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Datasheet for the decision of 25 July 2023

Case Number: T 0631/21 - 3.3.09

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Language of the proceedings: EN

Title of invention:
INJECTABLE IN-SITU CROSSLINKED HYDROGEL AND THE PREPARATION METHOD AND USE THEREOF

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

Opponent:
Croma-Pharma Gesellschaft m.b.H.

Headword:
Injectable hydrogel/BIOREGEN

Relevant legal provisions:
EPC Art. 100(b), 100(a), 54, 56
RPBA 2020 Art. 13(2)

Keyword:

Grounds for opposition - insufficiency of disclosure (no)
Novelty - prior disclosure - implicit features (no)
Inventive step - (yes)

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Case Number: T 0631/21 - 3.3.09

D E C I S I O N
of Technical Board of Appeal 3.3.09
of 25 July 2023

Appellant: (Patent Proprietor)	Bioregen Biomedical (Changzhou) Co., Ltd. No. 165 East East Road Changzhou, Jiangsu 213025 (CN)
Representative:	Haseltine Lake Kempner LLP One Portwall Square Portwall Lane Bristol BS1 6BH (GB)
Respondent: (Opponent)	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 11 February 2021 revoking European patent No. 2353612 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Haderlein
Members:	F. Rinaldi
	F. Blumer

Summary of Facts and Submissions

I. This decision concerns the appeal filed by the patent proprietor (appellant) against the opposition division's decision to revoke the European patent.

II. In the notice of opposition, the opponent (now respondent) had requested that the patent be revoked based on Article 100(a) EPC (lack of novelty and inventive step) and 100(b) EPC.

III. The following documents are relevant to the decision:

D1: WO 2008/077172 A2

D4: A. H. Krauland *et al.*, "Viscoelastic properties of a new in situ gelling thiolated chitosan conjugate", Drug Development and Industrial Pharmacy, 31, 2005, 885-893

D7: Experimental evidence (filed by the opponent, by letter dated 13 November 2020)

IV. In the decision under appeal, the opposition division decided, among other things, that the invention set out in the patent as granted was sufficiently disclosed and novel, but lacked inventive step.

V. On appeal, the appellant filed 14 auxiliary requests with the statement setting out the grounds of appeal, among other things.

VI. The respondent filed the following document after notification of the summons to oral proceedings:

B.B. Benson *et al.*, "The concentration and isotopic fractionation of oxygen dissolved in freshwater and seawater in equilibrium with the atmosphere", Limnology and Oceanography, 29(3), 1984, 620-632 (hereinafter: Benson *et al.*)

VII. The only claim relevant to the decision is claim 1 of the patent as granted (main request), which reads:

"*A method of preparing an injectable in-situ crosslinked hydrogel, characterized in that: [sic] it comprises the following* steps:

(1) filling a crosslinkable active solution into a container for injection of the hydrogel, wherein the crosslinkable active solution contains at least one kind of biocompatible macromolecules with more than two thiol groups on the side chain;
(2) sealing the container containing the crosslinkable active solution; and
(3) oxidizing the thiol groups into disulfide bonds to form the crosslinked hydrogel by oxygen dissolved in the crosslinkable active solution in the sealed container;

wherein the biocompatible macromolecule with more than two thiol groups on the side chain is a derivative of polysaccharides or proteins produced by one or more chemical modifications that includes at least one thiol modification."

VIII. The appellant's arguments relevant to the decision may be summarised as follows:

The invention set out in claim 1 was sufficiently disclosed. The patent's description set out how to

prepare a hydrogel in the sealed container for injection. Claim 1 was novel over example 3 of D1, which did not disclose at least step (3). Claim 1 also involved an inventive step. The objection of lack of novelty based on D4 and the document Benson *et al*. should not be considered on appeal.

IX. The respondent's arguments relevant to the decision may be summarised as follows:

The invention set out in claim 1 was not sufficiently disclosed. The patent did not teach how to control the oxygen content and obtain injectable hydrogels in the container. The experiments in D7 confirmed this. Claim 1 lacked novelty over D4 and example 3 of D1, which implicitly disclosed all the features of claim 1. Moreover, claim 1 lacked inventive step starting from example 3 of D1 as the closest prior art taken alone or in combination with D4.

X. Final requests:

The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted (main request) or on the basis of any one of auxiliary requests 1 to 14, all as filed with the statement setting out the grounds of appeal.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. *Patent*

1.1 The patent relates to a method for preparing an injectable hydrogel. The gelation process is completed in a syringe (paragraph [0012]).

1.2 The method set out in claim 1 involves the following steps:

(1) filling a container suitable for injection with a crosslinkable active solution which comprises macromolecules with thiol groups
(2) sealing the container containing the crosslinkable active solution
(3) oxidising the thiol groups into disulfide bonds to form the crosslinked hydrogel using oxygen dissolved in the crosslinkable active solution in the sealed container

2. *Admittance of the document Benson et al.*

2.1 The respondent filed the document Benson *et al*. after notification of the summons to oral proceedings. The document was filed to show that solubility of oxygen in water under atmospheric conditions was a well-known and long-studied phenomenon.

2.2 It is common general knowledge that oxygen dissolves in water under atmospheric conditions. This is not disputed and need not be demonstrated by evidence. However, whether oxygen is soluble in water under atmospheric conditions is not the relevant question in

the current case. Rather, what has to be answered is whether a hydrogel is formed in D1, and if so, where this happens.

2.3 The board also does not recognise that there may be exceptional circumstances, let alone cogent reasons, for filing this document.

2.4 Therefore, there is no reason to admit this document (Article 13(2) RPBA 2020).

3. *Main request - sufficiency of disclosure*

3.1 In the decision under appeal, the opposition division found that the invention complied with the requirement of sufficiency of disclosure.

3.2 The respondent contested this decision, arguing as follows:

- The "magic" of the invention, namely formation of the hydrogel, happened in step (3) of claim 1. According to this step, the container for injection was sealed and the crosslinking occurred without any external trigger or initiation of the reaction.
- Nevertheless, the patent did not teach how to control the oxygen content and obtain injectable hydrogels in the container. It was inevitable that crosslinking would start as soon as the thiol groups of the macromolecule in the crosslinkable active solution were exposed to ubiquitous oxygen.
- The experimental test in D7 demonstrated that a hydrogel composition produced in line with the patent in suit was not injectable.
- Therefore, the invention lacked sufficiency of disclosure.

3.3 It is observed that the invention as set out in claim 1 of the patent requires that a balance between two core aspects be struck, namely:

- forming a crosslinked hydrogel using oxygen dissolved in the crosslinking active solution in the sealed container (see step (3) of claim 1)
- while ensuring that the composition remains injectable (see preamble of claim 1)

3.4 Upon reading claim 1, the skilled person would learn that oxidising the thiol groups into disulfide bonds to crosslink the macromolecules in the active solution is a prerequisite for forming the hydrogel. The oxidation reaction which generates the disulfide bonds occurs at a molecular level. At the same time, a hydrogel calls for a particular, macroscopic structure. The patent specification discloses that a hydrogel requires a three-dimensional network structure. Gelation of the crosslinkable active solution is characterised by a reduction in or loss of fluidity (e.g. paragraph [0016] and example 4).

3.5 In view of this, the skilled person would understand that partial crosslinking of the macromolecules alone is not sufficient for a hydrogel to form. On the contrary, the crosslinkable active solution remains a fluid until a certain degree of crosslinking of the macromolecules is achieved so as to obtain a three-dimensional network structure. Only at this point is the hydrogel formed, which displays reduced fluidity.

3.6 Once the skilled person is aware of the invention and has read the patent, they would be able to simultaneously comply with the requirements of forming

the crosslinked hydrogel in the sealed container while ensuring that the composition remains injectable.

3.7 Clearly, a certain degree of trial and error might be necessary to achieve this result. The skilled person might even encounter occasional failure, as in the experiments in D7. However, the patent sets out what should be done to turn failure into success. Modifying the parameters to meet the requirements of claim 1 would be a matter of routine for the skilled person.

3.8 In detail, as the opposition division correctly explained in the decision under appeal, the patent presents the content of oxygen dissolved in the crosslinking active solution as key to the invention. How to adjust this parameter is extensively explained (claims 2 to 6; paragraphs [0031] to [0038], [0043] and [0044]; examples 7 to 9). The skilled person would also be aware that there are further parameters they can adjust to form a hydrogel in the sealed container. The measures that they can apply without resorting to inventive skill include increasing:

- the degree of thiolation
- the temperature of reaction
- the oxygen concentration in the crosslinkable active solution
- the molecular weight of the polymer
- the reaction time

3.9 In conclusion, the ground for opposition under Article 100(b) EPC does not prejudice maintenance of the patent.

4. *Main request - novelty*

4.1 The opposition division decided that claim 1 of the patent as granted was novel.

4.2 The respondent contested this decision. In its view, example 3 of D1 implicitly disclosed all the features of claim 1. Furthermore, it argued that claim 1 lacked novelty over D4.

4.3 The appellant argued that example 3 of D1 did not disclose several features of claim 1. The focus below is solely on step (3) of claim 1 (for wording see point VII above) as the distinguishing feature.

4.4 Novelty over D1

4.4.1 D1 relates to the use of a polymer containing thiol groups for preparing an implant for tissue augmentation. The implants are injectable, fluid, gel-like or semi-solid preparations which stay for at least several weeks at (or in the vicinity of) the site of application (claim 1 and page 4, second paragraph).

4.4.2 The disclosure of example 3 of D1 is quite concise. It reads:

"*The following preparation for intradermal applications was produced: 2 g thiol-group-containing hyaluronic acid was solved in sterile isotone phosphate buffer, stirred to form a partially crosslinked polymer, filled into syringes and sterilised. 0.1 ml of this formulation was injected intradermally into the back region of rabbits. The application produced a minimal local irritation which disappeared after one day. The depot formed by the thiol-group containing hyaluronic*

acid was tactually detectable over the whole examination period of two weeks."

4.4.3 Thus, example 3 discloses that a partially crosslinked polymer is formed before the preparation is filled into the syringe. As explained above in the context of sufficiency of disclosure (see above, point 3.4), a partially crosslinked polymer is a prerequisite for formation of a hydrogel. But this does not mean that because crosslinking occurs, a hydrogel is also directly and unambiguously disclosed. Example 3 does not disclose whether, and if so when, a gel is formed. It also does not describe what happens between the steps of sterilising the syringe and injecting the formulation, let alone how long the preparation stays in the syringe before it is injected. While the tactually detectable depot in the rabbit's back region may possibly be regarded as a gel, there is no indication as to when such a gel is formed.

4.4.4 In short, the disclosure of example 3 gives rise to the following four possibilities:

- a gel is formed before the preparation is filled into the syringe
- a gel is formed while the preparation is in the syringe
- a gel is formed after the preparation is injected into the rabbit's back
- no gel is formed

4.4.5 On this basis alone, example 3 does not directly and unambiguously disclose that a hydrogel is formed in the sealed container suitable for injection. Therefore, claim 1 is novel over example 3 of D1.

4.4.6 For completeness, the following additional observations are added.

4.4.7 Example 3 does not disclose whether the aqueous buffer with the partially crosslinked polymer includes significant amounts of oxygen. Even if this were the case, there is no disclosure that the amount of oxygen would be sufficient for a hydrogel to form while the preparation is in the syringe.

4.4.8 It was argued that example 4 of D1 disclosed an experiment which was carried out in the absence of oxygen. However, this does not lead (in a sort of argument from the contrary) to the conclusion that the preparation of example 3 implicitly includes oxygen, let alone in an amount sufficient for a hydrogel to form.

4.4.9 In any case, the aim in D1 seems to be to implant a polymer with thiol groups. In other words, the polymer is not crosslinked to a high degree. D1 underlines that a polymer that contains thiol groups is suitable for forming disulfide bonds and exerting an antioxidative action at the active site of the body (page 5, first full paragraph). Oxidation of the thiol groups may involve glutathione disulfide, which plays a decisive role in the detoxification of hydrogen peroxide. Reactive oxygen can be removed by analogous reactions.

4.4.10 Similarly, the last paragraph of page 5 discloses that all the thiol groups in the polymer are preferably available as free thiol groups, so that the polymer is crosslinked to a low degree or even not crosslinked at all. The crosslinking occurs afterwards under controlled conditions by changing the pH to

physiological pH values between pH 6 to 10.5 in the presence of oxygen.

4.4.11 The most straightforward interpretation of this passage is that crosslinking occurs after introduction of the polymer into the human or animal body, under the specific pH conditions of the tissue where the preparation is implanted. The respondent's argument that the pH conditions may be conveniently changed or adjusted in the syringe has no basis in the explicit disclosure of example 3, nor elsewhere in D1.

4.4.12 All these considerations reinforce the conclusion reached above in point 4.4.5 that D1 does not disclose step (3) of claim 1.

4.5 Novelty over D4

4.5.1 An objection as to novelty based on D4 is not discussed in the decision under appeal. It is manifest from the minutes that such an objection was not presented at the oral proceedings before the opposition division either. The appellant requested that this objection not be considered on appeal. The respondent did not demonstrate that this objection was admissibly raised and maintained in the proceedings leading to the decision under appeal.

4.5.2 Therefore, the respondent's objection represents an amendment to its appeal case within the meaning of Article 12(4) RPBA 2020.

4.5.3 Moreover, considering that the opposition division found the claimed subject-matter to be novel, the objection based on D4 could and should have been raised in the proceedings before the opposition division.

4.5.4 Thus, the objection of lack of novelty based on D4 need not be considered on appeal (Article 12(6) RPBA 2020).

4.6 To conclude, the ground for opposition under Articles 100(a) and 54 EPC does not prejudice maintenance of the patent.

5. *Main request - inventive step*

5.1 In the decision under appeal, the opposition division concluded that claim 1 lacked inventive step. The appellant contested this decision.

5.2 In the decision under appeal, example 3 of D1 is regarded as the closest prior art. The parties did not contest this choice. As explained above in point 4, claim 1 differs from example 3 of D1 at least in step (3).

5.3 This difference does not have a demonstrated technical effect over the closest prior art. However, it provides a different process for manufacturing preparations which include crosslinkable polymers.

5.4 The technical problem can be formulated as providing a further method for preparing (a semi-solid) formulation suitable for physiological applications.

5.5 The solution provided in claim 1 would not have been obvious to the skilled person.

5.5.1 Firstly, the closest prior art does not to indicate that a delay is intended between sterilising the formulation and injecting it. Instead, claim 1 of the patent in suit is directed to an entirely different

process for preparing the formulation to be injected, i.e. the hydrogel.

5.5.2 Secondly, there is no prior art that would prompt the skilled person to crosslink the polymer until gelation occurs in a sealed container for injection, using oxygen dissolved in the solution.

5.5.3 The respondent referred to D4, which disclosed gelation in a container. In this document, buffered chitosan-thioethylamidine solutions are incubated in closed vessels in a water bath at 37°C, in order to obtain gels with different degrees of crosslinking (page 888, left-hand column).

5.5.4 However, starting from D1, the skilled person would have had no motivation to consult D4. As explained above, D1 does not suggest that injectable gels can be generated in a syringe. The experiments described in D4 concern physiological, in-situ conditions (buffered, 37°C). They simulate conditions within a body and do not refer to a gelation process during storage. There is also no indication that the gels of D4 are intended to be injectable.

5.5.5 Therefore, D4 does not suggest forming an injectable crosslinked hydrogel using oxygen dissolved in a crosslinkable active solution in a sealed container suitable for injection.

5.5.6 None of the other cited documents teaches forming an injectable crosslinked hydrogel using oxygen dissolved in a crosslinkable active solution in a sealed container.

5.6 Therefore, the grounds for opposition under Article 100(a) and 56 EPC do not prejudice maintenance of the patent.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is maintained as granted.

The Registrar: The Chairman:

H. Jenney A. Haderlein

Decision electronically authenticated