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Datasheet for the decision of 18 December 2007

Case Number: T 0785/05 - 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. 54, 111(1)
EPC R. 116(1)
RPBA Art. 12(1)(a), 12(1)(b), 12(2), 13(1), 13(3)

Relevant legal provisions (EPC 1973):
EPC Art. 52(1), 54, 56, 100(a)
EPC R. 71a(1)
RPBA Art. 10a(1)(a), 10a(1)(b), 10a(2), 10b(1), 10b(3)

Keyword:
"Novelty - yes"
"Amendment to a Party's Case"
"Decision re-appeals - remittal (yes)"

Decisions cited:
T 1002/92

Catchword:
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Case Number: T 0785/05 - 3.3.03

D E C I S I O N
of the Technical Board of Appeal 3.3.03
of 18 December 2007

Appellant: (Patent Proprietor)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office dated 19 April 2005 and posted 6 May 2005 revoking European patent No. 1144459 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: R. Young
Members: A. Däweritz
E. Dufrasne

Summary of Facts and Submissions

I. The grant of European patent No. 1 144 459 in respect of European patent application No. 99 968 778.3, filed on 8 November 1999 as International patent application PCT/EP99/08481, which was published as WO-A-00/027887 on 18 May 2000, and claiming a priority of 11 November 1998 of an earlier patent application in Italy (MI982440), was announced on 2 October 2002 (Bulletin 2002/40). The patent was granted with eleven claims, reading as follows:

1. Cross-linked hyaluronic acids obtainable by reaction of the carboxylic groups of hyaluronic acid and a polyamine.
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 this decision, references to passages in the patent in suit as granted will be given underlined in squared brackets, those to passages in the application as filed will be shown in underlined italics, eg Claim [1], § [0001], Example [1], *Claim 1*, *page 1, line 1* and *Example 1*, respectively. "HA" means hyaluronic acid, "EDC" 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. "EPC" refers to the revised text of the EPC 2000, the previous version is identified as "EPC 1973".

II. On 1 July 2003, an opposition was filed, requesting revocation of the patent in its entirety for the grounds for opposition of Article 100(a) EPC 1973, ie for not complying with the provisions of Articles 52(1), 54 (novelty) and 56 (inventive step) EPC 1973.

(1) Five documents were cited, including

D1: K. Tomihata and Y. Ikada, "Crosslinking of hyaluronic acid with water-soluble carbodiimide", J.Biomed.Mater.Res. 37, (1997), pages 243 to 251 and

D2: WO-A-00/16818,

both of which were cited in support of the assertion of lack of novelty.

The Opponent argued, that "D1 clearly discloses the formation of cross-linked hyaluronic acids obtainable by reaction of the carboxylic groups of hyaluronic acid and a polyamine", in particular, by reacting HA and L-lysine methyl ester (Lys-Me) in an aqueous reaction medium additionally containing a water-soluble carbodiimide (WSC), such as EDC. More particularly, the Opponent referred to reaction equations (2), (3) and (5) shown on pages 249 and 250 of D1, according to which the carboxylic acid groups of HA formed, due to their reaction with the WSC, intermediate anhydride groups, which then reacted further with the Lys-Me to form a crosslinking group bound by two amide linkages to the HA. The polysaccharide films thus obtained would have a higher resistance against hydrolytic degradation than those crosslinked through an ester bond alone (Notice of Opposition, page 4).

(2) In reply to the Notice of Opposition, the Patent Proprietor disputed these arguments, cited four documents (letter dated 4 February 2004)

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;

D8: T. Pouyani et al., "Functionalized Derivatives of Hyaluronic Acid Oligosaccharides: Drug Carriers and Novel Biomaterials", Bioconjugate Chemistry, 5, 1994, pages 339 to 347; and

D9: P. Bullpitt et al., "New strategy for chemical modification of hyaluronic acid: Preparation of functionalized derivatives and their use in the formation of novel biocompatible hydrogels", J. Biomed. Mater. Res. 47, 1999, pages 152 to 169,

and reported the results of five experiments (pages 3 to 5 of the letter) explained with reference to sixteen IR- and NMR-spectra filed therewith. In its opinion, D1 was not an enabling disclosure for the preparation of the desired products. Therefore, its content would not anticipate the subject-matter claimed in the patent in suit. Rather, the conclusions drawn in D1 would have been based on a misinterpretation of IR data in the document and would, therefore, have been incorrect.

Rather, these experiments and D6 would show that the reaction of HA with EDC would yield a mixture of two isomeric N-acylureas, but would fail to provide HA crosslinked by the amine.

(3) In a further letter dated 18 February 2005, the Patent Proprietor filed further arguments and submitted an Auxiliary Request containing a set of eleven claims differing from the granted version, above, 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.

III. At the end of oral proceedings held on 19 April 2005, in which the Patent Proprietor had made the above Auxiliary Request its "only request" (No. I.8 of the decision), the Opposition Division revoked the patent in suit, because "the subject-matter of Claim 1 is not novel over D1" (No. II.4, page 4, end of paragraph 3). The decision was issued in writing on 6 May 2005.

(1) In the reasons for the decision, reference was made to the arguments of the Opponent, that in Claim 1 the claimed product had been defined in terms of a product-by-process claim and that an activator in the process did not change the resulting product. Since D1 disclosed the cross-linking of HA with Lys-Me under the formation of hydrolysis resistant amide-bonds, its products would fall within the scope of Claim 1.

(2) Furthermore, the Opposition Division held that, contrary to the opinion of the Patent Proprietor, D1 contained an enabling teaching for the person skilled in the art and that the Patent Proprietor had not discharged the burden of proof to show that this finding had not been correct.

(3) In particular, the experiments provided by the Patent Proprietor with its letter of 4 February 2004

(section II(2), above) would not have shown beyond any reasonable doubt that the teaching of D1 could not be carried out. The Opposition Division continued that, in these experiments, HA of lower molecular weight than the HA used in D1 had been used. However, it would have been known from D7, that the molecular weight of the acid had an essential influence on the cross-linking of the acid and diamines, and, according to the reasons for the decision, no evidence had been provided to demonstrate the contrary (No. II.4 of the decision).

(4) In these circumstances, the IR-spectra filed with the above letter and their interpretation were considered irrelevant for the assessment of novelty. Therefore, the Opposition Division concluded that the subject-matter of Claim 1 was not novel over D1.

(5) In view of this finding, the Opposition Division did not deal at all with the issue of inventive step. It only added a further remark to novelty over D2. This document would not anticipate the subject-matter of Claim 1, because it disclosed only an intermediate 1:1 HA-diamine adduct, which was then, in a second reaction, crosslinked over aldehydes or ester functionalities. According to two examples, the 1:1 acid-amine adduct was not a crosslinked "acid:diamine:acid product".

IV. On 22 June 2005, a Notice of Appeal was filed against this decision by the Patent Proprietor/Appellant. The prescribed fee was paid on the same date.

(1) In the Statement of Grounds of Appeal (SGA) received on 5 September 2005, the Appellant disputed the reasons given in the decision under appeal, requested that the decision under appeal be set aside and that the patent in suit be maintained in the form

of the above "Auxiliary Request" of 18 February 2005 (section II(3), above), annexed thereto as Enclosure 1.

(2) Each of two further Enclosures 2 and 3 contained a new experimental report.

(a) In Enclosure 2, the method of D1 was repeated with two types of HA films having different molecular weights (1.6 and 2.2 MDa, respectively) as starting material, each being reacted either with EDC alone or with EDC and Lys-Me ("samples 2 to 5"). In further experiments, a HA film of HA (180 kDa) according to Claim 1, crosslinked with diaminopropane by means of CMPJ (N-methyl chloropyridinium iodide) as the activator ("sample 6") and, as a comparison, a film of unmodified HA (2.2 MDa; "sample 1") were prepared. The films of samples 2 to 5 were then solubilised by hydrolysis in mild conditions (in which, according to D1, amide bonds would not be broken; see the Introduction of Enclosure 2), in order to get homogeneous solutions necessary for NMR measurements. However, subjecting sample 6 to the same treatment did not yield such a solution, but only "a suspension of completely swelled gel in a highly viscous solution", despite the lower molecular weight of the HA used therein (Enclosure 2, pages 4 and 5: "*RESULTS, 1.Hydrolysis*"). According to the Appellant, this showed that the amide bonds had been completely stable in these hydrolysis conditions.

On the basis of the NMR-spectra obtained from samples 1 to 5, from Lys-Me, from lysine-HA monoamide, from lysine diacetamide and from

mixtures thereof, which had been filed therewith, the Appellant pointed out in its "*CONCLUSIONS*" that, in the spectra of samples 2 to 5 (ie the samples prepared according to D1), no signals had been found which could be assigned to lysine diamide groups, and that the films obtained by the method of D1 had been "heavily contaminated by free lysine and dialkyl urea, notwithstanding the repeated dialysis cycles they were subjected to".

(b) Enclosure 3 included and referred to IR-spectra of (a) films made from two types of HA having 1.6 MDa (Spectrum 1A) and 2.2 MDa (Spectrum 1B), respectively, (b) films of the products of each of these HA types and EDC (Spectra 2A and 2B, respectively) and (c) films of products of each of these HA types reacted with EDC and Lys-Me (Spectra 3A and 3B, respectively). The films of each of the Spectra 2A, 2B, 3A and 3B had been prepared by the film immersion technique of D1 (page 244, right column). Those of Spectra 1A and 1B had been prepared as described in the left column of page 244 of D1. The film made from HA, EDC and Lys-Me (Spectrum 3A) was subjected to repeated dialysis with water to remove side-products or unbound adsorbed substances. The report (see its paragraph 1) explicitly refers to the procedure reported in D1. The "typical peaks of hyaluronic acid" in the region from 1560 to 1640 cm^{-1} of the IR-spectrum of HA were assigned to the stretching of the CO groups of amido and carboxylate groups and to the bending of the amido NH group. In the Spectra 2A and 2B of the HA + EDC products, an additional peak at 1700 cm^{-1} was assigned to acylurea carbonyl stretching, "thus

confirming the formation of the adduct (HA-EDC)". Each of the Spectra 3A and 3B additionally showed a very small shoulder at 1740 cm^{-1}, which was assigned to the ester carbonyl of Lys-Me. However, this gave, according to the Appellant, "no indication whether this is bound or physically trapped inside the HA film." ("Infrared Analysis" at the bottom of page 1 and in the first half of page 2 of Enclosure 3).

(3) Additionally, the Appellant referred again to its previous experiments (section II(2), above) and argued that these results would support its case, because the higher reactivity of the HA due to the lower molecular weight of the HA would have meant best conditions for the prior art method. Moreover, the results of all its experiments mentioned hereinbefore would have been in full agreement with the available knowledge derived from D6 to D9, according to which EDC alone would not be effective in promoting the formation of diamide bonds, due to "the notorious formation of unreactive intermediates (O-isoacyl-ureas converting to the more stable, non-reactive N-acyl-ureas)" (SGA: page 3, lines 19 to 21). Furthermore, the Appellant referred to four passages in D7, which indicated that acylureas had been obtained rather than amides, when "one chose to explore carbodiimide-promoted coupling of HA carboxylic group with simple aliphatic diamines" (page 232, right column, last paragraph preceding the EXPERIMENTAL PROCEDURES; page 237, left column, lines 15 to 17; page 238, left column, lines 14 to 16; and page 240, right column, paragraph 2 of the Conclusions).

Moreover, D9, "published after the relevant dates", provided, in the Appellant's view, final evidence for

the impossibility of achieving the formation of diamide bonds by using EDC, unless further scavengers for the intermediate O-acyl-iso-ureas such as 1-hydroxybenzo-triazole or N-hydroxysulfosuccinimide were present. Such compound had not, however, been used in D1.

V. In its letter dated 10 January 2006, the Respondent/ Opponent disputed the arguments of the Appellant in their entirety and supported the reasons for the revocation given in the decision under appeal.

(1) In particular, the Respondent reiterated its arguments that a claim to products defined in terms of a process was allowable only, if the products as such were patentable, and that the claim was silent about the kind of the crosslinking bonds. For anticipating the subject-matter of the actual product-by-process claims, it was not, according to the Respondent, necessary that only amide bonds were formed, but only that a certain amount of amide bond was obtained as clearly indicated in the specification of D1. The Respondent also maintained its previous arguments to novelty on the basis of D1, and it referred to the optional functional groups in the preferred diamine in Claim [3], ie hydroxy, carboxy, halogen, alkoxy and amino groups. Moreover, it put emphasis on the statement that the molecular weight of the HA would play an important and decisive role in the formation of an intermediate HA-acylurea. Thus, D7 would indicate that a low molecular weight of the HA would favour the forming of N-acylurea, whilst higher molecular weight HA would be less prone to rearrangement from O-acyl-(iso)urea of HA to the N-acylurea. Therefore, the use of high molecular weight HA (of 2000 kDa) had been proposed in D1, which was younger than D7, to provide

the O-acylurea as the reactive intermediate, which could be attacked by the nucleophilic diamines to form amide bonds, rather than the stable N-acylurea, which would form from a low molecular weight HA as used in D7 (600 kDa) or as in the additional experiments provided by the Patent Proprietor (240 kDa; section II(2), above). Nor would, according to the Respondent, the Appellant's additional experimental data prove the Appellant's case beyond any reasonable doubt (letter: page 9, last paragraph and page 10 and sections IV(2)(a) and IV(2)(b), above, respectively), since NMR spectra of crosslinked HA involved "many difficulties and problems, because of complexity of the structure and because of many different possibilities to change and adapt the various variables in order to point out some peaks and to decrease other peaks". This could be seen in two additional generic documents on NMR spectroscopy, in general, and on NMR spectroscopy of polymers (D14 and D15, filed with this letter; which played, however, no further role in these proceedings). Moreover, due to the threshold level of NMR spectra, a bond present at a low level would not be detected, because it would be covered by other signals or by the basic noise (letter: page 10, paragraphs 1 and 2).

(2) With regard to the Appellant's first experiments (sections II(2) and IV(3), above), the Respondent argued along the same lines as in its arguments to the NMR spectra mentioned in section V(1), above, pointed to the criticality of specimen preparation (film thickness and hydrolytic treatment thereof) and choice of the appropriate type of measuring device, and also questioned the validity of the interpretations of the IR-spectra by the Appellant, because no particulars such as the film thickness or the mounting of the films

in the IR apparatus had been given although "the preparation of the sample is particularly critical" (letter: page 10, penultimate line and following).

(3) Furthermore, the Respondent maintained its novelty objection on the basis of D2 and cited another document as being anticipatory for the claimed subject-matter:

D13: EP-A-0 566 118.

According to the Respondent, D13 disclosed a process for preparing a crosslinked modified polysaccharide, namely crosslinked HA, by means of a diamine or a polyamine. The Respondent pointed out that D13 indicated in many points that the crosslinking would occur through amidation (letter: page 16, 1st half).

VI. In a letter dated 19 October 2007, the Appellant, on the one hand, summarised its previous arguments and, on the other hand, further elaborated some aspects of its previous arguments, in particular those referring to its additional experiments provided. In this context, it criticised that, despite the fact that the onus of proof had been on the Opponent, the Respondent had, up to that date, not discharged this burden and had not submitted any experimental data to prove its case. On the basis of the results of its own experiments, the Appellant maintained its view that D1 did not contain any enabling disclosure for obtaining crosslinked HA, despite the speculations made in D1. Instead of crosslinked HA, only N-acylurea derivatives of HA would have been obtained therein (letter: No. 78).

(1) As regards D1, the Appellant summarised its arguments as follows (letter: No. 81):

Additionally, the Opponent has repeatedly pointed out that claim 1 is a product by process claim which is only novel if the product obtained by the process is novel. Of course, it is agreed to this statement. However, the Opponent draws the wrong conclusion therefrom that any process which might lead to similar products would need to be considered novelty destroying for claim 1. It is pointed out that it is not necessary according to claim 1 that only amide bonds are obtained, but it is completely sufficient in order to come to the conclusion that the subject matter of claim 1 is novel over D1 that amide bonds are formed at all whereas according to D1 no amide bonds are formed. There seems to be a misunderstanding on the Opponent's side. The argumentation is that there is a difference between the products obtained when following the teaching of D1 as compared to the process underlying the patent, in that according to the patent a product is obtained which predominantly contains amide bonds and the products according to D1 do not contain any detectable amide bonds. This consequently means that the products obtained according to D1 are different from the product according to claim 1 which is defined by the process by which it is obtained.

(2) The Appellant fully agreed to the comments in the decision under appeal on D2 (section III(5), above).

(3) The new novelty objection on the basis of D13 was disputed by the Appellant, who pointed out that this document had been referred to in § [0014]. In particular, it put emphasis on the fact that HA was mentioned in D13 only as one example for a long chain polyol, which could be used as an alternative to the long list of possible crosslinking agents such as diamines or polyamines, which could be used to crosslink suitable polysaccharides. HA was not, however, disclosed as belonging to the polysaccharide (Nos. 101, 102 and 105 of the letter). Nor did D13 refer to the use of an activator (No. 106).

(4) Furthermore, a clean copy of the Main Request (the claims of which were identical to those of the previous Auxiliary Request, sections II(3) and IV(1), above) and a new Auxiliary Request were attached. In this new Auxiliary Request, the new Claim 1 had been formed by combining Claims 1 and 3 of the above Main Request, except for "carboxy" having been deleted from the list of optional substituents of group A in the formula of

the diamine, and, furthermore, Claim 2 had been deleted and the remaining Claims 4 to 11 of the Main Request had been renumbered as Claim 2 to 9.

VII. In a letter dated 15 November 2007, the Respondent essentially reiterated its objections and arguments. Additionally, it submitted an experimental report

D17: "Tests Carried out According to the Teaching of D1 (Yakeda) and Determination of Free Amino Groups by TNBS Assay".

(1) In this report, experiments, ie Reaction A and Reaction B, respectively, were carried out according to the solution casting method, one of two methods equally efficacious for carrying out the reaction (letter: page 13, paragraph 2 to page 15 and the paragraph bridging pages 7 and 8). Furthermore, the content of free amino groups was determined by TNBS (2,4,6-tri-nitrobenzene sulphonic acid) assay (wherein the light absorbance at 420 nm was measured), a previously known method described in two publications submitted therewith, which did not play any further role. In each of these experiments, an aqueous solution of the Na salt of HA (1200 to 1400 kDa) and Lys-Me was prepared and adjusted to pH 4.75. Then, EDC was added thereto which resulted in a slight increase of the pH. During the reaction, aliquots of the mixture were withdrawn and the amount of free amino groups was determined, which decreased over the time of reaction, indicating, according to the Respondent, the increasing cross-linking of the HA by amidation. The final products were then purified to remove any unreacted Lys-Me and EDC, until the TNBS assay indicated the absence of free NH_2.

Despite a subsequent hydrolysis of the products at 25°C for 3h, the absorbance at 420 nm remained negligible. A stronger alkaline hydrolysis at 80°C for 3h, however, to hydrolyse all amide linkages in the products resulted in a significant absorbance at 420 nm. These findings were interpreted by the Respondent as proof for the HA having been completely crosslinked by covalent diamide bonds of the Lys-Me.

(2) The Respondent maintained its position that in D1 the HA had been crosslinked by means of Lys-Me diamide groups and disputed, with regard to its Figure 11, the interpretation of the IR-spectra by the Appellant that only N-acylurea would have been formed. Furthermore, it referred to Figure 12 of D1, according to which the product of HA + EDC + Lys-Me had shown higher resistance to hydrolysis than the product of HA + EDC.

(3) The Appellant's argument that the IR band at 1700 cm^{-1} in D1 was due to the formation of N-acylurea, from HA and EDC, but not to the ester of the cross-linked product, was disputed by the Respondent on the basis of the disclosure in D1 of the IR spectra of reaction products of poly(acrylic acid) and of poly-(L-glutamic acid), respectively, with WSC. The Respondent took the view that, if the reaction had stopped in these cases at the formation of the carboxyl groups/WSC, the same absorbances as with HA/WSC should have been found. Since the spectra had, however, been different, the Respondent concluded that no acylureas had been formed in these reactions and that WSC worked to activate the formation of the ester, since, upon addition of Lys-Me, the peak at 1700 cm^{-1} decreased, whilst the peaks of amide increased (2nd half of page 9).

VIII. Oral proceedings were held before the Board on 18 December 2007. In essence, both parties reiterated their previous arguments as submitted in writing. Therefore, only those points as presented during the hearing, which have been of particular importance for this decision, will be summarised herein below.

(1) Only at a very late stage shortly before the oral proceedings, had experimental results (D17) been filed by the Respondent, which, according to the Appellant, did not contain direct proof for the alleged structure of the products by IR- and NMR-spectrometry, but contained only indirect tests of the amino group content. In the reaction conditions used in this report (eg an insufficient amount of EDC was asserted by the Appellant), it would have been impossible that all amino groups could have reacted to amide groups. Moreover, the strong hydrolysis of the final products reported in D17 would, in any case, also have resulted in the hydrolysis of the acetylamide group inherently present in the glucosamine part of HA. Consequently, the final measurement of free amino groups after the hydrolysis could not be assigned to crosslinks of HA via lysine diamide groups.

(2) The Respondent explained the late filing of D17 with regard to the filing of new requests and further arguments concerning the nature of the crosslinking bonds and the question of whether D1 contained enabling disclosure with the Appellant's letter dated 19 October 2007 (sections VI to VI(4), above). Furthermore, the experiments of D17 could easily be repeated in a few days. Consequently, the filing of D17 could neither be considered as an abuse of procedure, nor as an action causing delay of the proceedings.

(3) By contrast, the Appellant pointed out that the Main Request had already been on file during the opposition procedure and that, therefore, there was no justification for the late submission of D17. Nor had there been any late action from the Appellant's side, in particular, no additional experiments after the filing of the Statement of Grounds of Appeal. Moreover, in view of the confusing facts and reasoning in D17 and the Respondent's letter filed therewith (section VII(1), above), which it could neither follow, nor comment on, and the late filing of D17, the Appellant requested that D17 not be admitted into the proceedings.

(4) In view of the arguments presented by both parties, the Board came to the conclusion not to admit D17 into the proceedings and announced this decision.

(5) As regards the substantive questions concerning the reasoning in the decision under appeal, the Appellant put emphasis on the fact that Claim 1 of the Main Request referred to crosslinked HA as the reaction product of the reaction of the HA and a polyamine, ie the reaction of the carboxylic acid group of HA and the amino groups of the "cross-linking polyamine" (§ [0021] and § [0032]), irrespective of the optional presence of any additional functional groups in the polyamine actually used.

(6) By contrast, the Respondent argued that in Claim 3 a number of functional groups of the amine were listed, eg hydroxy and carboxylic groups, which could react with HA. Whilst some amidation would certainly occur in the crosslinking reaction and the amino groups were very reactive, it could not be said that amide groups would be predominant in the claimed product.

(7) As regards the products of D1, the Appellant pointed out that the authors had only speculated about the nature of the reaction products, when they stated that the degradation of a film of the product of HA + Lys-Me + WSC was prolonged "probably because of amide bond formation as the crosslink" (Abstract of D1). In fact, they had, in the Appellant's view, never had a crosslinked HA in their hands. This would be confirmed by each of D6 to D9. Thus, in each of these documents, the respective authors had stated that the reaction of HA and EDC in the presence of an amine of diamine had failed to provide polymeric materials in which the amines had been incorporated (D6: page 5972, left column, paragraph 2 of the Introduction; D7: page 232, right column, last paragraph of the Introduction, page 240, right column, paragraph 2 of the Conclusions; D8: page 345, right column, Discussion; D9: page 153, right column, lines 10 to 22 and page 154, Figure 2). An HA, which was crosslinked via amidic bonds, was never obtained. Moreover, the Appellant pointed out that D1 was completely silent about the pH value applied in its method of crosslinking by film immersion. It would, however, be evident from Figure 2 in D9 that crosslinking of HA could not be achieved by means of EDC even when starting at an acidic pH value, necessary for the EDC activation. Rather, the activation of HA by means of EDC for crosslinking HA by amidation with diamines could only be achieved by adding further compounds such as N-hydroxysulfosuccinimide (NHS) or 1-hydroxybenzotriazole (HOBt). However, such compounds had not been used in D1.

(8) Then the Appellant referred to some of the individual IR absorptions and of the ^{13}C-NMR peaks in

the spectra in the first experimental report (section II(2), above). Thus, it argued that the NMR-"Spectrum nr. 8" of the reaction product of HA, EDC and Lys-Me (obtained in its Experiment 4 according to the film immersion method of D1 and determined after repeated washing steps) showed the same peaks as NMR-Spectra "nr.2" (prepared in its Experiment 1, according to D6) and "nr.6" (obtained in Experiment 3, according to the immersion method of D1) of the reaction products of HA and EDC. In particular, a peak in the range of 150 to 160 ppm, which could be found in each of Spectra nr. 2, nr. 6 and nr. 8, but not in Spectrum nr. 4 (non-crosslinked HA of Experiment 2 according to D1), was assigned by the Appellant to the carbonyl carbon atom of the N-acylureas, because in D6, the reaction product of HA and EDC had been identified as the mixture of two isomeric N-acylureas (wherein HA was linked to one of the NH-groups of the urea derived from EDC). In view of the teachings in D6 to D9, the Appellant, therefore, excluded that direct ester bonds between hydroxyl and carboxyl groups of HA (HA-COO-HA) could have been obtained in Experiments 1 or 3 (HA + EDC) and that the above peak at between 150 and 160 ppm could be assigned to the carbonyl carbon atom in such an ester bond.

Moreover, it would be evident from these findings, that the IR-peak at 1700 cm^{-1}, which could be found in each of IR-spectra "nr. 1" (product of Experiment 1), "nr. 5" (product of Experiment 3) and "nr. 7" (product of Experiment 4, repeatedly washed with ethanol/water), but not in "Spectrum "nr. 3"(non-crosslinked HA film of Experiment 2), could only be assigned to the carbonyl stretching in the N-acylurea (obtained in the reaction of HA and EDC in the presence or absence of Lys-Me). The Appellant believed that the authors of D1 had erred

when they had assigned the IR-peak of the acylurea CO-stretching to the CO-stretching of an ester bond.

Lys-Me as used in Experiment 4 could, according to the Appellant, be removed by washing, as confirmed in their Experiment 5 (peak at about 1740 cm^{-1}, assigned to the CO-stretching of the ester bond of Lys-Me, which vanished upon repeated washing: Spectra "nr. 10" and "nr. 11"). In the latter Experiment additional Lys-Me had been added after the termination of the reaction of Experiment 4, but before the subsequent washing steps.

The IR-peak at about 1650 cm^{-1}, found in all IR-spectra, was assigned by the Appellant to the CO-stretching of the acetylamide group on the glucosamine ring of HA.

The Appellant added, undisputed by the Respondent, that the above wave numbers of the IR-absorption of a given structural group could slightly differ in the spectra of different products (eg the CO-stretching of the ester group of Lys-Me at 1731 to 1740 cm^{-1}).

(9) Since the products obtained in Enclosure 3 (section IV(2)(b), above) showed the same pattern of IR-bands in the same region (in cm^{-1}), although two HA types with different molecular weights had been used (1.6 and 2.2 MDa, respectively; cf. D1: 1.5 MDa), the molecular weights of which had been higher than that of the HA in the above first experimental report (240 kDa), the Appellant argued, that the molecular weights of the HA used did not have the high influence on the reaction as attributed to in the decision under appeal and that their own assignments of these bands (above) were confirmed by these results.

Whilst acknowledging that Spectrum 3B of Enclosure 3 indicated that some minor bonding of Lys-Me to HA had occurred, which was also confirmed by NMR (see section VIII(10), below), the Appellant took the view that this did not amount to a disclosure of a crosslinked HA, but rather to the presence of some pendant Lys-Me groups bonded only by one of their amine groups to the HA. Most of the Lys-Me added to the reaction would, however, have remained as an additional component dissolved in the solution of the sample.

(10) In order further to explain its view on the basis of the results of Enclosure 2 (section IV(2)(a), above), the Appellant submitted marked and annotated copies of Figures 1A to 8 of this Enclosure.

As an initial remark, the Appellant pointed out again that the NMR measurements could only be carried out with solutions, so that solubilisation of the respective products was necessary. This had, however, to be achieved in mild conditions in order to prevent the cleavage of any amide bonds, in order to find out whether amidic crosslinks were, in fact, present in a sample. Whilst the products prepared according to D1 formed the required solutions in these conditions, the Appellant referred again to the fact that no solutions had been obtained in this way from the product according to the patent in suit (sample 6), because its amidic crosslinks prevented the required solubilisation (cf. section IV(2)(a), above).

In its explanations of the above spectra given at the hearing, the Appellant specifically referred to the separate sheets each of which showed one of Figures 1A, 1B, 5 and 6 of the Enclosure, containing NMR-spectra

inter alia of samples 1, 2, 3 and 5, respectively, as explained in the letter referred to in section IV(2)(a), above. On each of these sheets, a number of peaks within the range of from 0 to about 4.5 ppm was marked in colour. These peaks within one spectrum marked in one colour were assigned by the Appellant to a particular species contained in a given sample.

Thus, Fig. 1A, showed the spectra of HA (sample 1), of the product of HA + EDC (sample 2) and of the product of HA + EDC + Lys-Me (sample 3), each solubilised by mild hydrolysis of the ester group of Lys-Me to the (sodium) carboxylate ion group. In the spectrum of sample 3, the ^{1}H-peaks assigned by the Appellant to the five individual hydrocarbyl groups of the lysinate part of the molecule had been marked in blue. According to the Appellant, it was evident from a signal of the CH-group adjacent to the carboxylic group of the lysinate and bearing one of the two amino groups (peak 1' at about 3.9 to 4 ppm), that a small part of the lysine was linked to the HA via the amide group bonded to this CH-group, as opposed to a signal of the same CH-group of unbound sodium lysinate (peak 1 at about 3.1 ppm). A peak at about 2.4 to 2.5 ppm was assigned to the CH_2-group adjacent to the other free amino group of the lysinate.

Fig. 1B was indicated to show two measurements of sample 2 in different measuring conditions and allowed, according to the Appellant, the identification of those peaks belonging to one given species in the sample. Whilst the spectrum at the bottom of Fig. 1B showed only the signals of a derivative of N-ethyl-N'-(3-dimethylamino-propyl)-urea (derived from EDC), wherein HA was linked to the nitrogen of the N-ethyl-amino

group via an amidic bond, the upper spectrum showed the peaks of all compounds present in sample 2. Thus, the comparison of the two spectra allowed to assign in the upper spectrum those peaks (marked in green) to the hydrocarbyl groups of N-ethyl-N'-(3-dimethylamino-propyl)-urea itself (as shown on page 7 of Enclosure 2), and the other peaks in the spectrum marked in pink could thus be assigned to the N-HA-urea derivative.

In Fig. 5, showing the three spectra of the solubilised sample 5 as such (top) and under specific measuring conditions, ie selective excitation at either 3.96 (centre) or 2.47 ppm (bottom), respectively, the Appellant specifically referred to the triplet signal at 2.5 ppm which was assigned to the CH_2-group adjacent to the second amino groups of free lysinate and of HA-bound lysinate (linked by an amide group derived from the other amino group adjacent to its CH-group).

In Fig. 6, showing four different spectra, the spectra of lysine diacetamide and of free lysinate were compared with the spectrum of sample 5 and the spectrum of sample 5 containing additional free lysinate. According to the Appellant, the comparison of the spectra of the lysinate diacetamide and of the pure free lysinate allowed to identify the chemical shifting of the above CH-group upon amidation of the one amino group adjacent to it and the chemical shifting of the CH_2-group upon amidation of the other amino group adjacent to the CH_2-group. The comparison with the two further spectra derived from sample 5 would then confirm, that the peak at 2.5 ppm proved that the amino group adjacent to the CH_2-group of lysine had not been amidated, whilst after its amidation this peak would have disappeared. Hence, in the Appellant's view, the

lysine had never formed a diamide when reacted with HA and EDC, and consequently, this reaction had never yielded a crosslinked HA within the scope of Claim 1.

(11) The Appellant stressed in particular, that all its experimental data had been submitted prior to or together with the Statement of Grounds of Appeal (ie during the opposition procedure or at the begin of the appeal procedure) and that these results had never been refuted by the Respondent.

(12) The Respondent again argued that the product-by-process wording of Claim 1 did not specify the nature of the crosslinks. Having regard to the possible additional functionalities of the polyamine (in Claim 3), the claim would only require the presence of some amidation reaction having occurred in the preparation of the claimed product.

Concerning D1, the Respondent pointed out that spectra of its products and data about their degradation in Figure 12 had been given, which would have proved that a crosslinked HA had, in fact, been obtained in that document. Nor would D6 to D9, which (except for D9) had been published prior to D1, allow to conclude that in D1 the asserted results had not been reached. Rather, Figure 2 of D9 and also the spectra in Figure 15 of D1 would show that crosslinking by means of EDC would be possible, because the rearrangement of O-acylurea to N-acylurea would take longer than the crosslinking reaction. Furthermore, on page 246, right column of D1, reference was made to a pH of from 3 to 11. Lines 20 to 26 in the left column on page 247 would show that crosslinking of HA could be carried out by both methods disclosed in D1, ie by film immersion and by solution

casting. Due to the addition of amine, the pH of the initially acidic reaction mixture containing HA and EDC would be increased, so that the amine could act as a nucleophile capable of reacting with the activated carboxylic groups of HA.

(13) The debate on novelty was closed when it became apparent that the parties did not wish further comments on this topic. They then indicated to the Board that they would be prepared to continue with a discussion on inventive step, but left the decision in this respect to the discretion of the Board.

IX. The requests of the parties at this moment were as follows:

The Appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the Main Request or, in the alternative, of the Auxiliary Request, both filed with letter dated 19 October 2007.

The Respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. In view of the course of events in the opposition proceedings, *viz.* the only point addressed in the Communication pursuant to Rule 71a(1) EPC 1973/ Rule 116(1) EPC, and in view of the only issue dealt with in the decision under appeal, ie the question of novelty, the Board has limited its considerations in these appeal proceedings exclusively to this question,

initially with regard to the subject-matter according to the Main Request of the Appellant.

3. The primary basis for this decision is, therefore, the version of the claims of the Main Request as filed with the letter dated 19 October 2007. The wording of these claims is identical to the wording of the claims submitted with the letter dated 18 February 2005 under the heading of "Auxiliary Request" (sections II(3), IV(1) and VI(4), above). The only difference between these two requests resides in the amendment of the heading which now clearly identifies these claims as forming the "Main Request" of the Appellant.

3.1 As furthermore pointed out by the Appellant (section VIII(3), above), all evidence submitted by the Patent Proprietor was filed at the latest together with the Statement of Grounds of Appeal (section IV(1) to IV(3), above), ie in accordance with Articles 12(1)(a) and 12(2) of the Rules of Procedure of the Boards of Appeal (RPBA; OJ EPO 2007, 536; former Articles 10a(1)(a) and 10a(2) RPBA, OJ EPO 2004, 541). Therefore, the above Main Request and the experimental results presented by the Appellant provide the basis on which this decision can properly be based.

3.2 As regards the filing of D17 with the letter dated 15 November 2007 (section VII, above), the Board takes the view in accordance with Articles 12(1)(b) and 12(2) (former Articles 10a(1)(b) and 10a(2)) RPBA, that the Respondent has not presented its case in its reply to the Statement of Grounds of Appeal in a complete manner (letter dated 10 January 2006 (sections V to V(3), above). Hence, the filing of D17 constitutes an

amendment of the party's case in the sense of Article 13(1) RPBA (former Article 10b(1) RPBA).

3.3 At the oral proceedings on 18 December 2007 (sections VIII(1) to VIII(3), above), it became clear from the arguments of both parties that a number of new questions had arisen from D17 and that D17 was not a true repetition of the alleged crosslinking of HA as described in D1, page 244, "Crosslinking by film immersion" in conjunction with page 247, line 33 *et seq.*, but that its experiment had rather been carried out by "solution casting", including an initial adjustment of the pH value of the purely aqueous solution of HA salt of HA and Lys-Me·2HCl to 4.75 (section VII(1), above).

It is, thus, evident that the experiment of D17 differs from the relevant disclosure in D1 not only by the fact that a different method (solution casting instead of the film immersion in D1) had been used, but also that the reaction conditions had been modified. Thus, D1 does not contain any indication that, in its film immersion method, the pH of the aqueous solution of EDC and Lys-Me salt, which additionally contained ethanol, had been adjusted or changed prior to, during or after the immersion of the non-crosslinked HA film.

For these reasons alone, D17 cannot be accepted as a true repetition of the disclosure of D1 which could serve to further elucidate the relevant disclosure of the document, because D17 does not meet the requirements for the admissibility of new (late-filed) facts, evidence and related arguments into appeal proceedings, as set out in T 1002/92 (OJ EPO 1995, 605, No. 3.4 of the reasons).

The further argument of the Respondent allegedly demonstrating more clearly the *prima facie* relevance of D17, that, upon addition of the EDC to the acidic aqueous solution of HA and Lys-Me in its experiment, the pH value had spontaneously increased slightly and that this was indicative of the release of Lys-Me as a nucleophilic reactant from its dihydrochloride, which would then have reacted with the activated HA in an amidation reaction, does not remedy the above deficiencies of D17. Nor was it convincing that, in D17, Lys-Me was, in fact, released as a nucleophile in the above reaction conditions, let alone that it had crosslinked the HA by reaction with activated carboxyl groups of the HA, as asserted. This will become more evident from the further detailed consideration of D1 and the reaction allegedly disclosed therein in the context of D6, D8 and D9 and D2 herein below.

On the basis of these facts and findings, the Board decided not to admit D17 into the proceedings and announced this (section VIII(4), above; Articles 13(1) and 13(3); former Articles 10b(1) and 10b(3) RPBA).

4. As indicated in sections II(1) and V(3), above, documents D1, D2 and D13 formed the basis of the novelty objection raised by the Respondent.

4.1 In Document D13, a method is claimed for the production of a water-swellable, generally water-insoluble modified polysaccharide. Modified polysaccharides suitable for use in the invention of D13, which are generally water-soluble, are listed on page 3, lines 34 to 47. They encompass derivatives of eg cellulose, starch, carrageenan, agar, gellan gum, chitin, preferably carboxymethyl cellulose (CMC).

On page 4, lines 23 to 31, examples of crosslinking agents suitable for use in the method of D13 are mentioned. Desirably they are selected from diamines, polyamines, diols, polyols and mixtures of these compounds. Further specific members of this group of compounds are chitosan glutamate, type A gelantin, diethylenetriamine, ethylene glycol, butylene glycol, polyvinyl alcohol, HA, polyethylene imine, and their derivatives and mixtures thereof.

In all the examples of D13, CMC was used as the basis, which was crosslinked with one of the crosslinking agents mentioned above. Thus, Samples 39 to 43 of Table 1 describe the use of HA as the crosslinking agent for the CMC, whilst, in Samples 33 to 38 of the table, polyethylene imine and, in Samples 47 and 48 of Table 1 and 49 to 56 in Table 2, diethylenetriamine were used as alternative crosslinking agents for CMC.

The Board cannot derive from this document any hint, let alone any clear and unambiguous disclosure, on which a valid novelty objection against the subject-matter of Claim 1 could be based.

Consequently, the subject-matter of Claim 1 is novel over D13.

4.2 Intermediate document D2 (published on 30 March 2000) describes methods for chemically crosslinking high molecular weight HA to form polymerisable biodegradable materials. The methods are based on the introduction of functional groups into HA via the formation of an active ester at the glucuronic acid moiety of HA as an intermediate and the subsequent substitution with a side chain containing a nucleophilic group on one end

and a (protected) functional group on the other end. The introduced functional groups allow for crosslinking of the HA derivatives (D2: page 1, first paragraph, "TECHNICAL FIELD OF THE INVENTION").

4.2.1 A number of functional compounds, including diamines (page 21, formula VIII) are listed in the bridging paragraph of pages 24 to 25. Examples of HA derivatives functionalised with polyamino compounds can be found in Example 4 (diaminoethane), Example 5 (lysine methyl ester), Example 6 (L-histidine methyl ester) and Example 8 (diaminobutane). In each of Examples 4, 5 and 6, the reaction was catalysed by means of a combination of EDC/HOBt, in Example 8, a combination of EDC and of sodium N-hydroxysulfosuccinimide ($NHS \cdot SO_3Na$, cf. D9, Fig. 2) was used. None of these examples provided a crosslinked product. Rather, the HA derivatives functionalised as described above could then be crosslinked by addition of a further functional compound capable of reacting with the pendant functional groups of the above HA derivatives (Example 9). This crosslinking by reaction with an additional functional compound is referred to in Schemes 4, 5 and 6 (pages 16 to 18) and on from page 25, line 18 of D2, onwards.

4.2.2 In view of these facts and findings, the Board concurs with the final remarks of the Opposition Division in the last paragraph of No. II.4 of the decision under appeal concerning D2, that D2 is not novelty destroying for the subject-matter of Claim 1.

4.2.3 Moreover, according to page 20 of D2, second paragraph,

Direct carbodiimide-mediated coupling of amines to the carboxyl group of HA in an aqueous environment, e.g., with EDC (1-ethyl-3-[3-

dimethylaminopropyl] carbodiimide), does not yield the predicted product since the *O*-acyl isourea that is formed as a reactive intermediate rearranges rapidly to a stable *N*-acyl urea (Kuo et al., supra). We demonstrate that by "rescuing" the active *O*-acyl isourea by formation of a more hydrolysis resistant and non-rearrangable active ester intermediate, the coupling of primary amines to HA is possible.

This can be achieved eg by using HOBt or $NHS \cdot SO_3Na$ (section 4.2.1, above).

The above rearrangement of the acylurea is also referred to on page 6, lines 10 *et seq.* of the document, where it is additionally stated that "any amide formation that does occur is insignificant ..."

4.2.4 In the Board's view, this passage (published after D1) confirms the Appellant's arguments repeatedly brought forward with reference to D6 to D9 (sections IV(3) and VIII(7), above) and disproves the Respondent's arguments in this respect (sections VIII(12), above). Furthermore, the Respondent has not discharged the burden of proof for its assertion that the rearrangement of O-acylurea to N-acylurea would take longer than the crosslinking reaction.

4.2.5 It follows from these facts and findings that the subject-matter of Claim 1 is novel over D2.

4.3 The asserted anticipation of the claimed subject-matter by D1 has been based on two principal assertions: (i) the spectra in D1 would prove the identity of the products of D1 and those claimed; (ii) it would not have been demonstrated beyond doubt that the different methods as disclosed in D1 and as used in the patent in suit, respectively, would yield different products.

4.3.1 Document D1 is a publication titled "Crosslinking of hyaluronic acid with water-soluble carbodiimide" aiming

at the production of low-water content HA films when brought into contact with water. The experiments, in which HA was reacted with WSC (ie EDC), were carried out in two different ways, one by starting from HA films and the other by casting HA solutions. Reference was also made to the reaction of a HA film with WSC in the presence of Lys-Me. The product of this reaction would have prolonged the *in vivo* degradation of the HA film, "probably because of amide bond formation as the crosslink" (page 243, Abstract).

The latter reaction using Lys-Me (or L-lysine instead of Lys-Me, which was reported to give similar results, D1: page 248, right column, first paragraph) was carried out according to a method disclosed under the title "Crosslinking by film immersion" on page 244, right column. This method included the preparation of aqueous solutions of ethanol or acetone (at different concentrations of the organic solvent), addition of the WSC and Lys-Me to the mixtures and immersion of small pieces of non-crosslinked polysaccharide films in the mixtures for 24 h at 25°C. Thereafter, the pieces were washed in double-distilled water and dried. A few more details of this reaction and an interpretation of the results are given from page 247, right column, line 7 of the continuous text, to page 248, right column paragraph 1. Thus, different amounts of Lys-Me (cf. Figure 11) and 10 mM WSC had been added to an 80 vol% ethanol/20 vol% water mixture. The structures of the resulting products were interpreted on the basis of the IR spectra shown in Figure 11 by the authors of D1. They concluded from these spectra and from the result of an in vivo degradation in the subcutaneous tissue of rats as shown in Figure 12 of D1 (D1: page 250, left column, last paragraph), that these results would

strongly suggest "that an amide bone [*sic*] was formed between the carboxyl group of HA molecule and the amino group of L-lysine methyl ester" as shown in the first reaction scheme (5) depicted in the right column of that page. Below that scheme (5), reference was additionally made to the possibility that side chains could form in this reaction, each having a terminal amine group.

4.3.2 As mentioned in section 4.2.3, above, D2 contains statements obviously contrary to the above interpretation of the results of the reaction of HA, EDC and Lys-Me in D1 and also contrary to the Respondent's statement at the oral proceedings (for which no evidence has been made available), that the rearrangement of the O-acylurea to the N-acylurea would take longer than the crosslinking reaction (section VIII(12), above). Rather, these statements in D2 confirm the arguments of the Appellant, who had referred to similar statements in each of D6 to D9, that no amidation or, if any, very little amidation would occur, which would then result in pendant groups having amino end groups (sections II(2), IV(3), VIII(9), VIII(10), above, see also section 4.3.1, above).

4.3.3 As mentioned in section 4.3, above, assertion (i) of the Respondent concerning the products of D1 in question was based only on the authors' interpretation of a number of particular peaks of the IR-spectra (1560, 1700, 1740 and 2925 cm^{-1}), as given in D1, whilst the Appellant provided, in addition to IR-spectra (section II(2) and IV(2)(b), above), a number of NMR-spectra of their experiments, which allow to evaluate the form of a NMR-signal with regard to the electronic and chemical neighbourhood of the particular atom

corresponding to that signal (Enclosure 2; sections IV(2)(a), VIII(8) and VIII(10), above).

The Respondent's comments on the NMR-data referred to difficulties and problems in the NMR-spectroscopy, in general, and in the NMR-spectroscopy of polymers, in particular (section V(1), above), however without providing any evidence that assumptions to this end would have been valid for the experimental data of the Appellant. Nor did the Respondent refute the detailed explanations of the NMR- and IR-data given by the Appellant at the oral proceedings. Therefore, the Board has no reason not to accept the Appellant's interpretations of those data, in particular, the interpretations on the basis of the knowledge from D6, that two isomeric N-acylureas were the only products of the reaction of HA and EDC (section II(2) and VIII(8), above; Patent Proprietor's letter dated 6 February 2004, page 3) and that the spectra of the products of the reaction of HA, Lys-Me and EDC also confirmed the formation of N-acylureas or, at most, of HA having some pendant groups terminated by an amino group (section 4.3.2, above).

4.3.4 With regard to assertion (ii) (section 4.3, above) the Respondent stated with reference to the Guidelines for examination, that products defined in terms of a process are allowable only if the product as such is patentable, namely the cross-linked HA must be new and inventive, independently from the process through which it has been obtained (letter dated 10 January 2006; page 4, paragraph 1). In the Board's opinion, this does not, however, mean that a process as such and the reaction conditions in this process would have no influence on the structure and properties of its

resulting product and that they need not, therefore, be considered at all.

4.3.5 Thus, according to Enclosure 2 (section IV(2)(a), above), the product made according to the method defined in Claim 1 (ie using CMPJ as an activator), on the one hand, and the products prepared according to the method of D1 (using EDC), on the other hand, showed completely different behaviour when homogeneous solutions were to be prepared therefrom for NMR-spectroscopy. Thus, contrary to those samples prepared in accordance with D1, the product (sample 6) obtained in accordance with Claim 1 could not be solubilised to obtain the solution required for NMR-spectroscopy. In the Board's view, this can only mean that the structure of the product according to Claim 1 was different from the products prepared by the method of D1.

4.3.6 In the discussion at the oral proceedings, it was, moreover, accepted by the parties that the reaction of HA and EDC depends on the pH value. More particularly, it requires an acidic environment. However according to the explanation in the paragraph bridging pages 339 and 340 of D8, normal aliphatic and aromatic amines, eg a diamine, cannot, contrary to hydrazine, act as a nucleophile towards the reactive intermediate product as expected from the reaction of HA and EDC (ie the O-acylurea), because of its protonation, so that the authors' attempts to couple aliphatic and aromatic diamines to the carboxylate groups of HA having a molecular weight of 1.5 MDa (as in D1) by this route (using EDC) had failed (page 345, "DISCUSSION").

4.3.7 Despite this apparent importance of the pH value for the reaction between HA and EDC, D1 is completely

silent in this respect, as far as the film immersion method is concerned, whilst reference was made to an adjustment of the pH value by addition of diluted HCl or NaOH in the solution casting method (page 244, right column, paragraph 3). Nor does the simple reference, below, to a pH-range of from 3 to 11 in the reaction of HA and WSC provide the missing clear information for the immersion of a HA-film into a solution of WSC and Lys-Me (page 246 of D1, right column, paragraph 1):

> To examine the pH effect of the reaction medium on HA crosslinking, a medium was prepared from 20 vol % water of different pHs and 80 vol % ethanol. No significant difference in water content was observed for the resultant HA films when crosslinking was carried out at 25°C for 24 h in the medium containing 20 vol % water of pH 3–11 and 50 m*M* WSC.

In view of the disclosure of D6, as relied upon by the Appellant (sections VIII(8) and 4.3.3, above), this statement in D1 rather casts further doubts on the assertion of its authors, based only on their assignments of IR-peaks, that they had, in fact, obtained crosslinked HA films, instead of N-acylureas as identified in D6 and in the Appellant's experiments.

4.3.8 Moreover, it is made clear in D2 (sections 4.2.1 and 4.2.3, above) and confirmed in D9, Figure 2; section VIII(7), above), that the amidation of the carboxylic group of HA by activation by a WSC (*viz.* EDC) can only be achieved in the presence of a further compound such as HOBt or NHS·SO_3Na. However, D1 does not mention to use such a scavenger to prevent the rearrangement of the intermediate O-acylurea to inactive N-acylurea, let alone has any such compound been used in D1.

4.3.9 Consequently, the Board takes the view that assertion (ii) (section 4.3, above) does not support the allegation of lack of novelty either.

4.4 In view of the above facts and findings, the Board has come to the conclusion, even when taking into account that the Appellant had admitted that some amidation would have occurred in its experiments resulting in pendant amino groups, that no convincing argument, let alone any evidence has been made available by the Respondent, for its assertion that the final products of the reaction of HA, WSC and Lys-Me or L-lysine, as disclosed in D1, had been crosslinked HA within the scope of Claim 1.

4.5 Consequently, it follows from the findings in each of sections 4.1, 4.2.5, and 4.4, above, that the subject-matter of Claim 1 in novel.

5. By the same token, the above findings are also valid for the elaborations in the remaining Claims 2 to 11, all containing the features of Claim 1 incorporated.

This view is also valid for Claim 3, even in view of carboxy as an example of the optional substituents of the amino compounds, as referred to by the Respondent, because "carboxy" is not referring to an ester group, ie an alkoxy- or aryloxy-carbonyl group.

6. In view of the above findings, there is no need further to consider the Auxiliary Request of the Appellant.

7. As already indicated in section 2, above, the Board, in its discretion and in particular since the issue of inventive step, also raised in the Opposition (section II, above), was evidently not considered by

the first instance, has decided to make use of its powers under Article 111(1) EPC to remit the case for completion of examination of the opposition in this respect.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance for further prosecution on the basis of the Main Request filed with letter dated 19 October 2007.

The Registrar: The Chairman:

E. Görgmaier R. Young