Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 13 September 2022

Case Number: T 0638/19 - 3.3.07

Application Number: 11823038.2

Publication Number: 2614828

IPC: A61K31/573, C08B37/00, C08J3/075, A61P19/00

Language of the proceedings: EN

Title of invention:
LOW-MODIFICATION BIOCOMPATIBLE HIGH POLYMER SULFHYDRYL-MODIFIED DERIVATIVES, CROSS-LINKED MATERIAL THEREOF, AND USES OF SAID MATERIAL

Patent Proprietor:
Bioregen Biomedical (Changzhou) Co., Ltd.

Opponents:
Strawman Limited
Croma-Pharma Gesellschaft m.b.H.

Headword:
Disulfide-crosslinked hydrogels/BIOREGEN

Relevant legal provisions:
EPC Art. 56
RPBA Art. 12(4)
RPBA 2020 Art. 13(1)

Keyword:

Late-filed evidence - admitted (no)
Inventive step - obvious alternative
Late-filed requests - requests could have been filed in first instance proceedings (yes)

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 0638/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 13 September 2022

Appellant: (Patent Proprietor)	Bioregen Biomedical (Changzhou) Co., Ltd. East East Road 167 Building 5 Changzhou Jiangsu 213025 (CN)
Representative:	Haseltine Lake Kempner LLP Redcliff Quay 120 Redcliff Street Bristol BS1 6HU (GB)
Respondent: (Opponent 1)	Strawman Limited Orchard Lea Horns Lane Combe, Witney Oxfordshire OX29 8NH (GB)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Respondent: (Opponent 2)	Croma-Pharma Gesellschaft m.b.H. Industriezeile 6 2100 Leobendorf (AT)
Representative:	Schwarz & Partner Patentanwälte GmbH Patentanwälte Wipplingerstraße 30 1010 Wien (AT)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 21 December 2018 revoking European patent No. 2614828 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	J. Molina de Alba
	P. Guntz

Summary of Facts and Submissions

I. The decision under appeal is the opposition division's decision revoking European patent No. 2 614 828.

II. The documents cited in the opposition and appeal proceedings include the following:

D1: M.A. Serban et al., Biomaterials, 29(10), 2008, 1388-99
D2: WO 2005/056608
D4: K. Kafedjiiski et al., International Journal of Pharmaceutics, 343, 2007, 48-58

III. The decision was based on the claims of a main request and five auxiliary request. The opposition division held, among other things, that:

- the amendments of the main request did not comply with Rule 80 EPC
- the subject-matter of auxiliary request 1 was not inventive starting from D2 as the closest prior art
- auxiliary requests 2 to 5 were not to be admitted into the opposition proceedings

IV. The patent proprietor (appellant) filed an appeal against that decision.

With the statement of grounds of appeal, the appellant filed 14 sets of claims as its main request and auxiliary requests 0B, lA, lB, lC, 2A, 2B, 2C, 3A, 3B, 3C, 4A, 4B and 4C. The main request and auxiliary requests 0B, lB, 2B, 3B and 4B are identical to the

main request and auxiliary requests 1 to 5 on which the decision under appeal is based, respectively.

With a subsequent letter dated 23 November 2020, the appellant filed four additional sets of claims as auxiliary requests 1C', 2C', 3C' and 4C'. It also filed Appendix 1 and Appendix 2, which contain supplementary experimental data. Appendix 2 was corrected by letter dated 2 September 2022.

Claim 9 of the main request reads as follows:

"*9. Disulfide-bond cross-linked biocompatible macromolecule materials made from one or more mercapto-modified biocompatible macromolecule derivatives with a low degree of mercapto-modification, wherein the mercapto-modified biocompatible macromolecule derivative contains at least three mercapto groups in its side chain, and has a degree of mercapto-modification ≤ 4.5%; the mercapto-modified biocompatible macromolecule derivative refers to a derivative obtained by chemically introducing the mercapto group into the side-chain group of the biocompatible macromolecule; the degree of mercapto-modification refers to a percentage of the amount of the introduced mercapto group in the amount of the available side-chain group of the biocompatible macromolecule for modification; and the biocompatible macromolecule refers to chondroitin sulfate, dermatan, heparin, heparan, hyaluronic acid, dermatan sulfate, pectin, and carboxymethyl chitosan, polyaspartic acid, polytartaric acid, polyglutamic acid and polyfumaric acid, collagen, alkaline gelatin, acidic gelatin, elastin, core protein, polysaccharide laminin and fibronectin, or the salts thereof.*"

Claim 9 of auxiliary request 0B is identical to claim 9 of the main request.

Claim 1 of auxiliary request 1B differs from claim 9 of the main request in that the material has been specified to be a hydrogel.

Claim 1 of auxiliary request 2B differs from claim 1 of auxiliary request 1B in that the hydrogel is further defined as having a water content of more than 98% (weight/volume).

Claim 1 of auxiliary request 3B differs from claim 1 of auxiliary request 1B in that the biocompatible macromolecule is limited to hyaluronic acid or its salts.

Claim 1 of auxiliary request 4B differs from claim 1 of auxiliary request 1B in that it contains the limitations of auxiliary requests 2B and 3B.

Claim 1 of each of auxiliary requests 1A to 4A is identical to claim 1 of auxiliary requests 1B to 4B, respectively.

Claim 1 of auxiliary requests 1C to 4C differs from claim 1 of auxiliary requests 1B to 4B, respectively, in that it contains the following sentence at the beginning of the claim: "*For use in medicine as a biocompatible hydrogel which is storable without contraction and loss of dynamic viscosity*".

Claim 1 of each of auxiliary requests 1C' to 4C' is a reformulation of claim 1 of auxiliary requests 1C to 4C to reflect the usual wording of first medical use claims.

V. Opponents 1 and 2 (respondents 1 and 2) replied to the statement of grounds of appeal.

VI. The board scheduled oral proceedings, in line with the parties' requests, and gave its preliminary opinion.

VII. Oral proceedings were held before the board on 13 September 2022. At the end of the oral proceedings, the board announced its decision.

VIII. The appellant's arguments relevant to this decision can be summarised as follows.

Appendixes 1 and 2

Appendixes 1 and 2 did not change the appellant's case. They merely supplemented the data in the patent and supported the appellant's argument in the statement of grounds of appeal that the opposition division was wrong to consider that the molecular weight of the mercapto-modified macromolecules tested in the patent was decisive for establishing the technical effect produced by the difference with the closest prior art.

Neither were the appendixes late filed. During the written opposition proceedings, the appellant had no need to file additional evidence because the opposition division had given a positive preliminary opinion on the patent. At the oral proceedings, the opposition division changed its mind and considered that the comparative examples in the patent were not conclusive because they did not indicate the molecular weight of the tested macromolecules. The appellant could not file Appendixes 1 and 2 with the statement of grounds of appeal because they contained long-term stability tests

that were not concluded on that date. The first possible occasion for filing the appendixes was in response to the replies to the appeal. The respondents had enough time to prepare their case before the oral proceedings. Therefore, the appendixes were to be admitted into the appeal proceedings.

Main request and auxiliary request 0B

The subject-matter of claim 9 was novel over D2 because it resulted from an undisclosed series of selections. This included modifying the biocompatible macromolecule with a mercapto-group, selecting a modification degree of no more than 4.5% and cross-linking via disulfide bonds. The passages in D2 on page 23, lines 7 to 9 and lines 23 to 31 did not disclose the degree of modification of 0.1 to 5% as being the most preferred; the range 30 to 40% had the same level of preference. The embodiments cited by the respondents on pages 51 and 52 and in claim 69 illustrated a method of cross-linking mercapto-modified macromolecules in the presence of an oxidant. This was one among other cross-linking options and was not disclosed in combination with any specific degree of mercapto-modification.

The subject-matter of claim 9 was inventive starting from D2 as the closest prior art. It differed in that the degree of mercapto-modification of its macromolecules did not exceed 4.5%, while the mercapto-modified hyaluronic acid Carbylan-S illustrated in D2 had a degree of modification of 37.2%. Example 9 of the patent showed that a lower degree of mercapto-modification resulted in the formation of cross-linked materials (hydrogels) with improved long-term stability. This made the cross-linked materials of claim 9 particularly suitable for therapeutic

applications, as shown in Examples 10 to 13 of the patent. Therefore, the objective technical problem was the provision of a cross-linked material for biological use having improved properties.

The solution proposed in claim 9 was not obvious because D2 taught away from reducing the degree of mercapto-modification of its macromolecules. As shown in Tables 3 to 5 of D2, a reduction of the concentration of Carbylan-S reduced gel formation. A reduction of the degree of mercapto-modification had the same effect because fewer thiol moieties were available for cross-linking. Furthermore, the cross-linked materials that D2 tested for medical applications (Carbylan-SX and Carbylan-GSX, see page 100 and Figure 8) were not cross-linked by disulfide bond formation, as required by claim 9. On top of that, there was a prejudice in the prior art against using low degrees of mercapto-modification because they impaired effective cross-linking. This was confirmed by D4 (page 56, right-hand column, lines 21 to 26) and D1 (section 3.3). D4 associated a reduction of the degradation rate of a mercapto-modified hyaluronic acid with the degree of cross-linking via disulfide bonds. D1 attributed the inability of the macromolecule to cross-link to its low degree of mercapto-modification.

Auxiliary requests 1C to 4C

These claim requests were to be admitted. They did not change the appellant's case because claims 24 to 27 as granted were directed to medical uses, and the feature that the material was storable without contraction and loss of dynamic viscosity had been discussed in the opposition proceedings. Therefore, auxiliary requests

1C to 4C had been filed in due time with the statement of grounds of appeal.

Auxiliary requests 1C' to 4C'

These claim requests were filed at the first possible occasion in direct response to the clarity objections raised by the respondents against auxiliary requests 1C to 4C. They overcame the respondents' objection at first glance, so they were to be admitted.

IX. The respondents' arguments relevant to this decision can be summarised as follows.

Appendixes 1 and 2

The data in Appendixes 1 and 2 changed the appellant's case at a late stage of the proceedings and were not to be admitted. The appendixes were intended to address the lack of conclusiveness of the comparative examples in the patent owing to a lack of information on the molecular weight of the tested macromolecules. Respondent 2 had already pointed out this deficiency in its notice of opposition, and the matter had been discussed throughout the opposition proceedings. Therefore, the appendixes could have been filed during the opposition proceedings. Furthermore, the appellant waited until two years after the decision had been issued to file the appendixes. Even if they related to long-term stability tests, the appendixes could have been filed earlier. The appellant should have at least announced in its statement of grounds of appeal that it would be filing additional evidence. Moreover, the data in the appendixes do not support the appellant's contention that the molecular weight of the macromolecule is irrelevant since they lack essential

information such as the degree of cross-linking at testing. Even if the appendixes were considered to confirm the appellant's contention, the effect was not plausible from the application as filed.

Main request and auxiliary request 0B

The subject-matter of claim 9 was not novel over D2. The passage on page 50, line 31 to page 51, line 16 and claim 69 disclosed the coupling of two or more mercapto-modified macromolecules via a disulfide bond. These macromolecules were encompassed by claims 1 to 13 and 24 of D2, and therefore their degree of modification was within the ranges generally disclosed in D2. According to page 23, lines 7 to 9 and 25 and 26, the most preferred degree of modification was from 0.1 to 5%. This was essentially the same range as in claim 9 of the main request and contained the individualised value 0.1%.

If the subject-matter of claim 9 was regarded as novel, it was not inventive starting from D2 as the closest prior art. The cross-linked material of claim 9 had a lower degree of mercapto-modification than Carbylan-S in D2. The appellant had not demonstrated that this difference was associated with a technical effect; the results of the stability tests in Example 9 of the patent were not conclusive because the patent did not indicate the molecular weight of the tested polymers, an essential parameter for assessing viscosity. Therefore, the objective technical problem was the provision of an alternative disulfide-bond cross-linked biocompatible macromolecular material.

The cross-linked material of claim 9 was an obvious solution because its degree of mercapto-modification

was suggested in D2 (page 23, last paragraph). The appellant's allegation that there was a prejudice in the prior art against the use of low degrees of mercapto-modification had not been proven. D1 and D4 did not represent common general knowledge, and their statements allegedly linking low degrees of mercapto-modification to difficulties in gel formation were speculative. Moreover, if needed, the skilled person knew how to select the conditions for promoting gel formation, e.g. molecular weight, pH and temperature.

Auxiliary requests 1C to 4C

The appellant could have filed these claim requests, limited to medical uses, during the opposition proceedings. The fact that the opposition division had issued a preliminary opinion favourable to the appellant did not relieve the appellant of its duty to file fallback positions. The opposition division could deviate from its preliminary opinion, as indeed occurred. Furthermore, the appellant had had the opportunity to file additional claim requests at the oral proceedings before the opposition division, but none of the claim requests then filed was limited to a medical use. In addition, the wording of claim 1 of auxiliary requests 1C to 4C was unclear, and the feature "which is storable without contraction and loss of dynamic viscosity" raised issues of clarity and sufficiency of disclosure that had not been discussed in the opposition proceedings. Therefore, the requests were not to be admitted.

Auxiliary requests 1C' to 4C'

These claim requests were allegedly filed to overcome the objections raised against auxiliary requests 1A to

4C. However, they were not a legitimate response because they still contained the objected feature "which is storable without contraction and loss of dynamic viscosity".

X. The parties' final requests relevant to this decision were the following.

- The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of the main request or, alternatively, auxiliary request 0B.

  In the alternative, the appellant requested that auxiliary requests lA, lB, lC, lC', 2A, 2B, 2C, 2C', 3A, 3B, 3C, 3C', 4A, 4B, 4C and 4C' be admitted into the proceedings - with regard to auxiliary requests lB, 2B, 3B and 4B, it was primarily requested that the decision not to admit these requests (auxiliary requests 2 to 5 in the opposition proceedings) be reversed and, in the alternative, that the requests be admitted - and that the patent be maintained on the basis of any of these auxiliary requests.

  The appellant also requested that the appeal fee be reimbursed on the basis of an alleged substantial procedural violation committed by the opposition division.

- The respondents requested that the appeal be dismissed. In addition, they requested that none of auxiliary requests 1A to 4C' and Appendixes 1 and 2 be admitted into the proceedings.

Respondent 1 also requested that if Appendixes 1 and 2 were admitted and considered decisive for assessing inventive step, the appeal be stayed until decision G 2/21 was rendered.

Reasons for the Decision

1. The appeal is admissible. It meets the requirements of Articles 106 to 108 and Rule 99(2) EPC.

2. Admittance of Appendixes 1 and 2

2.1 Appendixes 1 and 2 were filed by the appellant in reaction to respondent 1's reply to the appeal (see the appellant's letter dated 23 November 2020, paragraph 108). Their admittance is to be assessed under Article 13(1) RPBA 2020 (see also Article 25(1) RPBA 2020), which provides that any amendment to a party's appeal case after it has filed its grounds of appeal or reply is subject to the party's justification for its amendment and may be admitted only at the discretion of the board. Article 13(1) RPBA 2020 also states that the board must exercise its discretion in view of, *inter alia*, the current state of the proceedings, the suitability of the amendment to resolve the issues which were admissibly raised by another party in the appeal proceedings and whether the amendment is detrimental to procedural economy.

2.2 Appendixes 1 and 2 contain experimental test results intended to counter the opposition division's view in point 50 of the decision under appeal that the comparative tests in Example 9 of the patent are not

conclusive. The opposition division based its view on the fact that the patent does not provide information on the molecular weight of the tested macromolecules. This position led the opposition division to reject the technical effect allegedly shown in Example 9 and ultimately resulted in the revocation of the patent for lack of inventive step. The opposition division adopted this view for the first time at the oral proceedings. In its communication in preparation for the oral proceedings (point 8), it had given a positive opinion on inventive step based on the technical effect allegedly demonstrated by the comparative tests in Example 9 of the patent. Therefore, the decision under appeal could have justified the filing of Appendixes 1 and 2 with the statement of grounds of appeal. However, the appendixes were not filed with the statement of grounds of appeal but later in the proceedings.

2.3 The appellant submitted that Appendixes 1 and 2 could not be filed with the statement of grounds of appeal because they contained long-term stability tests extending over six months. So the first possible occasion for filing them was in response to the replies to the appeal. Therefore, the appendixes could not be considered to be late filed. In addition, the appendixes did not change the appellant's case. They were merely an additional support to the argument in the statement of grounds of appeal that the molecular weight of the macromolecules was irrelevant to the properties of the hydrogels according to the invention.

2.4 These arguments are not convincing. First, the statement of grounds of appeal addressed the issue of the conclusiveness of the comparative tests in Example 9 of the patent (points 27 to 30 and 41). However, it did it exclusively by means of arguments, so the

subsequent filing of experimental evidence to support those arguments changed the appellant's case. Second, nothing in the statement of grounds of appeal suggested that the appellant intended to support its case with additional data from ongoing tests. If the appellant was carrying out tests to counter the opposition division's view in point 50 of the decision, it should have indicated this together with the reasons why the results could not be provided at that time. Without such an indication, the appellant's case was not complete. Furthermore, it is apparent from Appendix 2 that at least preliminary results could have been filed with the statement of grounds of appeal since an effect could already be observed after only one month. Consequently, Appendixes 1 and 2 changed the appellant's case and were late filed.

2.5 When considering the aspects mentioned in Article 13(1) RPBA 2020 for exercising its discretion, the board noted the following.

- Appendixes 1 and 2 do not show at first glance the effect intended by the appellant. As noted by respondent 1 (letter of 20 June 2022, page 28, paragraph 3), the appendixes lack essential information for assessing whether their results are conclusive. For instance, they fail to indicate the degree of cross-linking of the hydrogels at the time of testing.

- If Appendixes 1 and 2 were admitted and considered suitable for showing that the properties of the hydrogels according to the invention are independent of molecular weight, the plausibility of this new effect on the filing date would have to be discussed, and the case could need to be stayed

until decision G 2/21 is issued, to the detriment of procedural economy.

2.6 Therefore, the board decided not to admit Appendixes 1 and 2 into the appeal proceedings pursuant to Article 13(1) RPBA 2020.

3. Main request and auxiliary request 0B

3.1 Novelty over D2 - claim 9

Document D2 (abstract and page 2, lines 6 to 12) is directed to the modification of macromolecules such as hyaluronic acid by introducing at least one hydrazide-reactive group or an aminooxy-reactive group. This modification facilitates cross-linking of the macromolecule, and the obtained cross-linked material can be used in medical applications.

On page 23, D2 discloses possible degrees of modification when the macromolecule is a glycosaminoglycan, which may range from the substitution of a single hydroxyl group to 100% of the hydroxyl groups. For hyaluronic acid, page 23, lines 25 to 31 states:

"*In one aspect, 0.1% to 40%, 0.1% to 30%, 0.1% to 20%, 0.1% to 10%, or 0.1% to 5% of the primary hydroxyl groups of hyaluronan can be substituted. In another aspect, 0.1%, 0.5%, 1%, 2%, 3%, 5%, 10%, 15%, 20%, 25%, or 30% of the primary hydroxyl groups to 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the primary hydroxyl groups of hyaluronan can be substituted, where any lower endpoint can be combined with any upper endpoint.*"

Consequently, page 23 of D2 discloses two principal ranges for the degree of modification of hyaluronic acid: (i) 0.1 to 40%, or a smaller upper end point, and (ii) ranges having a lower end point of up to 30 to a minimum of 40% as the upper end point. The ranges 0.1 to 5% and 30 to 40% can be considered representative for the two respective principal set-ups. The choice of the range 0.1 to 5% constitutes a selection.

The respondents considered that this selection could be applied to the methods disclosed on pages 50 to 52 and in claim 69 of D2, which involve the cross-linking of two thiolated (i.e. mercapto-modified) macromolecules to produce a disulfide-bond cross-linked macromolecule. However, D2 also discloses cross-linking methods involving macromolecules which are modified with groups not containing sulphur atoms. Obviously, those methods do not produce disulfide-bond cross-linked macromolecules. For instance, D2 discloses the coupling of compounds by reaction between a thiolated macromolecule and a macromolecule modified with a thiol-reactive electrophilic group (see page 53, lines 10 to 13; page 53, line 31 to page 54, line 8; page 55, lines 12 to 21; page 56, lines 5 and 6; claims 33 to 36).

The ranges on page 23 of D2 are not disclosed for any specific modifying group. So they are not necessarily degrees of mercapto-modification since, as explained in the paragraph above, modifications with groups not based on sulphur are also envisaged in D2.
The respondents did not cite any passage in D2 associating the degrees of modification within the range 0.1 to 5% with mercapto-modification, let alone with cross-linking methods involving the formation of

disulfide bonds. Therefore, at least for this reason, D2 does not anticipate the subject-matter of claim 9.

3.2 Inventive step - claim 9

3.2.1 The patent (paragraphs [0001]) is directed to biocompatible macromolecules with a low degree of mercapto-modification. Upon cross-linking via disulfide bond formation, these macromolecules provide a material with a low degree of cross-linking that can be used in medicine.

3.2.2 It was common ground among the parties that D2 is a suitable starting point for the assessment of inventive step. This document (page 1, line 16 to page 2, line 12) concerns the modification of macromolecules for medical applications so that they can easily undergo cross-linking. An example of such macromolecules is hyaluronic acid, which can be modified to different degrees (page 23, last paragraph). When the macromolecule is modified by introducing thiol groups, cross-linking may occur by oxidative coupling, e.g. by air exposure (page 48, last paragraph to page 50, line 8). This is illustrated in D2 by the preparation of the product Carbylan-S, which is a hyaluronic acid modified with groups containing a terminal thiol (page 96, last paragraph to page 97, penultimate paragraph and Figure 5). Carbylan-S undergoes cross-linking in the presence of air, forming a hydrogel without the need of a cross-linker (page 98, last paragraph and page 99; Tables 3 to 5). This occurs by the formation of intermolecular disulfide bonds (page 49, lines 5 to 21 and page 50, lines 5 to 8).

The appellant calculated the degree of mercapto-modification of Carbylan-S from the ^{1}H-NMR spectrum in

Figure 6 of D2 (see Appendix A annexed to the statement of grounds of appeal). It obtained the result 37.2%, which was not contested by the respondents.

3.2.3 The parties agreed that the subject-matter of claim 9 differs from the hydrogels obtained by cross-linking of Carbylan-S in D2 (Tables 3 to 5) in the lower degree of mercapto-modification (no more than 4.5 vs 37.2%).

3.2.4 The effect produced by this difference was a matter of dispute.

The appellant defended that the results of the comparative tests in Example 9 of the patent demonstrated that the hydrogels obtained by cross-linking macromolecules with a lower degree of mercapto-modification were more stable. Table 5 of the patent showed that the dynamic viscosity of a hydrogel with a degree of mercapto-modification of 1.54% (Hydrogel 2) remained above 100 000 cps after six months at 40 °C while that of a hydrogel with a degree of mercapto-modification of 13.5% (Hydrogel 1) decreased sharply, falling to below 5 000 cps after two months. Table 5 also showed that Hydrogel 2 did not experience any contraction after six months while Hydrogel 1 contracted by 41.4%.

The respondents maintained that, as concluded by the opposition division in the decision under appeal, the results in Table 5 of the patent were not conclusive because the patent did not indicate the molecular weight of the tested macromolecules.

The board agrees with the respondents. It is a basic principle of rheology that viscosity is dependent on the molecular weight of the macromolecule in the fluid.

It is therefore apparent that, under the same conditions, the degradation of a macromolecule of low molecular weight results in a viscosity drop below a given level earlier than the same macromolecule with a higher molecular weight. Therefore, to assess whether a conclusion can be drawn from the comparative tests in Example 9 of the patent, it is necessary to know the molecular weight of the tested macromolecules. During the opposition and appeal proceedings, the appellant never provided these data, so it is uncertain to what extent the results in Table 5 of the patent are conclusive. As a consequence, the board cannot rely on these results for establishing the technical effect produced by a lower degree of mercapto-modification.

3.2.5 As the evidence on file is not suitable for demonstrating that the difference with the closest prior art brings about a technical effect, the objective technical problem has to be formulated as the provision of an alternative disulfide-bond cross-linked biocompatible macromolecular material.

3.2.6 This problem is credibly solved by the solution proposed in claim 9, i.e. by cross-linking a mercapto-modified biocompatible macromolecule with a degree of mercapto modification of no more than 4.5%. However, this solution was obvious from the teaching of D2.

D2 discloses on page 23, last paragraph some ranges of degrees of modification for hyaluronic acid, including 0.1 to 5% and 30 to 40%. This paragraph does not explicitly refer to a modification introducing thiol groups but to the substitution of primary hydroxyl groups in the hyaluronic acid with a hydrazide- or aminooxy-reactive group. However, D2 teaches that macromolecules are modified in two steps. In a first

step, a compound bearing a hydrazide-reactive or aminooxy-reactive group is introduced. Subsequently, the introduced group is reacted with a hydrazide-compound or aminooxy-compound bearing a functional group that facilitates cross-linking. Thus, the resulting macromolecule is modified with a functional group that facilitates cross-linking. If the group introduced for facilitating cross-linking contains a thiol group, it is apparent that the degree of modification with hydrazide-reactive or aminooxy-reactive groups referred to on page 23 of D2 is equivalent to the degree of mercapto-modification. Figures 3 to 5 of D2 illustrate this process for hyaluronic acid. Figures 4 and 5 show the modification with thiol groups.

As calculated by the appellant, Carbylan-S has a degree of mercapto-modification of 37.2%, i.e. within the range 30 to 40% disclosed on page 23 of D2. The skilled person seeking to provide a cross-linked material alternative to the Carbylan-S hydrogels in Tables 3 to 5 of D2 would consider it obvious to use a hyaluronic acid with a different degree of mercapto-modification but still within one of the ranges referred to in D2, e.g. 0.1 to 5%. In this way, they would arrive at the subject-matter of claims 9 in an obvious manner.

3.2.7 The appellant argued that D2 teaches away of the invention because Tables 3 to 5 (pages 99 and 100) show that reducing the concentration of Carbylan-S impairs gel formation, and a reduction of the degree of mercapto-modification would have the same effect. The appellant also noted that Carbylan-S gels were not tested for medical applications in D2; the tested materials (Carbylan-SX and Carbylan-GSX, see page 100

and Figure 8) were not cross-linked by disulfide bond formation as required by claim 9.

Furthermore, D4 demonstrated that there was a prejudice in the prior art against using low degrees of mercapto-modification because they were detrimental to an effective cross-linking. D4 associated a reduction in the degradation rate of thiolated hyaluronic acid with its degree of cross-linking via disulfide bonds (page 56, right-hand column, lines 21 to 26). This prejudice was confirmed by D1 (section 3.3), which attributed the inability of a mercapto-modified hyaluronic acid to form a gel to its low degree of derivatisation.

3.2.8 These arguments have not convinced the board.

D2 teaches that 0.1 to 5% is a workable range of mercapto-modification. The board does not dispute that a low degree of modification may be analogous to a low concentration of the macromolecule in that both circumstances require longer times for gel formation due to a reduced probability of disulfide bond formation. However, the knowledge that a higher dilution of thiol groups may delay cross-linking does not counter the teaching in D2 that degrees of mercapto-modification of 0.1 to 5% are workable. It is apparent from Tables 3 to 5 of D2 that, if needed, the time required for gel formation may be reduced by adjusting parameters such as temperature, pH or molecular weight. In fact, this was also the appellant's view in the statement of grounds of appeal (paragraph 78).

The fact that the Carbylan-S hydrogels in Tables 3 to 5 of D2 were not tested for medical applications does not teach away from disulfide-bond cross-linked materials

as possible solutions to the objective technical problem. Carbylan-S and its hydrogels were disclosed in D2 as embodiments according to the invention. The fact that there were other options for cross-linking (e.g. using a cross-linker) and that they were tested for medical purposes, does not render the option of reducing the degree on mercapto-modification of Carbylan-S less obvious as an alternative.

Regarding the alleged prejudice in the prior art, D4 and D1 are isolated publications which neither constitute common general knowledge nor present conclusions that could be understood by the skilled person as being generally applicable. Therefore, they cannot set a prejudice for the skilled person. The passage in D4 cited by the appellant (page 56, right-hand column, lines 21-26) states that a higher degree of cross-linking "additionally" reduces gel degradation. This observation merely suggests a preference for higher degrees of cross-linking, which cannot be equated with a higher degree of mercapto-modification, and this in no way sets a prejudice against low degrees of mercapto-modification. As to D1 (section 3.3), it gave three plausible explanations why a polymeric thiol was unexpectedly unable to undergo cross-linking. The low degree of derivatisation was only one of them. Furthermore, as noted here two paragraphs above, the skilled person was able to select conditions that promote cross-linking if this was insufficient. So the considerations in D4 and D1 could not deter the skilled person from using degrees of mercapto-modification within the lower range of D2.

3.2.9 The board therefore concludes that the subject-matter of claim 9 of the main request and auxiliary request 0B

does not involve an inventive step, contrary to Article 56 EPC.

4. Auxiliary requests 1A to 4A and 1B to 4B

4.1 Admittance

Auxiliary requests 1B to 4B were filed at the oral proceedings before the opposition division as auxiliary requests 2 to 5. The opposition division did not admit them. The requests were re-filed with the statement of grounds of appeal together with auxiliary requests 1A to 4A.

In view of the outcome of the assessment of inventive step in point 4.2.3 below, the board does not need to give details on its decision to not reverse the opposition division's decision not to admit auxiliary requests 1B to 4B and to take auxiliary requests 1A to 4A and 1B to 4B into account pursuant to Article 12(4) RPBA 2007.

4.2 Inventive step

4.2.1 In the written proceedings (statement of grounds of appeal, paragraphs 103 to 120), the appellant provided reasons why the additional limitations in auxiliary requests 1A to 4A and 1B to 4B conferred the claimed subject-matter with an inventive step.

Respondent 1 noted in its reply to the appeal (page 6) that the additional features in auxiliary requests 1B to 4B (auxiliary requests 2 to 5 before the opposition division) were already disclosed in D2.

In its communication in preparation for the oral proceedings (page 14, first paragraph, last sentence), the board noted that the additional limitations in auxiliary requests 1B to 4B did not provide any additional difference over the closest prior art.

4.2.2 At the oral proceedings, the board gave its preliminary opinion that the reasons why the subject-matter of the main request lacked an inventive step applied equally to auxiliary requests 1A to 4A and 1B to 4B. Nevertheless, the appellant did not wish to comment on this issue and referred to its written submissions.

4.2.3 Claim 1 of auxiliary request 1B differs from claim 9 of the main request in that the cross-linked material is specified as being a hydrogel. D2 discloses in Tables 3 to 5 hydrogels obtained by cross-linking Carbylan-S.

Claim 1 of auxiliary request 2B further requires that the hydrogel has a water content of more than 98% (weight/volume). This is also the case for the Carbylan-S hydrogels in Tables 3 to 5 of D2, which were prepared by dilution of Carbylan-S to final concentrations of 1.25% and lower.

Claim 1 of auxiliary request 3B limits the biocompatible macromolecule to hyaluronic acid or its salts. Carbylan-S is a mercapto-modified hyaluronic acid.

Claim 1 of auxiliary request 4B contains the limitations of auxiliary requests 2B and 3B.

Therefore, claim 1 of each of auxiliary requests 1B to 4B fails to provide additional differences over the closest prior art, and the reasons why the subject-

matter of claim 9 of the main request lacks an inventive step (Article 56 EPC) also apply to the subject-matter of claim 1 of auxiliary requests 1B to 4B.

This is also the case for claim 1 of each of auxiliary requests 1A to 4A, which is identical to claim 1 of auxiliary requests 1B to 4B, respectively.

5. Auxiliary requests 1C to 4C - admittance

5.1 Auxiliary requests 1C to 4C are directed to the hydrogels of auxiliary requests 1B to 4B for use in medicine. They also specify that the hydrogels are storable without contraction and loss of dynamic viscosity.

These claim requests were filed by the appellant with the statement of grounds of appeal, before the entry into force of the RPBA 2020. Their admittance is to be assessed under Article 12(4) RPBA 2007, which gives the board the power to hold inadmissible facts, evidence or requests that could (and should) have been presented in the opposition proceedings.

5.2 The claim requests on which the decision under appeal is based were primarily directed to products, namely a mercapto-modified biocompatible macromolecule or the material resulting from its cross-linking via disulfide-bond formation. The discussion of substantive matters in the decision under appeal dealt with the products as such and with the stability of their cross-linked materials; the use of the claimed products in medicine was not discussed at any point. Therefore, contrary to the appellant's view, the limitation of the subject-matter of auxiliary requests 1C to 4C to

products for use in medicine changed the appellant's case in appeal. The fact that claims 24 to 27 as granted related to uses in medicine does not change this situation since those claims were never the focus of the discussion in the opposition proceedings.

5.3 The appellant has failed to explain why it could not file auxiliary requests 1C to 4C in the opposition proceedings. The board agrees with the respondents that, in view of the objections raised in the notices of opposition, the requests could have been filed in the opposition proceedings as fall-back positions. This was the case even if the opposition division had given a positive opinion on the claim requests then on file since the opposition division could change its mind at any time, as indeed happened at the oral proceedings. Furthermore, after having changed its mind at the oral proceedings, the opposition division gave the appellant the opportunity to file additional claim requests. The appellant then filed four claim requests, none of which was primarily directed to a product for use in medicine. If the appellant had wanted to seek protection in this regard, it should have filed respective claims at least at that point in time.

5.4 Therefore, the board decided to hold auxiliary requests 1C to 4C inadmissible pursuant to Article 12(4) RPBA 2007.

6. Auxiliary requests 1C' to 4C' - admittance

These requests were filed by the appellant with its letter dated 23 November 2020 in response to the respondents' replies to the appeal. Their admittance is to be assessed under Article 13(1) RPBA 2020 (see also Article 25(1) RPBA 2020).

In their replies to the appeal, the respondents had objected, *inter alia*, to the clarity of claim 1 of each of auxiliary requests 1C to 4C because their drafting was not in line with the usual wording of first medical use claims. The claims of auxiliary requests 1C' to 4C' are those of auxiliary requests 1C to 4C reformulated to comply with the usual wording of first medical use claims.

As auxiliary requests 1C to 4C were not admitted under Article 12(4) RPBA 2007, at least the same reasons apply for not admitting auxiliary requests 1C' to 4C' under Article 13(1) RPBA 2020.

7. *Reimbursement of the appeal fee*

The appellant requested that the appeal fee be reimbursed for an alleged substantial procedural violation committed by the opposition division.

The board has come to the conclusion that the decision under appeal should be upheld and that the appeal should be dismissed. Therefore, a reimbursement of the appeal fee under Rule 103(1)(a) EPC is not justified. Even if the opposition division had committed a procedural violation (which is left open), it would not have been substantial, as required by Rule 103(1)(a) EPC, since it did not lead to a decision that had to be reversed by the board.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

2. The appeal fee is not reimbursed.

The Registrar: The Chairwoman:

B. Atienza Vivancos M. Pregetter

Decision electronically authenticated