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Datasheet for the decision of 14 April 2010

Case Number: T 0365/09 - 3.3.03

Application Number: 99968778.3

Publication Number: 1144459

IPC: C08B 37/08

Language of the proceedings: EN

Title of invention:
Cross-linked hyaluronic acids and medical uses thereof

Patentee:
Sigmar Italia S.p.A.

Opponent:
Fidia Farmaceutici S.P.A.

Headword:
-

Relevant legal provisions:
EPC Art. 56, 112, 112a

Keyword:
"Inventive step - ex post facto analysis"
"Inventive step - non-obvious combination of known features"
"Inventive step - problem and solution"
"Res judicata"

Decisions cited:
G 0001/97, G 0003/08, T 0254/86, T 0656/90, T 0843/91, T 0934/91, T 0785/05

Catchword:
Res judicata under EPC 2000 (reasons 2 to 2.2)

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0365/09 - 3.3.03

D E C I S I O N
of the Technical Board of Appeal 3.3.03
of 14 April 2010

Appellant: (Opponent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office dated 7 November 2008 and posted 8 December 2008 concerning maintenance of European patent No. 1144459 in amended form.

Composition of the Board:

Chairman: R. Young
Members: A. Däweritz
H. Preglau

Summary of Facts and Submissions

I. European patent No. 1 144 459, which had been granted in respect of European patent application No. 99 968 778.3, filed on 8 November 1999 as International patent application PCT/EP99/08481 and claiming the priority of 11 November 1998 of an earlier application in Italy (MI982440), had already been the matter of dispute in appeal case T 0785/05. In the decision of 18 December 2007 (not published in OJ EPO) terminating that appeal case, the Board set aside the previous decision of the Opposition Division, in which the above patent in suit had been revoked for lack of novelty, and remitted the case back to the first instance for further prosecution on the basis of the Main Request filed with the letter of 19 October 2007, which contained 11 claims and differed from their granted version only by Claim 1 reading as follows:

1. Cross-linked hyaluronic acids obtainable by reaction of the carboxylic groups of hyaluronic acid **activated by chloromethylpyridylium iodide** and a polyamine.

The further claims of the Main Request had the following wording:

2. Cross-linked hyaluronic acids according to claim 1 wherein the polyamine is a diamine.

3. Cross-linked hyaluronic acids according to claim 2 wherein the diamine has the formula

$$R_1NH\text{-}A\text{-}NHR_2$$

wherein A is a C_2 - C_{10} linear or branched alkylene chain, preferably a C_2 - C_6 chain, optionally substituted by hydroxy, carboxy, halogen, alkoxy and amino groups; a polyoxyalkylene chain $[(CH_2)_n\text{-}O\text{-}(CH_2)_n]_m$ wherein n is 2 or 3, m is an integer from 2 to 10; an aryl or hetaryl group, preferably 1, 4 or 1,3 disubstituted benzene; R_1 and R_2, which are the same or different, are hydrogen, C_1-C_6 alkyl, phenyl or benzyl groups.

4. Cross-linked hyaluronic acids according to claim 3 wherein A is a linear C_2 - C_6 alkylene or a chain of formula

$$[(CH_2)_n\text{-}O\text{-}(CH_2)_n]_m$$

wherein n is 2 and m is an integer from 2 to 10.

5. Cross-linked hyaluronic acids according to any one of claims 1 to 4 wherein the hydroxy groups are sulphated or hemisuccinylated.

6. Cross-linked hyaluronic acids according to any one of the previous claims in the form of gel.

7. Cross-linked hyaluronic acids according to any one of the previous claims in solid or semi-solid forms.

8. Complexes of zinc, copper or iron of the products of the claims 1-7.

9. The use of cross-linked hyaluronic acids derivatives of claims 6 and 8 as substitutes of synovial fluid, vitreous humor, as controlled-release matrices forms medicaments, as healing and antiadhesive agents.

10. The use of cross-linked hyaluronic acids derivatives of claim 7 for the preparation of vascular prosthesis, biohybrid organs, healing devices, ophthalmic and otological compositions, prosthesis, implants and medical devices.

11. Biomaterials comprising the cross-linked hyaluronic acids of claims 1-8.

In view of the order in T 785/05, the Board did not see any need to deal with the Auxiliary Request also filed with the Patent Proprietor's letter of 19 October 2007 (cf. T 0785/05, above, No. VI(4) and Reasons 6).

During the different stages of these opposition and appeal proceedings, altogether 20 documents were cited by the two parties, including

D1: K. Tomihata et al., "*Crosslinking of hyaluronic acid with water-soluble carbodiimide*", J. Biomed. Mater. res. 37, (1997), pages 243-251;

D3: WO-A-98/08 897;

D4: WO-A-95/24 429;

D5: EP-B-0 341 745;

D6: T. Pouyani et al., "*Solid-State NMR of N-Acylureas Derived from the Reaction of Hyaluronic Acid with Isotopically-Labeled Carbodiimides*", J. Am. Chem. Soc. 114 (1992), pages 5972 to 5976;

D7: J. Kuo et al., "*Chemical Modification of Hyaluronic Acid by Carbodiimides*", Bioconjugate Chemistry, 2 (1991), pages 232 to 241;

D10: W. Keese *et al.*, "*2-Chlor-1-methylpyridiniumjodid*", Biol. Chem. Hoppe-Seyler, 366 (1985), 1093 to 1095;

D12: T. Mukaiyama, "*New Synthetic Reactions Based on the Onium Salts of Aza-Arenes*", Angew. Chem. Int. Ed. Engl., 18 (1979), pages 707 to 721; and

D13: EP-A-0 566 118.

II. In this decision, references to passages in the patent in suit as granted will be given underlined in squared brackets, eg [0001]. References in underlined italics concern passages in the application as filed and as published in WO-A-00/027887, eg *page 1, line 1*.

The following abbreviations will be used herein below:

EPC 1973 European Patent Convention, 1973 version

EPC European Patent Convention as amended in 2000

Case Law	Case Law of the Boards of Appeal of the European Patent Office, 5th Edition (2006)
dec	reference to the decision (under appeal)
SGA	Statement of Grounds of Appeal
rej	reference to the rejoinder
HA	(or elsewhere: HY) hyaluronic acid
CMP	chloromethylpyridinium
CMPJ	CMP iodide, in the [patent] referred to as "*chloromethylpyridylium iodide*"
WSC	water-soluble carbodiimide, such as eg:
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Lys-Me	L-lysine methyl ester

III. On 18 July 2008, the Opposition Division continued the opposition proceedings by issuing a summons to oral proceedings to be held on 7 November 2008. In an annex to the summons, it informed the parties that, since novelty had been acknowledged by the Board in T 0785/05 (above), the issue to be discussed at the oral proceedings would relate to the question of inventive step. Furthermore, it indicated as its preliminary and non-binding position concerning this question that the presence of inventive step could presumably be acknowledged, irrespective of whether D1 or D5 would be used as the closest state of the art.

IV. In a letter of 5 September 2008, the Patent Proprietor reiterated its arguments to the issue of inventive step and requested that the patent be maintained on the basis of its Main request or, in the alternative, its Auxiliary Request, both as filed with its letter of 19 October 2007 (cf. section I, above).

V. By contrast, the Opponent disputed in a letter dated 29 September 2008, that the requirement of inventive step of the claimed subject-matter would not be met, and referred additionally to the revocation of another

case of the present Patent Proprietor by an Opposition Division for lack of novelty. That decision played, however, no role in the further proceedings.

VI. At the end of the above oral proceedings (section III, above), the Opposition Division announced its interlocutory decision, that "*Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the Convention. The currently valid documents are those according to the main request dated 19.10.07.*" (cf. the Minutes on "*EPO Form 2309.2 12.07CSX*").

(1) However, both the front sheet of the interlocutory decision, as issued in writing on 8 December 2008 ("*EPO 2327 12.07CXS*") and the "*EPO Form 2339 (Sheet 1) 12.07CSX*" as signed by the members of the Opposition Division, contained an "*Additional decision*", that the opposition of the present opponent was rejected as inadmissible.

By contrast, in both the first decision of the Opposition Division, which had been dealt with in T 785/05, above, and the interlocutory decision forming the basis of these appeal proceedings, the same wording was used in the respective Reasons 1 ("*II.1*") dealing with the admissibility of the opposition: "*The opposition is admissible because it meets all the requirements of Art. 99(1) and 100 EPC and of Rules 1(1) and 55 EPC.*"

(2) In II.2 of the interlocutory decision, it was pointed out that the question of novelty of the claimed subject-matter had already been decided in T 785/05.

(3) With regard to the issue of inventive step, the Opposition Division dealt in the reasons for the interlocutory decision not only with the arguments starting from D1, which it considered as being the

closest piece of prior art (D1 + D12 and D1 + D5; dec: II.3.1 to II.3.1.2), but - "*Assuming for the sake of a complete analysis that D5 is the closest prior art*" (dec: II.3.2) and "*Assuming that D13* (and *D3*, respectively) *could be considered as the closest prior art*" (dec: II.3.3 and II.3.4, respectively) - also with seven further lines of argument presented by the Opponent in its written submissions, starting from D5 (D5, D5 + D3, D5 + D13, D5 + D12; dec: II.3.2 to II.3.2.3), D13 (D13, D13 + D4; dec: II.3.3 and II.3.3.1) and D3 (dec: II.3.4), respectively.

(4) The Opposition Division held D1 to be the closest piece of prior art, because it "*shares with the patent in suite* [sic] *the most technical features and is directed to the same technical problem.*" Despite the fact that it had been established in T 785/05 that, contrary to its disclosure, D1 had not actually led to an amide cross-linked HA, it was considered as the best starting point for the assessment of inventive step. (dec: II.3.1).

(5) The technical problem was formulated as follows: "***The objective technical problem in view of D1 is the provision of homogeneous HA-product in a reproducible process****, furthermore a cross linked hyaluronic acid which has high biocompatibility, a high resistance to enzymatic degradation, a high capacity to absorb water and an ability to chelate metal ions (cf. patent page 3, lines 1-5)*", ie it comprised two aspects: the provision of the product and certain properties thereof (dec: page 4, lines 4 to 10).

(6) The solution of this problem was, according to the decision, the provision of a crosslinked HA which could be obtained by means of a specific activating agent, namely CMPJ (dec: page 4, lines 11 to 14), and which, as shown in [Examples 1 to 12], showed a high degree of swelling in water and could chelate metal ions. However,

when it was realised that D1 did not actually lead to amide crosslinked HA (cf. D6, page 5974, right column; D7, page 237 and T 785/05, above, Reasons 4.3.3, 4.3.5 and 4.3.6), it was not derivable from D1 itself nor from D1 in combination with D5 or D12, that it had been the WSC activator which had caused the problems. Nor did D1 contain an indication to using CMPJ as the activator for that reaction (dec: page 4, lines 16 to 26). Instead, there were ample possibilities available to the skilled person for optimising the crosslinking of HA (variation of pH or reaction temperature or the use of other external or internal crosslinkers).

(7) "*The skilled person would not end up within claim 1 by combining the documents D1 and D5*", because, whilst D1 tried to crosslink HA externally by its reaction with polyamines to polyamide groups, D5 disclosed the cross-linking of HA via intra- and intermolecular ester bonds and the activation of the carboxy groups by means of a compound chosen from a "*list of possible activators … which contains also carbodiimide as a member … Chloromethyl-pyridinium chloride (CMPCl) is mentioned as preferred … and CMPJ is used as activator in all the examples of D5*". When comparing D1 and D5, it would be apparent that the external crosslinker was missing from D5. Moreover, in view of the teaching in D5, that carbodiimides were useful activators, it was not apparent that the WSC should be replaced (dec: II.3.1.1).

(8) D12 referred to the activation of carboxylic groups in general, whilst D1 related to the complex macro-molecular HA. There was no indication in D12 that CMPJ would be a better activator than WSC. Nor would D12 be considered, since it did not deal with the crosslinking of HA for medical applications. In this connection, the

skilled person would have had more motivation to consult other documents (dec: II.3.1.2).

(9) As mentioned in section VI(3), above, the Opposition Division also dealt with the line of argument presented by the Opponent in further approaches on the basis of the following wordings of the problem: "***The objective technical problem in view of D5 is the provision of homogeneous HA-product in a reproducible process.***" (dec: II.3.2) and "***The objective technical problem in view of D13 is the provision of homogeneously cross linked polysaccharide product in a reproducible process.***" (dec: II.3.3), respectively.

(10) Considering the solution to the problem as offered in D5, it was evident that WSC was a good activator for the crosslinking reaction of D5. However, no reference or suggestion could be found therein concerning the use of a polyamine as an external crosslinker (dec: II.3.2).

(11) As regards the suggested combination of D5 and D13, it was held that, when starting from D5, it had to be decided at first that it was HA which was to be cross-linked externally, and, thereafter, polyamine had to be selected as the external crosslinking agent. D13 would not, however, give sufficient guidance to make these choices, since D13, which referred to modified poly-saccharides in general for use as superabsorbents, did not mention an activation for the crosslinking, let alone the use of CMPJ therefor. Moreover, HA was mentioned in D13 only as a crosslinking agent amongst others, such as polyamines and polyols (dec: II.3.2.1).

(12) Nor would a combination of D5 and D3 lead to the claimed subject-matter, because D3 neither indicated to use HA homopolymers nor suggested their activation by CMPJ (dec: II.3.2.2).

(13) Whilst D5 taught the crosslinking of HA by intra- or intermolecular ester bonds, D1 tried to crosslink HA externally with polyamines. The reader of D1 would realise, in the light of D5, that it was the WSC which was missing from D5, and he would not be motivated to crosslink HA externally with the help of polyamines, because D1 did not teach that external crosslinking would solve the posed problem (dec: II.3.2.3).

(14) D13 (used by the Opponent as a further starting point) referred to HA only as one of several different crosslinkers for polysaccharides (cf. section VI(11), above). The technical problem seen with regard to D13 was about the same as the problem to be solved with regard to D5 (see section VI(9), above). For its solution, one would have, firstly, to choose HA as the polysaccharide and, secondly, to activate HA by CMPJ. Neither choice was suggested in D13 (dec: II.3.3).

(15) With regard to the suggested combination of D13 and D4, it was held that D4 related to the modification of polysaccharides to esters, amides and thioesters via the formation of active ester intermediates, however, without mentioning polyamines as external crosslinking agents or CMPJ as an activator. Again several choices would have to be made, when starting from D13 as the closest state of the art: choice of HA as the substrate, choice of polyamines as the crosslinking agent and choice of CMPJ as the activator (dec: II.3.3.1).

(16) The technical problem to be solved with respect to D3 was the same, as quoted for D13 in section VI(9), above. Whilst D3 was concerned with HA copolymers which were crosslinked with polyamines, there was no indication to use HA homopolymer nor its activation by CMPJ (cf. section VI(6), above; dec: II.3.4).

(17) In summary, the Opposition Division concluded that the subject-matter of the Main Request (Claims 1 to 11) was inventive with respect to D1, D5, D13 and D3 and that the claims (sections I, IV and VI, above) thus met the requirements of the EPC (dec: II.3.5 and II.3.6).

VII. On 9 February 2009, a Notice of Appeal was filed by the Opponent with simultaneous payment of the prescribed fee. In the SGA, which was received on 10 April 2009, the Appellant requested that the decision under appeal be set aside and that the patent in suit be revoked.

(1) Firstly, the Appellant observed that on the cover sheet of the decision under appeal, there was a mistake in that it contained an additional decision that the opposition would be inadmissible, and it requested that this mistake be corrected.

(2) With regard to the merits of the claimed subject-matter, the Appellant maintained its objection of lack of inventive step and disputed the reasons given by the Opposition Division, as referred to in sections VI(3) to VI(16), above.

(3) On the basis of the documents listed in section I, above, the Appellant presented eleven different lines of argument, namely based on combinations of D1 and D12, D1 and D5, D5 and D12, D5 and D3, D5 and D13, D5 and D1, D3 and common general knowledge, D3 and D1, D3 and D4, D13 and D4 and, finally, D7 and D5 (cf. section VI(3), above).

(4) However, on page 4 of its SGA, the Appellant agreed to the finding in the decision under appeal that "*D1 has to be considered the closest prior art*", as it had the most technical features in common with the patent in suit and was directed to the same technical problem. More

particularly, the Appellant referred to II.3.1 in the decision under appeal (cf. sections VI(4) and VI(5), above), according to which D1 disclosed the cross-linking of HA with a diamine crosslinker (Lys-Me) in the presence of WSC and to the reaction schemes (2), (3) and (5) on pages 249 and 250 of D1.

Hence, the person skilled in the art would have known from D1 that it was possible to prepare in this way crosslinked HA having definitely improved properties in terms of hydration and degradation for use in bio-medical applications in comparison with non-crosslinked HA. The problem to be solved with respect to this document was seen in the provision of an alternative activating agent (SGA: page 14, paragraph 2).

Additionally the Appellant (O-01) referred to different parts of the patent in suit (SGA: pages 7 and 8), according to which (i) the activation could be achieved by conventional methods, only one of which was the use of CMPJ, and (ii) the crosslinking degree could be adjusted within broad limits by changing the amount of activator used. Moreover, these passages of the patent in suit would show that the solution of the technical problem was given by the crosslinking through formation of the amide bond and that it did not depend on the specific activator used. Moreover, the Appellant criticised that the Patent Proprietor had not filed any comparative examples, which would show that it was the use of CMPJ which would be the crucial requirement for the solution of the relevant technical problem.

With regard to the finding in the decision under appeal that there had been plenty of possible modifications, the Appellant argued that it was the simplest to use a different activator. The skilled person would in any

case look at first for a generic teaching about the activation of carboxy groups to be reacted with diamine (SGA: pages 9 and 10).

(5) Despite the acceptance of D1 as the closest piece of prior art (section VII(4), above), the Appellant nevertheless used D5, D3, D13 and D7, respectively, as further starting point for contesting inventive step (section VII(3), above).

(6) Thus, D5 (SGA: point 1.2) would teach to crosslink carboxy polysaccharides, in particular HA, via intra- or inter-molecular ester bonds by activating at first their carboxylic groups by means of an activating agent, such as CMP halides and preferably CMPCl as shown on page 4, lines 24 to 27 and 32 of D5. This activation would result in a substituent group highly reactive to the hydroxyl group of the same or other HA molecules thereby forming crosslinking ester or lactone bonds. According to D5, page 16, paragraph 1, free carboxylic groups of HA could be esterified in part or completely with mono- or polyvalent alcohols, eg "*amino alcohols, … as external crosslinkers (see page 7, lines 10 to 24)*" (SGA: page 16, lines 4 and 5). Moreover, apart from HA itself, its partial esters with mono- or polyvalent alcohols could be used as starting materials for the preparation of new crosslinked products of D5.

"*Considering D5 as the closest prior art, as also indicated by the Interlocutory Decision under Appeal at point 3.2, the only difference is in that no teaching would be present about the use of polyamines as 'external' cross-linker in D5.*" (SGA: page 16, paragraph 3). From D5, it would have been clear to the skilled person that it was possible to control the degree of crosslinking when carrying out

the process of D5, which would yield a homogeneous HA-product in an absolutely reproducible manner.

Contrary to the decision under appeal, the Appellant saw the remaining technical problem with respect to D5 hence in the provision of an alternative crosslinking agent (SGA: page 17, line 5).

(7) With regard to D3, the technical problem to be solved was seen in the SGA (point 1.3) in the choice of an alternative crosslinked polymer for biomedical use. The solution to this problem was seen in a process for crosslinking HA in the presence of a crosslinking agent consisting of a polyamine, a tri- or a diamine (D3: page 2, lines 6/7 and page 3, lines 13 to 21), the process being carried out by adding the activating agent and the crosslinking agent to the polycarboxylic polymers. The only difference from the patent in suit would reside in the presence of a further comonomer [*sic*] not being a polysaccharide and a polyamine during the preparation of the crosslinked product. However, the choice of crosslinked HA alone, without a second copolymer consisting of a second polycarboxylic polymer which was not a polysaccharide, was considered by the Appellant as being "*absolutely obvious in view of the common general knowledge or in view of the cited state of the art.*" (SGA: page 24, penultimate paragraph).

(8) In point 1.4 of the SGA, the Appellant started from D13 as the closest piece of prior art. It would clearly address the issues of providing crosslinked poly-saccharides and, in particular crosslinked HA, in an amidation reaction with a polyamine as the crosslinking agent. Additionally, reference was made therein to an optional formation of crosslinks by esterification resulting from self-crosslinking of the material and/or

from the presence of a crosslinking agent other than a diamine or polyamine. The only difference from the patent in suit would reside in the absence of a previous activation, in particular by CMPJ. "*The effect thereof is that the process is more reproducible and yields a more homogeneous product. The problem to be solved can therefore be seen as how to provide crosslinked .HA which are more homogeneous and can be made with higher reproducibility than those of D13.*" (SGA: page 30, paragraphs 3 and 4).

(9) In chapter 1.5 of the SGA, D7 was regarded as closest state of the art. In its introduction, D7 stated that studies about crosslinking HA and its coupling would be extremely important, because they would allow biomaterials to be obtained having surgical and medical value as long-lasting biomaterials and as potential drug-delivering vehicles. The skilled person was, since 1991, faced with the importance of chemically modifying HA by crosslinking or coupling with other molecules. The specific interest of the author of D7 was that of studying the possibility to activate, by action of carbodiimide, the reaction of the carboxy groups of HA with difunctional amines and thus to obtain undegraded HA with a free amine group. However, unexpectedly, he obtained functionalised and crosslinked HA. In the examples of D7, more particularly, urea derivatives, wherein the amine was not bound, were obtained by reacting carbodiimide, HA and diamine. However, the right column on page 239 of D7 (figure 8) referred to a specific synthesis allowing the preparation of stable crosslinked HA using HA and bis-carbodiimides, namely by using molecules with two amine groups which reacted with the carboxylic groups of HA. Therefore D7 would provide a clear teaching to

obtain very stable gels from HA crosslinked via "*bridge molecules through N atoms*".

The problem to be solved with regard to D7 was identified as the finding of an alternative activating agent for the carboxylic group to carry out the reaction indicated in D7. (SGA: page 33, paragraph 1).

(10) As addressed in section VII(3), above, the Appellant argued that the subject-matter of the patent in suit was obvious in the light of combinations of two of these documents (as referred to in sections VII(4) to VII(9), above), or in the light of one of these closest pieces of prior art in combination with D4 or D12, (cf. section VII(3), above).

(11) According to the SGA, page 28, D4 pertained to the same technical field. More particularly, it concerned the preparation of highly reactive esters which could be used for the preparation of a variety of modified carboxy polysaccharides, in particular, those obtained by reaction of these active esters with primary amines to amide derivatives, which were to be used in the bio-medical or pharmaceutical fields. The active esters had, according to the SGA, a high reactivity and selectivity with respect to amines.

The person skilled in this art would certainly carry out the reaction suggested in D3 (cf. section VII(7), above) by using the active esters of D4, without using the second copolymer of D3, when he wanted to prepare crosslinked HA. Thereby he would obtain exactly the solution taught by the patent in suit. Consequently, Claim 1 of the Respondent's requests did not meet the inventive step requirement (SGA: point 1.3c)).

(12) The same conclusion was drawn by the Appellant in point 1.4a) of the SGA with regard to the combination

of D13 relating to the crosslinking by amidation (cf. section VII(8), above) and D4 (cf. section VII(11), above) so as to provide crosslinked HA which was more homogeneous and could be made with higher reproducibility than the products of D13.

(13) Whilst admitting that other documents such as D6 and D7 taught that the activation with WSC could not bring about to get the amide bond, the Appellant argued that the skilled person would, in the knowledge of the advantages disclosed in D1 (which was younger than D6 and D7), have thought about optimising the crosslinking reaction with diamines (as disclosed in D1) by using an activating agent for the carboxyl group well-known from the state of the art, namely from D12. According to this document, the amidation reaction with primary or secondary amines would be made much easier by the use of weak bases. Therefore, he would certainly have used CMPJ and triethylamine (as in [0028] and [0032]) to activate the carboxylic group "*to obtain a complete reaction with the polyamine, reaction already taught by D1*" (SGA, the paragraph bridging pages 5/6).

The mechanism of the reaction between a carboxylic acid and "XMPJ" (X = Cl or Br) as shown in the scheme on page 708, left column of D12, would clearly indicate that an activated ester compound (*2*) thus formed could be attacked by a nucleophile. According to the end of the right column of that page, a carboxylic acid group activated by CMPJ (*1a*) would react with primary and secondary amines, when used as the nucleophile, to carboxamides in high yields (D12: Table 4), quantitative or >85%, depending on the amine.

"*Therefore a skilled person in the field, knowing both the teaching of the prior documents D1 and D12 and wanting to*

find an alternative activating agent compound … would have certainly used CMPJ in view of the clear indication present in D12 about the quantitative yields of such reactions." (SGA: point 1.1.a), namely, page 6, lines 12 to 18).

Therefore, the claimed subject-matter of the patent in suit did not involve an inventive step in view of the combination of the teachings of D1 and D12.

(14) In the SGA, point 1.2a), the Appellant saw the problem to be solved with regard to D5 in the provision of an alternative crosslinking agent (section VII(6), above). In view of D12, disclosing the use of primary and secondary amines in the preparation of carboxamides in high yields (see section VII(13), above), the person skilled in the art "*would have certainly tried diamines*", when "*wanting to find an alternative compound to carry out a nucleophilic substitution of the activated ester of HA obtained after treatment with CMPJ, with respect to the alcohols disclosed in D5*" (SGA: page 17, paragraph 3).

(15) In summary, it was, in the Appellant's opinion, obvious to combine the teachings of these different documents as listed in section VII(3), above, and thus to arrive at something within the operative claims.

VIII. In its rejoinder of 11 August 2009, the Respondent disputed all of the Appellant's arguments. Additionally, it filed clean copies of its Main Request (cf. sections I and VI(17), above), and three further limited Auxiliary Requests.

(1) Since none of these Auxiliary Requests played a role in the further proceedings there is no need further to refer to them in this decision.

(2) Primarily, the Respondent discussed the question of inventive step on the basis of D1 as the closest piece of prior art in combination with D12.

(3) In its considerations concerning D1, the Respondent referred to formulations in D1 such as "*probably because of amide bond formation as the crosslink (see Abstract of D1)*", "*… the following experiment was performed in an attempt to crosslink HA molecules through an amide bond which is more resistant against hydrolysis than the ester bond … (see page 247, right col. of D1)*", "*The plausible mechanism of crosslinking of HA … (see page 250, right col., lines 1 to 4 and Scheme 5 of D1)*" and "*This finding strongly suggests that an amide was formed … (see page 250, left col. lines 27-37 of D1; emphasis added)*". Based on these passages, the Respondent concluded, in a statement in No. 7 of the rejoinder (referring to an expected reduction of HA degradation, "*If HA molecules are crosslinked not only through ester but also through amide*" on "*page 248, column 1, 2nd para.*" of D1) that "*the Authors of D1 themselves merely had the intention to prepare mixed HA-cross-linked derivatives*", and that "*D1 is therefore of a highly speculative nature with regard to any crosslinked product actually obtained*" (rej: Nos. 4 and 6 to 10).

Moreover, "*The Board of Appeal in the decision of 20 March 2008 (T 785/05) and the Opposition Division in the decision of 8 December 2008 already came to the same conclusions …*", and reference was made to Reasons 4.3.2, 4.3.7, 4.3.8 and 4.5 in T 785/05, above, and also to II.3.1 in the decision under appeal (rej: Nos. 11 to 13).

(4) Having regard to the disclosure of D1, the Respondent saw the technical problem to be solved in the provision of "*homogeneously crosslinked HA, which is cross-linked in a reliable and reproducible manner through the formation of amid linkages and which has therefore a high biocompatibility, a high resistance to enzymatic degradation, a high capacity to absorb water and an ability*

to chelate metal ions (see page 3, lines 1 to 5 of the patent)" (rej: No. 14).

(5) The solution to this problem was seen by the Respondent in the provision of a crosslinked HA, which was obtained through the activation of the carboxylic groups of HA with a specific activating agent, namely CMPJ. Furthermore, the [examples] provided evidence that the crosslinked HA thus obtained contained amide linkages, but no ester bond, as could be taken from the IR data of [Example 1]. (rej: No. 15)

(6) By contrast, D1 merely taught the activation and crosslinking of HA in the presence of WSC, ie a completely different compound, in particular EDC, and "i*s highly speculative on the obtained product indicating that some amide bonds - along with ester bonds - might be obtained.*" (rej: No. 16).

(7) In the Respondent's opinion, the person skilled in the art had no motivation to change those reaction conditions of D1, let alone was there any hint how to change the same: "*Even if the person skilled in the art had contemplated to change the reaction condition, he would have been faced with a myriad of possibilities and Dl is completely silent which specific parameter might cause any problem, let alone how to change same. This has also been correctly analyzed by the Opposition Division in the decision of 8 December 2008:*
'The OD stresses on the fact that the skilled person starting from D1 would have had ample other possibilities to optimize the cross-linking of HA. For example the variation of pH or reaction temperature or the employment of other external or internal cross-linkers' (see section 3.1, Summary)" rej: No. 17).

IX. On 15 January 2010, the parties were summoned to oral proceedings. In an annex to the summons, the Board

pointed out that the opposition had already been the subject-matter of decision T 785/05 (above) and that it was evident to the Board that the passage concerning the "*Additional decision*" on the front sheet of the interlocutory decision under appeal (section VI(1), above) had clearly been added to that sheet in error, and that there was, therefore, apparently no need for the Board to send the case back to the Opposition Division for the formal correction of the front sheet under R 140 EPC (cf. section VII(1), above).

X. In a further letter dated 10 March 2010, the Appellant raised a new objection against the third Auxiliary Request under Articles 100(c) and 123(2) EPC (cf. sections VIII and VIII(1), above).

(1) Moreover, the Appellant modified its arguments brought forward with regard to the combination of D1 and D5, but indicated that it intended to maintain all its previous positions.

(2) The Appellant essentially reiterated its arguments to D1 as dealt with in section VII(4), above, but put additional emphasis on some further aspects. Thus, the Appellant pointed out that D1 taught that HA had to be crosslinked in order to slow down the hydrolytic degradation of HA and it "*discloses **two different types of crosslinking**, both obtainable using WSC, which allows the crosslinking, not remaining however bound to HA as crosslinking agent:*" (a) a direct ester bond derived from the reaction of COOH and OH groups; (b) "*in presence of a diamine in the reaction medium to obtain a crosslinked HA through a diamine bridge bound to COOH through an amide bond, definitely more resistant than the ester bond to the hydrolytic degradation (as indicated in the same D1)*". Then, the Appellant referred to the different ways the esterification (a) had been described (film immersion

and casting) and argued that, on the basis of the experience thus made, the person carrying out the experiments of D1 had tested the formation of crosslinked HA with diamines. However, apparently, "*He is not able to optimize a method of crosslinking through the formation of amide bonds starting from **HA solutions**, namely from **grams of HA dissolved** in water or in other solvents. In other words, the technician is bound to the form of the starting biomaterial and it cannot therefore obtained crosslinked HA in form of a powder, powder which could be then worked in different ways to obtain biomaterials in the wanted final form. Further D1 seems to teach that HA can be crosslinked with WSC as crosslinking agent, only working with high concentrations of HA.*" (letter: page 5, line 5 to page 6, line 9).

(3) The skilled person "*wanting to solve this technical problem, namely wanting to improve the reaction in the case of crosslinking through the formation of an amide bond, using a diamine, would have considered the teaching of document D5.*"

(4) Starting from this statement, the Appellant argued that the skilled person would learn from the comparison of Examples 19 and 3 of D5 that upon replacement of a carbodiimide by CMPJ in a reaction mixture containing the same HA concentration (in an amount similar to the concentrations as used in the patent in suit, ie equal to or less than 2% as in [Examples 4 and 5]), the same solvent (ie an aprotic solvent such as DMSO) the time required to obtain the same amount of crosslinking of HA (by formation of ester bonds) could be reduced by 2/3 (ie from 45 h to 15 h). Moreover, the reader would immediately notice that substantially all examples of D5 used CMPJ. In conclusion of the information in D5, the skilled person would know that it was possible to crosslink HA solutions at concentrations definitely

lower than those disclosed in D1 with very short reaction times and modulating the degree of cross-linking, simply by using CMPJ instead of carbodiimide, defined in D5 as being the preferred condensation agent to be used in aprotic solvent in the presence of triethylamine. In this way it would be possible to obtain crosslinked HA in powder form, which could then be worked up to the wanted final form of biomaterial.

Moreover, it was, according to the Appellant, well-known from other documents like D12 that CMPJ could be used not only to form ester bonds, but also in the formation of carboxamides bonds from COOH groups and amines.

(5) When starting from D1 and wanting to solve the technical problem, namely to improve the reaction in the case of crosslinking HA by an amide group and to provide crosslinked HA being more resistant to hydrolytic degradation than HA crosslinked through ester bonds, the person skilled in the art would, in view of these hints in D5, have directed his attention to the condensation agent and to the finding of an alternative activating agent to carry out the nucleophilic substitution of the activated ester of HA with a polyamine. He would certainly have used CMPJ instead of WSC ion view of the clear indication in D5 to use the salts of CMP as preferred activators.

XI. The oral proceedings took place on 14 April 2010.

(1) At the outset of the hearing, the parties were informed that the Board intended to concentrate the discussion at first on the Main Request, before, if need be, turning to the open questions concerning the auxiliary requests.

(2) When the Appellant was given the floor to present its case, it indicated that it would concentrate on two approaches to the question of inventive step, one based on D1, the other based on D5 as the respective closest pieces of prior art. Nevertheless, it confirmed that it maintained all the other approaches put forward in its SGA (section VII(3), above). The Appellant's arguments can be summarised as follows:

(3) The Appellant pointed out that Claim 1 was worded as a product-by-process claim which meant that the product *per se* had to be inventive. Moreover, it would be noteworthy that neither Claim 1 nor anything in the patent in suit indicated that the reaction of HA and polyamine would yield, let alone would be limited to a product containing only polyamide bonds. Nor did the claim contain any explanations or definitions concerning the reaction conditions necessary for actually obtaining the claimed product.

(4) According to D1, there were two conceivably possible ways for crosslinking HA, ie by formation of ester bonds or by formation of diamide crosslinking groups (in the well-known amidation reaction). As indicated on its page 250, amide groups would impart improved stability against hydrolytic degradation to the crosslinked HA. Such crosslinking groups would be obtained, according to D1, by the addition of WSC for activating the carboxylic groups of HA and subsequent amidation reaction with a diamine as shown in the reaction schemes (2), (3) and (5) on pages 249 and 250 of D1.

(5) When finding out that some different product was obtained when trying to carry out the amidation reaction as described in D1, as held in T 0785/05

(above, to which the Appellant did not agree), the person skilled in the art could not, nevertheless, simply forget the disclosure of D1, but would have tried to find out why the repetition of the amidation according to D1 had not been successful. In view of the high resistance of amide bonds against hydrolytic degradation, already mentioned (cf. section XI(4), above), he would not have abandoned the idea of crosslinking HA via reaction with polyamine, but would rather have tried to modify the reaction conditions described in D1 so as to obtain the product described therein, ie the crosslinked HA having improved resistance against enzymatic hydrolysis. Moreover, there had been an incentive to modify the method of D1 in order to deviate from the crosslinking treatment of a film to a more useful preparation of a crosslinked powder.

(6) The technical problem vis-à-vis D1 would, therefore, reside in the question of how the method of for cross-linking HA by using a diamine of D1 could be optimised.

(7) As it would have been clear to him, in particular due to a precise hint given in D1, that it was the reaction conditions in the first reaction step of the method of D1, ie the activation step of the carboxylic groups of HA, which had to be corrected, the person skilled in the art would have looked into D5 dealing with the activation of the carboxylic group in the same field of the art as in the patent in suit.

(8) In D5, he would have found a clear indication to the route to be taken for the improvement of the crosslinking of HA, the activation of the carboxylic group of the polysaccharide (HA) by the same method as used in polypeptide synthesis (D5, page 3, lines 29 to

30 and page 4, lines 16 to 18) and referred to a number of activators for this purpose. In particular, D5 referred to the CMP compounds as preferred activators for the carboxylic groups of HA. More particularly, the Appellant referred to the use of CMPJ in the examples of D5, and reiterated its arguments concerning Examples 3 and 19 of D5 concerning the advantageous effect of the replacement of carbodiimide by CMPJ (section X(4), above).

(9) Hence, the choice of an activator other than EDC (as in D1), namely the choice of CMPJ, would have been the first step when he had realised that the reaction had not worked. And in fact, it had only been the use of this specific activator of the carboxylic groups of HA which distinguished the teaching of the patent in suit (CMPJ) from that of D1 (EDC). This choice was even more obvious, according to the Appellant, having regard to D10 (relating to the polypeptide synthesis) and D12 (relating to the amidation of carboxylic acids) both suggesting CMPJ).

(10) Moreover, according to the patent in suit, (i) the above activation could be carried out with conventional methods and (ii) all activators were disclosed as being equivalent. Hence, the use of an activator other than the EDC used in D1 could not contribute anything to the question of inventive step.

(11) Starting from D5 as closest state of the art, the Appellant saw the technical problem to be solved vis-à-vis D5 in the finding of an alternative process for the crosslinking of HA, ie a method carried out in the presence of an polyamine compound in order to provide crosslinking groups having bonds to the HA molecules

stronger than ester bonds, ie amide bonds, as suggested on page 250 of D1 (cf. section XI(4), above).

(12) These arguments of the Appellant were disputed by the Respondent in their entirety.

(13) Firstly, D1 could be taken at face value according to the reaction scheme on page 250. On this basis, the skilled person would try to work in accordance with this teaching, which would, however, result in a complete failure as regards the aims as presented in [0017], in particular, as regards the provision of a homogeneous crosslinked HA product having a high resistance to enzymatic degradation, which could be obtained in a reproducible process.

(14) The problem to be solved with regard to D1 would not reside in the crosslinking via amide groups or the improvement of its preparation as referred to by the Appellant (cf. sections X(5), XI(4), XI(6) and XI(11), above), which features would rather be part of the solution to the problem. Instead, the formulation of the relevant problem, formulated without features of the solution, could only be based on the finding that the teaching as presented in D1 had failed and that, therefore a feasible modification of the crosslinking of HA, in general, had to be found.

Apart from the starting material, which could also, in the Respondent's view, be the reason for the problems occurring in D1, numerous process features could be changed. However, D1 did not provide any hint to this end.

(15) The solution found in the patent in suit consisted, according to Claim 1, of crosslinked HA as obtainable by the reaction of the carboxylic groups of HA, activated by CMPJ, with a polyamine. These products

showed a high degree of swelling as shown in the [examples] and were obtained in a much shorter reaction time ([Examples 1 to 3]: 30 min) than in D1.

(16) Therefore, the Respondent argued that the claimed subject-matter was inventive over D1 as such.

(17) Nor did D5 provide, according to the Respondent, any instruction to achieve the solution of the above relevant problem and thereby to arrive at something within the present claims. D5 spoke only about forming inner ester crosslinks of HA, thereby involving the activation of the HA carboxylic groups, which was also part of the disclosure of D1.

Even when taking into account that D1 additionally referred to amidation (which was not the case in D5), one would have had to find the right conditions for the formation of the second amide bonding (solvent, activator, prevention of the protonation of the amino group). It was difficult to get both amino groups of a diamine to react with the carboxylic group of HA. D5 did not provide any contribution to achieve a solution to the problems occurring when trying crosslink HA by means of an amidation.

(18) Moreover, in view of the long list of preferred activators in D5 (page 4, lines 16 to 36) including the carbodiimides (as used in D1), the person skilled in the art could not learn to change the activator, let alone that this would have been the crucial point.

(19) Nor could the comparison of D5's Examples 3 and 19 contribute to the solution of the relevant problem for several reasons: both examples related only to the formation of esters; hence, no conclusion could be derived therefrom for the amidation; in Example 19 a carbodiimide was used which was different from the WSC

used in D1; hence, no valid conclusion could be derived therefrom in respect to the question of the reaction duration. This latter finding would even be strengthened furthermore in view of the fact that, according to both examples of D5, a precipitation step was mandatory for the preparation of the respective esters.

(20) Moreover, the Respondent referred to the findings in decision T 785/05 (above) concerning the cross-linking via amide groups in the crosslinked HA as claimed, to the [examples] as proof for the superior quality of its products and to the different reaction conditions in the esterification in D5, Example 3 (30°C, 15 h) and in the amidation in the [examples] (0°C, in minutes).

(21) With regard to the reverse approach of the Appellant starting from D5, the Respondent argued that D1 did not provide any incentive to deviate from the esterification of D5 to an amidation, which had not worked.

(22) When the parties indicated that they did not want to make further submissions concerning the Main Request, the Chairman reaffirmed the requests of the parties at this moment, closed the debate on the Main Request and interrupted the oral proceedings for the final deliberation on the Main Request.

XII. At this moment, the requests were as follows:

The Appellant requested that the decision under appeal be set aside and the patent in suit be revoked.

The Respondent requested that the appeal be dismissed or, in the alternative, that the decision under appeal be set aside and the patent in suit be maintained on

the basis of the first, the second or the third Auxiliary Request, each containing Claims 1 to 9 and each being dated 11 August 2009.

Reasons for the Decision

1. *Admissibility*

1.1 As addressed in section I, above, the present case is the second appeal concerning the patent in suit.

1.2 In the first appeal T 785/05 (above), the decision of the Opposition Division as announced on 19 April 2005 and issued in writing on 6 May 2005 was set aside and the case was remitted to the first instance for further prosecution of the case on the basis of the Main Request filed on 19 October 2007 (see section I, above).

At the end of the continuation of the opposition proceedings (section VI(1), above, paragraph 2), the Opposition Division established in II.1 of the decision now under appeal, that the appeal was admissible, thereby using the same wording as in II.1 of its first decision in this case, dated 19 April 2005 (cf. section VI(1), above).

1.3 As in T 785/05, above, the Board has not seen any reason to contest these findings. Nor has the Board seen any need to remit the case to the Opposition Division for correction of the front sheet of the interlocutory decision (cf. section VI(1), above, paragraph 1), as already expressed by the Board in the annex to the summons (section IX, above).

1.4 In summary, the Board confirms the above findings in the reasons (II.1) of both decisions of the Opposition Division as quoted in section 1.2, above. By contrast,

the statement on the front sheet of the decision under appeal concerning the "*Additional decision*" is clearly erroneous and, therefore, null and void.

1.5 Moreover, as stated in the last paragraph on the front sheet (EPO Form 2327) of the interlocutory decision of 8 December 2008, informing the parties that the interlocutory decision was open to appeal according to Article 106(2) EPC, this appeal is clearly admissible.

Procedural issues

2. The question of lack of novelty, initially raised by the Opponent and already decided in case T 785/05 (above) was indirectly addressed again by reference to another case in the Opponent's letter of 29 September 2008 (section V, above). Hence, the Board has considered the question of whether the decision on novelty had become final (*res judicata*) or was again open to discussion.

2.1 According to the EPC 1973, a decision which had become final and the reasons on which this decision had been based (*ratio decidendi*), were no longer open to discussion, nor could the Board in a further prosecution of the same case depart therefrom (cf. T 934/91, OJ EPO 1994, 184; Reasons 2 and 3; T 843/91, OJ EPO 1994, 818, Reasons 6 to 6.3; and also Case Law, chapters VII.D.10.1 and VII.D.10.2).

These findings were confirmed by the Enlarged Board of Appeal in G 1/97 (OJ EPO 2000, 322), in particular Reasons 2(a), wherein, in its first paragraph, reference was made, first of all, to the suspensive effect of an appeal against a decision of a department of the EPO provided for by Article 106(1) EPC 1973 and then to the consequences of this effect: "*This effect prevents a decision from becoming final and is therefore*

limited to ordinary appeals, ie those against decisions which are not yet final (…). Since, …, ***decisions of the boards of appeal become final as soon as they are issued****, there can be no possibility of appeal under Article 106 EPC against these decisions. This is confirmed, moreover, by Articles 21 and 106 EPC, which do not include the boards of appeal in the list - which must be regarded as exhaustive - of departments whose decisions are open to appeal*" (emphasis added).

2.1.1 The only further question, which could still arise in this respect, was of whether these findings would still be applicable under the revised version of the EPC 2000.

2.1.2 As can most easily be seen in the OJ EPO, Special Edition 4/2007, "*Synoptic presentation EPC 1973/2000 - Part I: The Articles*", the wording of Articles 21 and 106, to which articles reference had been made in G 1/97 (above), has not been amended to "*include the boards of appeal in the list - which must be regarded as exhaustive - of departments whose decisions are open to appeal*." (cf. G 1/97, as quoted in section 2.1, above).

2.1.3 However, the question remains to be examined of whether the situation has changed by the introduction of the new Article 112a EPC "*Petition for review by the Enlarged Board of Appeal*".

2.1.4 A first difference between appeal and petition lies evidently in the fact that, unlike Article 106(1) EPC, Article 112a(3) EPC clearly excludes a suspensive effect of the petition.

2.1.5 Moreover, a petition for review can, according to Article 112a EPC, only be based on fundamental *procedural* violations or defects during the appeal proceedings, which do not include questions relating to patentability as defined in Chapter I of Part II

(Articles 52 to 57) of the EPC. This can be derived from the, in the Board's opinion, exhaustive list of fundamental procedural violations and defects in Article 112a(2) and Rules 104 and 105 EPC. This view has, in the meantime, been confirmed in G 3/08 of 12 May 2010 (OJ EPO ...., ..., Reasons 7.2.5).

2.2 Consequently, this Board takes the view that the rulings and *rationes decidendi* in the above decisions, in particular in G 1/97, are still valid under the revised provisions of EPC 2000. In other words, the facts and findings dealt with in T 785/05 (above) are not open to discussion in these appeal proceedings. Nor can arguments, which are contrary to the *ratio decidendi* or the result of decision T 785/05, be taken into account for the assessment of inventive step.

2.3 Hence, the matter to be decided in this case concerns only the question of whether the subject-matter as claimed in any one of the Respondent's requests (section XII, above) is based on an inventive step and, if the Main Request and the first and second Auxiliary Requests failed, furthermore the question of whether the third Auxiliary Request contravened or complied with Article 123(2) EPC (sections X and XI(1), above).

Main Request

3. *Problem and solution*

3.1 The patent in suit relates to crosslinked hyaluronic acids (HA) (cf. [0001]), which, according to [0017], are to have high biocompatibility, high resistance to enzymatic degradation, high capacity to absorb water with formation of visco-elastic characteristics dependent on the degrees of crosslinking and optionally of sulphation and/or hemi-succinylation, and the ability to chelate metal ions.

3.2 The solution resides, according to the claims under consideration, in the fact that the above advantageous properties are inherent to crosslinked HA obtainable by activation of the carboxylic groups of HA in a particular way, ie by means of CMPJ, and the subsequent reaction of these activated groups with polyamines.

Accordingly, data relating to the swelling degrees of hydrated gels in relation to the crosslinking degree, rheological properties, biocompatibility and the chelating ability were provided in the [examples]. Moreover, the Patent Proprietor provided further experimental results together with its reply to the Notice of Opposition (letter dated 4 February 2004) and with its SGA dated 5 September 2005 in the first appeal (Enclosures 2 and 3) to demonstrate the different nature of the claimed products in comparison with prior art products (in particular those according to D1). According to these experimental results, the products of D1 did not contain amide crosslinks. The arguments presented at that stage by both parties were reported in decision T 785/05 (above), Facts and Submissions II(2), IV(2)(a), IV(2)(b), IV(3), V to V(2), VI(1) and VIII(8) ff and were dealt with in Reasons 4.3 to 4.3.7.

3.3 The question of inventive step, yet to be decided in this case, is assessed in proceedings before the EPO, in general, according to the so-called problem-solution approach in several steps: Firstly, it must be established which document qualifies for being the closest prior art; secondly, the technical problem to be solved vis-à-vis this document is identified and it is investigated whether this problem has credibly been solved. Thirdly, it is decided whether the solution

found can be derived in an obvious way from the cited documents (cf. Case Law, Chapter I.D.2).

3.4 As mentioned in sections VII(3) and XI(2), above, the Appellant disputed the presence of an inventive step on the basis of D1, D3, D5, D7 and D13 referred to as the closest prior art at different stages of this case.

3.5 Consequently, it is therefore necessary at first to identify the document qualified therefor.

3.5.1 "*As is generally recognized in the jurisprudence of the Boards of Appeal, in cases where a claimed invention is attacked on the basis of more than one prior document each belonging to the same technical field as the claimed invention, the closest prior art is the prior document, starting from which the claimed invention could most easily have been made by a skilled person at the filing date. As stated in decision T 254/86, OJ EPO 1989, 115, in paragraph 15, 'the objectively closest state of the art is the most promising springboard towards the invention which was available to the skilled person.' In each case, the objective choice of the closest prior art document depends upon the nature of the claimed invention and of the disclosures in the relevant prior documents.*" (T 656/90 of 13 November 1991, not published in OJ EPO, Reasons 1.1).

3.5.2 As shown in sections VII(3) to VII(9), above, in the present case, the "*claimed invention is attacked on the basis of more than one prior document*" of this kind. Hence it must be established, from which of D1, D3, D5, D7 and D13 "*the claimed invention could most easily have been made by a skilled person at the filing date*", or in other words, which of the prior art documents "*is the most promising spring board towards the invention …*" and thus must be considered as being the closest state of the art (cf. section 3.5.1, above).

3.5.3 In connection with this question, it appears to be appropriate to consider the documents, cited in these appeal proceedings, and their gist in relation to their time sequence of their publication dates.

3.5.4 In 1979, "*New Synthetic Reactions Based on the Onium Salts of Aza-Arenes*" were suggested in D12, cited as a secondary document (cf. section 3.4, above), referring *inter alia* to CMP compounds and their use for activating carboxylic acids in a first step of their reaction to esters, amides and thiol esters. None of the compounds considered in this document was a polymer.

3.5.5 In D10, published in 1985, CMPJ was described as being a particular coupling agent for the synthesis of different peptides (of up to four amino acid unities, cf. the Table on page 1094) "*synthesized with protected di- and trifunctional amino acids*" (Summary).

3.5.6 In 1989, D5, as the first document dealing with the crosslinking of HA, suggested to crosslink this polymer by formation of ester or lactonic bonds between a first portion of 1 to 100% of its carboxyl groups and hydroxyl groups of the same or different HA molecules and, if present, further to esterify the second portion of carboxyl groups of the HA with aliphatic, araliphatic, cycloaliphatic or heterocyclic alcohols (Claim 1 of D5). Any further remaining free carboxyl groups could be in neutralised form (cf. D5, page 5, lines 2 and 3), eg with sodium chloride (cf. its examples). The above alcohols were further explained in the passage on from page 6, line 51 to page 8, line 37, as optionally containing functional groups such as amino, hydroxyl, aldehyde, keto, mercapto, carboxy or derivatives thereof, eg dihydrocarbyl amino groups. Furthermore, the above list of alcohols included

bioactive active functional groups containing compounds, such as sterols, cholic acids, steroids and their derivatives, hormones and vitamin alcohols, which according to page 20 of D5, first paragraph, could be useful in the pharmaceutical and medical field.

According to its Claim 25, the process for the preparation of the crosslinked HA included, as a first step, the treatment of the HA with an activating agent selected from those generally used in peptide synthesis or 2-halogen-N-C_1-C_6 alkyl-pyridine or chloroaceto-nitrile for the activation of its carboxyl groups. A list of activator groups and individual activators was given on its page 4, line 16 *et seq*. including besides others carbodiimides and CMP compounds. In most of its examples CMPJ was used, except for Example 19, wherein the activator used was a carbodiimide.

It is noteworthy that, in all the examples of D5, the crosslinked product was precipitated, whether salified by addition of sodium salt or not (Example 7). Moreover, it is apparent that a number of esters formally derived from alcohols as mentioned above were not prepared by esterification of HA with a free alcohol, but were made in different reaction routes. Thus, even the partial *ethyl* esters of crosslinked HA were not prepared from HA and ethanol, but were prepared by alkylation of free carboxyl groups of HA with ethyl iodide in the presence of $N(C_2H_5)_3$, ie in basic conditions (cf. Examples 8, 9, 10, 13 and 18), before carrying out the crosslinking esterification step. Partial esters of crosslinked HA containing cortisone were prepared analogously by reacting the bromo-derivative of cortisone with HA in the presence of $N(C_2H_5)_3$ (NEt_3)(Examples 11 to 13). The partial esters with carteolol, kanamycin or amikacin groups,

respectively, were prepared by reacting the crosslinked HA precipitate in suspension with basic carteolol (Example 15), kanamycin sulphate (Example 16) or basic amikacin (Example 17).

In each of the examples the amounts of the respective reagent (eg halide or sulphate) was added in stoichiometric amounts for the desired degree of esterification (in percent). Thus, based on 10 mEq of HA, 2.5 mEq of C_2H_5I were added in Example 8 to provide 25% of ethyl ester groups. The same relation is found in the other examples. The same is true for the amounts of the NEt_3/CMPJ combination eg in D5's Examples 6 to 10 (cf. D12, the reaction scheme of page 708, left column).

In view of these findings, the Board cannot accept that, in the context of its teaching concerning, besides the crosslinking of HA by direct esterification of carboxyl and hydroxyl groups of HA, the partial or total esterification of free groups of HA with mono or polyvalent alcohols, D5 would disclose "*the use of aminoalcohols, like aminoethanol or aminopropanol as external crosslinker (see page 7, lines 10-24)*" (SGA, page 12, lines 15 to 19), since D5 is completely silent about the reaction route by which HA should be "*esterified*" with functional alcohols. There is not a single example demonstrating esterification with the alcohols of page 7, as implied by the wording in Claim 1 of D5 ("*the second portion of carboxyl groups … are esterified with … alcohols*"). Nor is mention made in D5 of any amidation or of any crosslinking of HA involving an external crosslinking agent.

Any interpretation of the disclosure D5 in this direction, as suggested in the quotation from the SGA mentioned in the preceding paragraph, can only be based

on improper hindsight, ie in the knowledge of the patent in suit.

3.5.7 According to D7, published in 1991, describing the "*Chemical Modification of Hyaluronic Acid by Carbodiimides*" an acidic environment is needed to catalyze the well-known amidation reaction in protein modifications with primary amines, presumably through the protonation of the carbodiimide nitrogen (pH 4.75). However, when attempting to react diaminohexane and HA activated by EDC in order to build an amide linkage between HA and the diamine at the same pH, the experiment failed: "*the only significant products observed were the acylureas.*" (D7, page 236, "*Results and Discussion*", in particular, right column, line 4 *et seq.* below Figure 2, Figure 4 and page 238, left column, first complete paragraph).

3.5.8 This finding was confirmed in D6, published 1992.

3.5.9 In 1993, D13 was published, which related to a process for the preparation of "*water-swellable, water-insoluble*" (D13, page 3, line 8) modified polysaccharides and their products, more particularly to a crosslinking process and its crosslinked product (Claim 1), which was a "*natural-based, highly absorbent material, suitable for personal care absorbent products*" (D13, page 3, lines 5 to 7). The crosslinking agent to be used was an organic compound capable of reacting with a carboxyl or hydroxyl group of the polysaccharide, ie in an esterification or amidation reaction, by heat-treatment at temperature of from 100 to 200°C (Claims 6, 10, 11 and 12), however, without referring to activation of carboxyl groups by reaction with an activating agent. Nor was HA mentioned in D13 as a polysaccharide starting material. It was only mentioned within a list of crosslinking agents on page 4, lines 23 to 31, as an

alternative to diamines, polyamines, diols, polyols and mixtures thereof, but D13 never taught to react at least two of these crosslinking agents with one another.

In accordance with the purpose of the crosslinked product of the claimed process, the polysaccharide starting materials contemplated in D13 were "*cellulose, starch, carrageenan, agar, gellan gum, chitin, and the like, and mixtures thereof. The preferred modified polysaccharide is a carboxyalkyl polysaccharide.*
Suitable carboxyalkyl polysaccharides for use in the present invention include carboxyalkyl celluloses such as carboxymethyl cellulose, carboxyethyl cellulose, carboxyalkyl carrageenan, carboxyalkyl agar, carboxyalkyl gellan gum, and the like, and mixtures thereof. The preferred carboxyalkyl polysaccharide is a carboxyalkyl cellulose with the preferred carboxyalkyl cellulose being carboxymethyl cellulose." (D13, page 3, lines 40 to 51).

In view of this finding, D13 cannot be considered as being the closest state of the art either.

3.5.10 Document D4, cited as a secondary document and published in 1995, related to highly reactive esters of carboxy polysaccharides, eg HA, and derivates of these compounds which could, in an intended diagnostic use, be further reacted with polypeptides or protein (page 3). However, emphasis was put in the document on the fact that the "*active esters of carboxy polysaccharides and their semisynthetic derivatives have been obtained without any undesired side reactions, such as the formation of intra- and inter-chain bridges, which lead to the phenomenon known as auto-crosslinking*". The alcohols used as the esterifying agent in aprotic conditions were aromatic, substituted aromatic, aromatic heterocyclic alcohols, a N-hydroxylamine or a combination of these compounds (Claim 1), more particularly, fluoro-,

chloro- or nitro-substituted aromatic alcohols, hetero-cyclic alcohols, or N-hydroxylamines (Claims 4 to 10 and 23 to 26).

However, no mention was made in D4 of any activating agent as described in any one of the documents referred to herein above or to crosslinking of HA.

3.5.11 In 1997, D1 was published, according to which HA could be activated by reaction with a WSC, such as EDC, and could then be crosslinked by reaction with Lys-Me. The interpretation of the results of this reaction were based on IR spectra and on an *in vivo* degradation experiment using a HA film which "*revealed that the film crosslinked in the medium containing lysine ester underwent slower degradation than that without lysine ester. This finding suggests than an amide bone was formed between the carboxyl group of HA molecule and the amino group of L-lysine methyl ester*" and it was asserted that the addition of Lys-Me to the reaction medium containing WSC could produce polysaccharide films having higher resistance against hydrolytic degradation than those crosslinked through an ester bond alone (D1, page 250, last paragraphs of both columns).

This document was already discussed in great detail with regard to the question of novelty in T 785/05 (above). Reference is, therefore, made to the relevant passages in that decision, which are incorporated herein by reference, in particular to Reasons 4.3 to 4.3.7 of that decision for the further details.

3.5.12 On 5 March 1998, finally, D3 was published, describing crosslinked copolymers on the basis of at least two non-crosslinked polycarboxylic polymer components and a crosslinking agent having at least two amino functional groups. The first polymer component included at least

one polycarboxylic polysaccharide, degradable by microbial flora, such as HA or, as used in all its examples, chondroitin sulphate; the other comprised at least one polycarboxylic polymer not being a polycarboxylic polysaccharide, eg a polycarboxylic acrylic polymer (Claims 1, 3 to 6). The first step of the crosslinking reaction is an activation of the carboxyl groups of the starting polymers by an activating agent as conventionally used in peptide synthesis, such as carbodiimides, quinoline derivatives or mixed anhydrides. Particularly preferred is EDC (D3, page 5, last paragraph).

The invention of D3 differs from the gel of a document referred to in D3, page 1, lines 6 to 11, by the presence of the second polymer and the fact that no crosslinking agent had been used for the preparation of that gel ("*un gel à base d'acide hyaluronique : mais ce gel ne comprend, dans sa structure, que de l'acide hyaluronique et aucun autre polymère polycarboxylique. Par ailleurs, aucun agent de réticulation est utilisé par la préparation de ce gel.*"). In other words the presence of the second polymer component not being a polysaccharide is an indispensible feature of the subject-matter of D3.

Hence, D3 cannot form the "*most promising springboard towards the invention*" (cf. sections 3.5.1 and 3.5.2, above), which would require to omit this feature.

3.6 As shown above, within the list of all the documents cited in these appeal proceedings, only in D5, D7, D6, D1 and D3 (in the order of their time sequence) had the possibility of crosslinking HA been envisaged. Hence, none of the further documents, including D13, mentioned by the Appellant as a possible starting point for the

assessment of inventive step can, in the Board's view, be considered as the closest prior art.

3.7 Moreover, D5 was the latest of all the documents cited during these appeal proceedings, which considered CMP compounds as appropriate activators, when including at all a reference to an activator for the carboxylic groups. Nevertheless, D5 cannot, in the Board's view, be regarded as being the closest state of the art for the reasons already provided in section 3.5.6, above.

3.8 All further documents in this series, ie those published between 1989 (D5) and 11 November 1998 (the priority date of the patent in suit), referred only to other types of activator compounds such as in particular carbodiimides, eg WSC or EDC.

3.9 In view of the fact that the experiments in both D7 and D6, wherein the authors tried to crosslink HA with polyamines by amidation after activation of HA with EDC, were complete failures, neither document qualifies for the closest state of the art either.

3.10 Nor can D3 qualify for the closest piece of prior art for the reasons set out in section 3.5.12, above.

3.11 In the decision under appeal and in the SGA, D1 had been identified as being the closest piece of prior art, because "*it shares with the patent in suit the most technical features and is directed to the same technical problem*" (sections VI(4) and VII(4), above). In the present circumstances and in view of the above findings concerning the other documents cited, the Board accepts D1 to be considered as the closest piece of prior art.

3.12 The relevant technical problem can be seen in the provision - in a reliable and reproducible manner - of homogeneous HA products containing crosslinks, which

products show high water-swelling degrees of their hydrated gels in relation to their degrees of crosslinking, particular rheological properties, high biocompatibility and the ability to chelate metal ions such as eg copper. These goals were in fact achieved as demonstrated in the [examples] ([0073], [0081] and [0085] to [0088], sections VI(5) and 3.2, above).

4. *Inventive step*

It remains to be decided whether the claimed solution of the above problem (sections 3.1 and 3.12, above) derives in an obvious way from the cited documents.

4.1 Document D1 itself does not provide any information or suggestion to the reader, that modifications in the measures described therein might be necessary in order to obtain HA crosslinked by amide-bonded crosslinking groups, let alone to obtain such crosslinked HA which provides the necessary properties (cf. section 3.12, above). Nor does it provide any hint, in which direction any or which modification should be applied to the disclosure or teaching of D1 for this purpose (cf. the Respondent's arguments referring to in sections VIII(3) to VIII(4), VIII(6) and VIII(7), above). Rather, the reader would have derived from the Abstract of D1, that HA could apparently be crosslinked successfully by amidation with Lys-Me when using a WSC as an activator for the carboxyl groups of HA.

4.1.1 However, as elaborated in great detail in T 785/05 (above), this assumption expressed in D1 turned out in the event to be wrong. When repeating the treatment of HA as described in D1, no HA containing amide-bonded crosslinks had been obtained by the Patent Proprietor/ Respondent in these experiments, the results of which have never been convincingly refuted.

4.1.2 Thus, the Appellant has failed to provide any evidence for this allegation, eg by providing experimental results confirming the alleged results reported in D1, that HA crosslinked by Lys-Me via amide bonds had shown an improved resistance against hydrolytic degradation. Consequently, the Board cannot accept the Appellant's argument that the claimed products could only be alternative products to those of D1, in particular, since D1 as such did not provide the desired product having eg a good swelling behaviour (in contrast to forming a solution as shown in the tests of the Respondent's Enclosure 2; section 3.2, above).

4.1.3 Consequently, the person skilled in the art was left alone when trying to verify the alleged results of D1.

In other words, D1 itself cannot render the claimed subject-matter obvious.

4.2 Nevertheless, the Appellant suggested in its latest submissions in writing and at the oral proceedings on the basis of D1, when the person skilled in the art realised that (s)he did not succeed in obtaining the results alleged in D1 (sections X to X(5) and XI(3) XI(11), above), that D5 would provide a clear hint to modify the process of D1 by replacing the WSC by CMPJ in order to improve the crosslinking of HA and thereby to arrive at something within the scope of the claims.

4.2.1 As already shown in section 3.5.6, above, D5 did not even consider a crosslinking reaction by means of di- or polyamine compounds as crosslinking agents, as allegedly carried out in D1. Instead D5 is clearly limited to esterification reactions of HA, including its crosslinking by esterification, which included, within a series of reaction steps (cf. eg Example 11), the activation of the free carboxyl groups of HA by

means of an activator selected from a list of different kinds, even including the class of carbodiimides which had been used in D1 (identified therein as WSC and EDC).

4.2.2 As already addressed above with regard to D1, the skilled reader of D1 could not identify which modification/s was/were to be made, once (s)he had realised that the desired product could not be obtained by the method disclosed in D1. Consequently, (s)he could derive even less from D5, that it was the activator which was to be replaced.

4.2.3 Any conclusion that the desired product solving the relevant technical problem would be obtained when using the specific activator compound, ie CMPJ, for enhancing the crosslinking of HA with di- or polyamines can, in view of the above facts and findings concerning D1 and D5, only be drawn in the knowledge of the claimed subject-matter, in other words by applying hindsight.

4.2.4 Consequently, D5 cannot provide an incentive either to solve the relevant technical problem by modification of the teaching of D1 so as to arrive at something within the ambit of Claim 1. In other words, it does not render the claimed subject-matter obvious.

4.3 The same arguments are held to be valid with regard to D12 (1979) and D10 (1985), respectively, both of which had been published long before the publication of D1 (the article was received by the Journal in September 1995). Apart from the other reasons above concerning the question of which modification/s of the teaching of D1 would have been obvious, this long period between the above publication dates and the filing of D1 demonstrates even more, that the use of CMP compounds in the crosslinking of HA was not the obvious alternative to the use of carbodiimides.

4.4 Moreover, the other documents addressed in section 3.8, above, ie those published after D5 (ie those considered in sections 3.5.7 to 3.5.10 and 3.5.12, above), cannot render the use of CMPJ in the crosslinking of HA obvious either, because they did not refer at all to the use of an activator in their respective reactions (D13, D4) or they also, like D1, made use of carbodiimides (D6, D7, D3).

Whilst D13 mentioned HA only as an alternative crosslinking agent to polyamines, D4 referred to the preparation of activated polymers, but not to crosslinked HA.

Furthermore, as pointed out in section 3.6, above, from amongst these further documents, only D6, D7 and D3 envisaged the crosslinking of HA with polyamines, but none of them provided an indication that the relevant technical problem (section 3.12, above) might be solved by modifying the teaching in D1 in accordance with their respective teaching, which in the case of D3 (which additionally required the presence of a further polymer not being a polysaccharide) clearly pointed to the use of EDC (ie the same activator as used in D1), whereas D6 and D7 had shown that the use of this compound had led to failure instead of providing the desired product.

4.5 In summary, the Board has come to the conclusion that, whilst it gave the impression at first sight to be the closest prior art, a closer examination of D1 showed that it neither provided the necessary teaching as such for finding the solution to the relevant technical problem (ie the crosslinked HA showing the desired properties), nor gave any hint in which way, chosen from amongst all conceivable possibilities, its

teaching ought to be modified for this purpose. Nor did any one of the further documents provide such a hint, let alone a clear teaching.

Consequently, neither D1 itself, nor D1 in combination with those other documents discussed herein before, singly or in any combination with one another, render the subject-matter as claimed obvious. In other words, the subject-matter of Claim 1 is based on an inventive step.

4.6 By the same token, this finding is also valid for the further Claims 2 to 11, all of which include the features and limitations of Claim 1.

5. It follows therefrom that the requirements of the EPC are met by the claims of the Main Request.

Auxiliary requests

6. As the Main Request is successful, there is no need for the Board further to consider any of the auxiliary requests filed by the Respondent with its rejoinder (cf. section VIII, above).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

(E. Görgmaier) (R. Young)