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**Datasheet for the decision
of 7 May 2010**

Case Number: T 0232/08 - 3.3.04

Application Number: 98911246.1

Publication Number: 0918535

IPC: A61K 38/16

Language of the proceedings: EN

Title of invention:

Sustained-release composition of drugs encapsulated in microparticles of hyaluronic acid

Patentee:

LG Life Sciences, Ltd.

Opponent:

Quadrant Drug Delivery Limited

Headword:

Microparticles of hyaluronic acid/LG LIFE SCIENCES

Relevant legal provisions:

EPC Art. 56

RPBA Art. 13(1)(3)

Keyword:

"Admission of new objection of lack of novelty (no)"

"Main request - inventive step (no)"

Decisions cited:

-

Catchword:

see points 2 to 8



Case Number: T 0232/08 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 7 May 2010

Appellant: Quadrant Drug Delivery Limited
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Respondent: LG Life Sciences, Ltd.
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
30 November 2007 concerning maintenance of
European patent No. 0918535 in amended form.

Composition of the Board:

Chairman: C. Rennie-Smith
Members: G. Alt
M. Wieser

Summary of Facts and Submissions

- I. The opponent (hereinafter "appellant") lodged the appeal against the decision of the opposition division according to which European patent No. 0 918 535, entitled "Sustained-release composition of drugs encapsulated in microparticles of hyaluronic acid" could be maintained in amended form pursuant to Article 102(3) EPC 1973 on the basis of the first auxiliary request.
- II. The opposition was based on Article 100(a) EPC, lack of novelty and lack of inventive step.

In the decision under appeal the opposition division decided that claim 1 of the main request before it, claims 1 to 9 as granted, did not involve an inventive step, but that claims 1 to 9 of the first auxiliary request before it met all requirements of the EPC. In particular the opposition division held that the claimed subject-matter was not obvious over the disclosure in any of documents D1 or D2 alone or over the disclosure in document D2 in combination with document D1. Document D1 did not indicate microparticles made of hyaluronic acid having the claimed size. Document D2 disclosed microparticles made of hyaluronic acid but only in admixture with a biodegradable polymer.

- III. With the statement of the grounds of appeal the appellant filed documents D6 to D16 as evidence that the particle size recited in claim 1 was common general knowledge. The statement contained arguments as to why the claimed subject-matter involved an inventive step

when starting from document D1 as the closest prior art document.

IV. Oral proceedings were summoned to be held on Monday, 19 April 2010. In a communication accompanying the summons the board informed the parties that document D2 could be a starting point for the valuation of inventive step preferable to document D1.

V. In a telefax submission received on Friday, 16 April 2010 at 11.06 h the patent proprietor (hereinafter "respondent") requested rescheduling of the oral proceedings since its clients' flight to Europe had been cancelled due to the ash cloud arising from the eruption of a volcano in Iceland.

In a telefax communication sent on 16 April 2010 at 13.18 h the board refused the respondent's request noting that the representative (whose firm is based in Munich), would be able to attend the oral proceedings. The board also informed the parties that it would however permit an interruption of the proceedings in order to allow the respondent's representative to contact its clients by telephone for consultation, if so needed.

In a telefax submission received on 16 April 2010 at 16.49 h the appellant also requested a postponement of the oral proceedings due to the ash cloud.

At the oral proceedings on 19 April 2010 only the respondent's representative was present, the appellant's representative being unable to attend the proceedings due to the cancellation of its flight as a

consequence of the volcanic ash cloud. Due to the exceptional circumstances the board adjourned the oral proceedings until 5 May 2010 or the earliest possible date thereafter without having heard the respondent on the substance of the case.

VI. The oral proceedings were continued on 7 May 2010, both parties' representatives being present.

VII. The appellant requested that the decision under appeal be set aside and that the patent be revoked.

The respondent requested that the appeal be dismissed, i.e. that the patent be maintained on the request held to be allowable by the opposition division.

VIII. Claim 1 of the respondent's request read:

"1. A sustained-release drug composition essentially consisting of microparticles of hyaluronic acid or an inorganic salt thereof; and a protein or peptide drug and a stabilizer, encased in said microparticles, said microparticles having an average size ranging from 0.1 to 40µm and the stabilizer being selected from the group consisting of a polysaccharide, protein, amino acid, inorganic salt, surfactant and a mixture thereof, wherein the microparticles are prepared by spray-drying."

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

D1 EP-A-0 486 959

D2 EP-A-0 522 491

D11 EP-A-0 737 472

D15 US 5,538,739

D16 PDA Journal of Pharmaceutical Science and Technology, vol. 49, no. 4, 1995, Takada, S. et al.: "Application of spray drying technique in the production of TRH-containing injectable sustained-release microparticles of biodegradable polymers"

X. The appellant's arguments, as far as they are relevant for the present decision, may be summarised as follows:

Although the argument, that the subject-matter of claim 1 lacked novelty in the light of the disclosure in document D11, was presented for the first time at the oral proceedings, it should be considered since novelty was a ground of opposition in these proceedings.

Inventive step

Document D2 was the closest prior art document. It disclosed a gel-like composition consisting of components falling under the definition of the components in claim 1 and this composition could be dried by lyophilisation.

The problem to be solved was the provision of an alternative, dry hyaluronic acid-based sustained-release preparation for the delivery of water-soluble drugs.

The solution according to the patent was to apply an alternative drying technique, i.e. spray-drying which inevitably resulted in microparticles.

Spray-drying was commonly known in the art as evidenced for example by documents D11, D15 and D16.

Document D11 disclosed in particular spray-drying of compositions comprising natural hyaluronic acid.

Thus, spray-drying was an obvious alternative to drying by lyophilisation disclosed in document D2. Therefore the subject-matter of claim 1 did not involve an inventive step.

XI. The respondent's arguments, as far as they are relevant for the present decision, may be summarised as follows:

The appellant presented the argument, that the subject-matter of claim 1 lacked novelty in the light of the disclosure in document D11, for the first time at the oral proceedings. Moreover, the appellant had not relied at all on the ground of opposition of lack of novelty in the statement of the grounds of appeal. Therefore, the argument should not be considered.

Inventive step

Document D2 was the closest prior art document.

The problem to be solved was the provision of microparticles for sustained release based on hyaluronic acid or salts therefore having improved sustained-release properties.

The data in the patent, in particular Figures 6 and 7, established the improved properties of the microparticles of the invention.

The skilled person knew that hyaluronic acid was a highly viscous and hygroscopic substance which would therefore tend to agglomerate in the spray-drying apparatus. Therefore, the skilled person would not have attempted to spray-dry such a substance.

Document D2 did not teach spray-drying of a composition consisting of a drug, a stabilizer and hyaluronic acid. Insofar as document D2 related to particles, they included a further biodegradable polymer. Spray-drying was not specifically mentioned in relation to their preparation.

Document D11 dealt with sustained-release particles for vaccination. The skilled person would not have considered the teaching of this document when trying to solve the underlying problem since it related to a technical field different from that of the patent.

Both documents D15 and D16 dealt with polymers different from hyaluronic acid. The skilled person would not have derived from them any teaching concerning problems connected with spray-drying of hyaluronic acid.

Thus, the skilled person would not have considered spray-drying for producing microparticles from hyaluronic acid. Consequently, the claimed subject-matter involved an inventive step.

Reasons for the decision

Admission of documents D6 to D16

1. The appellant submitted documents D6 to D16 with the statement of the grounds of appeal. The respondent did not raise an objection against their admission. The board too sees no reason not to admit these documents.

Lack of novelty on the basis of document D11

2. In accordance with Article 12(2) of the Rules of Procedure of the Boards of appeal (RPBA) "the statement of grounds of appeal and the reply shall contain a party's complete case. They shall set out clearly and concisely the reasons why it is requested that the decision under appeal be reversed, amended or upheld and should specify expressly all the facts, arguments and evidence relied on".
3. Article 13(1) RPBA leaves it to the discretion of the board to admit amendments to a party's case after it

has filed its grounds of appeal or reply. Aspects to be looked at when exercising the discretion are according to Article 13(1) RPBA inter alia the complexity of the new subject-matter, the current state of the proceedings and the need for procedural economy.

4. However, a stricter criterion is applied to amendments sought to be made after oral proceedings have been arranged. According to Article 13(3) RPBA these amendments "shall not be admitted if they raise issues which the Board or the other party or parties cannot reasonably be expected to deal with without adjournment of the oral proceedings." Thus, the parties' right to be heard and/or procedural economy take precedence over other considerations.
5. The objection of lack of novelty based on document D11 was raised for the first time during the whole opposition and appeal proceedings at the oral proceedings before the board.
6. Although lack of novelty was mentioned as a ground of opposition and was dealt with in the decision under appeal, it was not relied on at all in the statement of the grounds of appeal. Furthermore, document D11 was only introduced during the appeal proceedings and then only in the context of inventive step and even then only as evidence of common general knowledge of particle size (see section III above). Thus, in the board's view, the respondent had every reason to believe that novelty was no longer pursued as a ground of opposition in the appeal and that document D11 formed only a limited part of the appellant's case on inventive step.

7. Moreover, in the board's view the disclosure in document D11 of possibly novelty-destroying subject-matter is not particularly striking. This view is supported by certain of the appellant's submissions: although the summary of the teaching in document D11 submitted with the statement of the grounds of appeal (see page 8) mentions hyaluronic acid, spray-drying and a particle size range falling under the one mentioned in claim 1, the document is only cited in the context of inventive step. Further, the appellant conceded at the oral proceedings that the novelty-destroying character of the disclosure in document D11 only occurred to it during preparation for oral proceedings. Therefore, in the board's view, it cannot be expected that the respondent would have foreseen the objection of lack of novelty on the basis of document D11 itself.

8. In all the circumstances of the present case, the board considers that the respondent's right to be heard with regard to the novelty-objection based on document D11 would have been respected only if the oral proceedings had been adjourned or the case had been remitted to the department of first instance in order to allow the respondent adequate consideration of the appellant's objection.

Consequently, applying Article 13(3) RPBA, the board has decided not to allow the appellant to present its novelty objection based on document D11.

Inventive step

9. The invention according to claim 1 relates to a sustained-release drug composition consisting of
- (a) microparticles of hyaluronic acid or an inorganic salt thereof having an average size ranging from 0.1 to 40 μ m;
 - (b) a protein or peptide drug; and
 - (c) a stabilizer being selected from the group consisting of a polysaccharide, protein amino acid, inorganic salt, surfactant and a mixture thereof,
 - (d) wherein the microparticles are prepared by spray-drying.

The respondent's technical expert explained at the oral proceedings that, physically, the composition according to claim 1 is a dry powder resembling flour.

10. It is established case law that the closest prior art for assessing inventive step is a document disclosing subject-matter conceived for the same purpose as the invention under consideration and having the most relevant technical features in common (Case Law of the Boards of Appeal, 5th edition, 2006, I.D.3.1).
11. With regard to the subject-matter of claim 1 document D2 is the closest prior art document. This is not in dispute between the parties.

- 11.1 Document D2 discloses gel-like, vacuum-dried or lyophilized, i.e. freeze-dried sustained-release compositions comprising
- (a) a pharmacologically active polypeptide, except erythropoietin, secreted by the animal body or its derivative or a chemically synthesised pharmacologically active substance;
 - (b) a water-soluble species of hyaluronic acid or its nontoxic salt; and
 - (c) a water-soluble protein injectable into body fluids without showing any substantial pharmacological activity (see page 2, lines 15 to 24 and page 7, lines 1-3, 29-30, 32-33, 34 and 38).
- 11.2 Document D2 also discloses sustained-release compositions in the form of particles. They are prepared as follows (page 7, lines 38 to 42): "The liquid form or the lyophilisate powder form of the composition of the present invention dissolved or dispersed in a solution of biodegradable polymer such as poly(lactic-glycolic)acid copolymer, poly(hydroxybutyric acid), poly-(hydroxybutyricglycolic)acid copolymer, or the mixture of these can be formulated, for example, to films, microcapsules, microspheres, or nanocapsules (nanospheres) according to the well-known methods".
- 11.3 As to the effect, it is stated on page 7, lines 54 to 58 that "[t]he water-soluble composition of the present invention is excellent in producing a prolonged effect. Even a low concentration of hyaluronic acid can produce

the effect to a satisfactory extent. As a result, a small-gauge needle can be used, whereby pain in patients can be reduced. The composition has a low viscosity and therefore the possibility of bubble formation is much reduced. Thus, the composition can be used with ease in clinical practice."

12. In the respondent's view the problem arising vis-à-vis the teaching in document D2 is to provide microparticles for sustained release based on hyaluronic acid or salts thereof having improved sustained-release properties. It submits that the improved properties of the claimed composition are demonstrated by the results summarized in Figures 6 and 7 of the patent in dispute.
13. If the problem arising in relation to the closest prior art document is formulated as the improvement of the teaching in that document, there should be evidence that the claimed subject-matter indeed achieves these beneficial effects (Case Law of the Boards of Appeal, 5th edition, 2006, I.D.4.2).
14. In the assay of the patent, of which the results are given in Figure 6 (see page 6, "Test Example 5"), the microparticle-preparation of the invention containing human growth hormone (hGH) is administered to a group of rabbits, while the control group does not receive hGH. Hence, this assay does not provide a comparison with any of the sustained-release preparations disclosed in document D2 and is consequently not appropriate to establish an advantage over the closest prior art document D2.

15. In the assay entitled "Comparative Example 2" on page 9 of the patent, the results of which are summarized in Figure 7, the activities of Eutropin - a commercially available hGH formulation for aqueous injection (see paragraph [0036]) -, a hyaluronic-acid-based, hGH-containing gel formulation and hGH-containing microparticles of the invention are compared. The gel formulation is prepared by adding sodium hyaluronate having a molecular weight of 2,000,000 d to a 5mM saline buffer solution (PBS) containing hGH (see paragraph [0074]). For injection the gel formulation is emulsified with cottonseed oil (see paragraph [0075]).

15.1 The preparation according to document D2 contains in addition to hyaluronic acid and the drug as a mandatory constituent "a water soluble protein injectable into body fluids without showing any substantial pharmacological activity" (see above point 11.1). Such a compound is not present in the gel formulation according to "Comparative Example 2" (see above point 15). Thus, "Comparative Example 2" does not include a comparison with the gel formulation according to the closest prior art document D2. Consequently, also Figure 7 is not appropriate to establish an advantage over the closest prior art.

16. The board does not see any other evidence before it, either in the patent or in any other document, to support an advantageous effect of the claimed preparation over any of the preparations disclosed in document D2.

16.1 In particular, a preparation corresponding to either the gel or the microparticles according to document D2

is not used in any of the other assays disclosed in the patent.

16.2 Also a direct comparison of the results presented in document D2 with those in the patent is not appropriate.

Firstly, the hyaluronic acid used in the assays according to document D2 has a molecular weight of 1,470,000 d (see experimental examples 1 to 6 and preparations of Examples 1, 36, 39, 49, 50, 51), whereas the molecular weight of hyaluronic acid in the microparticles disclosed in the examples of the patent is 1,000,000 d or 2,000,000 d. It is stated in the patent that the release of the protein is dependent on the molecular weight of hyaluronic acid (paragraph [0027]). Thus, the difference in molecular weights between hyaluronic acid in document D2 and the patent cannot be disregarded.

Secondly, the release of different proteins is assayed in the patent and in document D2, i.e. while the patent discloses tests with hGH, document D2 discloses in vivo experiments with human basic fibroblast growth factor mutein CS23, insulin, human granulocyte colony stimulating factor and interferon alpha or parathyroid hormone (see Experimental Examples 1 to 6). Some of these proteins, for example, insulin or parathyroid hormone, have a molecular weight considerably lower than that of hGH. The board is convinced that the size of a protein, its tertiary structure and also its charge influence its rate of diffusion through the hyaluronic acid matrix.

17. Hence, in summary, a beneficial effect of the claimed preparation over any of those disclosed in document D2 has not been established. Thus, the board does not agree with the respondent's formulation of the problem to be solved.

18. Rather, the board considers that in view of the teaching in document D2, in particular the dried compositions, the problem to be solved by the patent may be formulated as the provision of an alternative, dry hyaluronic-acid-based sustained-release preparation for the delivery of water-soluble drugs.

19. The solution to this problem is the composition characterized in claim 1.

The patent presents ample evidence that this problem is solved by preparations falling under the definition of the claim.

20. At the oral proceedings in the context of the assessment of the obviousness of the subject-matter of claim 1, neither of the parties has accorded any relevance to features in the claim relating to the particle size, the protein or peptide drug, or the stabilizer.

Thus, the board is solely concerned with the question whether or not the skilled person aiming at preparing an alternative, dry sustained-release preparation would have considered it obvious to provide a composition obtained by spray-drying.

21. Spray-drying is a commonly known method used for drying polymeric substances. Documents D15 and D16 report spray-drying processes for the production of sustained-release microparticles of biodegradable synthetic polymers such as polylactic or polyglycolic acid or copolymers thereof (see document D15, column 3, lines 37 to 40; column 7, last paragraph, continued in column 8; column 9, last paragraph; document D16, the whole document). Document D15 generally mentions in column 3, line 36 that the polymer matrix may be a "natural polymer" without giving specific examples however.

22. Document D16 advertises spray-drying as a particularly advantageous drying method.

"As reported previously, the spray drying method is very convenient as the process is quite fast and allows for the use of mild conditions (13, 14)." (page 180, first column, lines 18 to 20).

"From the point of efficiency of production, 10 g of microparticles could be produced within 3 minutes by spray drying, while in-water drying required 24 hours including the freeze drying process. An ideal method for the preparation of biodegradable microparticles should be simple, reproducible, rapid, little dependent on the solubility characteristics of the drug and polymer, and easy to scale-up (15). Therefore, a spray-drying method was preferable for mass production." (page 182, second column, lines 13 to 18).

23. The respondent submits that in the particular case of natural hyaluronic acid the skilled person would not

have applied spray-drying because of the known high viscosity and hygroscopic character of hyaluronic acid. The skilled person would have expected the material to adhere to the inside wall of the spray-drying apparatus and/or to agglomerate in the outlet spraying nozzle.

24. However, the board is not persuaded by this submission in view of the teaching in document D11.

Document D11 relates to a vaccine formulation consisting of microparticles. The particles are prepared by coating the antigen with a water-soluble substance to obtain a powdered "core particle" which is subsequently coated with a hydrophobic bio-degradable polymer to obtain the final microparticle (page 4, lines 54 to 56).

On page 5, lines 11 to 13 it is explained that "[t]he core particle is prepared by dissolving or dispersing the antigen in a solution obtained by dissolving a water-soluble substance in a suitable aqueous solvent, e.g., water or a buffer, and drying the mixture by a spray drying or a freeze drying method."

On page 5, lines 18 to 22 it is stated that "[e]xemplary water-soluble substances include water-soluble saccharides such as glucose, xylose, galactose, fructose, lactose, maltose, saccharose, alginate, dextran, **hyaluronic acid**, chondroitin sulfate [...]." (emphasis added).

25. Thus, document D11 discloses spray-drying as a drying procedure for compositions which comprise natural hyaluronic acid.

26. The respondent furthermore argues that the skilled person would not have considered the teaching in document D11 since it relates to a different field, i.e. to "vaccination", while the patent relates to "treatment" and therefore the compounds encased in the matrix according to document D11 serve a purpose different from that in the patent.

26.1 However, the skilled person would infer from the disclosure in document D11 (see page 5, lines 1 to 10), that the compound to be delivered to the body according to document D11, i.e. the "antigen" is (essentially) proteinaceous and thus of the same nature as the "drug" according to the patent. The skilled person aiming at providing an alternative, dry hyaluronic acid-based sustained-release preparation for the delivery of water-soluble drugs would therefore consider that the actual effect caused by the active compound of the composition to be administered to the patients body is not a criterion for the selection of the method for drying the composition. Consequently, in the board's view, the skilled person would have paid attention to the teaching in document D11.

27. Thus, in summary, the skilled person would have considered a hyaluronic-acid-based, sustained-release preparation dried by spray-drying as an obvious alternative to one dried by lyophilisation or vacuum-drying as disclosed in document D2.

28. Hence, the subject-matter of claim 1 is obvious in view of a combination of documents D2 and D11 and therefore does not involve an inventive step.

The requirements of Article 56 EPC are not fulfilled.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chair:

P. Cremona

C. Rennie-Smith