 to 26, has to be read under this light: "any desired glycan structure" does not necessarily mean that the end preparation is 100% uniform in terms of said glycan.

8.4 Inventive step

8.4.1 The present patent is directed at preparations comprising serum proteins such as Factor VII and Factor IX. Said polypeptides, which are involved in coagulation or fibrinolysis, are "useful therapeutic agents to treat a variety of pathological conditions" (paragraph [0004]). However, in order to avoid "the many disadvantages of using human plasma as a source of pharmaceutical products, it is preferred to produce these proteins in recombinant systems" (paragraph [0005]). In order to avoid the problems associated with recombinant systems, such as the production of different arrays of glycoforms which may in turn lead to changes in immunogenicity and in vivo clearance (paragraphs [0005] and [0006]), the patent aims at providing "preparations comprising recombinant human Factor VII or modified Factor VII or Factor VII-related polypeptides that contain predetermined glycoform patterns" (paragraph [0006]).

8.4.2 Document D7, which discloses the manufacturing and clinical development of recombinant human activated Factor VII, was considered by both parties and by the opposition division as the closest prior art. The difference to the claimed subject-matter is that the preparation according to D7 does not contain the glycoform with Xyl-Xyl-Glc at Serine 52 in a proportion of at least 85%; rather, although not explicitly stated, it appears that, by reference to document D1 (reference 37 of D7), this glycoform constitutes roughly one third of the total amount of Factor VII (D7, page 376, right-hand column, last paragraph to page 377, left-hand column, line 3).

8.4.3 Example 8 of the patent shows in Table 1 (page 20) that there is increased Factor VII specific activity for peak fraction 15 in comparison to the starting material and to fraction 10: 61 IU/ug against 53 IU/ug and 44 IU/ug, respectively. In paragraph [0149], peak fraction 15 is described as comprising "a low content of Glc-O-Ser52-rFVIIa and a high content of Xyl-Xyl-Glc-O-Ser52-rFVIIa", while peak fraction 10 is described as containing "a high content of Glc-O-Ser52-rFVIIa and a low content of Xyl-Xyl-Glc-O-Ser52-rFVIIa". There is, however, no indication whatsoever of the percentage amounts of each of the glycoforms, and it therefore cannot be concluded that peak fraction 15 corresponds to a preparation as claimed (i.e. with at least 85% of the Xyl-Xyl-Glc-O-Ser52 glycoform). Nevertheless, it can be stated that the patent does predict an increase of specific activity for fractions comprising more of the Xyl-Xyl-Glc-O-Ser52-rFVIIa glycoform. This is then corroborated by the post-published data of D12, which show an increase of specific activity for fractions BHK-rFVII 5 and CHO-rFVII 4, comprising respectively 86% and 88% of the Xyl-Xyl-Glc-O-Ser52-rFVIIa glycoform (Table 2 of D12), in comparison to the starting material BHK-rFVII and CHO-rFVII, respectively (Table 3). The recombinant FVII used in D7 is expressed in BHK cells as well, meaning that at least this set of data of D12 allows direct comparison to D7's preparations.

8.4.4 The technical problem can thus be formulated as the provision of a preparation of human Factor VII that has a homogeneous glycoform pattern and an increased specific activity in comparison to the preparation of D7. The solution is the subject-matter as claimed, and the board is satisfied that the problem is plausibly solved.

8.4.5 While the importance of the O-glycosylation sites for Factor VII activity was known (e.g. D1, D2, D4, D9), there is no teaching or suggestion in the prior art that increasing the proportional amount of the Xyl-Xyl-Glc-O-Ser52 glycoform in human Factor VII preparations would lead to an increase in the specific activity. Hence, the board comes to the conclusion that the claimed solution to the technical problem would not be obvious for the skilled person.

8.4.6 The appellant-opponent essentially argued that the technical problem as formulated was not plausibly solved in the patent, because the definition of Factor VII still included inactive polypeptides (paragraph [0043]), and also because Example 8 did not plausibly demonstrate that a preparation as claimed indeed had an increased specific activity. Hence, following decision T 1329/04, the post-published data were not suitable to establish that the problem had been solved. Additionally, even if the problem could be considered solved, then the solution was obvious in view of D1, referred to in D7, which discussed the importance of glycosylation at Serine 52 for Factor VII activity.

8.4.7 The board notes that, while the passage of paragraph [0043] of the patent indeed includes inactive Factor VII as polypeptides of the invention, the skilled person would understand that the present claims, directed to pharmaceutical compositions, should comprise active rather than inactive polypeptides. Moreover, as discussed above, the board considers that Example 8 plausibly shows that human Factor VII preparations with an increased proportional amount of the Xyl-Xyl-Glc-O-Ser52 glycoform have an improved specific activity. Since the patent already plausibly

shows that the problem has been solved, post-published data such as D12 can be used as further evidence (in accordance with decision T 1329/04). As to the obviousness of the solution, the board fails to see any suggestion, either in D7 or in any other available document of the prior art, pointing towards the claimed solution.

8.4.8 The subject-matter of claim 1 of auxiliary request 3 thus involves an inventive step pursuant to Article 56 EPC. The same is also true for dependent claim 2. As to independent claim 3, this claim is directed to a method to produce a preparation as defined in claim 1 and, accordingly, also involves an inventive step, for the same reasons as discussed for claim 1. The same applies to dependent claims 4 to 6.

9. Description amendments

9.1 Added subject-matter

9.1.1 According to Article 123(2) EPC, a European patent application or European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed. The "gold standard" (G 2/10, OJ EPO 2012, 376) for assessing compliance with Article 123(2) EPC is that any amendment to the parts of a European patent application or a European patent relating to the disclosure (description, claims and drawings) is subject to the mandatory prohibition on extension laid down in Article 123(2) EPC and can therefore only be made within the limits of what a skilled person would derive, directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of these documents

as filed (G 3/89, OJ EPO 1993, 117; G 11/91, OJ EPO 1993, 125).

9.1.2 The appellant-opponent objected to the amendments made to paragraph [0145] of the description as granted as contravening Article 123(2) EPC, essentially arguing that, while it was apparent that there was an error in the application as filed, it was not beyond reasonable doubt that the resolution of the contradiction as done in the patent was the correct one.

9.1.3 The passage objected to in paragraph [0145] of the description as granted differs from the corresponding passage of the description as originally filed (page 40, lines 21 to 23) as follows (changes marked by the board): "The peaks containing the O-glycopeptides of rFVIIa are eluted after approx. 67-70 min where the ~~1st~~ 2nd peak contains O-glycopeptides with a xylose-xylose-glucose linked to serine 52, and the ~~2nd~~ 1st peak contains O-glycopeptides with a glucose linked to serine 52". It is part of Example 7, which discloses how "The O-glycoform pattern can be analysed by tryptic peptide mapping of rFVIIa". The whole disclosure of the experimental procedure is written in the present tense, which renders it clear that it is not the description of an experiment that has been made but rather an experiment to be performed. In contrast thereto, paragraph [0149], which is part of Example 8 and is identical to the corresponding passage of the description as filed (page 41, line 21 to page 42, line 2), discloses the actual performance of the experiment. It teaches that "Purified Glc-O-Ser52-FVII was identified in the peak fraction, fraction 10 (Figure 5), obtained by reloading fraction 'A' onto the second HIC step" and that "Purified Xyl-Xyl-Glc-O-Ser52-FVII was identified in the peak fraction, fraction 15

(Figure 6), obtained by reloading fraction 'B' onto the second HIC step". As is apparent from the paragraph just above (paragraph [0148] in the description as granted; page 41, lines 13 to 20, in the description as filed), fraction A corresponded to the "fractions containing the first peak", while fraction B corresponded to "fractions containing the second major peak". Paragraph [0149] then further discloses that "The identification was obtained by tryptic peptide mapping of rFVIIa as described in Example 7 (Figures 7A and 7B) and by total mass analysis of rFVIIa as described in Example 7 (Figures 8A and 8B)" and that "Both analyses showed a high content of Glc-O-Ser52-rFVIIa and a low content of Xyl-Xyl-Glc-O-Ser52-rFVIIa in the peak fraction, Fraction 10, and a low content of Glc-O-Ser52-rFVIIa and a high content of Xyl-Xyl-Glc-O-Ser52-rFVIIa in the peak fraction, Fraction 15". Figures 7A and 7B, and in accordance with their legend in paragraph [0015] of the description as granted (page 3, lines 23 to 26, of the description as filed) again confirm that fraction 10 (obtained from the first peak) contains the Glc-O-Ser52 O-glycopeptide while fraction 15 (obtained from the second peak) contains the Xyl-Xyl-Glc-O-Ser52 O-glycopeptide. Accordingly, Example 8 and the corresponding Figures 7A and 7B provide compelling evidence that the first peak contains the glucose O-glycopeptide while the second peak contains the xylose-xylose-glucose O-glycopeptides, and constitute the basis for the amendment done in paragraph [0145] of the description as granted, which is hence considered directly and unambiguously derivable from the application as filed.

9.1.4 The board notes that the appellant-opponent's arguments are not that the amendment added subject-matter which was not directly and unambiguously derived from the

application as filed, but rather that there was another alternative correction possibility to solve the inconsistency present in the description. Hence, although the objection is made under Article 123(2) EPC, the line of argument is based on the requirements applicable for the correction of errors in documents filed with the EPO pursuant to Rule 139 EPC. However, independently of whether the disputed amendment to the description was originally made with the aim of correcting an obvious error, the conclusions of the board that it was made within the limits of what a skilled person would derive, directly and unambiguously, from the whole of these documents as filed are still valid.

9.1.5 The description as granted thus fulfils the requirements of Article 123(2) EPC.

9.2 Adaptation of the description

During the oral proceedings, the description was further adapted to bring it into conformity with the claimed subject-matter of auxiliary request 3.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent as amended in the following version:

   - claims 1 to 6 filed as auxiliary request 3 with the letter dated 9 September 2013,
   - description: pages 2, 2a, 3 to 13 filed at the oral proceedings of 28 August 2018 and pages 14 to 20 of the patent specification, and
   - drawings: figures 1 to 8b of the patent specification.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated