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Datasheet for the decision of 12 June 2012

Case Number: T 1850/09 - 3.3.10

Application Number: 01110038.5

Publication Number: 1161958

IPC: A61L 2/02, A61K 39/395

Language of the proceedings: EN

Title of invention:
A method for the inactivation of viruses

Patentee:
Omrix Biopharmaceuticals Ltd.

Opponent:
Octapharma AG

Headword:
Method for the inactivation of viruses/OMRIX

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (yes)"

Decisions cited:
-

Catchword:
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Case Number: T 1850/09 - 3.3.10

D E C I S I O N
of the Technical Board of Appeal 3.3.10
of 12 June 2012

Appellant: (Opponent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 10 July 2009 rejecting the opposition filed against European patent No. 1161958 pursuant to Article 101(2) EPC.

Composition of the Board:

Chairman: P. Gryczka
Members: J.-C. Schmid
D. S. Rogers

Summary of Facts and Submissions

I. The Appellant (Opponent) lodged an appeal against the decision of the Opposition Division rejecting the opposition against European patent No. 1 161 958 pursuant to Article 101(2) EPC, independent claim 1 reading as follows:

"1. A method for the inactivation of viruses present in a biological liquid preparation comprising the steps of:

(a) treating the biological liquid preparation with a solvent-detergent combination, at concentration and under conditions which are sufficient to inactivate lipid-coated viruses;
(b) removing solvent-detergent reagents from the liquid preparation by passing the liquid preparation obtained in (a) on a chromatographic packing composed of silica beads which pore volume is filled with three-dimensional cross-linked hydrophobic acrylic polymer; and
(c) passing the liquid product of step (b) through a filter having a pore size from about 15 nm to about 70 nm."

II. The Appellant's notice of opposition requested revocation of the patent in suit in its entirety on the ground of lack of inventive step (Article 100(a) EPC), based *inter alia* on the following documents:

(1) Stucki M. et al.: "Characterisation of a chromatographically produced anti-D immunoglobulin product", Journal of Chromatography B., vol. 700, (1997), pages 241-248,

(2) Burnouf-Radosevich M. et al.: "Nanofiltration, a New Specific Virus Elimination Method Applied to High-Purity Factor IX and Factor XI Concentrates", Vox Sanguinis, vol. 67, no. 2, (1994), pages 132-138,

(3) Guerrier L. et al.: "Specific sorbent to remove solvent-detergent mixtures from virus-inactivated biological fluids", Journal of Chromatography B., vol. 664, (1995), pages 119-125, and

(4) US-A-5 486 293.

III. According to the Opposition Division each of the documents (1) to (3) could be used as the closest prior art. Documents (1) and (2) were similar in respect of the fundamental principle used for removing the solvent/detergent reagent. The protein of interest present in the biological liquid was bound to the chromatographic material and the solvent/detergent was removed with the flow-through. The protein was then eluted and subjected to nanofiltration. Starting from document (1) or (2) as the closest prior art to the invention, the technical problem underlying the patent-in-suit was the provision of an alternative method of virus inactivation. The skilled person had no reason or motivation to modify the procedure of document (1) or (2) by substituting the chromatographic process steps intended for concentrating the proteins of interest and increasing safety, with different chromatographic steps providing no concentration of the proteins or increase in safety. The Opposition Division therefore held that

the claims as granted satisfied the requirement of inventive step (Article 56 EPC).

IV. In the statement of the grounds for appeal, the Appellant submitted that the subject-matter of claim 1 lacked an inventive step starting either from document (1), (2) or (3). Document (1) described a process for preparing an anti-D immunoglobulin product wherein enveloped and non-enveloped viruses were inactivated by a solvent/detergent treatment, removal of the solvent and detergent and nanofiltration. The solvent detergent was removed by a cation-exchange chromatography. Document (2) also disclosed a method for the elimination of viruses comprising a solvent/detergent treatment, removal of the solvent/detergent reagent by an anion exchange chromatography, and a nanofiltration step. The method of claim 1 of the patent-in-suit differed from the method of documents (1) or (2) only by a different chromatographic material to remove the solvent and detergent used in the virus inactivation step. Document (3) related to the removal of solvent detergent in plasma products and reported the benefits of a new chromatographic packing, namely SDRHyperD as a very powerful and attractive sorbent to compete with existing classical methods. It was therefore obvious for the skilled man to replace the weak cation-exchange chromatography by the chromatographic package suggested in document (3), thus arriving at the claimed subject-matter without the exercise of inventive skill. A chromatographic material to remove solvent and detergent from biological fluids and comprising a cross-linked hydrophobic polymer network was also known from document (4).

The Appellant therefore concluded that the claimed subject-matter was the obvious combination of documents (1) or (2) with documents (3) or (4).

V. With the reply to the statement of the grounds for appeal dated 12 April 2010, the Respondent filed auxiliary requests 1 to 4 and in support of its argumentation, it furthermore relied *inter alia* on document:

(15) Yiantsios et al.: "The effect of colloid stability on membrane fouling", Desalination, vol. 118, (1998), pages 143-152.

The Respondent's arguments can be summarized as follows.

Document (1) was the closest prior art to the invention. The essential difference between the teaching of document (1) and the claimed invention was the principle by which the solvent/detergent reagents were removed from the biological liquid preparation. The technical problem underlying the invention was the provision of an alternative method for the inactivation of viruses in a liquid biological preparation.

The skilled person would not have considered to apply the method to remove the solvent/detergent reagent disclosed in document (3) in the process according to document (1) comprising a nanofiltration step to follow. In fact, in document (3) a chromatographic packing made of silica beads in which the pore volume was filled with a three dimensional cross-linked hydrophobic acrylic polymer named SDR-HyperD was investigated for its ability to remove a mixture of the solvent tri-n-

butylphosphate (TBP) and the detergent Triton X-100 from virus-inactivated biological samples. It was apparent from table 1 of document (3) that this chromatographic package only achieved removals of 99.92% and 95.2% of TBP and Triton X-100 respectively in bovine serum. It was indicated in this document with reference to table 2 that a larger amount of sorbent or a smaller load enhanced the removal efficiency of the chromatographic system to a quantitative level. However this table also revealed a removal of only 95.5% Triton X-100. It was known that protein aggregates were dispersed by detergents in biological samples, thus forming colloids. However, according to document (15), colloids were known to cause the clogging of membranes during nanofiltration. This phenomenon of clogging was shown in tables 1 and 2 of the patent-in-suit. Thus, the skilled person would have expected that the chromatographic method for removing the solvent/detergent reagent disclosed in document (3) would not be compatible with a subsequent nanofiltration step and hence would not have contemplated modifying the purification process for removing solvent and detergent of document (1) by replacing the there disclosed method by that described in document (3).

Taking into account all technical aspects of the purification scheme described in document (1), the skilled person would not have combined document (1) with document (3), since there was no reasonable expectation that the flow-through of the SDR-HyperD column would be suitable for the following nano-filtration step. Thus the claimed process involved an inventive step.

VI. With the letter dated 5 June 2012, the Appellant announced that it would not attend the oral proceedings before the Board scheduled for 12 June 2012. It did not take position either on the Respondent's fresh auxiliary requests 1 to 4, or on the Respondent's written arguments.

VII. The Appellant requested in writing that the decision under appeal be set aside and that the patent be revoked.

The Respondent requested that the appeal be dismissed and the patent be maintained as granted or, subsidiarily, that the patent be maintained on the basis of one of the auxiliary request 1 to 4 filed with the letter dated 12 April 2010.

VIII. At the end of the oral proceedings held on 12 June 2012 in the absence of the Appellant the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

Main request (patent as granted)

The sole objection raised by the Appellant against the patent-in-suit is lack of inventive step.

2. *Inventive step*

2.1 *Closest prior art*

The patent-in-suit is directed to a method for the inactivation of viruses present in a biological liquid preparation comprising the steps of

(a) treating the biological liquid preparation with a solvent/detergent composition;

(b) passing the liquid preparation obtained in (a) on a chromatographic packing composed of silica beads which pore volume is filled with three-dimensional cross-linked hydrophobic acrylic polymer; and

(c) passing the liquid product of step (b) through a nanofilter .

Document (1) discloses a method for the production of a liquid-stable anti-D immunoglobulin preparation including the steps of inactivating lipid-coated viruses by a solvent/detergent treatment, chromatographic purification and nanofiltration to remove non-enveloped viruses.

The Board considers, in agreement with the Respondent, that document (1) represents the closest state of the art, and, hence the correct starting point in the assessment of inventive step. Document (2) has the same relevant teaching as document (1) and therefore could equally be taken as the closest prior art to the invention.

The Opposition Division and the Appellant had also considered document (3) as a possible starting point for the assessment of inventive step. However, this

document fails to disclose the step of nanofiltration to remove non-enveloped viruses, with the consequence that document (3) represents prior art which is further away from the patent-in-suit than document (1) or document (2).

2.2 *Technical problem underlying the patent-in-suit*

In view of this state of the art the objective problem underlying the patent in suit, as submitted by the Respondent during the appeal proceedings, consists in providing an alternative method for the inactivation of viruses in liquid biological preparations.

2.3 *Solution*

The patent in suit proposes as the solution to this problem the process according to claim 1 which is characterized by the fact that the removal of the solvent-detergent reagent from the liquid preparation is carried out by passing the liquid preparation obtained in step (a) on a chromatographic packing composed of silica beads which pore volume is filled with three-dimensional cross-linked hydrophobic acrylic polymer.

2.4 *Success*

The Appellant never disputed that the claimed method did not solve the problem of providing an alternative to the known method for the inactivation of viruses. The Board, in view of tables 2, 5 and 8 of the patent-in-suit, is satisfied that this problem has been successfully solved.

2.5 *Obviousness*

It remains to decide whether or not the proposed solution to that objective problem underlying the patent in suit is obvious in the light of the state of the art, in other words, whether it was obvious to replace the ion exchange chromatography present in the method of document (1) by a chromatography on a packing composed of silica beads which pore volume is filled with three-dimensional cross-linked hydrophobic acrylic polymer.

Starting from document (1) or (2), the Appellant only addressed documents (3) and (4) in order to object to obviousness. According to the Appellant it was obvious for the skilled man to replace the weak cation-exchange chromatography disclosed in document (1) by the chromatographic package described in documents (3) or (4), thus arriving at the claimed subject-matter without the exercise of inventive skill.

The Appellant's arguments imply, as a prerequisite, that the skilled person would have taken documents (3) or (4) into consideration in order to solve the problem underlying the invention. However, in the method according to document (1), as well as in the claimed method, the step of purification of the biological sample is directly followed by the step of passing the liquid product of the chromatography (step b) through a filter having a pore size from about 15 nm to about 70 nm, which requires a colloids free liquid to avoid clogging of the filter (see e.g. figures 3 to 9 of document (15)). However, colloids in biological samples

comprising proteins are *inter alia* generated by the formation of micelles due to the presence of detergent in the sample. This explains why the removal of the solvent/detergent reagent is carried out in document (1) by binding the target proteins to the column matrix and by washing away the solvents and detergents in the flow-through, achieving a quantitative removal of the solvent/detergent reagent, i.e. there remains less than 1 µg/ml detergent (Triton X-100) in the biological sample (see the paragraph bridging page 244 and 245).

Documents (3) and (4) disclose a method to remove the solvent/detergent reagent by passing the biological sample through a chromatographic packing composed of silica beads which pore volume is filled with three-dimensional cross-linked hydrophobic acrylic polymer (SDR-HyperD chromatographic packing). This chromatographic separation works on a fundamentally different principle than that disclosed in the closest prior art, since the solvent/detergent reagent is retained on the chromatographic material and the target protein eluates, with the consequence that this method does not remove quantitatively the solvent/detergent reagent added in the biological sample during the first step of inactivation of the viruses. As a matter of fact, only about 95.2% of the detergent (Triton X-100) is removed from a bovine serum by the method disclosed in document (3) (see table 1 and 2) and at best 96.58% (Triton X-100) is removed from the human plasma by the method disclosed in document (4) (see examples 9 and 10). Accordingly, taking account of the requirement of purity imposed by the nanofiltration step (c) to follow, the skilled person would not have considered the chromatographic material disclosed in document (3) or

(4) as a suitable replacement for the ion exchange chromatography used in the methods disclosed in document (1) or (2)).

Hence, the Board comes to the conclusion that the subject-matter of claim 1 involves an inventive step.

Auxiliary requests 1 to 4

3. Since the main request is considered to be allowable, it is not necessary to decide on the lower-ranking auxiliary requests 1 to 4.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar The Chairman

K. Boelicke P. Gryczka