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Datasheet for the decision of 19 February 2019

Case Number: T 1095/15 - 3.3.10

Application Number: 07867783.8

Publication Number: 2111239

IPC: A61L15/32, A61L15/38, A61L26/00, A61L24/10

Language of the proceedings: EN

Title of invention:
GELATIN-TRANSGLUTAMINASE HEMOSTATIC DRESSINGS AND SEALANTS

Patent Proprietor:
Lifebond Ltd.

Opponent:
GELITA AG

Headword:

Relevant legal provisions:
EPC Art. 100(a), 56

Keyword:
Inventive step - (no) - all requests

Decisions cited:

Catchword:

Europäisches Patentamt
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Case Number: T 1095/15 - 3.3.10

D E C I S I O N
of Technical Board of Appeal 3.3.10
of 19 February 2019

Appellant: (Patent Proprietor)	Lifebond Ltd. Industrial Park 7 Ha-Eshel 30889 Caesarea (IL)
Representative:	Fuchs Patentanwälte Partnerschaft mbB Westhafenplatz 1 60327 Frankfurt am Main (DE)
Appellant: (Opponent)	GELITA AG Uferstrasse 7 69412 Eberbach (DE)
Representative:	Hoeger, Stellrecht & Partner Patentanwälte mbB Uhlandstrasse 14c 70182 Stuttgart (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 30 March 2015 concerning maintenance of the European Patent No. 2111239 in amended form.**

Composition of the Board:

Chairman	P. Gryczka
Members:	R. Pérez Carlón
	F. Blumer

Summary of Facts and Submissions

I. Both the opponent and the patent proprietor appealed the interlocutory decision of the opposition division concerning the maintenance of European patent No. 2 111 239 on the basis of the first auxiliary request then pending. In this decision, the parties are referred to as the appellant-opponent and the appellant-patent proprietor.

II. Notice of opposition had been filed on the grounds of added subject-matter (Article 100(c) EPC), insufficiency of disclosure (Article 100(b) EPC), and lack of novelty and inventive step (Article 100(a) EPC).

III. The documents filed during the opposition proceedings include the following:

D1: McDermott *et al*, "Mechanical Properties of Biomimetic Tissue Adhesive Based on the Microbial Transglutaminase-Catalyzed Crosslinking of Gelatin", *Biomacromolecules* **2004**, 5, *1270-1279* and

D4: WO 2008/006545 A2.

The experimental evidence filed included D16 and D17, filed by the appellant-opponent with its statement of grounds of appeal.

IV. The opposition division concluded, *inter alia*, that the sealing agent of claim 1 of the patent as granted was not novel over D4, which was prior art as defined in Article 54(3) EPC. With respect to the sealing agent of claim 1 of the first auxiliary request then pending,

document D1 was the closest prior art. It disclosed a sealing agent having a transglutaminase composition with specific gelatin cross-linking activity of 15 U/g of gelatin. The problem underlying the claimed invention was to provide a sealing agent with increased burst pressure resistance. The solution, characterised by a cross-linking activity of from 40 U to 200 U/g of gelatin, was not obvious having regard to the prior art.

V. Claim 1 of the patent as granted (main request) reads as follows:

"A hemostatic or body fluid sealing agent wherein said agent comprises a composition of gelatin and a transglutaminase composition wherein said transglutaminase composition has a specific gelatin crosslinking activity of from 40U to 200 U/gm of gelatin and in which the weight ratio of gelatin to transglutaminase composition is in a range of from 1:1 to 300:1;
characterised in that *said agent when applied to a wound site cross links between gelatin chains and endogenous collagen of tissue extracellular matrix to create a barrier to fluid leakage or bleeding."*

VI. With its statement setting out the grounds of appeal, the appellant-patent proprietor filed its first, second and fourth to eighth auxiliary requests. The third auxiliary request was filed by letter dated 8 August 2018.

Claim 1 of the auxiliary requests contains all the features of claim 1 of the patent as granted and adds the following:

First auxiliary request

"wherein the activity of the transglutaminase is measured prior to use and/or manufacture of said composition with the hydroxamate method or Nessler's assay."

Second auxiliary request

"wherein the activity of the transglutaminase is measured prior to use and/or manufacture of said composition with the hydroxamate method or Nessler's assay [...]

with the proviso that the agent is not example composition 4-2 and not example composition 4-4 of WO 2008/006545 A2."

Third auxiliary request

"wherein the transglutaminase is calcium independent"

Fourth auxiliary request

"wherein the transglutaminase is a microbial transglutaminase"

Fifth auxiliary request

"wherein said microbial derived transglutaminase is isolated from one or more of Streptoverticillium baldaccii, Streptomyces hygroscopicus, Escherichia coli or Streptoverticillium mobaraensis"

Sixth auxiliary request

"wherein the gelatin has a bloom of at least 250"

Seventh auxiliary request

"wherein the transglutaminase composition has a specific activity level of at least 40 U/g"

Eighth auxiliary request

"wherein the transglutaminase composition comprises a stabilizer or filler".

VII. The arguments of the appellant-patent proprietor relevant for the present decision were as follows:

Document D1 was the closest prior art. The problem underlying the claimed invention was to provide a hemostatic or body fluid sealing agent having enhanced burst resistance. The claimed solution was characterised by requiring a specific gelatin crosslinking activity of from 40 U to 200 U/g of gelatin. Document D1 taught a number of variables which could affect the final properties of an adhesive, but failed to teach any connection between enzyme activity and burst resistance. For this reason, the claimed solution according to claim 1 of all requests was inventive.

VIII. The appellant-opponent agreed on the choice of the closest prior art, the definition of the problem to be solved and the claimed solution. However, it considered that, having regard to D1, it would have been obvious for the skilled person to vary the enzyme activity to enhance burst resistance. For this reason, it considered the claimed solution not to be inventive.

IX. Oral proceedings before the board of appeal took place on 19 February 2019.

X. The final requests of the parties were as follows:

- The appellant-patent proprietor requested that the decision under appeal be set aside and the patent be maintained as granted (main request) or, subsidiarily, that the patent be maintained in the form of one of the first to eighth auxiliary requests; the first, second and fourth to eighth auxiliary requests having been filed with the statement setting out the grounds of appeal dated 6 August 2015, the third auxiliary request having been filed with a letter dated 8 August 2018.

- The appellant-opponent requested that the decision under appeal be set aside and that European patent No. 2 111 239 be revoked.

XI. At the end of the oral proceedings, the decision was announced.

Reasons for the Decision

1. The appeal is admissible.

Inventive step (all requests)

2. Claim 1 of the main request is directed to a hemostatic or body fluid sealing agent comprising a composition of gelatin and a transglutaminase (TG) composition. The sealing agent, applied to a wound, is capable of cross-linking between gelatin and endogenous collagen. Claim 1 requires the TG composition to have a specific gelatin cross-linking activity of from 40 U to 200 U/g

of gelatin and a defined weight ratio of gelatin to TG composition.

The parties did not contest the interpretation of the opposition division that the feature "said transglutaminase composition has a specific gelatin crosslinking activity of from 40U to 200U/gm of gelatin" relates to the enzyme activity in units "U" per gram of gelatin in the sealing agent.

3. Closest prior art

The opposition division and the parties considered that document D1 was the closest prior art. The board sees no reason to differ.

It has not been disputed that document D1 discloses sealing agents which differ from those of claim 1 only by virtue of the specific cross-linking activity of TG composition per gram of gelatin. D1 only discloses sealing agents in which this activity is 15 U/g.

4. Technical problem underlying the invention

The appellant-patent proprietor defined the technical problem underlying the claimed invention as how to provide a hemostatic or body fluid sealing agent having enhanced burst resistance.

5. Solution

The solution to this technical problem is the claimed sealing agent, characterised in that it requires a specific gelatin cross-linking activity of from 40 U to 200 U/g of gelatin.

6. Success

The appellant-patent proprietor relied on experimental evidence D16 and D17, filed by the appellant-opponent in these appeal proceedings, to show that the problem formulated in point 4. above had been credibly solved by the features of claim 1.

These results show that sealing agents containing 15 U of TG per gram of gelatin have a lower burst pressure maximum than those according to claim 1, having 40 U/g or 141 U/g. The problem is thus credibly solved by the sealing agent of claim 1.

7. It thus remains to be decided whether the proposed solution to the objective problem defined above is obvious from the prior art.

Document D1 is a scientific publication disclosing tissue adhesives on the basis of gelatin and TG, which can be used for stopping bleeding (page 1270, left column, second line) and represented an alternative to fibrin-based sealants (Scheme 1; page 1271, second paragraph). D1 shows that gelatin-TG systems provided higher adhesive strengths than fibrin sealants.

Document D1 discloses different mechanical properties of this adhesive. It provides information on cross-linking time (Figure 3) and its variation with gelatin bloom and concentration (page 1273, last paragraph). It also provides data on Young's modulus (Figure 4), which correlates with cohesive strength (page 1276, left column, lines 20-21) at different gelatin bloom and concentration values (Table 1). D1 acknowledges a high variability of the results obtained, which is common when testing adhesives, in particular on biological

samples (page 1276, left column, lines 6-11).

D1 is a preliminary study teaching the combination of gelatin and TG as a promising material for the preparation of soft tissue adhesives. The skilled reader would have recognised from D1 that the properties of the adhesive could be improved.

D1 discloses variables which would have a bearing on such properties. On page 1274, left column, lines 3-6, it indicates that "it should be possible to adjust the gel time by adjusting the mTG activity or adding other ingredients (not investigated here)". The following paragraph (page 1274, left column, lines 29-31) indicates that the adhesive's flow properties and gel strength can be controlled by the enzyme activity, gelatin bloom and gelatin concentration.

From these variables, the authors of D1 have tested the influence of gelatin bloom (Figures 2, 3 and 4) and gelatin concentration (Figures 3 and 4).

Even though D1 does not directly refer to burst pressure resistance, the appellant-patent proprietor acknowledges (point II.3 of its statement of grounds of appeal) that this property is linked to properties disclosed in D1, such as cohesive strength (Young's modulus), adhesive strength (page 1275, left column, second full paragraph) and polymerisation speed (page 1273, last paragraph). D1 discloses that each of these properties is expected to vary with enzyme activity.

Although D1 does not predict how enzyme activity will affect any of these properties, it would have been obvious for the skilled person to study its influence on TG-gelatin sealing agents and thus arrive at the

claimed invention without using inventive skills.

7.1 For these reasons, the hemostatic or body fluid sealing agent of claim 1 is not inventive within the meaning of Article 56 EPC, with the consequence that the ground of opposition set in Article 100(a) EPC precludes the maintenance of the patent as granted.

The appellant-patent proprietor acknowledged that the same arguments apply, *mutatis mutandis*, to the sealing agents of claim 1 of all the auxiliary requests on file, which were in fact filed in response to other objections raised by the appellant-opponent.

7.2 The appellant-patent proprietor argued that D1 concluded that gel time was convenient. The skilled person would not have taken any measurement which could decrease gel time such as increasing enzyme activity. A too low gel time could lead to an unsuitable adhesive strength. In any case, the skilled person would not have increased enzyme activity by a factor of three.

Although D1 does not disclose the effect of enzyme activity in a soft tissue adhesive, it indicates that it will vary the properties of such an adhesive. For this reason alone, it would have been obvious for the skilled person to study this influence.

By carrying out such experiments, the skilled person would have arrived at results such as those disclosed in experimental evidence D17. On realising that an increase of the enzyme activity implies an increase in burst resistance, the skilled person would have continued increasing enzyme activity until the effect is maximised. By doing so, they would have arrived at the enzyme activities required by clam 1 without using

inventive skills.

This argument is thus not convincing.

7.3 The appellant-patent proprietor also argued that sealing agents with more than 200 U/g were too brittle and could break. For this reason, the upper limit was a purposeful selection which also contributed to an inventive step.

However, the issue here is whether the skilled person would have arrived at an embodiment of the claimed invention, regardless of whether the upper limit of enzyme activity was linked to a decrease of the desired properties of the sealing agent. This argument is also not convincing.

Conclusion

8. The ground of opposition defined in Article 100(a) EPC precludes the maintenance of the patent as granted or on the basis of the auxiliary requests 1-8.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

C. Rodríguez Rodríguez P. Gryczka

Decision electronically authenticated