BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

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File Number: T 300/90

Application No.: 83 301 740.3

Publication No.: 0 091 258

Title of invention: Method for stabilizing tumor necrosis factor and a stable aqueous solution or powder containing said factor

Classification: A61K 35/12

D E C I S I O N
of 16 April 1991

Proprietor of the patent: Asahi Kasei Kogyo Kabushiki Kaisha

Opponent: BASF AG

Headword: Stabilizing TNF/ASAHI

EPC Article 56

Keyword: "Inventive step of main request (no) - obvious solution"
"Patent maintained on the basis of auxiliary request"

Headnote

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number : T 300/90 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 16 April 1991

Appellant : (Opponent)
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Respondent : (Proprietor of the patent)
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Decision under appeal :
Decision of Opposition Division of the European Patent Office dated 20 February 1990 rejecting the opposition filed against European patent No. 91 258 pursuant to Article 102(2) EPC.

Composition of the Board :

Chairman : A. Nuss
Members : U. Kinkeldey
C. Holtz

Summary of Facts and Submissions

I. European patent No. 91 258 was granted with 10 claims on European patent application No. 83 301 740.3.

Claim 1 reads as follows:

"1. A method for stabilising Tumour Necrosis Factor, which comprises adding to an aqueous solution or powder containing Tumour Necrosis Factor an effective amount of at least one stabilising agent selected from albumin, gelatin, globulin, protamine and a salt of protamine."

II. The Appellants (Opponents) filed a notice of opposition against the European patent requesting revocation of the patent as far as a stabilising agent albumin was concerned on the grounds that the claimed process was lacking novelty and inventive step (Article 100(a) EPC) in the light of eleven prior art documents, each of which disclosed the use of albumin as a stabilising agent for a variety of different substances.

III. The Opposition Division rejected the opposition and maintained the patent as granted.

The reasons for maintaining the patent were in essence the following:

(i) The eleven documents submitted by the Appellants related to the successful use of human serum albumin (HSA) inter alia for the stabilisation of certain proteins. The stabilisation of the Tumour Necrosis Factor (TNF) was not disclosed in any of these eleven documents. The addition of an effective amount of albumin to an aqueous solution or powder containing TNF was, therefore, new.

(ii) The problem to be solved in the patent in suit was the stabilisation of the protein Tumour Necrosis Factor (TNF).

None of the said eleven documents pertained to this problem. Any of these documents, to be convincing per se, would have to show that it was obvious from its teaching that albumin would stabilise TNF. This was not the case and it was not shown that there was an obvious structural or any other link between TNF and any protein referred to in one of the said eleven documents. There seemed to be important differences between TNF and the proteins referred to in one of the eleven documents.

Thus it appeared that the problem had not been posed by the prior art and that the solution had not been known, in that the man skilled in the art would not have been able to say, with an acceptable certainty, that it would have solved the problem, even if it had been shown that albumin was an almost universal stabiliser. The fact that it was now possible to stabilise TNF in such a manner and to such a suprising extent that it could now be submitted to all the preparation steps it needed, were valuable results which should decisively facilitate the industrial development of TNF. This result could not have been foreseen from the prior art, at least in its full extent and the means leading to it deserved, therefore, protection by a patent. The subject-matter of Claim 1 was, therefore, said to meet the requirement of Article 56 EPC.

IV. The Appellants filed a notice of appeal against this decision and submitted a statement of grounds.

Oral proceedings took place on 6 April 1991.

During the appeal proceedings the Appellants argued essentially as follows:

(i) It was state of the art to stabilise proteins with HSA. This view was supported by the eleven prior art documents submitted during the procedure before the Opposition Division. There is further evidence for this fact in document (12) (US-A-3 637 640). The use of albumin for that purpose was thus a standard method. Therefore, this use was not even new.

(ii) As far as an inventive step was concerned, it was self-evident that a skilled person, confronted with the problem to stabilise a protein in a first step would certainly work within the standard method being common general knowledge and thus use albumin which already proved to be successful in stabilising proteins in many known cases. The list of documents showing the use of albumin for stabilising proteins could be easily extended. It was thus the evident and trivial step to try albumin in solving the problem of stabilising TNF. The fact that albumin might not have worked in the case of the protein human tissue plasminogen activator as described in document (14) (Collen, D. et al., Thromb. Haemostas. (Stuttgart), 48, 294-296 (1982) firstly does not contravene this view; and secondly the patentees themselves filed in 1985 a patent application in Japan claiming the use of HSA

to stabilise plasminogen activators whereby it was documented that there are at least contradicting opinions about the stabilisation of plasminogen activators by HSA.

An inventive step, as required by Article 56 EPC, thus, was not in existence as far as HSA as stabilising agent was concerned.

The Appellants declared at oral proceedings that the above objections were only raised in respect of HSA as stabilising agent.

V. In response to the statement of grounds, the Respondents maintained the claims as granted as a main request and filed a new set of claims no longer containing albumin as stabilising agent (auxiliary request).

During the appeal proceedings the Respondents argued to the main request which contained albumin as a stabilising agent in the main claim as follows:

(i) Although eleven documents taught that HSA might be useful to stabilise certain proteins, there was no indication that it might be used to stabilise TNF.

Despite the fact that in document (12) it was stated that it was well known that highly purified proteins are best stabilised with small amounts of other proteins or nucleoproteins, each protein actually required a different type of stabiliser. A stabiliser which was highly effective with one protein often was completely ineffective with others.

In the light of the discussed prior art documents it was apparent that the subject-matter of the claims of the patent in suit were novel.

(ii) Inventive step might be discussed in terms of the problem to be solved at the priority date of the patent in suit which was the stabilisation of TNF. Although it might have been shown in a document that HSA could be used to stabilise certain proteins, there was no indication that HSA would successfully stabilise TNF. Consequently, there was no suggestion that HSA could stabilise TNF. This substance has neither origins nor activity that were similar to the proteins of any of the citations.

Furthermore, it was known from document (14) that HSA did not stabilise every protein, for example it did not stabilise human tissue-type plasminogen activator.

The combined teaching of the prior art was that proteins might have been suitable as stabilisers for a biologically active substance such as TNF. However, this resulted in no more than an invitation to perform experiments which were not at all likely to succeed.

The main claim of the auxiliary request excluded the only contested stabiliser albumin from the list of stabilising agents and reads as follows:

"1. A method for stabilising Tumour Necrosis Factor which comprises adding to an aqueous solution or powder containing Tumour Necrosis Factor an effective amount of

at least one stabilising agent selected from a gelatin, a globulin, a protamine and a salt of protamine."

VI. The Appellants request that the decision under appeal be set aside and that the European patent No. 91 258 be revoked.

The Respondents request that the appeal be dismissed and the patent be maintained (main request); alternatively that the patent be maintained on the basis of Claims 1 to 9 as filed on 29 November 1990 (auxiliary request).

Reasons for the Decision

1. The appeal is admissible.

Main Request

2. **Novelty**

The Appellants contested novelty of the use of albumin to stabilise proteins, but admitted that before the date of priority of the patent in suit it was not known to stabilise TNF with albumin.

Since this in fact is the case and none of the prior art documents described the stabilisation of TNF with albumin, Claim 1 is novel.

3. **Closest prior art and the problem**

3.1 After consideration of the prior art documents cited during the proceedings, the Board considers, in agreement with the patent in suit, that prior art to be the closest which described the detection, purification and chemical

characterisation of TNF, represented for example by Br.J. Cancer, 42, 416-422 (1980). This prior art is discussed in the description of the patent in suit on page 2, lines 7 to 26. On lines 40 and 41 of the same page of the patent in suit it is stated that the present inventors had found that the activity of highly purified TNF markedly dropped on storing, freezing, thawing and lyophilizing it. This disadvantage, objectively discovered only by the patentees, arises from the necessity to highly purify the crude TNF induced in a mammal or tissue culture system. This necessity thus created a new problem.

3.2 The mentioned prior art was not submitted before the Opposition Division or during appeal proceedings and thus it might be a question whether or not this prior art can be considered by the Board in these proceedings. In the present case the Board is of the opinion that for the examination of an inventive step it is necessary to objectively examine the complete prior art on file for equally objectively finding out the problem which was to be solved by the claimed subject-matter. The Board follows with this view the decision T 536/88 "Staubdichte Faltschachtel" of 14 January 1991 (to be published) stating that documents cited and discussed in the patent in suit are in principal not automatically subject-matter of an opposition appeal proceedings. If, however, as concluded in that decision, a prior art document in a European patent is discussed as the closest and most essential prior art, which forms the basis for the technical problem mentioned in the description of the patent in suit, this prior art document is subject-matter in an opposition appeal proceedings, even if it was not expressly mentioned within the time limit for the opposition.

3.3 In view of the above, the problem underlying the patent in suit can thus be seen in the stabilisation of highly purified TNF, as already set out in the impugned decision and not contested by the parties either before the Opposition Division or during appeal proceedings.

4. **The solution**

The proposed solution according to Claim 1 as granted comprises the addition to an aqueous solution or powder containing TNF an effective amount of at least one stabilising agent selected from an albumin, a gelatin, a globulin, a protamine and a salt of a protamine.

The indicated problem has been solved by the claimed proposal. This becomes in particular apparent from Tables 1 and 2 of the patent in suit where the stabilising effect of **inter alia** HSA is shown under various conditions and by a comparison with the results of experiments carried out without the stabilising agents. It is evident that HSA is effective in stabilising TNF. This was not contested by the Appellants.

5. **Inventive step** (Article 56 EPC)

5.1 The Board notes that the problem to stabilise TNF arose only when it was possible to purify the crude TNF to a high degree. Only then was it recognised that the activity of highly purified TNF markedly dropped on storing, freezing, thawing and lyophilizing it. Since none of the prior art documents mentioned in the description which describe the isolation, purification and characterisation of TNF discovered a markable decrease of activity of the TNF there was no need for stabilisation of TNF prior to the recognition of the difficulty to stabilise highly purified TNF. However, once a technical level is reached

which allows TNF to be purifyied to a high degree, the skilled person is challenged with the problem to stabilise TNF.

5.2 From the prior art mentioned in the description of the patent in suit and referred to above it was known that TNF is a protein. Consequently the skilled person, when trying to solve the problem of stabilising a protein, would certainly turn to this technical field and would, therefore, arrive at the prior art represented by the documents submitted by the Appellants with their opposition.

5.3 An analysis of these documents has been done by the Opposition Division in its impugned decision. From this analysis it is apparent that HSA had been used for the stabilisation of a number of different proteins like blood factor IX, acetylcholinesterase and orgotein.

5.4 Even if document (14), which relates to the purification of human tissue-type plasminogen activator describes on page 295, left column that the addition of 0.5% HSA did not improve the stability of the said protein, it is nevertheless stated in the following paragraph of the mentioned document that "omission of the saturation with albumin led to loss of all activity". Therefore, the Board is not convinced that HSA has no stabilising effect on this specific protein.

5.5 In document (12), column 1, lines 37 to 39 it is expressly stated that it was well-known that highly purified proteins are best stabilised with small amounts of other proteins or nucleoproteins, such as albumin and DNA. This remark is a statement to well known background prior art in this US-patent, issued in 1972. This shows that already since that time albumin represents the most common

stabilising agent to be used when stabilisation of a protein is required.

5.6 The fact that document (14) may show that albumin is not suitable to stabilise each and every protein does not establish a technical prejudice against the use of albumin in the case of stabilising the protein TNF. The gist of all prior art documents disclosing the ability of albumin to stabilise proteins is not that each and every protein can be stabilised by this substance but rather that normally albumin was indeed suitable to stabilise proteins. This is thus what the man skilled in the art will normally expect to happen. However, even if one interprets the disclosure of document (14) such that albumin might not have been successful in stabilising the human tissue-type plasminogen activator - which, in the Board's opinion, has not been clearly established - such an interpretation cannot form the basis for a well accepted technical prejudice in the art in the absence of further corroborating evidence (cf. T 19/81, OJ EPO 1982, 51). A prejudice of this kind could possibly be accepted if for example the prior art had already established that the protein TNF could not be stabilised by albumin and that in spite of this teaching one was successful in stabilising TNF with albumin. The facts here are different. Rather, in the present case, where it is common general knowledge that a certain substance (HSA) is normally suitable to stabilise proteins, the skilled person will not be prevented from trying this all-round stabilising agent with TNF. The man skilled in the art would, therefore, easily have found out that this known stabilising agent could successfully be used in the case of TNF, like with many other proteins.

5.7 Since it was, therefore, the evident, obvious and trivial step to solve the problem of stabilising highly purified

TNF by the use of a most common stabilising agent, which is albumin, this alternative of Claim 1 of the main request lacks an inventive step.

The main request has thus to be rejected.

Auxiliary Request

6. **Amendments (Article 123(2) and (3) EPC)**

6.1 From the set of claims according to the auxiliary request albumin as a stabilising agent for TNF is excluded.

This is a limitation of the claims compared to the main request which does not give rise to any objections with regard to the above Article.

6.2 From the beginning of the opposition proceedings the Appellants exclusively requested revocation of the patent in suit to the extent that albumin is used for stabilising TNF. The extent of the opposition was thus limited to one specific embodiment of a claim. The Appellants clearly declared that they do not object to the claims of the auxiliary request, which exclude albumin as a stabilising agent for TNF. In these circumstances, the Board sees no reason to further investigate the auxiliary request, under Article 114 EPC.

Thus, the patent in suit is maintained on the basis of the claims according to the auxiliary request.

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 on the basis of Claims 1 to 9 as filed on 29 November 1990, and a description to be adapted accordingly.

The Registrar: The Chairman.

P. Martorana A. Nuss

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