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D E C I S I O N
of 2 June 2003

Case Number: T 0308/99 - 3.3.2

Application Number: 86306046.3

Publication Number: 0224987

IPC: A61K 47/36

Language of the proceedings: EN

Title of invention:

Drug delivery systems based on hyaluronan, derivatives thereof
and their salts and method of producing same

Patentee:

Biomatrix, Inc.

Opponent:

Biomatrix Inc.
FIDIA, S.p.A.

Headword:

Hyaluronan/BIOMATRIX

Relevant legal provisions:

EPC Art. 52(1), 54, 56, 83, 84, 100, 111(1), 123(2),(3)
EPC R. 57(a)

Keyword:

"Novelty (yes): claimed use reflects a newly discovered
technical effect"

"Inventive step (no): claimed use is based on a thoroughly
obvious property of known substances; slightly enhanced
effects associated with the claimed use in comparison with
substances used in the state of the art emerge from obvious
tests - no indication of an inventive step"

Decisions cited:

G 0002/88, G 0006/88, G 0009/91, T 0296/87

Catchword:

-



Case Number: T 0308/99 - 3.3.2

DECISION
of the Technical Board of Appeal 3.3.2
of 2 June 2003

Appellant:
(Opponent)

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Representative:

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Respondent:
(Proprietor of the patent)
and Former Opponent I

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Representative:

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Decision under appeal:

Interlocutory decision of the Opposition
Division of the European Patent Office posted
11 May 1999 concerning maintenance of
European patent No. 0224987 in amended form.

Composition of the Board:

Chairman: U. Oswald
Members: G. F. E. Rampold
P. Mühlens

Summary of Facts and Submissions

I. The respondent is proprietor of European patent No. 0 224 987 ("the patent") which was granted with 21 claims on the basis of European patent application No. 86 306 046.3. Claim 1 as granted read as follows:

"The use of a polymeric component as an agent for slowing the release of a substance having pharmacological activity in the preparation of a composition for therapeutic treatment, said polymeric component being a water-soluble or water-insoluble hyaluronan or hylan, other than a water-insoluble cross-linked hyaluronan gel formed using divinyl sulfone as cross-linking agent."

II. Oppositions were originally filed by the patent proprietor against its own patent (former opponent I) which sought maintenance of the patent in amended form, and by the appellant (opponent II) which sought revocation of the patent in its entirety on the grounds of lack of novelty and inventive step (Articles 54, 56 and 100(a) EPC) and also on the ground of insufficient disclosure (Articles 83 and 100(b) EPC).

III. With its letter dated 23 December 1996, the proprietor (former opponent I) withdrew its opposition.

IV. Of the numerous documents cited during the first-instance opposition and subsequent appeal proceedings, the following are referred to in the present decision:

- (1) H. G. Hassan et al, "Effects of Adjuvants to Local Anaesthetics on Their Duration, III. Experimental Studies of Hyaluronic Acid", Acta Anaesthesiol. Scand. 1985:29, pages 384 to 388;
- (2) EP-A-0 138 572
- (3) EP-A-0 197 718 (State of the Art under Article 54(3) EPC)
- (4) EP-A-0 216 453 (State of the Art under Article 54(3) EPC)
- (5) EP-A-0 161 887
- (6) GB-A-2 151 244

V. During prosecution of the case before the opposition division the proprietor filed amended claims by way of main and auxiliary requests. In its decision posted on 11 May 1999, the opposition division maintained the European patent in amended form pursuant to Articles 102(3) and 106(3) EPC on the basis of claims 1 to 20 filed on 24 April 1996 with the proprietor's letter of 23 April 1996 and an accordingly amended description filed on the same date, with page 2 of the description further amended during the oral proceedings held before the opposition division on 22 March 1999.

The claims as maintained by the opposition division read as follows:

- "1. The use of a polymeric component as an agent for slowing the release of a substance having pharmacological activity in the preparation of a composition for therapeutic treatment, said polymeric component being a water-soluble hylan or a water-insoluble cross-linked hyaluronan other than a water-insoluble cross-linked hyaluronan gel formed using divinyl sulfone as cross-linking agent.
2. The use in accordance with claim 1, wherein the polymeric component is hylan and comprises an aqueous hylan solution.
3. The use in accordance with claim 2, wherein the said substance is dissolved or dispersed in the aqueous solution.
4. The use of a polymeric component as an agent for slowing the release of a substance having pharmacological activity in the preparation of a composition for therapeutic treatment, said polymeric component being a solution of a water-soluble hylan or hyaluronan in the form of a viscoelastic putty.
5. The use in accordance with any one of claims 2-4, wherein the hyaluronan or hylan concentration is from 0.05 to 4% by weight.
6. The use in accordance with any one of claims 2-5, to prepare a composition in the form of an injectable product or a topical product such as pharmaceutical eye drops.

7. The use to prepare a topical product in accordance with claim 6, wherein the hyaluronan or hylan has a molecular weight of at least 1×10^6 and the concentration of hyaluronan or hylan is from 0.05 to 2% by weight.
8. The use in accordance with any one of claims 2-7, wherein the said substance is serotonin, or salicylic acid.
9. The use in accordance with claim 1, wherein the water-insoluble cross-linked hyaluronan is a cross-linked gel of hyaluronan.
10. The use in accordance with claim 1, wherein the water-insoluble cross-linked hyaluronan is in the form of a molecular cage and the substance is dispersed within said molecular cage.
11. The use in accordance with claim 1, wherein the said substance is covalently bonded to the macromolecules of hyaluronan or hylan.
12. The use in accordance with claim 11 to prepare a gel of cross-linked hyaluronan and gentamicin covalently attached thereto.

13. A drug delivery system comprising a polymeric component, a selected amount of at least one substance having biological or pharmacological activity and a support or substrate for said polymeric component, wherein said polymeric component is a water-soluble hylan or water-insoluble cross-linked hyaluronan.
14. A drug delivery system in accordance with claim 13 and comprising (a) a membrane formed of a gel of hyaluronan containing gentamicin or mydriacyl, or (b) a membrane formed of a gel of hyaluronan and chondroitin sulfate containing gentamicin.
15. A drug delivery system in accordance with claim 13 and comprising a porous polymeric sponge for example a polyurethane sponge, said sponge having a hyaluronan gel immobilized therein together with said substance, preferably serotonin.
16. A drug delivery system in accordance with claim 14 and comprising a cotton gauze, said gauze having a hyaluronan gel immobilized therein together with said substance, preferably gentamicin.
17. A method of obtaining a product as defined in claim 2, comprising either (a) dissolving or dispersing the said substance in a water or saline solution of water-soluble hylan, or (b) mixing a solution or dispersion of the substance with a hylan solution.

18. A method of obtaining a product as defined in claim 4, comprising adding the said substance to a solution of hyaluronan or hylan and adjusting the pH of the resulting mixture to about 2.5.
 19. A method of obtaining a product as defined in claim 9, comprising (a) placing the gel into a solution of the said substance and allowing the substance to diffuse into the gel whereby a product having the substance uniformly dispersed therethrough is obtained; (b) dehydrating the gel and placing the dehydrated gel into a solution of the substance to cause reswelling of the dehydrated gel, said substance being diffused into the gel while the reswelling occurs; or (c) placing a concentrated gel in a solution of said substance and allowing the gel to swell in said solution whereby the substance is diffused into the gel while it is swelling.
 20. A method in accordance with claim 19, wherein said dehydrating is effected by treating the gel with a water miscible solvent, preferably ethanol, isopropanol or acetone, or by drying."
- VI. The essence of the reasoning in the decision of the opposition division was as follows:

The ground of opposition referred to in Article 100(b) in conjunction with Article 83 EPC was raised by opponent II for the first time after expiry of the nine-month opposition period. In the absence of the proprietor's approval, the opposition division saw with reference to decision G 9/91 (OJ EPO 1993, 408) no

reason to consider the late-filed ground of insufficiency of disclosure in the opposition proceedings.

It was further noted in the decision under appeal that the experimental evidence, filed with the letter of opponent II dated 22 February 1999, was not admitted into the first instance opposition proceedings on the grounds that it had been submitted late and that it would have been impossible for the proprietor to reproduce the findings in good time for the oral proceedings scheduled to take place on 22 March 1999.

As regards novelty, the opposition division considered that the scope of amended claim 1 (see V above) had been appropriately restricted to establish novelty of the claimed subject-matter in the patent vis-à-vis the state of the art according to any of citations (1) to (6).

As regards inventive step, the opposition division concluded in the decision under appeal that either one of citations (1) or (2) represented the closest state of the art, since both of them taught that hyaluronic acid or its salts were useful as drug release controlling agents for slowing the rate of drug release in drug delivery systems. In that decision it was recalled that citations (5) and (6) already disclosed both water-soluble cross-linked and water-insoluble cross-linked hyaluronic acid derivatives which were prepared by cross-linking hyaluronic acid, or a salt thereof, with a variety of cross-linking agents. It was also recalled that citations (5) and (6) taught the use of such cross-linked hyaluronic acid derivatives for a

number of different medical or cosmetic purposes or as a material for various prosthetic devices, but that there was no hint or suggestion in citations (5) and (6) that water-soluble cross-linked hyaluronic acid derivatives, such as hylan, or water-insoluble cross-linked hyaluronic acid derivatives would be useful in slowing the rate of drug release in drug delivery systems. Since, moreover, the comparative experiments submitted by the respondent provided in the opposition division's opinion appropriate evidence that both water-soluble hylan or water-insoluble cross-linked hyaluronic acid derivatives were more effective in slowing the rate of drug release than prior art water-soluble hyaluronans, the claimed subject-matter in the patent in suit was found to meet the requirements of inventive step.

VII. The appellant (opponent II) filed a notice of appeal on 21 July 1999 and paid the appeal fee on the same date and filed a statement of grounds of appeal on 21 September 1999. With its reply of 22 May 2000 to the appeal statement, the respondent filed arguments and additional comparative experiments supporting its request for the appeal to be dismissed.

VIII. In the board's communication of 26 May 2003, the rapporteur informed the parties that claim 13 maintained by the opposition division (corresponding to claim 14 as granted) which related to a product (drug delivery system) *per se* (see V above) was to be considered as the broadest claim then on file and that the parties should be prepared to discuss the patentability of this claim during the oral proceedings with respect to both novelty and inventive step. The

rapporteur expressed his preliminary opinion that the disclosure of citation (5), - see especially the disclosure from page 7, line 5 to page 8, line 9 - provided for a cosmetic composition comprising a cross-linked hyaluronan and including substances having therapeutic activity and, accordingly, also for a drug delivery system.

In reply, by facsimile letter of 29 May 2003, the respondent submitted an amended claim 13 to replace claim 13 as maintained by the opposition division. The modified claim corresponded to claim 13 maintained (see V above), with the following additions indicated in bold italic letters below:

A drug delivery system **for slowing the release of a substance having biological or pharmacological activity** comprising a polymeric component <.....>, wherein said polymeric component is a water-soluble hylan or water-insoluble cross-linked hyaluronan.

- IX. Oral proceedings were held on 2 June 2003. Following a detailed discussion of both the formal aspects and substantive merits of all independent claims 1, 4, 13 and 17 to 19 as maintained by the opposition division (see V above), the respondent withdrew towards the end of the hearing its previous request and presented, instead, an amended set of 11 claims forming its sole remaining request.

- X. The respondent's current request consists of one single independent claim corresponding to claim 1 as maintained by the opposition division and dependent claims 2 to 11 corresponding to dependent claims 2

and 3 and 5 to 12 as maintained by the opposition division (see V above). Consequently, **in comparison with the claims as maintained by the opposition** the current set of claims has been amended as follows:

- (a) former independent claim 4 and all former claims from claim 13 onwards, i.e. claims 13 to 20 (see V above), have been deleted in the present set of claims;
- (b) dependent claims 2, 3 and 5 to 12 (see V above) have been renumbered consecutively in the present set of claims as dependent claims 2 to 11;
- (c) the references in present dependent claims 4 to 11 have consequentially been amended to take into account deletion of former independent claim 4.

XI. The appellant's arguments, submitted in writing during the oral proceedings as regards the issues relevant to the present decision, can be summarised as follows:

The conclusions reached in decisions G 2/88 (OJ 1990, 93) and G 6/88 (OJ EPO 1990, 114) as to the novelty of a "second non-medical use" were not applicable to product claims. It followed that the proposed amendment to claim 13 by insertion of the particular intended use for the claimed drug delivery system (see VIII above) could not render the claim's subject-matter novel vis-à-vis the state of the art according to citation (5).

Citations (1) to (4) disclosed already the use of hyaluronic acid and salts and water-soluble and water-insoluble esters thereof in drug delivery systems to

provide a slow release of drug from the system. The appellant submitted that the extremely broad definition of the hyaluronan derivatives used in present claim 1 as "a water-soluble hylan or a water-insoluble cross-linked hyaluronan" was, in the absence of any indication of the degree of cross-linking, insufficient to delimit the claimed use in the patent vis-à-vis the state of the art according to citations (1) to (4). Consequently, the subject-matter of claim 1 lacked novelty.

The closest state of the art under Article 54(2) EPC was in the appellant's judgment either one of citations (1) or (2) since both of them taught that hyaluronic acid or its salts were useful as drug releasing controlling agents for slowing the rate of drug release in drug delivery systems. In the absence of a clear distinguishing feature in claim 1 vis-à-vis the state of the art according to (1) and (2), it was in the appellant's opinion difficult to determine the objective problem underlying the claimed invention.

In paragraph 3.2 of its statement of the grounds of appeal the appellant considered that the problem in relation to citations (1) and (2) was "to provide a hyaluronic acid based drug vehicle having improved release delaying properties" [as compared with the state of the art according to (1) or (2)]. The appellant, on inquiry by the board at the hearing, confirmed that it considered the problem defined in its appeal statement to be superseded at this stage of the proceedings and that it did not wish to continue discussion of inventive step on the basis of this problem. It argued that the comparative evidence

provided by the respondent in the course of the opposition and subsequent opposition appeal proceedings was insufficient to demonstrate that the beneficial technical effects allegedly associated with the use of the hyaluronan derivatives broadly defined in claim 1, namely that their use as a drug delivery vehicle provided the benefit of a significantly slower drug release as compared with hyaluronic acid or its salts used in (1) and (2), can be credibly achieved over the whole range claimed. In this respect, the appellant expressed its doubts as to whether, for example, a water-soluble hylan, which has a relatively low degree of cross-linking but is nevertheless covered by claim 1, would indeed exhibit slower drug release properties than the prior art systems disclosed in citations (1) and (2). The appellant admitted, however, that no evidence in support of its allegation was available in the proceedings.

In view of its above observations, the appellant redefined during the hearing the problem to be solved by the claimed invention as that of providing alternative delayed-release drug delivery systems to those disclosed in (1) and (2). A skilled person seeking a solution to this problem would have known from citation (1) that the addition of hyaluronic acid or sodium or ammonium hyaluronate to different local anaesthetics was found to produce a pronounced increase of the duration of the pharmacological effects exhibited by these anaesthetics. Similarly, citation (2) taught that the use of hyaluronic acid as a vehicle for the medicament pilocarpine nitrate caused a significant prolongation of the medicament's activity. The appellant submitted that those skilled in the art,

knowing the state of the art according to (1) and (2), would have expected that the cross-linked hyaluronan derivatives broadly defined in present claim 1 would likewise exhibit valuable properties as drug release controlling agents. It concluded therefrom that the claimed subject-matter in the patent did not involve an inventive step.

XII. The counter-arguments submitted in writing and orally by the respondent as regards the issues relevant to the present decision were essentially the following:

The appellant's objection of lack of novelty was unfounded. The amendments made to the claims in the course of the opposition and subsequent opposition appeal proceedings had the effect of excluding water-soluble hyaluronan in the claimed invention. The claims required that the agent which was used to slow the release of a drug must be either a water-soluble hylan or a water-insoluble cross-linked hyaluronan. The amendments were made to distinguish the claimed subject-matter in the patent from citation (1), which described experiments in which solutions of sodium or ammonium hyaluronate were found sometimes to prolong the effects of various local anaesthetics. The sodium or ammonium hyaluronates used in (1) were water-soluble hyaluronans in the terminology of the present patent.

Citations (2) and (3) similarly suggested the use of water-soluble hyaluronans to prolong the effect of a drug. Of these only citation (2) was a prior publication, citation (3) being in the state of the art only in the sense of Article 54(3) EPC. Citation (4) which was likewise comprised in the state of the art

under Article 54(3) EPC was solely concerned with esters of hyaluronic acid, which might be fully water-soluble or poorly water-soluble depending of the degree of esterification. The insoluble esters of (4) were therefore not water-insoluble cross-linked hyaluronans to which the present claims related.

Moreover, by deleting independent process claim 4 (see V and VIII above) and granted claims 13 to 20 (see V and VIII above), the respondent had made every effort to dispel any of the board's and the appellant's remaining doubts about the novelty of the claimed subject-matter in the patent. Accordingly the claims maintained in the current sole request were undoubtedly novel vis-à-vis citations (1) to (6).

As regards inventive step, the respondent submitted that the problem as generally defined in the patent itself was to provide a drug system based on hyaluronic acid which provided a slow release of drug from the system. In the light of the state of the art according to citations (1) and (2), however, the problem needed to be more closely defined as being to provide improved delayed release drug systems based on hyaluronic acid. The delayed drug delivery systems now claimed had a number of important technical advantages over those using water-soluble hyaluronans as taught in (1) and (2), for example:

- the present compositions in general exhibited much slower drug release than the prior art;

- the rate of drug release from the present compositions could be more readily controlled to much an optimum for the drug concerned; and
- the claimed invention provided much greater flexibility in the design of a drug delivery vehicle meeting specific end-use requirements than was possible employing a water-soluble hyaluronan as taught in the cited prior art.

As evidence that the present compositions using either water-soluble hylan or water-insoluble cross-linked hyaluronan as the retarding agent exhibited a significantly slower rate of drug release than the prior art, the respondent made reference to (a) the comparative test data filed on 6 December 1993 with the respondent's letter of 3 December 1993, (b) Experiment 5 (using formaldehyde-cross-linked HA) filed on 24 April 1996 with the respondent's letter of 23 April 1996, and (c) Experiments 1 to 5 filed on 23 May 2000 with the respondent's letter of 22 May 2000.

None of the prior published citations relied upon by the appellant taught or suggested the claimed invention. If they described the property of slowing drug release, they were solely concerned with water soluble hyaluronan. If, on the other hand, they related to water-insoluble cross-linked hyaluronan, ie as do citations (5) and (6), then they were totally silent about the hyaluronan having any properties useful in the present invention. It was simply not to be expected that hylan or water-insoluble cross-linked hyaluronan would have the enhanced properties as drug release

controlling agents demonstrated in the course of the opposition and subsequent opposition appeal proceedings.

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

The respondent requested that the patent be maintained in amended form on the basis of claims 1 to 11 filed in the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

Admissibility of the respondent's request

2. Although the respondent's current sole request was presented for the first time during the hearing before the board and was, accordingly, filed late, the board considers that it should be admitted into the proceedings.

As regards deletion of independent claims 4 and 13 and the corresponding dependent claims (see VIII above), the respondent submitted that this was prompted by the discussion in the oral proceedings concerning the patentability of the subject-matter of these claims in the light of citations (1) and (5). As regards deletion of all independent "method claims" 17, 18 and 19 and dependent claim 20 (see VIII above), the respondent submitted that this was a response to the importance attached by the board during the hearing to the problem

of assessing the novelty and inventive step of these claims, in view of the references in claims 17, 18 and 19 to a product as defined in preceding "use claims 2, 4 and 9", respectively, although no such product is defined in the "use claims" referred to in claims 17 to 19 (see V above). These assertions appear, *prima facie*, correct. Although the board does not condone such lateness *per se*, the board considers it justified in the present case to exercise its discretion in favour of the respondent because the amendments were prompted by the discussion in the oral proceedings and their impact on the current request (see X above) was immediately clear to the board and the appellant. Moreover, the appellant did not challenge the admissibility of the respondent's late-filed request.

- 2.1 The amendments to the claims in the respondent's present request can fairly be said to be occasioned by grounds for opposition specified in Article 100(a) EPC and to constitute a bona fide attempt on the part of the respondent to overcome the appellant's objections of lack of novelty and inventive step raised in the opposition and appeal statements. The proposed amendments to the granted patent are thus also admissible under the terms of Rule 57a EPC.

Allowability of the amendments

3. The amendments (a), (b) and (c) to the respondent's current request (see X above) are found to comply with the formal requirements of Articles 84 and 123(2) and 123(3) EPC and are accordingly allowable.

Patentability; Introductory Remarks

4. The following introductory remarks most of which can also be found in the introductory portion of the patent specification, may contribute to a better understanding of both the claimed subject-matter in the patent and the disclosures in the cited state of the art:

4.1 The term "**hyaluronan**" is a synonym for the more traditional term "**hyaluronic acid**"; both terms are used in the patent interchangeably for the designation of a well known, naturally occurring, high molecular weight glycosaminoglycan having a repeating disaccharide unit consisting of D-glucuronic acid and N-acetylglucosamino-2-acetamido-2-desoxy-D-glucose joined by 1->3 glucosidic bond; these disaccharide units are joined to form an unbranched, uncross-linked polysaccharide chain by 1->4 glucosidic bonds.

Both terms "**hyaluronan**" and "**hyaluronic acid**" are hereinafter abbreviated "**HA**".

4.2 **HA** is an **uncross-linked, water-soluble** naturally occurring **polysaccharide**. It is found in animal tissues such as umbilical cord, vitreous, synovial fluid, rooster combs, skin, etc. The molecular weight of purified HA has been reported in the literature to be within the range of 50 000 to 8×10^6 depending on the source, method of isolation and method of determination of molecular weight. HA usually occurs as the sodium salt.

- 4.3 **Hylan** is a **cross-linked**, but nevertheless **water-soluble derivative of HA**. It is prepared by subjecting HA to a cross-linking reaction *in situ*, that is, in the animal tissue from which it is obtained before its extraction from such tissue. Hylan is soluble notwithstanding its cross-linked nature because the degree of cross-linking **is relatively low** as compared to more cross-linked HA. Suitable cross-linking agents for preparing hylan are, for example, formaldehyde, glutaraldehyde or glyoxal (see patent specification, page 2, lines 13 to 17).
- 4.4 Claim 1 relates to the use of either a **water soluble hylan**, i.e. a **water-soluble cross-linked HA derivative** (see 4.3 above), or a **water-insoluble cross-linked HA derivative**, other than a water-insoluble cross-linked HA gel formed using divinyl sulfone as cross-linking agent, as a drug release controlling (retarding) agent for slowing the rate of drug release in *drug delivery systems*.

Prior Art relating to cross-linked HA

5. Both **water-soluble cross-linked HA derivatives** and **water-insoluble cross-linked HA derivatives** and their uses for a number of different medical and non-medical applications are already known in the state of the art according to citations (5) and (6).
- 5.1 Citation (6) discloses **water-insoluble, cross-linked HA derivatives** which are made by subjecting HA to treatment with a cross-linking agent selected from formaldehyde, dimethylolurea, dymethyloethylene urea, ethylene oxide, a polyaziridine, a polyisocyanate or divinyl sulphone. It is taught that the water-insoluble

cross-linked HA derivatives disclosed in (6) can be used in numerous *in vivo* applications, such as various prosthetic devices, including artificial heart valves, vascular grafts, etc. They can also be used to modify various polymer articles which themselves can be used in numerous *in vivo* applications (see (6): especially page 1 lines 1 to 41).

5.2 On the other hand, citation (5) discloses both **water-soluble cross-linked HA derivatives** and **water-insoluble cross-linked HA derivatives**. The solubility or insolubility in water of cross-linked HA derivatives disclosed in (5) depends on the molar ratio of the HA or a salt thereof to the polyfunctional epoxy compound used in (5) as the cross-linking agent, for example a halomethyloxirane compound such as epichlorohydrin or epibromohydrin, or a bisepoxy compound such as 1,2-bis(2,3-epoxypropoxy)ethane, a diglycidyl ether or bisphenol A (see especially page 5, line 16 to page 6, line 6). This means that - as in the case of water-soluble hylans in present claim 1 - the degree of cross-linking of water-soluble cross-linked HA derivatives disclosed in (5) **is relatively low** as compared to more cross-linked HA.

5.3 A number of valuable properties and capabilities are ascribed to the cross-linked HA derivatives disclosed in (5), making them useful for a broad variety of different medical or cosmetic purposes, including in particular the following:

- use as arthritis treating agents (see paragraph bridging pages 6 and 7);

- use as ophthalmologic agents for the treatment of difficult retinal detachment to treat and restore e.g. retinal ablation with proliferation retinopathy of vitreous body, retinal detachment with huge dehiscence, proliferation traction retinal detachment or dehiscence-originated retinal detachment with diabetic rhenophaty (see page lines 5 to 19);
- use as the active ingredients of skin cosmetics (see page 7, line 20 to page 8, line 4);
- use as a drug delivery system comprising skin cosmetics in conjunction with substances having therapeutic activity (see page 8, lines 5 to 7: "also, the present skin cosmetics [comprising a cross-linked HA] may be blended with allantoin or its derivative which may be employed as a **dermatological disease treating agent**".)

5.4 Citation (5) must thus be considered **as representing the closest prior art** available in the proceedings because it is the only document before the board relating to both **water-soluble cross-linked HA derivatives** and **water-insoluble cross-linked HA derivatives and** their use for a number of different medical or cosmetic purposes, including their use as a drug delivery system comprising skin cosmetics in conjunction with substances having therapeutic activity (see 5.2 and 5.3 above)

Problem and Solution

6. In the light of the disclosure in (5) as representing the closest state of the art, the problem to be solved by the claimed invention can be seen to be to find for both the water-soluble cross-linked HA derivatives and water-insoluble cross-linked HA derivatives a further usable property in addition to the ones specified in (5). It is the normal task of the skilled person to be constantly occupied with the investigation of additional usable properties exhibited by known, widely applicable biological substances, such as polysaccharides, in order to find further valuable applications for such substances, for example, in the field of pharmacy or chemistry. According to claim 1, this problem is solved by their proposed use as a vehicle (drug release controlling agent) which provides a slow release of a drug from a drug delivery system.

6.1 That water-soluble **hylan**, i.e. **a water-soluble cross-linked HA derivative** - see 4.3 and 4.4 above, exhibits useful slow drug release properties can be derived, *inter alia*, from the following experimental data provided by the respondent in the course of the opposition and subsequent opposition appeal proceedings:

- Experiment 1 in Appendix A filed on 6 December 1993 with the respondent's letter of 3 December 1993

- Experiments 1 to 5 filed on 23 May 2000 with the respondent's letter of 22 May 2000.

That **water-insoluble** (but non-DVS) **cross-linked HA** - see 4.4 above - exhibits useful slow drug release properties can be derived from the experimental data in Experiment 5 (using formaldehyde-cross-linked HA) filed on 24 April 1996 with the respondent's letter of 23 April 1996.

- 6.2 In view of test data reported in the respondent's above-mentioned experiments and in the absence of any evidence to the contrary, the board accepts that the stated problem has been credibly solved within the whole area claimed. Although the board admits that the definition of the HA derivatives in claim 1 is extremely broad, covering the complete spectrum of water-soluble HA derivatives with a negligible degree of cross-linking (hylans) to highly cross-linked ones which are insoluble in water, the onus of proof that the problem has not been solved over the whole range claimed was in any case on the appellant at this stage and no such evidence has been provided.

Novelty

7. The technical teaching of claim 1, i.e. use of water-soluble hylan or a water-insoluble cross-linked HA derivative as a vehicle (drug release controlling agent) which provides a slow release of a drug from a drug delivery system, differs from the technical teachings described in citations (5) and (6) and referred to in detail in points 5.2 and 5.3 above. It may be true that any practice of the particular teaching in (5) - use a drug delivery system comprising cosmetics in conjunction with substances having therapeutic activity (see 5.2 above) - must also result

in an unintentional and unnoticed sustained release of the therapeutically active substance used. However, the achievement of this particular effect (slow release of drug from the system) deliberately and purposefully was taught for the first time in the patent. This effect represents a technical effect within the meaning of decisions G 2/88 (loc. cit.) and G 6/88 (loc. cit.), which is necessary to establish novelty, under Article 54(1) EPC, of the claimed subject-matter vis-à-vis the prior art. In accordance with the principles laid down in cited decisions of the Enlarged Board of Appeal, the fact of certain substances (here water-soluble hylan and water-insoluble cross-linked HA) being known cannot preclude the novelty of a hitherto unknown use of those substances, even if the new use does not require any technical realisation other than that for a hitherto known use of the same substances. The claimed solution in the patent is therefore novel within the meaning of Article 54(1) EPC.

- 7.1 The appellant objected to this finding. It submitted that citations (1) to (4) already disclosed the use of uncross-linked HA and salts and water-soluble and water-insoluble esters thereof as drug vehicles that are useful in slowing the rate of drug release from a delivery system and that, in the absence of any indication of the exact degree of cross-linking of the HA derivatives used as the vehicles in claim 1, the claimed subject-matter in the patent was not clearly delimited from the cited state of the art. Although the board agrees with the appellant's submission that the definition of the HA derivatives in claim 1 is extremely broad, covering the complete spectrum of water-soluble HA derivatives with a negligible degree

of cross-linking (hylans) to highly cross-linked ones which are insoluble in water, the state of the art according to citations (1) to (4) is, however, **completely silent** as to the use of a **cross-linked HA derivative of any degree of cross-linking**. It follows therefrom that the claimed use in the patent cannot be said to be anticipated by the state of the art according to citations (1) to (4).

Inventive Step

8. The claimed solution must therefore be examined to see whether it is also based on inventive step.

8.1 Long before the contested patent's priority date, it was generally known to specialists that certain polymeric substances and, in particular, a series of polysaccharide compounds, such as dextrans, are useful in slowing the rate of drug release in drug delivery systems (see, for example, the references to the use of dextrans as vehicles in drug delivery systems - see citation (1), page 384, left-hand column).

Moreover, prior to the priority date, it was already known from the state of the art according to (1) and (2) that other polysaccharide compounds, namely HA and its sodium or ammonium salts, also have excellent properties as drug release controlling agents in drug delivery systems comprising a pharmacologically active substance selected from various local anaesthetics (see (1): the whole document) or pilocarpine nitrate (see (2): especially page 27, last paragraph). HA and its salts cause a significant prolongation of action of pharmacologically active substances owing to their

ability to delay the release of the substances from the system. It is also already taught in (1) that the duration of action was found to be directly related to the viscosity of the local anaesthetic solutions modified by addition of HA and that increasing the viscosity of local anaesthetic solutions by addition of HA seems to be a feasible method in the search for longer acting local anaesthetic preparations (see page 387, left-hand column, last full paragraph; page 388, last paragraph).

- 8.2 In the light of the above-mentioned teaching in the state of the art, coupled with the fact that polysaccharide compounds in general have been widely used for many years as retarding agents in drug delivery systems, the skilled person had, in the board's judgment, every reason to expect that at least some, if not all, of the cross-linked HA derivatives falling within the broad definition in claim 1 (covering the complete spectrum of water-soluble slightly cross-linked HA derivatives (hylans) to highly cross-linked ones (which are insoluble in water) would exhibit qualitatively at least the same or improved low drug release properties as shown for HA itself and its salts in (1) and (2). In view of the structural closeness of water-soluble hylans to water-soluble HA and its salts in the cited art, the skilled person would have expected that HA derivatives in accordance with present claim 1 exhibit the stated properties as drug release controlling agents and would have suggested their use for the claimed purpose.

8.3 In the board's view, the cited state of the art according to (1) and (2) contains a clear suggestion to choose water-soluble cross-linked and water-insoluble cross-linked polysaccharide compounds disclosed in (5) as drug release controlling agents in drug delivery systems for slowing the release of a substance having pharmacological activity from the system. The appellant has failed to provide any reasoned argument, let alone convincing technical explanation, as to why, for example, a water-soluble, slightly cross-linked HA derivative (hylan) according to present claim 1 should exhibit entirely different properties to HA or its salts when used as a drug release controlling agent.

8.4 In the present situation, the prior art pointed the notional skilled person in the direction of the claimed use, and it only remained to confirm experimentally by a small number of routine tests that the thoroughly obvious result, namely that water-soluble hylans and water-insoluble cross-linked HA according to claim 1 can act as drug release controlling agents, was in fact obtained. However, the necessity of experimentally confirming a reasonably expected result does not render an invention unobvious.

The board is aware that the respondent has found in the comparative tests referred to in 6.1 above some slightly enhanced effects associated with the use of water-soluble hylans and a water-insoluble (but non-DVS) cross-linked HA as drug release controlling agents in comparison with HA or its salts and esters used in the cited state of the art. If, as here, the aim was to find for known water-soluble cross-linked HA derivatives (ie hylans) and water-insoluble cross-

linked HA derivatives a further usable property (see 6 above), the first self-evident step - before any thought is given, say, to finding some other valuable properties for these HA derivatives - is to test whether they exhibit that property which would have been expected and envisaged by the skilled person in the light of the cited state of the art and which in the present case is, as shown above, straightforwardly obvious. Such tests are routine. According to established case law of the boards of appeal (see eg T 296/87, OJ EPO 1990, 195) enhanced effects cannot be adduced as evidence of inventive step if they emerge from obvious tests. Since, in the present case, tests with the HA derivatives defined in claim 1 were obvious in view of the task at hand, discovery of some slightly enhanced effects exhibited by these HA derivatives as compared with HA and its salts used in (1) and (2) for the same purpose cannot be regarded as an indication of inventive step.

- 8.5 It follows from the foregoing that the subject-matter of claim 1 does not involve an inventive step, contrary to the requirements of Article 52(1) in conjunction with Article 56 EPC. Since a decision can only be taken on each request as a whole, there is no need to look into the patentability of any of the dependent claims.

Order

For these reasons it is decided that:

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

The Registrar:

The Chairman:

A. Townend

U. Oswald