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Datasheet for the decision of 23 April 2015

Case Number: T 2544/11 - 3.3.03

Application Number: 00901776.5

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Language of the proceedings: EN

Title of invention:
PROCESS FOR THE PRODUCTION OF MULTIPLE CROSS-LINKED HYALURONIC ACID DERIVATIVES

Patent Proprietor:
Mentor Biopolymers Limited

Opponent:
Q-Med AB

Headword:

Relevant legal provisions:
EPC Art. 54, 56, 84, 123(3)

Keyword:
Novelty - Main request (no) - auxiliary request (yes)
Claims - clarity - auxiliary request (yes)
Amendments - auxiliary request - allowable (yes)
Inventive step - auxiliary request (yes)

Decisions cited:
G 0003/14

Catchword:

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Case Number: T 2544/11 - 3.3.03

D E C I S I O N
of Technical Board of Appeal 3.3.03
of 23 April 2015

Appellant: (Patent Proprietor)	Mentor Biopolymers Limited Research Avenue North, Heriot-Watt Research Park Edinburgh EH14 4AP (GB)
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Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 10 October 2011 concerning maintenance of the European Patent No. 1149116 in amended form.**

Composition of the Board:

Chairman	B. ter Laan
Members:	O. Dury
	R. Cramer

Summary of Facts and Submissions

I. The appeals by the opponent and the patent proprietor lie against the interlocutory decision of the opposition division posted on 10 October 2011 maintaining in amended form European patent No. EP 1 149 116, based on application No. 00 901 776.5, corresponding to the international application published as WO 2000/046253.

II. The application as filed contained 23 claims, of which claims 1, 3, 4, 15 and 21 read:

"1. A process for the preparation of multiple cross-linked derivatives of hyaluronic acid, which process comprises cross-linking HA via two or more different functional groups."

"3. A process according to claim 1 or claim 2 wherein the crosslinking is effected by means of two or more different bonds selected from ether, ester, sulfone, amine, imino and amide bonds."

"4. A process according to any of claims 1 to 3 wherein the cross-linking agent is selected from formaldehyde, glutaraldehyde, divinyl sulfone, a polyanhydride, a polyaldehyde, a polyhydric alcohol, carbodiimide, epichlorohydrin, ethylene glycol diglycidylether, butanediol diglycidylether, polyglycerol polyglycidylether, polyethylene glycol diglycidylether, polypropylene glycol diglycidylether, or a bis-or poly-epoxy cross-linker."

"15. Multiple cross-linked HA obtainable by a process according to any of claims 1 to 14."

"21. A product comprising multiple cross-linked HA according to any of claims 15 to 20."

III. The granted patent contained 24 claims, of which claims 1 and 3 read (additions as compared to claims 1 and 4 of the application as filed, respectively, are indicated in **bold**, deletions in ~~strikethrough~~:

"1. A process for the preparation of multiple cross-linked ~~derivatives of~~ hyaluronic acid **(HA)**, which process comprises cross-linking HA via two or more different functional groups, **wherein said cross-linking is effected by contacting HA with one or more chemical cross-linking agents so as to form two or more different types of functional bonds, between HA molecules, and wherein said two or more different types of functional bonds are selected from ether, ester, sulfone, amine, imino and amide bonds.**"

"3. A process according to claim 1 or claim 2 wherein the cross-linking agent is selected from formaldehyde, glutaraldehyde, divinyl sulfone, a polyanhydride, a polyaldehyde, a polyhydric alcohol, carbodiimide, epichlorohydrin, ethylene glycol diglycidylether, butanediol diglycidylether, polyglycerol polyglycidylether, polyethylene glycol ~~diglycidylether~~, polypropylene glycol diglycidylether, or a bis-or poly-epoxy cross-linker."

IV. A notice of opposition against the patent was filed, in which the revocation of the patent was requested on the grounds of Art. 100 (a) EPC (lack of novelty, lack of an inventive step as well as lack of industrial application pursuant to Art. 52(1)(4) and Art. 57 EPC 1973), Art. 100(b) EPC and Art. 100(c) EPC.

V. With the decision under appeal the patent was maintained on the basis of the sixth auxiliary request filed during the oral proceedings before the opposition division, comprising 11 claims of which claim 1 read (additions as compared to claim 1 of the application as filed are indicated in **bold**, deletions in ~~strikethrough~~; in order to facilitate the reading of the present decision, some features of the claim are indicated as separate paragraphs, which was not the case in claim 1 as submitted):

"1. A process for the preparation of multiple cross-linked ~~derivatives of~~ hyaluronic acid **(HA)**, which process comprises cross-linking HA via two or more different functional groups,

wherein said cross-linking is effected by contacting HA with one or more cross-linking agents so as to form two or more different types of functional bonds, between HA molecules, wherein said two or more different types of functional bonds are selected from ether, ester, sulfone, amine, imino and amide bonds,

wherein, in said process, a first cross-linking reaction is carried out and a further cross-linking agent, which may be the same or different from the first, is added to the reaction mixture to effect the second cross-link

and wherein the cross-linking agent is selected from formaldehyde, glutaraldehyde, divinyl sulfone, a polyanhydride, a polyaldehyde, a polyhydric alcohol, carbodiimide, epichlorohydrin, ethylene glycol diglycidylether, butanediol diglycidylether, polyglycerol polyglycidylether, polyethylene glycol

diglycidylether, polypropylene glycol diglycidylether, or a bis-or poly-epoxy cross-linker."

Claim 7 read:

"7. A process according to any of claims 1 to 6 wherein the crosslinking of each type of functional group is effected sequentially."

Claims 2-6 and 8-11 were dependent on claim 1.

VI. The decision under appeal was based, *inter alia*, on the following documents:

D1: WO 98 02 204
D3: EP 0 341 745
D5: K. Tomihata and Y. Ikada, J. Biomed. Mater. Res., 37, pages 243-251, 1997
D6: WO 87/07 898

In its decision, the opposition division considered that

- the main request and auxiliary request 3 did not fulfil the requirements of Art. 123(2) EPC because of the presence in claim 1 of the term "chemical" before "cross-linking agents" (see granted claim 1);
- auxiliary requests 1 and 4 did not fulfil the requirements of Art. 123(3) EPC because of the deletion of the term "chemical";
- each of auxiliary request 2 and 5 was anticipated by D5 and D6;
- auxiliary request 6 met the requirements of the EPC. An inventive step was in particular acknowledged starting from D6 as the closest prior art.

VII. On 9 December 2011 the opponent (appellant 1) lodged an appeal against the above decision. The prescribed fee was paid on the same day. With the statement setting out the grounds for the appeal, received on 9 February 2012, the opponent requested that the patent be revoked.

Further arguments were submitted with letters of 29 June 2012 and 15 September 2014.

VIII. On 19 December 2011 the patent proprietor (appellant 2) lodged an appeal against the above decision. The prescribed fee was paid on the same day. With the statement setting out the grounds for the appeal, received on 17 February 2012, the patent proprietor requested that the patent be maintained in amended form according to any of main requests A to D, or alternatively to any of auxiliary requests 1A to 1D and 2A to 2D.

Claims 1, 14 and 18 of main request A read (in claim 1, additions as compared to claim 1 of the application as filed are indicated in **bold**, deletions in ~~strikethrough~~):

"1. A process for the preparation of multiple cross-linked ~~derivatives of~~ hyaluronic acid **(HA)**, which process comprises cross-linking HA via two or more different functional groups, **wherein said cross-linking is effected by contacting HA with one or more cross-linking agents so as to form two or more different types of functional bonds, between HA molecules, wherein said two or more different types of functional bonds are selected from ether, ester, sulfone, amine, imino and amide bonds.**"

"14. Multiple cross-linked HA obtainable by a process according to any of claims 1 to 13."

"18. A product comprising multiple cross-linked HA according to any of claims 15 to 20."

Auxiliary request 2D (11 claims) was identical to auxiliary request 6 on which the contested decision is based.

Further arguments were submitted with letters of 3 July 2012, 10 April 2014 and 19 February 2015.

IX. With a communication dated 18 February 2015 in preparation for oral proceedings to be held on 23 April 2015, the Board set out its preliminary view of the case. The following documents were further cited:

D13: Encyclopedic Dictionary of Polymers, Ed. by J. W. Gooch, "cross-linking agent(s)";
D14: Stoeckhert "Kunststoff Lexikon", 8. Auflage, 1992, "Vernetzungsmittel" (cross-linking agents)

X. With a letter of 20 March 2015, the opponent submitted further arguments and filed

D15: Merriam-Webster Dictionary, online edition, 15.03.2015, "agent"
D16: Dorland's Illustrated Medical Dictionary, 27th Ed., 1988, page 37, "agent"
D17: US 5 800 541
D18: X. Zhao and C. Locket, "Double Crosslinked Hyaluronan and its medical Applications" in

Hyaluronan, Vol. 1, 2005, ed. EA Balazs and VC Hascall, Matrix Biology Institute, New Jersey, USA, pages 451-455.

XI. With a letter of 23 March 2015, the patent proprietor submitted further arguments.

XII. During the oral proceedings held on 23 April 2015 the patent proprietor withdrew each of main requests B-D, auxiliary requests 1A-1D and auxiliary requests 2A-2C.

XIII. The patent proprietor's arguments, as far as relevant for the present decision, may be summarised as follows:

Main request A

Novelty

a) D5 disclosed the crosslinking of hyaluronic acid using either carbodiimide, which led to crosslinking by ester bonds only, or a combination of carbodiimide and either L-lysine methyl ester or L-lysine, which led to crosslinking by amide bonds only, as clearly indicated in the abstract of D5. It could not be concluded from D5, in particular not from Fig. 11, that crosslinking by both ester and amide bonds effectively took place. There was further no evidence on file that the assumption made in the paragraph bridging the columns on page 248 in connection with Fig. 12 of D5 was effectively realised. Besides, there was no evidence that, should ester bonds be formed, they would not be purely intra-molecular i.e. that the ester bond so formed did indeed contribute to crosslinking.

b) D6 disclosed a process for the preparation of crosslinked hyaluronic acid comprising an epoxy-activation stage, removal of unreacted epoxy activator and a drying stage, in which crosslinking only occurred in the drying stage. In the activation stage a polyepoxy compound was bound to hyaluronic acid through a single type of bond (ether or ester) using either acidic or basic reaction conditions, a neutral pH being undesirable. Similarly, the drying step could also be performed using basic, acid or neutral pH conditions, which would also lead to a single type of bond (ether or ester). The description of D6 dealt with polysaccharides in general, hyaluronic acid being only cited as an example among others. Therefore, a process according to claim 1 could only be arrived at after making a series of choices within D6 (hyaluronic acid, different pH conditions for the activation and the drying step). There was further no evidence on file that two types of crosslinking bonds were effectively obtained in the examples of D6.

c) D6 also described the addition of polysaccharide(s) after the activation stage. However, the skilled person would not consider that polysaccharides were crosslinking agents in the sense of the patent in suit.

d) Therefore, the subject-matter of main request A was novel over D5 and D6.

Auxiliary request 2D

Clarity

e) The question whether, due to the wording of the claim, the cross-linking agents used in any of the process stages mentioned in claim 1 were limited to those specified in the list indicated in claim 1 also applied, in the same context, to granted claim 3. Therefore, following decision G 3/14, that feature could not be objected to as lacking clarity.

f) The feature "a first cross-linking reaction is carried out ... to effect the second cross-link" was to be read in its broadest sense, meaning that it encompassed simultaneous, step-wise and/or sequential addition of the crosslinking agents. That reading was broader than the sole sequential addition according to claim 7. That a claim had a broad scope did not mean that it was unclear.

g) The application as filed only disclosed cross-linking agents according to the list specified in claim 1. Therefore, it was clear from the application as filed that only those compounds were meant, for any step of the claimed processes.

Art. 123(3) EPC

h) According to common general knowledge and as confirmed by D13 and D14, crosslinking agents were chemical compounds, contrary to heat or irradiation. D17 was a patent document, which, according to EPO case law, could not be seen as reflecting common general knowledge. Therefore, the deletion in claim 1 of "chemical" as compared to granted claim 1 did not contravene the

requirements of Art. 123(3) EPC.

Novelty

i) L-lysine methyl ester according to D5 was not a cross-linking agent as specified in claim 1.

j) Since polysaccharides were not crosslinking agents in the sense of the patent in suit, the passage in D6 was not relevant so that D6 did not disclose the addition of further cross-linking agents to the reaction mixture.

k) Therefore, novelty over D5 and D6 was given.

Inventive step

l) In view of the problem addressed in the patent in suit D5 was the closest prior art, not D6.

m) The problem to be solved was to provide a process for the preparation of multiple cross-linked hyaluronic acid having a higher degree of cross-linking and improved resistance to digestion and free radicals.

n) The solution was a process according to claim 1, which differed from D5 in the nature of the further crosslinking agent.

o) The examples of the patent in suit showed that the problem was effectively solved. In that respect, the hyaluronic acid obtained in example CHA-6 (Table 1) was water soluble, which showed that only a single type of bond remained, as explained in paragraphs [0031]-[0032] of the patent in suit.

The hyaluronic acid obtained in example CHA-12 (Table 2 of the patent in suit) which was obtained using a similar sequence of steps as for CHA-6, was not water soluble but exhibited a higher water absorption capacity than the examples illustrative of claim 1: that result showed that both ether and ester bonds had been obtained and that the problem had been solved.

p) D5 taught that L-lysine methyl ester was essential in order to obtain two types of crosslinking bonds and that more amide bounds were obtained when using more L-lysine methyl ester (or L-lysine). Therefore, D5 provided no motivation to use a different crosslinking agent than L-lysine methyl ester, in particular not a compound as specified in claim 1.

The processes of D6 and D1 were incompatible with that of D5. Therefore, the combination of D5 with either D6 or D1 relied on hindsight.

q) Since D10 and D11 were both late-filed and not *prima facie* highly relevant, they should not be admitted to the proceedings and the opponent's objection made in writing based on a combination of each of D5 or D6 with either D10 or D11 should not be considered.

r) For those reasons, auxiliary request 2D was inventive.

XIV. The opponent's arguments, as far as relevant for the present decision, may be summarised as follows:

Main request A

Novelty

a) The reaction schemes in D5 showed the preparation of hyaluronic acid crosslinked by both ester and amide bonds. There was no evidence on file that only intra-molecular ester bonds were formed and no justification had been provided to explain why that might be the case.

Should it be concluded that D5 disclosed the formation of intra-molecular ester bonds only, the question arose if the patent in suit was sufficiently disclosed and if it taught how to achieve inter-molecular ester bonds.

b) D6 disclosed a multistage process for the preparation of hyaluronic acid crosslinked with both ether and ester bonds, which were formed using different pH conditions (basic or acidic) in the epoxy-activation stage and the drying stage, respectively. When neutral conditions were used in the activation stage, both types of bonds were made. In the activation stage, it could not be prevented that both partial crosslinking (only one epoxy functional group of the epoxy activator reacts with hyaluronic acid) and full crosslinking (both epoxy groups react with hyaluronic acid) took place.

c) According to D6, further polysaccharides could be added to the reaction mixture which amounted to a further crosslinking of hyaluronic acid by the polysaccharides by two different types of bonds. In that respect, although the further

polysaccharides reacted primarily with the epoxy-activator rather than directly with hyaluronic acid, they were considered to be crosslinking agents in the same manner as the L-lysine methyl ester of D5. In that respect, D5 described that L-lysine methyl ester only crosslinked to hyaluronic acid when carbodiimide was also present.

d) Therefore, the subject-matter of main request A was not novel over D5 and D6.

Auxiliary request 2D

Clarity

e) The process defined in claim 1 comprised a step of contacting hyaluronic acid with "one or more cross-linking agents" and further required that “the” cross-linking agent “is” selected from a list of components. Should at least two cross-linking agents be used, it was not clear whether that formulation imposed that each of those had to be selected within the list specified in claim 1 or whether it was sufficient that at least one of those cross-linking agents was to be chosen within said list.

f) The same objection applied concerning the cross-linking agent to be used in the first and second crosslinking reactions defined in the feature now being present in claim 1. Considering that said feature did not make part of any granted claim, the conclusions of decision G 3/14 did not apply and a clarity objection could be made in that respect.

Art. 123(3) EPC

g) As derivable from D3 or D17, the term "cross-linking agent" encompassed both chemical compounds as well as heat or irradiation. Therefore, the deletion of the word "chemical" before "cross-linking agents" from the wording of granted claim 1 contravened the requirements of Art. 123(3) EPC.

Novelty

h) Should the crosslinking agents used in any step of the claimed process be limited to those specified in claim 1, novelty over D5 was given.

i) Polysaccharides were polyhydric alcohols, which were mentioned in the list of cross-linking agents of claim 1. Considering that claim 1 set no limits in respect of said polyhydric alcohols, it also encompassed polymeric compounds such as polysaccharides. That crosslinking agents could be polymeric was acknowledged in the patent in suit. Consequently, as explained for main request A, (See XIV c) above), claim 1 was anticipated by D6.

Inventive step

j) Either D5 or D6 represented the closest prior art.

k) The process being claimed was at most to be distinguished from that disclosed on page 8 of D6 in that two crosslinking agents as specified in claim 1 were used. Since D6 explained that other compounds than polysaccharides were bound into the

material in the same manner (page 8, second paragraph), D6 taught that a second crosslinking agent could be added at the same time as or at a later stage than the first crosslinking agent. Therefore, starting from D6, the claimed method was obvious.

l) In the absence of any comparison with D5, the problem to be solved over D5 resided in providing a further, alternative process for preparing multiple cross-linked hyaluronic acid.

m) It was obvious to solve that problem by using, in the process of D5, an additional crosslinking step according to the teaching of D6. The same was valid regarding the combination of D5 and D1.

n) It was also obvious to solve that problem by adding the further cross-linking agent glutaraldehyde to the gels obtained in D5 or D6 to effect a further crosslinking, as taught in either D10 or D11.

o) Example CHA-6 of the patent in suit (Table 1) was a process according to claim 1 that resulted in a water soluble hyaluronic acid. That non-working embodiment cast serious doubts on the enablement of the process over the whole breadth of the claims.

p) Therefore, auxiliary request 2D was not inventive.

XV. Appellant 1 (opponent) requested that the decision under appeal be set aside and that the patent be revoked.

Appellant 2 (patent proprietor) requested that the decision of the opposition division be set aside and that the patent be maintained in amended form according to main request A, or alternatively according to auxiliary request 2D, both filed with its statement of grounds of the appeal.

XVI. The Board announced its decision at the end of the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

Main request A

2. Novelty

2.1 The opponent argued that each of D5 and D6 anticipated the subject-matter of claim 1.

2.2 Operative claim 1 is directed to a process for the preparation of multiple crosslinked hyaluronic acid in which

(a) crosslinking takes place via two or more functional groups;

(b) use is made of one or more chemical crosslinking agents;

(c) crosslinking is effected so as to form two or more different types of functional bonds, as specified at the end of claim 1.

2.3 D5 discloses two embodiments for crosslinking hyaluronic acid, using either water soluble carbodiimide alone or a combination thereof with L-lysine methyl ester or L-lysine (abstract; paragraph bridging both columns on page 248).

2.3.1 It was not disputed by the parties that the crosslinking of hyaluronic acid takes place via two different functional groups, namely hydroxyl and carboxyl groups, as illustrated in reaction scheme (1) of D5. Therefore, above feature (a) is disclosed in D5.

2.3.2 According to the patent in suit (paragraphs [21] and [24]), carbodiimide is cited as a suitable crosslinking agent. That is confirmed by e.g. D13 and D14, which are both technical dictionaries illustrating common general knowledge and according to which a crosslinking agent is defined as a substance that promotes or regulates intermolecular covalent bonding between polymer chains. In that respect, D14 indicates that crosslinking agents must not mandatorily be incorporated in the crosslinked product e.g. can also behave as an activator. That definition is neither in contradiction with the disclosure of the patent in suit nor with any of the cited documents. Therefore, according to that definition, carbodiimide when used alone as disclosed in the first embodiment of D5, although not being incorporated in the final crosslinked hyaluronic acid polymer (D5: page 243, bottom of the right column; page 249, reactions 2-4) is a “cross-linking agent”.

There is no evidence on file that the term "**chemical** cross-linking agent" (emphasis by the Board) has any accepted definition or clear, unambiguous meaning in the art, in particular that it represents a limitation of the term "crosslinking agent". There is in

particular no evidence to corroborate the patent proprietor's argument, provided e.g. during the examination or opposition proceedings, according to which a "chemical" cross-linking agent is limited to those agents that are incorporated in the final cross-linked product. Such a definition would, in addition, be in contradiction with D14.

Therefore, the water soluble carbodiimide and both lysine compounds disclosed in D5 are all "chemical crosslinking agents" according to claim 1 so that above feature (b) is disclosed in all processes of D5, in particular in the processes using a combination of carbodiimide and a lysine compound.

2.3.3 It is specifically indicated in D5 that an experiment was performed "in an attempt to cross-link hyaluronic acid molecules through an amide bond", in which cross-linking of a hyaluronic acid film was performed using various amounts of L-lysine methyl ester or L-lysine in the presence of water soluble carbodiimide (D5: page 247, right column; Figs. 10-11; page 248: top of right column). In that respect it is in particular concluded that Fig. 11 shows a reduction in the absorption at 1700 cm^{-1} (which corresponds to the ester bond: see D5, page 249, bottom of the right column) and an increase in the absorption at 1740 and 1560 cm^{-1}, suggesting that the amide bond is "actually formed by an addition of L-lysine methyl ester to the reaction medium" (D5: paragraph below Fig. 11).

The assumption made on page 248 of D5 (left column, first sentence of the paragraph above Fig. 12) that hyaluronic acid molecules are cross-linked not only through ester bonds but also through amide bonds is further corroborated by Fig. 12 which, according to D5,

provides evidence for the contribution of the amide bond to cross-linking of hyaluronic acid when lysine ester is added to the reaction medium (page 248: top of right column). Therefore, D5 discloses that both types of crosslinking bonds (ester and amide) are indeed formed.

That reading is further confirmed by the last sentence on page 250 of D5 ("... than those cross-linked through an ester bond **alone**", emphasis by the Board). The Board does not share the patent proprietor's opinion according to which said sentence only referred to the basis for comparison and did not imply that the material with which this was compared necessarily also contained ester crosslinks. That sentence is to be read considering the whole teaching of D5, which, as explained above in respect of Figs. 11-12, is that the use of carbodiimide together with L-lysine methyl ester leads to the formation of both ester and amide crosslinking bonds.

Although it is indicated on page 249 of D5 (paragraph below compound (4)) that it is unclear whether the reaction leading to intra-molecular or inter-molecular ester bonds prevails when using carbodiimide crosslinking agents, the conclusion of D5 is that inter-molecular ester bonds must be present (page 248: second sentence of the section "Discussion"). There is further no evidence on file that the process of D5 may lead to intra-molecular ester bonds only. Nor did the patent proprietor provide any explanation why that would be the case. Considering in addition that claim 1 of main request A does not set any limit to the amount of crosslinking bonds present for each type of bond, the patent proprietor's argument that D5 did not directly disclose inter-molecular ester bonds, in

particular in respect of the second embodiment, cannot be followed.

The mere fact that the last sentence of the abstract reads, in respect of the second embodiment, "because of amide bond formation as **the** crosslink" (emphasis by the Board), is not sufficient to refute the conclusions drawn from the disclosure of D5 as a whole, in particular the clear teaching derived from Figs. 11-12. That argument of the patent proprietor was, in the absence of further evidence to corroborate that assumption, not followed.

Although the opposition division already concluded that the presence of both amide and ester bonds in crosslinked hyaluronic acid was effectively disclosed in Fig. 11 and on page 248 of D5, no further evidence was provided by the patent proprietor in appeal to refute that conclusion.

Therefore, the process of D5 in which use is made of both a carbodiimide and a lysine compound not only satisfies above feature (c), but also its combination with above features (a) and (b).

2.3.4 Under these circumstances, D5 anticipates claim 1 of main request A.

2.3.5 Since the process according to operative claim 1 is not novel, the products of that process cannot be novel either. Therefore, also the subject-matter of claims 14 and 18 is not novel over D5.

2.4 D6 discloses a process for the production of materials of cross-linked polysaccharides containing carboxyl groups, characterised in that in a first step the

polysaccharide is activated with a bi- or polyfunctional reagent, whereupon excess reagent is removed and the activated polysaccharide is then dried in a second step so as to form an insoluble crosslinked material (claim 1). Preferably, the polysaccharide is hyaluronic acid (claim 5; page 4, lines 3-4; examples 1-14 and 18-25) and the activating reagent is a bi- or polyfunctional epoxide (claim 2; page 4, first full paragraph).

The initial epoxy activation is performed in such a way that gel formation is avoided and either leads to ester bonds, ether bonds or both, depending on the pH conditions (page 4, full paragraphs 2-3). According to page 4, full paragraph 2 and the examples, the activation step is performed under diluted conditions. Preferably, the activation is carried out in an alkaline medium while the drying is performed in acidic conditions (claim 3). According to claim 7 and page 6, first paragraph, the final product, i.e. the cross-linked polysaccharide, contains both ester and ether bonds.

Such processes using specifically hyaluronic acid are described in examples 1-14 and 18-25 of D6. The final products are considered to be "gels" (last paragraph on page 8; first paragraph on page 9) or "gel films" (examples 2-4).

2.4.1 The epoxy-activator according to D6 satisfies the definition of a “cross-linking agent” given in section 2.3.2 above, which is also confirmed by the teaching of D6 (as explicitly mentioned on page 10, line 4 and page 12, examples 13-14 of D6) and/or by operative claim 3, in which epoxy compounds such as epichlorohydrin and

butanediol diglycidyl ether are specifically mentioned.

2.4.2 D6 discloses that the polysaccharides obtained are cross-linked via two different types of bonds, namely ether and ester bonds (claim 7). It is further disclosed on page 6, first paragraph, that using basic and acidic conditions in the activation and drying steps, respectively, or the other way round, in particular leads to crosslinking by ether and ester bonds. In that respect, it is further derivable from the last paragraph on page 1 and the first paragraph on page 2 of D6, as well as from the conclusions already drawn in respect of D5 (see section 2.3.1 above) that such double crosslinking is made via two different functional groups of hyaluronic acid, namely hydroxyl and carboxyl groups. That conclusion is also in line with paragraphs [0020] and [0022]-[0023] of the patent in suit.

That such a double crosslinking (ether and ester bonds) via two different functional groups (hydroxyl, carboxyl) in particular occurs for hyaluronic acid is explicitly disclosed in claim 8 of D6 and is further derivable from the fact that hyaluronic acid is the preferred polysaccharide disclosed in D6 (page 4, lines 3-4; examples 1-14 and 18-25). Besides, the processes used in examples 1-7 and 9-18 of D6 are considered to be in line with those indicated on page 6, first paragraph of D6 and are, thus, expected to lead to hyaluronic acid crosslinked by both ether and ester bonds. No evidence was provided by the patent proprietor to refute that conclusion. Nor was any convincing explanation given in that respect, in particular during the oral proceedings before the Board.

The patent proprietor's argument according to which there was no evidence that two types of bonds are effectively obtained in D6, in particular in the examples, is therefore in contradiction with the disclosure of D6. In the absence of any evidence to corroborate said argument, the patent proprietor's argument cannot be followed.

2.4.3 For those reasons, the process disclosed in the first paragraph on page 6 of D6 and applied to the most preferred embodiment of hyaluronic acid, as well as the examples of D6 dealing with hyaluronic acid, anticipate the subject-matter of claim 1. Since the process is not novel, its products cannot be novel either, so that claims 14 and 18 of main request A also lack novelty.

2.5 Consequently, main request A is not allowable because it lacks novelty over both D5 and D6.

Auxiliary request 2D

3. Art. 123(3) EPC

3.1 The sole objection raised by the opponent concerns the deletion in claim 1, as compared to granted claim 1, of the term "chemical" before "cross-linking agents".

3.1.1 According to the definition given above (see section 2.3.2), a crosslinking agent is a substance, i.e. a chemical compound, not heat or irradiation as argued by the opponent. Although it is agreed that crosslinking may be induced by heat and irradiation, there is no evidence on file that the skilled person would consider those means as substances, i.e. as "cross-linking agents". It is further questionable whether one would consider that heat/irradiation is "contacted with"

hyaluronic acid when used, as specified in claim 1.

That reading is also in line with the meaning given to the term "cross-linking agent" in the application as filed: the last part of the paragraph bridging pages 4 and 5 of the application as filed reads "as described in more detail hereinbelow"; page 5, line 23 goes on with a list of chemical compounds suitable as crosslinking agents. Nowhere does the application as filed disclose heat or radiation for crosslinking.

3.1.2 The opponent argued that D17 (col. 15, lines 19-21) implicitly disclosed heat/radiation as crosslinking agents. However, that argument relies on one sentence present in a single patent document. Such a disclosure is not sufficient to depart from the general understanding of that term according to common general knowledge, which is illustrated by the definitions given in the technical dictionaries D13 and D14.

3.1.3 D15 and D16, both submitted by the opponent, relate to the meaning of the term "agent", which is defined as encompassing anything producing an effect. However, the term "agent" is more generic than the term "crosslinking agent" used in claim 1. D16 clearly shows that terms such as "adregenic blocking agent", "agent orange", "alkylating agent", "chelating agent" or "reducing agent" concern more specific definitions that are only related to "substances". On the basis of the evidence on file, it is concluded that, in the same manner, the more specific definition provided in D13 and D14 limits crosslinking agents to "substances" and excludes means such as heat or irradiation.

3.1.4 The passage of D3 (page 3, lines 46-50) relied upon by the opponent, also does not provide any definition of

the term "crosslinking agent" but rather exemplifies heat or irradiation as "an agent which activates the carboxy function".

3.1.5 Further to the deletion of the term "chemical", the definition of the crosslinking agent specified in claim 1 of auxiliary request 2D further imposes that the crosslinking agent is selected from a specific list of chemical compounds. Therefore, the deletion of "chemical" is in fact compensated by the more specific definition now being present in claim 1.

3.1.6 However, there is no evidence on file that the term "**chemical** cross-linking agent" (emphasis by the Board) has any accepted definition or clear, unambiguous meaning in the art, in particular that it represents a limitation of the term cross-linking agent. There is in particular no evidence on file to corroborate the patent proprietor's argument, provided e.g. during the examination or opposition proceedings, according to which a "chemical" cross-linking agent is limited to those agents that are incorporated in the final cross-linked product. Such a definition would, in addition, be in contradiction with D14.

3.2 In that light, it cannot be considered to have been shown that the term "chemical" before "cross-linking agents" in granted claim 1 implied any limitation in respect of the meaning of the term "crosslinking agent" that would not be fulfilled by the definition of the crosslinking agents now being present in claim 1.

Therefore, it was not shown that the deletion (as compared to granted claim 1) of the term "chemical" before "cross-linking agents", effectively leads to an extension of the protection conferred by the patent in

suit that would contravene the requirements of Art. 123(3) EPC.

4. Art. 84 EPC

4.1 According to decision G 3/14 (see e.g. catchword), in considering whether, for the purposes of Art. 101(3) EPC, a patent as amended meets the requirements of the EPC, the claims of the patent may be examined for compliance with the requirements of Art. 84 EPC only when, and then only to the extent that the amendment introduces non-compliance with Art. 84 EPC.

4.2 Claim 1 of auxiliary request 2D mainly differs from claim 1 as granted in the addition of the following features:

(i) "wherein, in said process, a first cross-linking reaction ... to effect the second cross-link";

(ii) "and wherein the cross-linking agent is selected from formaldehyde ... or poly-epoxy cross-linker".

4.3 Considering the wording of claim 1 as a whole, the process according to claim 1 is defined *inter alia* as comprising a step of contacting hyaluronic acid with "one or more cross-linking agents" (which was already present in granted claim 1) and further requires that "the" cross-linking agent "is" selected from … (above amendment ii).

4.3.1 During the appeal proceedings, the question arose whether or not said wording of claim 1 imposes that, for the claimed processes in which at least two cross-linking agents are used, each of those had to belong to

the list specified in claim 1 (amendment ii) or whether it was sufficient that at least one of those crosslinking agents was chosen within said list.

4.3.2 However, following the conclusions of decision G 3/14, since that issue had already been present in the same context in granted claim 3 (since it depends on granted claim 1), it may not be objected to under Art. 84 EPC.

4.3.3 Regarding the meaning of claim 1, according to standard practice, the wording of the claim should be read in a technically sensible way and taking into account the whole disclosure of the patent. In the present case, considering that the patent in suit only discloses crosslinking agents according to the list now specified in claim 1 (see paragraphs [21]-[27] and [33]; examples), there is no reason to consider that the first crosslinking agent should be selected from a first list and that the second or any other crosslinking agents could be any other crosslinking agent.

4.4 The feature "wherein, in said process, a first cross-linking reaction ... to effect the second cross-link" (see above amendment i), was taken from the description (page 7, second paragraph of the application as filed) and was not present in any of the granted claims. Therefore, claim 1 may be examined for compliance with Art. 84 EPC but only to the extent that this amendment introduces non-compliance with Art. 84 EPC (see G 3/14 above).

4.4.1 The opponent argued that, since amendment i) referred to two cross-linking agents, the same issue as discussed in section 4.3.1 above arose also in respect of the combination of amendments i) and ii).

However, said objection is considered to be directed to the nature of the crosslinking agent to be used in both reaction steps, i.e. the alleged lack of clarity arises not because of amendment b) but because of amendment c) as identified above, which is not objectionable for lack of clarity as explained above (G 3/14). In other words, the lack of clarity relied upon by the opponent is not introduced by amendment ii).

Furthermore, following the conclusion drawn in section 4.3.3, the processes now being claimed are limited to those using only crosslinking agents belonging to the list now being specified in claim 1. Therefore, the skilled person is in a position to identify, in respect of the nature of the crosslinking agents to be used, when he is working within or outside the claim.

Under these circumstances, it is considered that the opponent has not shown how amendment ii) introduces non-compliance with Art. 84 EPC.

4.4.2 Regarding the meaning of the features constituting amendment ii), it was clarified during the oral proceedings before the Board that the process now being claimed encompasses those in which the addition of the second crosslinking agent may take place at any stage of the process, the process so defined encompassing embodiments directed to simultaneous as well as sequential crosslinking reactions, as indicated in paragraph [29] of the patent in suit. The process of claim 1 is, thus, broader than that of claim 7.

4.5 For those reasons, none of the objections submitted by the opponent amounts to a lack of clarity pursuant to

Art. 84 EPC.

5. Art. 83 EPC

5.1 On page 2 of the opponent’s statement of grounds of appeal it is stated that the appeal is based on the ground according to Art. 100(b) EPC. However, that objection was not substantiated.

5.2 The opponent's (conditional) remark in respect of enablement made in writing (see section XIV a) is merely speculative. It is further not supported by any evidence and primarily depends on the patent proprietor’s interpretation of D5.

5.3 The opponent's "doubts" mentioned in section XIV o) above are related to the issue whether the claimed technical effect is present over the whole scope of the claims, which is an issue of inventive step, not sufficiency.

5.4 In the absence of any substantiation of the opponent's objection of insufficient disclosure, that issue is not open to discussion.

6. Art. 54 EPC

6.1 As explained in section 4.3.3 above, the wording of claim 1 is read as limiting the crosslinking agents used in any step of the process to those specified in claim 1. D5 only discloses processes using as cross-linking agents a combination of carbodiimide with either L-lysine methyl ester or L-lysine. Since neither L-lysine methyl ester nor L-lysine belong to the list of crosslinking agents specified in claim 1, D5 does

not anticipate the subject-matter now being claimed.

6.2 The opponent's novelty objection in respect of D6 was based on the argument that a first crosslinking occurred during the epoxy-activation stage and a second crosslinking took place during the addition of polysaccharides as disclosed in the second paragraph of page 8 of D6.

6.2.1 There is no evidence on file showing that it can be excluded that at the end of the epoxy-activation step according to D6, a certain amount of hyaluronic acid is already cross-linked, although not in an amount sufficient to cause gelation, which is indeed indicated on page 3, first full paragraph of D6. However, "no gelation" cannot be equated with "no crosslinking" but has to be understood as meaning that there is not enough crosslinking to lead to gel formation. Similarly, the sentence in the last paragraph on page 6 of D6 ("the second = crosslinking reaction step") means that crosslinking mainly occurs during said second step (drying) but it does not exclude that some crosslinking occurs in the first (activation) step. Therefore, it can be accepted that at least some crosslinking may take place during the epoxy-activation stage of D6.

6.2.2 Should, according to the teaching of the second paragraph on page 8 of D6, a further polysaccharide be used and become crosslinked to the hyaluronic acid in a second crosslinking reaction, the crosslinked hyaluronic acid so prepared would exhibit a structure of the type HA-X-P-X-HA (HA = hyaluronic acid; X = epoxy activator; P = further polysaccharide) as explained on page 8 of the opponent's submission dated 29 June 2012 as well as during the oral proceedings before the Board. Under those circumstances, said

"further polysaccharide" does not crosslink hyaluronic acid on its own, but only through the epoxy activator. Consequently, said further polysaccharide cannot be considered as a cross-linking agent, in line with the opposition division's conclusion (page 9, lines 16-17 of the contested decision).

During the oral proceedings before the Board, the opponent argued that the further polysaccharide according to D6 should be considered as a crosslinking agent for the same reason as for the L-lysine methyl ester used in D5. In that respect, D5 discloses two different crosslinking mechanisms: whereas carbodiimide leads to crosslinking of hyaluronic acid without becoming incorporated therein (D5: reaction schemes on page 249), L-lysine methyl ester, in combination with compounds (2) and (3) which are derivatives of the carbodiimide, crosslinks hyaluronic acid via covalent bonds as shown on page 250 (product (5)). However, since those mechanisms lead either to products of the type HA-HA or HA-L-HA (HA = hyaluronic acid; L = L-lysine methyl ester), none of those mechanisms corresponds to the reaction mechanism relied upon by the opponent. Therefore, the reaction mechanisms of D5 and that relied upon by the opponent in respect of page 8 of D6 are not identical. Consequently, it cannot be concluded that D5 shows that the "further polysaccharides" according to page 8 of D6 are crosslinking agents in the sense of the patent in suit.

Under those circumstances, D6 does not directly and unambiguously disclose a process for the preparation of multiple crosslinked hyaluronic acid in which a further crosslinking agent, which may be the same as or different from the first, is added to the reaction

mixture to effect the second crosslink.

6.2.3 Therefore, the subject-matter of claim 1, as well as that of claims 2-11 depending thereon, is novel over D6.

7. Art. 56 EPC

7.1 Closest prior art

7.1.1 Whereas the patent proprietor considered D5 as the closest prior art document, the opponent argued that both D5 or D6 were equally suited.

7.1.2 According to standard practice, the closest prior art for assessing inventive step is the prior art disclosing subject matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (see Case Law of the Boards of Appeal of the EPO, 7th Ed., 2013, I.D.3.1).

7.1.3 The patent in suit deals with a process for the production of multiple crosslinked hyaluronic acid derivatives with a high degree of crosslinking (i.e. low water absorption capacity) and improved biostability (paragraphs [5], [16] and Table 4 of the patent in suit).

D5 discloses a process for the production of hyaluronic acid with improved resistance to hydrolysis (Fig. 12; page 250: left column, last paragraph; last sentence on page 250).

D6 aims at preparing hyaluronic acid with controlled

degradability (page 1, first paragraph; last paragraph on page 2). In particular, the idea of D6 is to use low quantities of the epoxy-activator cross-linking agent in order to improve control of the product's degradability (page 2, last paragraph; page 5, first paragraph; page 7, second paragraph; examples), which goes against the aim of the patent in suit to provide a high crosslinking density.

Therefore, in view of the problem addressed in the patent in suit, D5 represents a more suitable starting point than D6 so that D5 constitutes the closest prior art.

7.2 Problem to be solved in view of the closest prior art

During the oral proceedings before the Board, the patent proprietor, relying on the patent in suit (section 7.1.3 above), formulated the problem to be solved as that of providing a process for the preparation of multiple crosslinked hyaluronic acid having a higher degree of cross-linking, and improved resistance to digestion and free radicals.

7.3 Solution

The solution proposed by the patent in suit resides in a process according to claim 1, which differs from that of D5 in using a combination of crosslinking agents that are all to be selected within the list specified in claim 1, which is not disclosed in D5.

In view of the conclusion drawn in section 4.4.2 above, the process step of adding a further crosslinking agent to the reaction mixture in order to effect the second crosslink, is not a distinguishing feature over D5

because the process according to claim 1 encompasses both simultaneous as well as sequential crosslinking of each type of functional group.

7.4 Success of the solution

7.4.1 In the absence of any comparison between the process now being claimed and that of D5, there is no evidence on file to support an improvement over D5 as relied upon by the patent proprietor.

Table 4 of the patent in suit compares double crosslinking with single crosslinking of hyaluronic acid. It does not provide any comparison with the closest prior art. Nor is it related to the distinguishing feature identified in section 7.3 above.

Under these circumstances, the problem effectively solved has to be reformulated in a less ambitious manner and can only be seen as to provide a further process for the preparation of multiple crosslinked hyaluronic acid.

7.4.2 Examples 1 (CHA-2, CHA-8, CHA-5), example 2 (CHA-11, CHA-12), example 3 (CHA-17, CHA-19) and examples 4-6 of the patent in suit show processes leading to multiple crosslinked HA.

7.4.3 Reference example CHA-6 of the patent in suit (Table 1) illustrates a process comprising all features of claim 1 but leading to a product that dissolves in water. In the process of example CHA-6, ester bonds are formed in the first crosslinking step (epoxy crosslinking agent under acidic conditions) and ether bonds are formed in the second crosslinking step (epoxy crosslinking agent under basic conditions). According

to paragraphs [0031]-[0032] of the patent in suit, with that sequence of crosslinking steps, the ester bonds do not withstand the reaction conditions of the second crosslinking. The question, thus, arises, if reference example CHA-6 is a process according to claim 1 which does not solve the problem as reformulated in section 7.4.1. However, should the product obtained in example CHA-6 be crosslinked via a single type of bond, then the process would not fall under the scope of claim 1, which requires that cross-linking takes place so as to form two or more different types of functional bonds. Therefore, reference example CHA-6 can not show that the above problem is not solved on the whole scope of the claims. The same is valid regarding the example of D18, of which the opponent argued that it did not work.

Example CHA-12 of the patent in suit also concerns a process in which ester bonds were formed in the first crosslinking step and ether bonds in the second crosslinking step. It leads to gel products i.e. not soluble in water (contrary to CHA-6). However, there is no evidence on file that said product does not contain two types of crosslinking bonds via two different functional groups as defined in claim 1. Therefore, example CHA-12 also does not show that the problem defined above is not solved.

From the sequence of reactions involved in examples CHA-3 and CHA-9 (Table 1 of the patent in suit) and considering the teaching of paragraph [0022] of the patent in suit, it is to be expected that only ether crosslinking bonds would be formed in those examples. Therefore, those examples do not illustrate claim 1 and no conclusion may be drawn from those examples in respect of the achievement or not of the problem to be

solved.

On the basis of those considerations, it can therefore not be concluded from the examples of the patent in suit that the problem identified above is not solved over the whole scope of the claims, as argued by the opponent.

7.4.4 Under these circumstances and in the absence of any evidence to the contrary, it is accepted that the technical problem defined in section 7.4.1 above is effectively solved.

7.5 Obviousness

7.5.1 The question remains to be answered if the skilled person desiring to solve the above identified problem, would, in view of the prior art, have modified the disclosure of the closest prior art D5 in such a way as to arrive at the claimed subject matter.

7.5.2 D5 itself only discloses the combination of carbodiimide and either L-lysine methyl ester or L-lysine as crosslinking agents and therefore fails to provide any motivation to use, in addition to carbodiimide, a different crosslinking agent belonging to the list specified in claim 1. Besides, the reaction scheme indicated on page 250 of D5 shows that the crosslinking reaction leading to amide bonds involves the reaction of the lysine compound with carbodiimide derivatives. D5 does not suggest that the same reaction would take place if the lysine compounds were replaced by any of the components listed in claim 1.

7.5.3 As shown above (sections 2.3 and 2.4), the processes for the preparation of multiple crosslinked hyaluronic

acid disclosed in D5 and D6 are completely different: whereas D5 teaches a single process step using a combination of two crosslinking agents, D6 discloses a multistage process using a single crosslinking agent. Besides, D5 teaches that a high crosslinking density is achieved by increasing the amount of lysine compound, whereas D6 advises not to use high amounts of crosslinking agent, which are even removed from the reaction medium between the activation and the drying stages. Therefore, the skilled person would have had no reason to combine D5 and D6.

7.5.4 The opponent argued that it would be obvious to solve the above problem by performing a process according to D6 on the products obtained from D5. However, the products of D5 are hyaluronic acid that is already crosslinked. There is no reason why the skilled person would contemplate using such products as starting materials in a process according to D6.

7.5.5 During the oral proceedings before the Board the opponent also considered the combination of D5 and D1.

D1 (e.g. claim 1) deals with a process for improving the mechanical properties and structural integrity of a shaped medical device comprising a polymeric hydrogel, said process comprising:

a) providing a crosslinked polymeric hydrogel composition containing a non-ionic crosslink structure, said hydrogel polymer characterized as being ionically crosslinkable and having a primary shape;

b) imparting a secondary shape to said hydrogel polymer composition; and

c) subjecting said hydrogel polymer to ionic crosslinking conditions to ionically crosslink said hydrogel polymer while retaining said secondary shape.
However, D1 fails to disclose the combination of technical features according to operative claim 1, in particular

- a process performed with hyaluronic acid (which is only cited in a list of alternatives on page 4, line 4),
- wherein cross-linking occurs via two or more different functional groups,
- wherein two or more different types of functional bonds selected from the list specified in operative claim 1 are formed.

Besides, the second step of the process of D1 concerns an ionic crosslinking step (above step c)) and the aim of D1 is that the ionic crosslinking bonds can be easily and selectively removed (page 5, lines 14-18), which is contrary to the aim of the patent in suit to provide multiple crosslinked hyaluronic acid having improved stability.

Therefore, not only is the combination of the processes of D1 and D5 not obvious in view of the problems addressed in both documents, but that combination would also not lead to the process now being defined in claim 1. For that reason, the opponent's argument would appear to have been made in the knowledge of the solution provided by operative claim 1 and it fails to convince.

7.5.6 The opponent's objection concerning the combination of D5 with either D10 or D11 made in writing, was not pursued during the oral proceedings before the Board.

Upon a question by the Board whether the opponent wanted to submit any other arguments than those discussed herein above, the opponent replied in the negative.

The issue of admissibility of D10 and D11 had been discussed by both parties in writing. The Board had clearly indicated both in its communication (section 4.3) and at the beginning of the oral proceedings that admissibility issues would have to be discussed during the oral proceedings if late-filed documents were considered to be relevant for the appeal proceedings by one of the parties. Since during the oral proceedings neither of the parties offered comments on that issue, the opponent's arguments based on the combination of D5 and each of D10 and D11 are considered to be no longer pursued.

7.5.7 For those reasons the subject-matter of claim 1, as well as that of claims 2-11 depending thereon, is inventive.

8. In view of the above, auxiliary request 2D is allowable. Since auxiliary request 2D is identical to auxiliary request 6 on which the contested decision was based, both appeals have to be dismissed.

Order

For these reasons it is decided that:

Both appeals are dismissed.

The Registrar: The Chairman:

B. ter Heijden B. ter Laan

Decision electronically authenticated