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Datasheet for the decision of 29 September 2010

Case Number: T 1280/08 - 3.3.04

Application Number: 99955389.4

Publication Number: 1084147

IPC: C07K 16/06

Language of the proceedings: EN

Title of invention:
Process for producting immunoglobulins for intravenous administration and other immunoglobulin products

Patentee:
Statens Serum Institut

Opponent:
Octapharma AG

Headword:
Immunoglobulin products/STATENS SERUM INSTITUT

Relevant legal provisions:
EPC Art. 56
RPBA Art. 12, 13

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main request - admissibility, inventive step (yes)"

Decisions cited:
T 0633/97, T 1074/06

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1280/08 **-** 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 29 September 2010

Appellant I: (Patent Proprietor)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 29 February 2008 concerning maintenance of the European patent No. 1084147 in amended form.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: M. Wieser
B. Claes

Summary of Facts and Submissions

I. Appeals were lodged by the Patent Proprietor (Appellant I) and by the Opponent (Appellant II) against the interlocutory decision of the Opposition Division according to which the European patent No. 1 084 147 could be maintained in amended form (Article 102(3) EPC 1973).

II. The patent had been opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and under Article 100(b) EPC.

The Opposition Division decided that the subject-matter of claim 12 of the main request before it, namely claims 1 to 22 as granted, was not novel contrary to the requirements of Article 54 EPC. However, it decided that claims 1 to 19 of the first auxiliary request met all requirements of the EPC.

III. The Board expressed its preliminary opinion in a communication dated 18 March 2010. Oral proceedings were held on 29 September 2010.

IV. Appellant I requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 11 of the main request filed at the oral proceedings.

Appellant II requested that the decision under appeal be set aside and the patent be revoked.

V. Claim 1 of Appellant I's main request is identical to claim 1 as granted and reads as follows:

"1. A process for purifying immunoglobulin G (IgG), from a crude immunoglobulin-containing plasma protein fraction, which process comprises the steps of:

(a) preparing an aqueous suspension of the crude immunoglobulin-containing plasma protein fraction;

(b) adding a water soluble, substantially non-denaturating protein precipitant to the said suspension of step (a) in an amount sufficient to cause precipitation of a high proportion of non-immunoglobulin G proteins, aggregated immunoglobulins and particles including potentially infectious particles such as virus particles, without causing substantial precipitation of monomeric immunoglobulin G, thereby forming a mixture of a solid precipitate and a liquid supernatant;

(c) recovering a clarified immunoglobulin G-containing supernatant from the mixture of step (b);

(d) applying the clarified immunoglobulin G-containing supernatant of step (c) to an anion exchange resin and subsequently a cation exchange resin, wherein the anion exchange resin and the cation exchange resin are connected in series and wherein the buffer used for the anion exchange chromatography and the cation exchange chromatography is the same buffer, the pH of said same buffer is below 6.0.

(e) washing out protein contaminants and the protein precipitant from the cation exchange resin of step (d) with a buffer having a pH and ionic strength sufficient to remove the contaminants from the resin without causing substantial elution of immunoglobulin G;

(f) eluting immunoglobulin G from the cation exchange resin of step (e) with a substantially non-denaturating buffer having a pH and ionic strength sufficient to cause efficient elution of the immunoglobulin G, thereby recovering an immunoglobulin G-containing eluate;

(g) performing a dia/ultrafiltration on the immunoglobulin G-containing eluate of step (f) to concentrate and/or dialyse the eluate, and optionally adding a stabilizing agent;

(h) adding a virucidal amount of virus-inactivating agent to the immunoglobulin G-containing dia/ultrafiltrated and optionally stabilized fraction of step (g) resulting in a substantially virus-safe immunoglobulin G-containing solution;

(i) applying the immunoglobulin G-containing solution of step (h) to an anion exchange resin and subsequently to a cation exchange resin;

(j) washing the cation exchange resin of step (i) with a buffer having a pH and ionic strength sufficient to wash out the protein contaminants and the virus-inactivating agent from the resin without causing substantial elution of immunoglobulin G;

(k) eluting immunoglobulin G from the cation exchange resin of step (j) with a substantially non-denaturating buffer having a pH and ionic strength sufficient to cause efficient elution of the immunoglobulin G, thereby recovering an immunoglobulin G-containing eluate; and

(l) subjecting the immunoglobulin G-containing eluate of step (k) to dia/ultrafiltration to lower the ionic strength and concentrate immunoglobulin G of the solution, and adjusting the osmolality by adding a saccharide."

Dependent claims 2 to 11 refer to preferred embodiments of the process of claim 1 and are identical to claims 2 to 11 as granted.

VI. The following documents are referred to in this decision:

(1) EP 0 447 585

(3) US 5 177 194

(4) US 5 593 675

(5) DE 3 430 320

(7) WO94/29 334

(8) "An improved chromatography method for production of IgG from human plasma", Andersson I., et al, XXIII Congress of the International Society of

Blood Transfusion, Amsterdam, The Netherlands, 2 to 8 July 1994; pages 1 to 4

(9) Biotechnology of Blood Proteins, vol.227, 1993, pages 207 to 212

(13) EP 1 268 551

(30) US 4 849 508

(31) Preparative Biochemistry, vol.14, no.1, 1984, pages 1 to 17

VII. The submissions made by Appellant I, as far as they are relevant to the present decision, may be summarised as follows:

The main request consisted of claims 1 to 11 as granted with claims 12 to 22 as granted being deleted. This request, which was a straightforward attempt of the Patentee to deal with critical issues, did not raise any new point not known from the beginning of the appeal procedure. It should therefore be admitted into the proceedings.

The provision of a new process for purifying IgG from plasma was not an easy task due to the high complexity of the starting material and the fragility of the immunoglobulins, which were the reasons that the outcome of any purification step was unpredictable.

None of the various prior art documents cited by Appellant II contained any hint to provide a purification process comprising the working steps

disclosed in claim 1. When starting from the disclosure in document (8), which could be considered to represent the closest prior art, but which resulted in the provision of a non-satisfactory end product, the skilled person was given no hint, neither in document (8) itself nor in any other prior art document on file, to amend the described purification process and to arrive at the process of claim 1 in an obvious way.

VIII. The submissions made by Appellant II, as far as they are relevant to the present decision, may be summarised as follows:

Appellant I's main request was filed only at the oral proceedings. There was plenty of time for filing this request at an earlier date. The necessity to file this request was foreseeable, at the latest after the Board had communicated its preliminary opinion in a communication half a year before the oral proceedings. Therefore the request was late filed and should not be admitted into the procedure.

Contrary to Appellant I's assertion, IgG was not a fragile but a rather robust molecule. The outcome of purification steps, like ion exchange chromatography, which per se were well known in the art, was therefore far from being unpredictable. The skilled person trying to provide a purification process for the production of IgG preparations for intravenous administration would have been aware of the processes disclosed in documents (1), (3) to (5) and (7) to (9). When staring from the disclosure in document (8) he/she would have chosen to add a further anion chromatographic step and would have

arrived at the subject-matter of claim 1 in an obvious way.

Reasons for the Decision

Admissibility of the main request

1. Appellant I's main request consists of claims 1 to 11 as granted. Claims 12 to 22 as granted have been deleted. The request was been filed in the afternoon of the oral proceedings held on 29 September 2010 before the Board.

2. Appellant II argued that this request could have been filed at a much earlier date, at the latest after the Board had communicated its preliminary opinion in a communication half a year before the oral proceedings. Therefore the request should not be admitted into the proceedings.

3. The statement of the grounds of appeal and, in cases where there is more than one party, the reply to other parties' submissions shall contain a party's complete case (Article 12(2) of the Rules of Procedure of the Boards of Appeal (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. The discretion shall be 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 (Article 13(1) RPBA).

4. Thus, among other matters, the decision to admit a new request into the proceedings should be governed by a general interest in the appeal proceedings being conducted in an effective manner, i.e. dealing with as many of the issues raised by the parties as possible, while still being brought to a close within a reasonable time (see decisions T 633/97 of 19 July 2000, point 2 and
T 1074/06 of 9 August 2007, point 11).

5. The main request filed by Appellant I at oral proceedings is distinguished from the main request filed with the grounds for appeal, claims 1 to 22 as granted, only in so far as claims 12 to 22 have been deleted. This amendment does not raise any additional technical or legal issue that neither the Board nor Appellant II could have expected to deal with.

Therefore, in order to conduct the appeal proceedings in an effective manner, the Board exercises its discretion and admits Appellant I's main request into the proceedings.

Novelty and Sufficiency of disclosure - Article 54 and 83 EPC

6. During the entire appeal procedure Appellant II has not put forward any objection under Articles 54 and 83 EPC with regard to the subject-matter of claims 1 to 11 of the main request. The Board also has none.

Inventive step - Article 56 EPC

7. Claim 1 refers to a process for purifying IgG comprising steps (a) to (l) (see section V above).

Each of documents (1), (3) to (5) and (7) to (9) discloses a method for the purification of IgG preparations. The processes disclosed in these prior art documents make use of well known protein purification methods such as, amongst various others, ion exchange chromatography. However, each purifying procedure referred to in these prior art documents differs from that of claim 1 with regard to the nature and/or number and/or sequence of the specific process steps.

8. In accordance with the problem and solution approach, the Boards of Appeal have developed certain criteria for identifying the closest prior art constituting the starting point for the assessment of inventive step.

The Boards have repeatedly pointed out that the closest prior art is normally represented by a document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications.

Where several cited documents all belong to the same technical field as the claimed invention, the closest prior art is that which on the filing date would most easily have enabled the skilled person to make the

invention (see Case Law of the Boards of Appeal of the EPO, 6th Edition, 2010, I.D.3.1 and I.D.3.4).

9. The Board, having carefully studied the different purification processes disclosed in the cited prior art documents, comes to the conclusion that, in application of the criteria developed by the Boards of Appeal, document (8) represents the closest state of the art.

The purification procedure of claim 1 is distinguished from the procedure disclosed in the diagram on page 2 of document (8) by the following features:

– the same buffer, having a pH below 6.0, is used to load a first anion exchange resin and a first cation exchange resin in step (d), and

– a second anion exchange resin is employed before the second cation exchange resin in step (i).

The Opposition Division also considered document (8) to represent the closest state of the art (see point 2.1.3 of the decision under appeal). Appellant I (see its letter of 26 August 2008, page 6) and Appellant II (see its letter of 26 February 2009, paragraph bridging pages 6 and 7) share this opinion.

10. It is known from post-published document (13) (see paragraph [0007]) that the product obtained by the purification process of document (8) does not fulfil the FDA and EU requirements for intravenous drugs.

The problem underlying the patent in suit is seen in the provision of an improved process for purifying IgG for intravenous administration.

11. Considering the high purity of the product obtained (example 2) and the results from clinical trials (example 3) the Board is satisfied that the technical problem has been solved by the subject-matter of claims 1 to 11.

12. Appellant II argued that a skilled person trying to improve the process of document (8) would certainly consider to add a further chromatography step, and in detail an anion chromatography. It referred to the disclosure in document (31) which on page 9, second paragraph describes the positive effects of anion chromatography on purity and stability of IgG preparations.

13. The Board has no doubt that anion chromatography belongs to the methods which are well known in the art to be useful for the purification of proteins and especially of IgG preparations. However, claim 1 does not generally refer to chromatographic purification process but to a process comprising twelve defined working steps to be carried out in a given sequence. Two times within this sequence, namely in steps (d) and (i) the IgG containing solution is applied to an anion exchange resin and subsequently to a cation exchange resin.

Neither the closest state of the art, document (8), nor document (31) or any other document on file contain any hint that would encourage the skilled person to amend

the teaching in document (8) and to arrive at the process according to claim 1 in an obvious way.

14. Appellant II furthermore argued that the individual process steps of claim 1 were per se known to a skilled person working in the field of protein purification and their effect on the treated materials was foreseeable. It referred in this respect to the disclosures in documents (1), (3) to (5) and (7) to (9). Consequently, the provision of a method merely consisting of a juxtaposition of known working steps, which produced a pure end-product, which was by no way surprising, lay within the normal abilities of a skilled person and did not require any inventive activity. This was all the more so as IgG, contrary to argument presented by Appellant I, was not an extremely fragile but rather a robust molecule, as could be seen from document (30), which disclosed in column 11, lines 22 to 30, that IgG preparations were able to tolerate very harsh conditions.

15. The passage in document (30) relied on by Appellant II refers to the influence of pH on the formation of IgG aggregates. It is shown that within a wide range of acidic pH values (4.0 to 5.5) "acceptable aggregate concentration (<5%) were achieved".

This disclosure does not convince the Board that IgG is a molecule which can be purified with a foreseeable result by known protein purification steps in whatever sequence they are used.

For instance the effects caused by the presence of varying amounts of different dominant contaminants

which have to be removed at an early stage, the competition between higher charged proteins and IgG for the binding sites of ion exchange resins and the presence of lipoproteins, are hard to predict and cannot be generally foreseen. Therefore, the effect caused by the addition of a specific purification step (here an additional anion chromatography) at a specific position of a known IgG purification protocol is not predictable.

16. The purification process according to claim 1 is therefore not derivable in an obvious way from the disclosure in document (8), either if taken alone or in any combination with another prior art document on file.

The subject-matter of claims 1 to 11 meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of claims 1 to 11 of the main request filed at the oral proceedings on 29 September 2010 and a description to be adapted thereto.

The Registrar | The Chairman

C. Eickhoff | C. Rennie-Smith