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**Datasheet for the decision
of 9 September 2010**

Case Number: T 1994/07 - 3.3.10

Application Number: 00970914.8

Publication Number: 1223990

IPC: A61L 27/22

Language of the proceedings: EN

Title of invention:

Formulations of hyaluronic acid for delivery of osteogenic proteins

Patentee:

Genetics Institute, LLC, et al

Opponent:

Biopharm Gesellschaft zur biotechnologischen Entwicklung von Pharmaka mbH

Headword:

Bone growth-promoting compositions/GENETICS INSTITUTE

Relevant legal provisions:

EPC Art. 56

Relevant legal provisions (EPC 1973):

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Keyword:

"All requests: Inventive step (no): improvement not credible in the absence of evidence - obvious alternative"

Decisions cited:

T 0020/81, T 0249/88, T 1053/93, T 0318/02

Catchword:

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Case Number: T 1994/07 - 3.3.10

D E C I S I O N
of the Technical Board of Appeal 3.3.10
of 9 September 2010

Appellant:
(Patent Proprietor)

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Decision under appeal:

Decision of the Opposition Division of the
European Patent Office posted 18 September 2007
revoking European patent No. 1223990 pursuant
to Article 102(1) EPC 1973.

Composition of the Board:

Chairman: R. Freimuth
Members: C. Komenda
J.-P. Seitz

Summary of Facts and Submissions

I. The Appellant (Patentees) lodged an appeal on 27 November 2007 against the decision of the Opposition Division of 18 September 2007 which revoked the European patent Nr. 1 223 990.

II. Notice of Opposition had been filed by the Respondent (Opponent) requesting revocation of the patent in its entirety on the grounds of lack of novelty and lack of inventive step pursuant to Article 100(a) EPC and insufficient disclosure of the invention (Article 100(b) EPC). *Inter alia* the following documents were submitted in the opposition proceedings:

(2) WO-A-97 32591,

(4) Vercruysse, K.P. et al., "Hyaluronate Derivatives in Drug Delivery", *Critical Reviews in Therapeutic Drug Carrier Systems*, 15(5); (1998), pages 513 to 555, and

(6) US-A-5 336 767.

III. The decision under appeal was based on claims 1 to 9 as granted, independent claim 1 read as follows:

"1. A composition for injectable delivery of osteogenic proteins comprising a pharmaceutically acceptable admixture comprising

(a) an osteogenic protein; and

(b) an injectable hyaluronic acid ester."

IV. The Opposition Division held that the invention was disclosed in a manner sufficiently clear for a skilled person to carry out the invention. Further, the

decision under appeal stated that the subject-matter of the claims of the patent in suit was novel over the cited prior art. Starting from document (2) as closest state of the art the objective technical problem was to provide alternative bone growth formulations. As the use of hyaluronic acid esters in drug delivery systems. was already known from either of documents (4) or (6) the claimed subject-matter constituted an obvious solution to the above mentioned technical problem. Therefore, the subject-matter of the claims did not involve an inventive step.

- V. Together with its statement of the grounds for appeal dated 24 January 2008 the Appellant submitted auxiliary requests I to III and with letter dated 8 July 2010 submitted auxiliary requests IV to VIII.

Auxiliary request I contained 7 claims, independent claim 1 of which was identical in wording with claim 1 as granted, but contained as additional feature "and (c) a pore former."

- VI. The Appellant argued that starting from document (2) as closest prior art the objective technical problem was to provide compositions for delivery of osteogenic proteins for improved bone growth. The solution to this problem was the use of esters of hyaluronic acid. Although esters of hyaluronic acid were already known from documents (4) and (6), the skilled person would not have considered to use these esters as carriers for the pharmaceutical compositions, since he knew from documents (4) or (6) that the esters of hyaluronic acid exhibited higher stability against degradation, which resulted in longer residence times in the tissue.

According to document (2) an excessive residence time of the compositions in the tissue could inhibit the formation of bone tissue. In view of the auxiliary requests the Appellant argued that the addition of pore formers led to further improvements concerning the bone formation. This was also not to be expected from the prior art, as sucrose and sodium citrate in combination with hyaluronic acid did not form pores and therefore, did not lead to improved bone formation. During the Oral Proceedings before the Board on 9 September 2010 the Appellant withdrew its auxiliary requests II to VIII.

- VII. The Respondent did no longer challenge insufficiency of disclosure and novelty. With regard to inventive step he argued that starting from document (2) as closest state of the art the problem could be formulated as providing alternative compositions comprising osteogenic proteins. The solution, which was the use of hyaluronic acid esters was already taught in documents (4) or (6). The teaching in document (2) that an excessive residence time in the tissue had a negative effect on the desired bone growth did not represent a deterrent from using carriers other than hyaluronic acid, since document (4) clearly taught that chemical modification of the hyaluronic acid derivatives allows to tailor the compositions for their intended use. In particular, document (4) taught that the formation of esters and the degree of esterification influenced the residence time of the composition in the tissue. Document (4) further exemplified that the hyaluronic acid ethyl ester having an esterification degree of 75% was completely reabsorbed within thirty days, which was an acceptable duration according to document (2) and

the patent in suit. The allegation of the Appellant that the use of sucrose or sodium citrate in compositions comprising hyaluronic acid as disclosed in document (2), did not lead to the formation of pores were not supported by the facts.

VIII. The Appellant requested that the decision under appeal be set aside and that the patent be maintained as granted (main request), or subsidiarily, on the basis of auxiliary requests I as submitted with letter dated 24 January 2008.

The Respondent requested that the appeal be dismissed.

IX. At the end of the oral proceedings before the Board the decision was announced.

Reasons for the Decision

1. The appeal is admissible.
2. *Insufficiency of disclosure of the invention and novelty*

Insufficiency of disclosure of the invention and novelty were no longer at issue in this appeal. The Board is satisfied that the patent in suit discloses the invention in a manner sufficiently clear and complete to be carried out by a person skilled in the art and that the claimed subject-matter is novel over the cited prior art. Although raised as grounds for opposition by the Appellant, these issues were no

longer in dispute before the Board. Hence, no detailed reasoning needs to be given.

Main request and auxiliary request I

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

Starting from the wording of claim 1 as granted the only modification in claim 1 of auxiliary request I resides in the presence of "(c) a pore former" as additional feature, which is based on claim 2 as granted and claim 3 as originally filed. Thus, the subject-matter of claim 1 of auxiliary request I constituted merely a combination of granted claims 1 and 2. As this additional technical feature restricts the scope of granted claim 1, the amendments made to claim 1 of auxiliary request I fulfil the requirements of Article 123(2) and (3) EPC.

4. *Inventive step*

The subject-matter of claim 1 of auxiliary request I corresponds to a combination of granted claims 1 and 2 and, thus, relates to the same subject-matter as dependent claim 2 of the main request. Therefore, the argumentation in view of claim 1 of the auxiliary request I, as set out below, applies *mutatis mutandis* to the subject-matter of claim 2 of the main request.

- 4.1 The patent in suit is directed to a composition, which comprises a pharmaceutically acceptable admixture of an osteogenic protein and an injectable hyaluronic acid ester for delivery of osteogenic proteins and for enhancing bone growth. Similar compositions are already

known from document (2). The decision under appeal and both parties to the present appeal proceedings conceded that this document represents the closest state of the art and the Board sees no reason to depart from this finding.

- 4.2 Document (2) discloses a bone growth-promoting composition comprising hyaluronic acid and a growth factor, which composition is injectable. The composition may further contain excipients such as sodium citrate or sucrose (claim 1; page 3, lines 8 and 12; page 3, lines 33 to 35; Examples 1 and 2).
- 4.3 Having regard to this prior art document, the Appellant submitted that the technical problem underlying the patent in suit was to provide compositions to improve bone formation (see paragraph [0011] of the patent specification).
- 4.4 As solution to this problem the patent in suit proposes the composition according to claim 1, which is characterized by the use of hyaluronic acid esters. According to the Appellant the formation of pores in the presence of the pore former does only occur in presence of the hyaluronic acid ester, but not in combination with hyaluronic acid.
- 4.5 In order to support that the solution proposed by the patent in suit successfully solves the technical problem mentioned above (Paragraph 4.3 *supra*) the Appellant referred to example 3 of the patent specification.

4.5.1 In example 3 three compositions according to the invention were tested, which comprised an osteogenic protein mixed with benzyl esters of hyaluaronic acid having various esterification degrees. None of the compositions used hyaluronic acid as described in the closest prior art document (2) instead of a hyaluronic acid ester characterising the invention. The Appellant did not provide any evidence demonstrating that the purported improvement in bone formation is causally linked to the use of hyaluronic acid esters instead of hyaluronic acid, as a direct comparison with the compositions of document (2) using hyaluronic acid is missing. Therefore, an improved bone formation due to the use of hyaluronic acid ester instead of hyaluronic acid, as alleged by the Appellant, has not been demonstrated.

4.5.2 Based on the bone formation within pores in example 3 (patent specification, page 5, line 31), the Appellant alleged that only the newly formed bone resulting from the compositions using hyaluronic acid esters according to the invention showed bone formed within pores, whereas in document (2) no pore formation was mentioned. A porous matrix would exhibit a higher surface area for the release of growth factor and the pores would allow the migration of biomass, which resulted in an improved bone formation. As document (2) did not disclose pore formation the improved bone formation could not be observed with the compositions using hyaluronic acid instead of its esters.

However, whether or not pores are formed is not the problem to be solved (see paragraph 4.3 *supra*), but is rather a technical insight as to how the bone formation

might work. Consequently, it is of no relevance whether or not the formation of pores is addressed in document (2) as the problem to be solved *vis-à-vis* that document according to the Appellant was to provide compositions which improve bone formation. To imply from the fact that document (2) is silent on the presence of absence of pores that no pores were formed in the prior art and any purported consequence deduced thereof, such that less bone formation occurred, is mere speculation what the Board cannot sanction.

4.5.3 Further, the Appellant alleged that the sodium citrate and sucrose, which were labelled pore formers in the patent in suit, would not induce the formation of pores in the bone-forming compositions of document (2), since these prior art compositions were based on hyaluronic acid, which had a too low viscosity. Consequently, the bone formation in document (2) was poor. When sodium citrate and sucrose were used in compositions having higher viscosities, such as the compositions according to the patent in suit using esters of hyaluronic acid, they would form pores and, thus, lead to an improved bone formation.

However, the first composition of example 2 of document (2) comprises hyaluronic acid, bFGF as osteogenic protein and sodium citrate and sucrose, which latter compounds the patent in suit labels pore formers. The test results summarized in Table 4 on page 10 demonstrate that this first composition in Table 4, is very effective in the formation of woven bone. Therefore, the allegation of the Appellant that the compositions of document (2) showed poor bone formation is not supported by the facts.

Irrespective of the above findings, since a fair comparison between a comparative composition reflecting document (2) and a composition according to the patent in suit differing from each other exclusively in the distinguishing feature of the invention, namely the use of esters of hyaluronic acid instead of the acid itself, is missing (see paragraph 4.5.1 *supra*) the alleged improvement in bone formation over the compositions of the closest prior art is not credible.

- 4.6 According to the jurisprudence of the Boards of Appeal, alleged but unsupported advantages cannot be taken into consideration for the determination of the problem underlying the claimed invention (see e.g. decision T 20/81, OJ EPO 1982, 217, point 3 of the reasons, last sentence).

As in the present case the purported improvement relating to bone formation has not been shown, the solution proposed by the patent in suit does not successfully solve the alleged technical problem (see paragraph 4.3 *supra*).

- 4.7 Consequently the objective problem underlying the patent in suit has to be reformulated in a less ambitious way as consisting merely in the provision of alternative bone-growth compositions.

- 4.8 It remains to be decided whether or not the proposed solution to the objective technical problem mentioned above (see paragraph 4.7 *supra*) is obvious in view of the state of the art.

4.9 Document (6) teaches in column 9, lines 5 to 9 that esters of hyaluronic acid may be used for typical indications of hyaluronic acid itself, such as for intra-articular injections. In column 14, line 10 it is indicated to use hyaluronic acid esters in combination with growth factors. Therefore, replacing the hyaluronic acid in the compositions of document (2) by hyaluronic acid esters known from document (6) for the same purpose can only be seen as lying within the routine activity of the skilled person faced with the mere problem of providing alternative bone-growth compositions. Thus acting routinely, the skilled person would arrive at the claimed invention without having to exercise any inventive activity.

4.9.1 The Appellant argued that document (2) indicated on page 3, lines 29 to 32 that, if the composition persists at the site of desired bone growth for an excessive period of time, the bone formation may be inhibited or even blocked completely. The teaching of document (4), page 533, penultimate paragraph, last but second sentence, indicated that the residence time of hyaluronic acid esters was 90 days or longer, thus exceeding the acceptable residence time of 30 days indicated in document (2) on page 3, line 24. Thus, a skilled person would not have considered to replace hyaluronic acid in the compositions of document (2) by their esters.

However, document (4) teaches on page 515, lines 5 to 8, that chemical modification of the hyaluronic acid allows its physicochemical properties to be tailored according to the desired applications and that it has a significant impact on the clearance of the hyaluronic

acid derivative. On page 532, first paragraph, it is taught that the degree of enzymatic degradation may be influenced by chemical modification, namely by the formation of esters with varying degrees of esterification. On page 533, penultimate paragraph, last but one sentence, an ester of hyaluronic acid is exemplified, namely its ethyl ester with an esterification degree of 75%. This particular ester is completely resorbed after 30 days, which is within the acceptable residence time indicated in document (2). Therefore, it is irrelevant whether alternatives having longer residence times are within the disclosure of document (4), as document (4) teaches alternatives falling within the residence time of only 30 days. Therefore, a skilled person would not be deterred from considering hyaluronic acid esters taught in documents (4) and (6) as solution for the technical problem of providing alternative bone-growth compositions thereby arriving at the claimed compositions without exercising any inventive ingenuity.

- 4.9.2 The Appellant disputed these findings and submitted that the passage on page 515, second paragraph of document (4) did apply to hyaluronic acid bioconjugates. Moreover, page 515 only referred to unspecified derivatives of hyaluronic acid, but not to its esters with the consequence that this section would not address hyaluronic acid esters now claimed.

However, this argument is not supported by the facts, since the first sentence of the second paragraph of page 515 distinguishes between derivatisation of hyaluronic acid on the one hand and hyaluronic acid bioconjugates on the other hand. The following

sentences then address each of both alternatives separately, whereby the alternative addressed first relates to the chemical modification of hyaluronic acid, bioconjugates being addressed later as second alternative. Though the type of chemical modification of the hyaluronic acid is not specified on page 515, the teaching on page 532, first paragraph of document (4) makes plain, that the esters of hyaluronic acid are encompassed therein.

- 4.9.3 The Appellant further stated that the hyaluronic acid esters mentioned on page 533, penultimate paragraph of document (4) were only administered as gauzes or films, which required surgical implantation and were not injectable as required for the claimed bone-growth compositions. Therefore, a skilled person would not consider this teaching for solving the technical problem underlying the invention.

However, document (6) already teaches that esters of hyaluronic are suitable for replacement of hyaluronic acid in injectable compositions (column 9, line 9). Thus, the skilled person was not deterred from combining the teaching of document (6) with the closest prior art composition known from document (2), thereby arriving routinely at the claimed subject-matter.

Notwithstanding these findings, the Appellant's allegations are inconsistent with the teaching on pages 532 and 533 of document (4), which makes plain that the residence time of hyaluronic acid esters is modified by the structure of the ester groups used and by the degree of esterification. Thus, document (4) indicates

that the residence time is rather dependent on the type of chemical modification of the hyaluronic acid.

- 4.9.4 The Appellant further argued that the solubility of the hyaluronic acid esters was different from that of hyaluronic acid. Therefore, it would not have been predictable whether or not a composition of a hyaluronic acid ester and a growth factor would show a similar release profile as a composition comprising hyaluronic acid and a growth factor.

However, for providing a solution to the problem of providing an alternative bone-growth composition no certainty of success is necessary. In order to render a proposed solution obvious it is sufficient to establish that the skilled person would have followed the teaching of the prior art with a reasonable expectation of success (see decisions T 249/88, point 8 of the reasons; T 1053/93, point 5.14 of the reasons; and T 318/02, point 2.7.2 of the reasons, neither published in OJ EPO).

In the present case, the Board cannot agree with the Appellant's argument that due to some purported uncertainty about the predictability of the release profile of the growth factor, the skilled person would not have contemplated to use hyaluronic acid esters instead of hyaluronic acid in order to provide alternative bone-growth compositions. Document (6) clearly teaches that hyaluronic acid esters are suitable for the replacement of hyaluronic acid in injectable compositions. Consequently, the arguments of the Appellant are not convincing.

4.10 For these reasons, the Board concludes that the subject-matter of claim 1 of the auxiliary request I is obvious from document (2) in combination with document (6) and does not involve an inventive step pursuant to Article 56 EPC.

As the subject-matter of claim 1 of the auxiliary request is the same as that of claim 2 of the main request, the considerations and the conclusions drawn for auxiliary request I apply *mutatis mutandis* to the main request with the consequence, that the main request does also not involve an inventive step according to Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar

The Chairman

C. Rodríguez Rodríguez

R. Freimuth