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D E C I S I O N
of 10 January 2002

Case Number: T 0235/97 - 3.3.2

Application Number: 91902955.3

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Title of invention:
Improved cyclodextrin based erythropoietin formulation

Patentee:
JANSSEN PHARMACEUTICA N.V.

Opponent:
Roche Diagnostics GmbH

Headword:
Aqueous solution of erythropoietin/JANSSEN

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main and first and second auxiliary request - inventive step - no - obvious to try a known stabilizer for another protein"

Decisions cited:
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Catchword:
-

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Case Number: T 0235/97 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 10 January 2002

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 23 December 1996 revoking European patent No. 0 513 072 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: U. Oswald
S. U. Hoffmann

Summary of Facts and Submissions

I. European patent No. 513 072, based on the international application No. PCT/EP91/00173 was granted on the basis of 13 claims.

Claim 1 reads as follows:

"A pharmaceutical composition comprising an aqueous solution of erythropoietin and β- or γ-cyclodextrin wherein one or more of the hydroxy moieties of the anhydroglucose units of the cyclodextrin have been replaced by a radical of formula

$$-O-[Alk-O-]_n-H \qquad (I),$$

wherein Alk represents a straight or branched chain C_{1-6}alkanediyl radical wherein optionally one hydrogen atom of said radical Alk may be replaced by a hydroxy group; and "n" ranges from 1 to 5, and wherein the average molar substitution (M.S.) is in the range of 0.3 to 0.8."

II. Opposition was filed against the granted patent by the Respondent (Opponent) alleging lack of novelty and lack of inventive step under Article 100(a) EPC.

Of the documents cited during the proceedings the following remain relevant to the present decision:

(7) Brewster E.M. et al., Journal of Parenteral Science and Technology, Vol. 43, No. 5, (1989), pages 231 to 240.

(9) US-A 4 824 938.

(10) EP-A 0 178 576.

(12) Journal of Parenteral Science and Technology, Vol. 42, Technical Report No. 10 Supplement 1988, pages 4 to 26.

(13) EP-A 178 665.

III. In its decision dated 23 December 1996 the Opposition Division revoked the patent under Article 102(1) EPC for lack of inventive step.

In the light of the disclosure of the prior art, particularly of document (7) the Opposition Division concluded that the skilled person would have expected hydroxyalkylated β- or γ- cyclodextrin to act as a stabilizer for erythropoietin (EPO) in aqueous solutions. Furthermore, the Opposition Division considered that the effect of preventing adsorption on container walls could only be considered as a bonus effect when solving the essential part of the technical problem, which was the stabilisation of EPO in aqueous solutions in general.

Since the use of hydroxyalkylated cyclodextrin led in an obvious way to improved aqueous solutions of EPO, the subject matter of the main and auxiliary requests did not involve an inventive step.

IV. The Appellant (Proprietor of the patent in suit) lodged an appeal against the said decision and filed a first and second auxiliary request on 30 April 1997 and 7 December 2001 respectively.

V. Oral proceedings took place on 10 January 2002 during which the Appellant filed a new *main request* comprising a claim 1 which differs from claim 1 as granted by the additional feature "*...and wherein the weight-by-weight ratio of cyclodextrin to erythropoietin is 7500:1 to 700:1.*"

Claim 1 of the *first auxiliary request* differs from the main request in that the derivatized cyclodextrin compound is specified as *hydroxypropyl-ß-cyclodextrin* and the *average molar substitution* range is restricted to *0.35 to 0.5*.

Claim 1 of the second auxiliary request differs from the first auxiliary request in that the *weight-by-weight ratio of cyclodextrin to erythropoietin* is restricted to *6000:1 to 1000:1*.

VI. The Appellant took the view that document (10) should be considered as the closest prior art since this document related to aqueous solutions comprising EPO as the active ingredient and disclosed a solution to the problem of adsorption of EPO on the walls of the containers. According to the teaching of document (10) the most effective additive for preventing the adsorption of EPO on the walls was human serum albumin (HSA). However HSA did not provide the long term stability of EPO in the aqueous solution. Accordingly, in the Appellant's view the problem underlying the patent in suit was the provision of aqueous solutions of EPO which were more stable and did not adsorb on the walls.

In order to support inventive step, the Appellant made reference to document (12) as representing common general knowledge in the field of protein stabilisation.

In the light of the disclosure of document (9), the skilled person would have concluded that cyclodextrin was not suitable for the stabilisation of proteins since experimental work with this stabilizer gave only poor results.

Concerning the disclosure of document (7) on which the appealed decision was mainly based, the Appellant held that most of the drugs tested according to the worked examples of this prior art represented small molecules which could not be compared with proteins in terms of stability. Also the proteins reported in document (7) were not comparable with EPO. In particular insulin, which was mentioned in the appealed decision, was not glycosylated like EPO, and consequently showed completely different behaviour in solution. Furthermore, insulin was tested with 2-hydroxypropyl-β-cyclodextrin (2-HPCD) only in order to measure its ability of inhibiting protein aggregation and not in relation to the stabilisation of insulin over time. The Appellant emphasised that document (7) expressly referred to document (12) (document 51 in document (7)), and that the skilled person did not carry out an extrapolation of stabilizer effects for a certain protein when trying to stabilize a different protein.

As regards the disclosure of document (13) a document suggested as closest prior art by the Board, the Appellant held that Example 4 of the patent in suit clearly showed an improvement in the compositions of the patent in suit in comparison with formulations as taught by this prior art. Taking into account the improvement shown in comparison with the most effective stabilizer in document (13), namely HSA, the problem was seen as providing EPO formulations with improved stability over time.

As regards the auxiliary requests the Appellant explained that the parameters defining the subject-matter of these requests came closer to the examples of the patent in suit than those of the main request and thus the claims of these requests more precisely reflected the advantageous effects of the stabilisation of EPO.

VII. The Respondent took the view that the problem underlying the patent in suit was in general the conservation of the biological activity of EPO in aqueous solutions.

Accordingly, document (10) which exclusively related to the adsorption of EPO on the container wall did not represent the closest prior art when considering the problem of the stability of the biological activity of EPO.

Regarding the stability aspect, document (7) came closer to the invention. This document was not restricted to the stabilisation of small molecules and clearly taught the stabilisation of large proteins such as tumour necrosis factor or macrophage colony stimulating factor by using 2-HPCD as an additive.

Although it was accepted that the cyclodextrin compounds as disclosed in document (9) showed poor stabilisation effects, there was no prejudice on the basis of the teaching of this prior art against the use of the cyclodextrin compounds as defined in the patent in suit, since the cyclodextrin compounds of document (9) were not derivatized and thus were not comparable with those of the alleged invention.

Furthermore, the Respondent argued that document (7) expressly mentioned the use of 2-HPCD as a stabilizer and also disclosed the more specific degree of substitution (MS) of 2-HPCD as defined in the auxiliary requests. The range of weight ratios as further restricted in the claims of the auxiliary requests, did not form the basis of an invention but must be considered as the result of a normal optimisation by the skilled person.

VIII. The Appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed during the oral proceedings or auxiliarily on the basis of the first auxiliary request filed on 30 April 1997 or on the basis of the second auxiliary request filed on 7 December 2001.

The Respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. The Board sees no formal objections on the basis of Articles 123(2) and (3) EPC as well as Article 84 EPC to the main, first and second auxiliary requests since the claims of these requests are clearly formulated, adequately supported by the original disclosure and do not extend the protection conferred when compared to the claims as granted.

This was not contested by the Respondent.

3. The Respondent also did not raise objections under Article 54 EPC to the currently claimed subject-matter and, since the Board agrees to the Opposition Division's point of view that at least the claimed range of weight-by-weight ratio of the cyclodextrin derivatives to EPO imparts novelty to the subject-matter of each of the requests there is no need to discuss this matter in detail.

Main request

4. In the course of the oral proceedings the parties discussed documents (7), (10) and (13) as a starting point for the assessment of inventive step.

4.1 The Respondent was of the opinion that document (7) should be taken as the closest prior art since this document specifically refers to the use of hydroxyalkyl-ß-cyclodextrin as stabilizing agent for large proteins. The Board, although recognising the high relevance of this document as to the disclosure of advantageous non-toxicity and the solubility effects of derivatized cyclodextrin in comparison with non-derivatized compounds (see paragraph 4.8 below), does not share this opinion since this document does not disclose an aqueous solution of EPO, the essential part of the pharmaceutical composition of the patent in suit.

4.2 As mentioned in the introductory part of the patent specification on page 1, lines 17 to 27, and accepted by both parties in the course of the oral proceedings, it was known to the person skilled in the art at the priority date of the patent in suit that aqueous solutions of erythropoietin (EPO) show a decrease in bio-activity due, on the one hand, to a chemical and/or structural degradation of EPO which occurs in the solution and, on the other, to a substantial adsorption of EPO on the inner surface of the container or syringe during storage.

4.3 Documents (10) and (13) both relate to the stabilisation of aqueous EPO solutions.

Document (10), suggested as closest prior art by the Appellant, relates specifically only to the problem of the wall adsorption whereas document (13) addresses in general the problem of stabilisation of EPO in aqueous solutions.

Moreover, the specification of the patent in suit on page 1, lines 40 to 46, makes a direct reference to document (13), being relevant prior art, and the worked examples of the patent in suit contain comparative tests using human serum albumin (HSA), one compound of the aqueous stabilizing composition of document (13) (see also page 2, line 26 of the published application).

4.4 In the light of these facts, document (13) is considered as the closest prior art.

In order to formulate stable formulations of EPO, which are recognised to be easily inactivated by environmental factors such as temperature and humidity, document (13) proposes the addition of **one or more stabilizers** selected from the group of polyethylene glycol, protein, sugar, amino acid, inorganic salt organic salt and sulfur-containing reducing agent (see particularly page 1, lines 6 to 30). The stabilised EPO may be formulated in liquid or solid dosage forms (see particularly page 2, lines 1 to 5). Examples 4 to 6 and 11 on pages 7 and 8 of document (13) contain human serum albumin as a protein additive in a composition comprising a combination of stabilizers for EPO.

According to the description of the patent in suit, the use of the stabilizers envisaged in document (13) does not guarantee the long term functional stability of EPO (see page 1, particularly lines 44 to 46).

Thus, the problem underlying the patent in suit can be seen in the provision of improved EPO formulations i.e. formulations with an overall better long term stability in aqueous solution.

4.5 The said problem is solved by the aqueous solution as defined in claim 1 of the main request, in particular by a derivatized cyclodextrin stabilizer wherein one or more of the hydroxy moieties of the anhydroglycose units of cyclodextrin are replaced by a defined radical (formula (I)).

4.6 The test results of worked Examples 4 and 5 on pages 7 to 9 of the patent in suit clearly show that hydroxypropyl-β- or γ-cyclodextrin provide greater stabilisation after 18 or 20 days than HSA. These examples refer to an overall stabilisation effect without making any distinction between the different possible sources of degradation.

More particularly taking into account the comparative experiments referred to in Table 1 and Table 2 of said Examples 4 and 5 of the patent in suit, the Board is thus satisfied that the problem as defined above is plausibly solved.

4.7 The Appellant tried to formulate the technical problem as also including the prevention of adsorption of EPO on the wall.

However, Example 6 on pages 9 and 10 of the patent in suit shows that as regards the effect of prevention of adsorption of EPO on the wall there is no difference between HSA and the cyclodextrin derivatives of the patent in suit (see particularly page 10, Table 3, and lines 31 and 32).

These results were expressly confirmed by the Appellant at the oral proceedings.

As a matter of fact, the alleged effect of prevention of adsorption of EPO on the wall based exclusively on the cyclodextrin derivatives of the patent in suit cannot form part of a separate problem underlying the patent in suit in comparison with the effects achieved by the use of HSA as described in document (13).

Accordingly, in the light of this prior art there is no reason to split up the problem underlying the patent in suit in separate types of stabilizing effects.

4.8 Therefore, the question remains whether the skilled person, in the light of the disclosure of the available prior art, would get an incentive to replace human serum albumin by the specific cyclodextrin derivatives as defined in the patent in suit in order to solve the above stated problem.

4.9 The skilled person faced with the problem as defined above would also take into account prior art relating in general to stabilizers and/or solubilizers for parenteral formulations containing particular proteins and/or peptides.

Document (7) represents such prior art and is of particular relevance since it also relates to the use of modified cyclodextrin as stabilizers and/or solubilizers in parenteral formulations of various drugs, in particular proteins and peptides (see page 231 "Abstract").

This document mentions that chemically modified cyclodextrin such as 2-hydroxypropyl-ß-cyclodextrin (2-HPCD) is a potent complexing agent which may be useful in stabilizing proteins. Furthermore, when compared to

non derivatized cyclodextrin, hydroxyalkyl-cyclodextrin offers the advantage of not being toxic (see page 231 "Introduction"). Different proteins have been tested in order to show an effect not only on their solubility but also on their stability in terms of biological activity. For example, studies performed on IL-2, tumour necrosis factor (TNF) and macrophage colony stimulating factor (M-CSF) showed that these proteins retained 100% of their biological activity in the presence of 2-HPCD. Insulin, which was chosen as a model because of the great need to produce an insulin product which is stable over a long period of time, was also tested (see page 238, left column, last paragraph, up to right column, last paragraph, first sentence).

After a presentation of the results obtained with the different proteins, the authors of document (7) came to the conclusion that "*...2-HPCD demonstrates many of the characteristics desirable in a parenteral excipient. It is non-toxic, it can improve the solubility and stability of many drugs and it is easily available via derivatization of beta-cyclodextrin. Complexes formed between drugs and this starch appear to rapidly dissociate after i.v. administration and as a result there is no mitigation of the biopotency of drugs delivered using this technology. This preliminary evidence suggests, therefore, that this material is useful and should be pursued*" (see page 239, left column, last paragraph).

Having regard to this clear and strong suggestion to pursue tests on the basis of the teaching of document (7), the Board is convinced that the skilled person faced with the problem as defined above and knowing both documents (7) and (13) would have tried with a reasonable expectation of success to use 2-HPCD as

stabilizer in aqueous EPO solutions, knowing in particular that he would at the same time overcome the toxicity problems linked to the use of HSA.

4.10 Contrary to the Appellant's point of view the Board sees no prejudice against the claimed solution on the basis of the disclosure of document (12) contained in document (7) as a cross reference and showing that proteins employed in parenteral formulations may vary tremendously in their properties. It is highly probable that a skilled person trying to improve the unsatisfactory results obtained with one stabilizer would first try to replace completely the unsatisfactory ingredients and would not fall back on a combination of the unsatisfactory ingredient with other stabilizers already known as components in aqueous EPO solutions. In view of the toxicity problems linked to the administration of HSA he would in any case be encouraged to find a product which is described as being non-toxic.

Moreover, the skilled person would note in particular that the authors of document (7), even in the light of the warning in document (12) of the specificity of the behaviour of each protein, nevertheless give an express and strong hint to pursue the tests with 2-HPCD.

When coming to the above conclusions, the Board did not overlook that document (7) describes a large palette of stabilizing and solubilizing effects by testing inter alia small molecule drugs and the effect of inhibiting protein aggregation of insulin, which is not a glycosylated protein like EPO. However, once there is such a strong expectation of success when continuing experimental work, it is most unlikely that there would be a particular prejudice against tests with EPO for a skilled person.

The Board is convinced that in the present case the skilled person would try to complete the palette of tested drugs proposed in document (7) by EPO.

Also, the teaching of document (9), referred to by the Appellant in favour of an inventive step, is not so relevant that the skilled person would not try what is strongly suggested by document (7). In fact, document (9) clearly relates to non-derivatized cyclodextrin (see particularly column 3, Table I, and column 5, Table II) with all the disadvantages known from document (7) and thus the skilled person would indeed set aside this document, but only so as not to continue tests with pure cyclodextrin. Therefore, contrary to the Appellant's argumentation, document (9) can be regarded as a further incentive to continue test series with the modified cyclodextrin of document (7).

The Board has consequently come to the conclusion that the replacement of HSA by the derivatized cyclodextrin of the invention in order to increase the stability of EPO in aqueous solution was obvious to a skilled person. The claimed formulations therefore lack the required inventive step under Article 56 EPC.

4.11 The Appellant was of the opinion that it could not be foreseen that the modified cyclodextrin would also prevent adsorption on the walls of the recipients.

In fact such consideration could be of value for a process or a use claim.

However, the use of modified cyclodextrin to prevent wall adsorption is not the subject-matter of the claim in the present case.

5. Auxiliary requests

No particular effects have been shown for the specific use of hydroxypropyl-ß-cyclodextrin and the more restricted range of molar substitution of this stabilizer as well as for the more restricted weight-by-weight ratio of the essential components in the composition according to claims 1 of auxiliary requests 1 and 2.

Accordingly, the Board can only conclude that the problem underlying the patent in suit in relation to these requests is the same as for the main request.

Document (7) already proposes, as modified cyclodextrin, hydroxypropyl-ß-cyclodextrin which is the stabilizer according to the auxiliary requests. In the light of the known prior art as discussed above, the choice of the rest of the more restricted parameters defining the aqueous EPO solution can only be regarded as the result of a normal optimisation process carried out by the skilled person without the exercise of inventive skill.

Under these circumstances the findings under paragraph 4 above also apply to the auxiliary requests.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Townend P. A. M. Lançon