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**Datasheet for the decision
of 3 December 2019**

Case Number: T 1166/16 - 3.3.07
Application Number: 09740822.3
Publication Number: 2349314
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A61K47/26, A61K48/00, A61K38/16
Language of the proceedings: EN

Title of invention:

LYOPHILIZED RECOMBINANT VWF FORMULATIONS

Patent Proprietor:

Baxalta Incorporated
Baxalta GmbH

Opponent:

Brunner, John Michael Owen

Headword:

LYOPHILIZED RECOMBINANT VWF FORMULATIONS/Baxalta Incorporated
and Baxalta GmbH

Relevant legal provisions:

EPC Art. 56
RPBA Art. 12(4), 12(2)

Keyword:

Main request - Inventive step (No)

Auxiliary request - Admission into the proceedings (No)

Decisions cited:

Catchword:



Beschwerdekammern
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Case Number: T 1166/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 3 December 2019

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 10 March 2016
revoking European patent No. 2349314 pursuant to
Article 101(3)(b) EPC.**

Composition of the Board:

Chairman J. Riolo
Members: D. Boulois
 C. Schmidt

Summary of Facts and Submissions

- I. European patent No. 2 349 314 was granted on the basis of a set of 14 claims.

Independent claim 1 as granted read as follows:

"1. A stable lyophilized pharmaceutical formulation of a recombinant von Willebrand Factor (rVWF) comprising: (a) a rVWF; (b) one or more buffering agents; (c) one or more amino acids; (d) one or more stabilizing agents; and (e) one or more surfactants; wherein the formulation is prepared by lyophilizing a solution comprising

(a) said rVWF comprising a polypeptide selected from the group consisting of:

- a) the amino acid sequence set out in SEQ ID NO: 3;
- b) an analog, fragment or variant of a) which is capable of causing agglutination of stabilized platelets in the presence of ristocetin, or of binding to Factor VIII;
- c) a polypeptide encoded by the polynucleotide set out in SEQ ID NO: 1;
- d) an analog, fragment or variant of c) which is capable of causing agglutination of stabilized platelets in the presence of ristocetin, or of binding to Factor VIII; and
- e) a polypeptide encoded by a polynucleotide that hybridizes to the polynucleotide set out in SEQ ID NO: 1 under moderately stringent hybridization conditions;

(b) said buffer comprising a pH buffering agent in a range of about 0.1 mM to about 500 mM and having a pH is in a range of about 2.0 to about 12.0;

(c) said amino acid at a concentration of about 1 to about 500 mM;

(d) said stabilizing agent at a concentration of about 0.1 to about 1000 mM; and

(e) said surfactant at a concentration of about 0.01 g/L to about 0.5 g/L."

- II. The patent was opposed under Article 100 (a), (b) and (c) EPC on the grounds that its subject-matter lacked novelty and inventive step, was not sufficiently disclosed, and extended beyond the content of the application as filed.
- III. The appeal lies from the decision of the opposition division to revoke the patent. The decision was based on the claims as granted as main request, auxiliary requests 1, 2, 4 and 5 filed with letter dated 23 October 2015 and on auxiliary request 3 filed during the oral proceedings before the opposition division on 4 December 2015.
- IV. The documents cited during the opposition proceedings included the following
D8: Prescribing information for Advate®
- V. According to the decision under appeal, the main request and auxiliary requests 1 and 2 did not meet the requirements of Article 123(2) EPC.

Claim 1 of auxiliary request 3 differed from claim 1 as granted by the suppression of the feature "of causing agglutination of stabilized platelets in the presence of ristocetin" characterizing feature b) and d). D8 was considered to be the closest prior art for the assessment of inventive step. The differences laid in the nature of the buffer and the amount of mannitol.

The opposition division considered that the problem of providing a stable lyophilized rVWF composition was not plausibly solved over the whole scope of the claim on view of the term "analog" in claim 1. The problem was seen as the provision of an alternative composition and the solution was obvious.

Auxiliary requests 4 and 5 lacked inventive step for the same reasons, since the claim recited that "the rVWF comprises the amino acid sequence set out in SEQ IND No3", which open language did not exclude possible analogs and/or derivatized peptides.

- VI. The patent proprietor (hereinafter the appellant) filed an appeal against said decision. With its statement of grounds of appeal dated 15 July 2016, the appellant filed a main request and auxiliary requests 1-7.
- VII. In its reply to the statements of ground of appeal dated 1st December 2016, the opponent (hereinafter the respondent) requested that the main request and auxiliary requests 1, 2, 5, 6, and 7 not be admitted into the proceedings.
- VIII. A communication from the Board, dated 29 July 2019, was sent to the parties. In this, it was considered in particular that the main request did not appear to be inventive over D8, and that applied also to auxiliary requests 1-4. The Board noted also that auxiliary requests 5-7 had not been commented by the appellant, in particular as regards inventive step.
- IX. With a letter dated 24 September 2019, the appellant filed a main request and auxiliary requests 1 to 3 corresponding respectively to the auxiliary requests 4-7 filed previously with letter dated 15 July 2016.

Independent claim 1 of the main request read:

"1. A stable lyophilized pharmaceutical formulation of a recombinant von Willebrand Factor (rVWF) comprising: (a) a rVWF; (b) one or more buffering agents; (c) one or more amino acids; (d) one or more stabilizing agents; and (e) one or more surfactants; wherein the formulation is prepared by lyophilizing a solution comprising:

(a) said rVWF comprising a polypeptide selected from the group consisting of:

- a) the amino acid sequence set out in SEQ ID NO: 3;
- b) an analog of a) which is capable of binding to Factor VIII;
- c) a polypeptide encoded by the polynucleotide set out in SEQ ID NO: 1;
- d) an analog of c) which is capable of binding to Factor VIII; and
- e) a polypeptide encoded by a polynucleotide that hybridizes to the polynucleotide set out in SEQ ID NO: 1 under moderately stringent hybridization conditions;

(b) , wherein the buffering agent of the solution is citrate at a concentration of 15 mM and the pH is about 7.3;

(c) wherein the amino acid is glycine at a concentration of about 15 mM in the solution;

(d) wherein the stabilizing agents are trehalose at a concentration of about 10 g/L in the solution and mannitol at a concentration of about 20 g/L in the solution; and

(e) wherein the surfactant is TWEEN-80 at about 0.1 g/L in the solution."

Independent claim 1 of auxiliary requests 1-3 read as follows, the main difference(s) compared with claim 1 of the main request shown in bold:

Auxiliary request 1

"1. A stable lyophilized pharmaceutical formulation of a recombinant von Willebrand Factor (rVWF) **consisting of:** (a) a rVWF; (b) one or more buffering agents; (c) one or more amino acids; (d) one or more stabilizing agents; and (e) one or more surfactants; wherein the formulation is prepared by lyophilizing a solution, **comprising:** **wherein the rVWF comprises the the amino acid sequence set out in SEQ ID NO: 3;** wherein the buffering agent is citrate at a concentration in the solution of about 15 mM at about pH 7.3; wherein the amino acid is glycine at a concentration of about 15 mM in the solution; wherein the stabilizing agents are trehalose at a concentration in the solution of about 10 g/L in the solution and mannitol at a concentration in the solution of about 20 g/L in the solution; and wherein the surfactant is TWEEN-80 at about 0.1 g/L in the solution."

Auxiliary request 2

Compared to claim 1 of auxiliary request 1, the subject-matter of claim 1 of auxiliary request 2 has been further amended by the feature "**for intravenous administration**".

Auxiliary request 3

"1. A stable lyophilized pharmaceutical formulation of a recombinant von Willebrand Factor (rVWF) comprising: (a) a rVWF; (b) one or more buffering agents; (c) one or more amino acids; (d) one or more stabilizing agents; and (e) one or more surfactants; **for use in a method of treatment of von Willebrand's disease**, wherein the formulation is prepared by lyophilizing a solution, **comprising:**
wherein the rVWF comprises the the amino acid sequence set out in SEQ ID NO: 3; wherein the buffering agent is citrate at a concentration in the solution of about 15 mM at about pH 7.3; wherein the amino acid is glycine at a concentration of about 15 mM in the solution; wherein the stabilizing agents are trehalose at a concentration in the solution of about 10 g/L in the solution and mannitol at a concentration in the solution of about 20 g/L in the solution; and wherein the surfactant is TWEEN-80 at about 0.1 g/L in the solution."

X. Oral proceedings took place on 3 December 2019.

XI. The arguments of the appellant may be summarised as follows:

Main request - Inventive step

Document D8 had been chosen by the opposition division as closest prior art. Claim 1 differed from this prior art in that citrate was used as a buffer and glycine was used as the amino acid. Moreover, the formulation of D8 was a formulation for Factor VIII, and not for vWF. This further difference had an impact on inventive step assessment, since Factor VIII and von Willebrand Factor were two different molecules and the person skilled in the art would not have turned to a

formulation for a chemically different molecule if faced with the object of providing a stable formulation of von Willebrand factor.

The Advate® formulation of D8 comprised very small amounts of von Willebrand factor, which were present only as a consequence of von Willebrand factor being co-purified with FVIII in the respective purification process. The von Willebrand factor in Advate® "...would not have any clinically relevant effect in patients with von Willebrand's disease" as disclosed in D8 under the heading "Indications and Usage". Thus, vWF in this D8 formulation had no clinical significance whatsoever; the formulation of Advate® had not been designed with the goal to keep VWF stable. Thus, no conclusion on stability of VWF whatsoever could be drawn from this document.

Moreover, the invention was plausibly solved over the scope of all claimed active ingredient. Claim 1 gave a structural identification of the vWF to be employed in this invention; namely SEQ ID NO:3. It did allow for a certain amount of variation, by allowing e.g. analogs. However, even these analogs had to fall into the definition as given in the specification, had to be a vWF molecule and to fall under the additional functional test of binding to Factor VIII. The present claims gave structural plus functional limitations and thus clearly fulfilled the requirements of the EPC.

The examples also supported the present claims. The main request was delimited to the following excipients: citrate buffer, glycine, mannitol, trehalose and Tween 80. Example 1 was a shaking experiment, and the samples

which had the best results were samples 40 and 41 and both comprise Mannitol and Tween 80 in citrate buffer.

Example 2 determined the impact of stress caused by repeated freezing and thawing. There was a clear tendency that those formulations comprising the recombinant vWF in citrate buffer, with mannitol and Tween 80 as excipients, showed particularly good results.

In example 3 further lyophilization experiments were designed to assess the ability of various formulations to allow the formation of a lyo-cake which dissolved in less than 10 minutes and resulted in a clear solution. Either Citrate or HEPES buffer in combination with an amino acid provided the best results.

The resultant formulation, which had all the excipients as now claimed, was subjected to accelerated and long-term stability testing in example 4 and confirmed that a very stable recombinant vWF formulation had been designed.

Taking D8 as closest prior art, as it had been selected by the opposition division, the problem to be solved would thus be the provision of an improved formulation.

The differences between claim 1 of the present main request and D8 were a different active ingredient to be stabilized, the use of citrate as a buffer instead of Tris as a buffer and the additional use of glycine.

The solution to the above mentioned object was thus the replacement of the active ingredient Factor VIII by

rVWF, the replacement of Tris as a buffer, and the addition of the amino acid glycine.

It was totally unclear where the person skilled in the art would have found any disclosure whatsoever to point him or her to this specific selection of new features over D8. The art of actually making a stable lyophilized formulation for one specific protein, was indeed extremely complex. As it could be seen in the field, each and every formulation for each and every protein was different, and different even if the protein in question has changed from plasma to recombinant protein.

The claimed solution was inventive for this reason.

Admission of auxiliary requests 1-3 into the proceedings

The patentee was confronted to several objections raised under Article 123(2) EPC, and said requests were a response to these objections. Claim 1 of all auxiliary requests had been narrowed by self-evident amendments, such as the introduction of the term "consisting of". There did not constitute a fresh case and should therefore be admitted into the proceedings.

XII. The arguments of the respondent may be summarised as follows:

Main request - Inventive step

The Opposition Division used D8 as the closest prior art for the problem-solution approach. The appellant disagreed with this selection of the closest prior art on the grounds that D8 concerns a "chemically different

molecule" because the formulation in D8 contained only a small amount of VWF in combination with FVIII and because this small amount of VWF would not have a clinically relevant effect in patients with von Willebrand's disease.

However, claim 1 did not specify the amount of VWF in the formulation, and nor did it relate to a particular medical use. Therefore, the Advate formulation disclosed in D8 was an appropriate starting point because it was a stable lyophilised formulation comprising rVWF.

The differences between the formulation in claim 1 and the Advate formulation in D8 were (i) the use of a citrate buffer instead of a Tris buffer and (ii) the use of glycine instead of histidine as the amino acid. The concentrations of the buffer and the amino acid used in the Advate formulation fell within the broad ranges in claim 1, so there was no difference in connection with these concentrations.

There was no technical effect associated with these differences. The examples indeed only related to rvWF, while claim 1 encompassed analogs of the amino acid sequence ID No 3 and the polypeptide encoded by the polynucleotide set out in SEQ ID No 1, as well as polypeptides encoded by a polynucleotide that hybridizes to the polynucleotide set out in SEQ ID No 1. The appellant's assertion that different proteins required different stabilizing formulations raised serious doubts that the claimed excipients would result in stable formulations for all analogs or polypeptides claimed, since they could differ substantially in size and structure from the full length rvWF, which is the only protein tested in the examples of the contested

patent. The alleged technical could therefore not be considered to be credibly solved across the whole scope of the claims.

Moreover, there were no comparative data relative to the prior art formulations as disclosed in D8, and the alleged effect was not demonstrated.

The objective technical problem in view of D8 is the provision of an alternative lyophilised formulation comprising VWF.

The use of a citrate buffer and glycine as the amino acid were obvious alternatives to the Tris buffer and histidine amino acid in D8 because these excipients were common in the field of protein formulation.

Therefore, claim 1 lacked an inventive step in view of D8.

Admission of auxiliary requests 1-3 into the proceedings

These requests did not correspond to any request submitted before the opposition division. They had been filed initially as auxiliary requests 5-7 and were not substantiated in the statement setting out the grounds of appeal of the patentee. There was indeed no explanation in said statement of grounds of appeal why and how the amendments made to the initial auxiliary requests 5-7, now auxiliary requests 1-3, addressed the grounds of opposition and the decision of the opposition division. A party had to substantiate why amended claims overcome the objections, and this was not done, even after the Board issued its preliminary opinion and mentioned that the appellant did not

comment initial auxiliary requests 5-7. Said auxiliary requests should therefore not be admitted into the appeal proceedings.

XIII. Requests

The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request, submitted with the letter of 24 September 2019, or on the basis of one of the auxiliary requests 1, 2 or 3, submitted with the same letter.

The respondent requested that the appeal be dismissed. It also requests that auxiliary requests 1 to 3 not be admitted into the proceedings.

Reasons for the Decision

1. Main request - Inventive step

1.1 The invention relates to stable lyophilised compositions of recombinant VWF.

1.2 The opposition division considered D8 as the closest prior art in its decision.

D8 is a monography of the medicament Advate®. Said medicament is a lyophilised composition comprising a recombinant Factor VIII, which is co-expressed with VWF during production to help stabilise it in culture. Said composition comprises therefore a recombinant anti-hemophilic factor, small amounts of VWF, 38 mg/ml of mannitol, 10 mg/ml of trehalose, 12 mM histidine, 12 mM Tris Buffer and 0.15 mg/ml polysorbate 80 (see D8, "Description"). Advate is available in single-dose

vials of 250 to 3000 IU of the recombinant factor VIII rAHF and contains no more than 2 ng of VWF/IU rAHF; as disclosed in D8 said VWF will not have any clinically relevant effect in patients with von Willebrand disease.

Even if it is clear that the composition disclosed in D8 was designed to stabilize a recombinant Factor VIII and contained effective amounts of said recombinant Factor VIII and only minor amounts of VWF, it remains that the composition as claimed is not restricted by the amount of VWF, and comprises also compositions with a minor amounts of VWF, such as the composition disclosed in D8. Accordingly, the amount of VWF cannot constitute a difference as argued by the appellant.

Hence, the composition disclosed in D8 does not comprise a citrate buffer and glycine as claimed.

- 1.3 According to the appellant, the problem is defined as the provision of an improved formulation.
- 1.4 The solution is a lyophilized composition of rVWF comprising in particular a citrate buffer and glycine,
- 1.5 The appellant relied on the examples of the contested patent to support the alleged effect.
 - 1.5.1 Said examples do however not provide a comparison with compositions as disclosed in D8. For this reason alone already, the examples cannot support the alleged effect.
 - 1.5.2 Moreover, the formulations tested in examples 1-4 of the contested patent comprise only full length rVWF represented by SEQ ID No 3, while claim 1 of the main

request relates not only to rVWF having the amino acid sequence set out in SEQ ID NO: 3, but also to an analogs thereof capable of binding to Factor VIII, to a polypeptide encoded by the polynucleotide set out in SEQ ID NO: 1 and to an analog thereof capable of binding to Factor VIII; and even to a polypeptide encoded by a polynucleotide that hybridizes to the polynucleotide set out in SEQ ID NO: 1 under moderately stringent hybridization conditions.

Analog as claimed include a wide range of structurally different proteins, such as chemically modified polypeptides, fusion proteins, and even PEGylated analogs; examples thereof are given in the description of the contested patent in paragraphs [0038]-[0044].

It is commonly known that proteins different in size and structure undergo different degree of denaturation during lyophilization and storage and thus require different formulations for the lyophilization and for the storage.

If the stabilization of a polypeptide with the full length rVWF represented by SEQ ID No 3 is credible in view of the experiments of examples 1-4, this credibility disappears when considering a polypeptide of the remaining claimed alternative rVWF b)-e).

This lack of credibility was confirmed by the appellant's own arguments when assessing the obviousness of the solution, by the statement that the art of actually making a stable lyophilized composition for one specific protein is extremely complex and that it was not true that the existence of one stable protein formulation does not constitute enough information to provide suitably stabilized formulations

for all further lyophilized proteins, as this one known formulation could have been applied to all further proteins.

- 1.5.3 Hence, it is not credible that the alleged improvement in stability would apply to lyophilized compositions comprising analogs as defined in b) and d) of different size or structure or the polypeptides according to the definitions c) and e).

It is therefore impossible to conclude that the claimed invention solves the technical problem of improved stability for all the possible claimed polypeptides, and, at best, the problem has to be redefined as the provision of an alternative lyophilized composition.

- 1.6 Since the problem consists in the provision of an alternative lyophilized composition, it belongs to the normal activity of the skilled person to accomplish routine modifications.

In the present case, citrate is commonly known as a buffering agent, and glycine is also commonly known as buffering or bulking agent. The replacement of a Tris buffer and of histidine in the composition disclosed in D8 for obtaining a composition which, at best, presents an equivalent stability by other known alternative excipients, such as a citrate buffer and glycine is obvious and cannot involve an inventive step.

- 1.7 Consequently, the main request does not meet the requirements of Article 56 EPC.

2. Auxiliary requests 1-3: Admission into the proceedings

- 2.1 Auxiliary requests 1-3 have been filed with the letter dated 24 September and correspond to former auxiliary requests 5-7 filed with the statement of grounds of appeal.
- 2.2 Auxiliary requests 1 and 2 are based on auxiliary requests 4 and 5 submitted during the opposition proceedings, wherein however the term "comprising" has been amended to "consisting of"; these requests do therefore not correspond to any request submitted before the opposition division. Said auxiliary requests 4 and 5 submitted during the opposition proceedings were found to lack inventive step in the opposition proceedings.

Auxiliary request 3 comprises a claim 1 wherein the format has been changed from a product format to a second medical use format, wherein the rVWF is used in a method for treating von Willebrand disease. Such request does not correspond to any request filed or discussed during the opposition proceedings.

- 2.3 The statement of grounds of appeal discuss the conformity of the amendments made to auxiliary requests 5-7 with the requirements of Article 123(2) EPC, but is silent as to the requirements of inventive step of said auxiliary requests. There is indeed no explanation in said statement of grounds of appeal why and how the amendments made to former auxiliary requests 5-7 addressed the grounds of inventive step and more particularly the decision of the opposition division, this despite the fact that auxiliary requests 4 and 5 submitted during the opposition proceedings and on which at least auxiliary requests 5 and 6 are based, were found to lack inventive step.

In its communication, the Board mentioned its concern that auxiliary requests 5-7 filed with the statement of grounds of appeal had not been commented by the appellant in its statement of grounds of appeal as regards inventive step. The appellant did not provide any response to this point, even when filing again the same requests as new auxiliary requests 1-3.

- 2.4 According to Article 12(2) RPBA, the statement of grounds of appeal and the reply shall contain a party's complete case. They shall set out clearly and concisely the reasons why it is requested that the decision under appeal be reversed, amended or upheld, and should specify expressly all the facts, arguments and evidence relied on.

This is obviously not the case here, since the notice of appeal does not indicate the merits of the auxiliary requests at least to the assessment of inventive step. The reply to the Board's communication mentioning this deficiency did also not contain any further argument as to the assessment of inventive step of said auxiliary requests. This puts the Board and the other party in a situation where arguments on inventive step of said auxiliary requests would be presented and discussed for the first time during oral proceedings.

Since everything presented by the parties shall be taken in account by the Board only if and to the extent it relates to the case and meets the requirements in Article 12(2) RPBA, the Board exerts its discretionary power and does not admit auxiliary requests 1-3 in to the proceedings (Article 12(4) RPBA).

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar:

On behalf of the Chairman

(according to Art. 8(3) RPBA):



B. Atienza Vivancos

D. Boulois

Decision electronically authenticated