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Datasheet for the decision of 29 April 2021

Case Number: T 1740/16 - 3.3.04

Application Number: 10720211.1

Publication Number: 2421549

IPC: A61K38/17, A61L27/52, A61L27/22, A61K38/01

Language of the proceedings: EN

Title of invention:
Silk fibroin hydrogels and uses thereof

Patent Proprietor:
ALLERGAN, INC.

Opponent:
Tufts University

Headword:
Silk fibroin hydrogels/ALLERGAN

Relevant legal provisions:
EPC Art. 113(1), 123(2)

Keyword:
Right to be heard - substantial procedural violation (no)
Amendments - all claim requests - extension beyond the content of the application as filed (yes)

Decisions cited:
G 0002/10

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 1740/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 29 April 2021

Appellant: (Opponent)	Tufts University Ballou Hall Medford MA 02155 (US)
Representative:	Haseltine Lake Kempner LLP Redcliff Quay 120 Redcliff Street Bristol BS1 6HU (GB)
Respondent: (Patent Proprietor)	Allergan Inc. 2525 Dupont Drive Irvine, CA 92612 (US)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 11 May 2016 concerning maintenance of the European Patent No. 2421549 in amended form.**

Composition of the Board:

Chairman	A. Chakravarty
Members:	D. Luis Alves
	L. Bühler

Summary of Facts and Submissions

I. European patent EP 2 421 549, entitled "*Silk fibroin hydrogels and uses thereof*", was granted on European patent application No. 10 720 211.1, filed as an international application published as WO 2010/123947 (in the following "application as filed").

II. The patent was opposed under Article 100(a) EPC, on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), insufficiency of disclosure (Article 100(b) EPC) and added subject-matter (Article 100(c) EPC).

III. The opposition division decided that, account being taken of the amendments in the form of the main request, the patent and the invention to which it related met the requirements of the EPC (Article 101(3)(a) EPC).

IV. The opponent (appellant) filed an appeal against that decision. The patent proprietor is respondent to this appeal.

V. In their statement setting out the grounds of appeal, the appellant contested the reasoning of the opposition division with regard *inter alia* to added subject-matter (Article 123(2) EPC). They also filed documents D44 to D46.

VI. In their reply to the statement setting out the grounds of appeal, the patent proprietor (respondent) re-filed sets of claims of a main request and auxiliary requests 1 to 5, all identical to those pending before the opposition division. The main request corresponds

to the request considered allowable by the opposition division.

VII. Claim 1 of the main request and of auxiliary requests 1 to 5 is reproduced below. In auxiliary requests 1 to 5 difference to the main request is underlined by the board.

Claim 1 of the **main request** reads:

"1. A hydrogel formulation comprising:

a) a gel phase, the gel phase including hydrogel particles comprising a substantially sericin-depleted silk fibroin and an amphiphilic peptide, wherein the particles have a particle size from 10 µm to 1000 µm in diameter; and

b) a carrier phase."

Claim 1 of **auxiliary request 1** reads:

"1. A hydrogel formulation comprising:

a) a gel phase, the gel phase including hydrogel particles comprising a substantially sericin-depleted silk fibroin and an amphiphilic peptide, wherein the particles have <u>been milled to</u> a particle size from 10 µm to 1000 µm in diameter; and

b) a carrier phase."

Claim 1 of **auxiliary request 2** reads:

"1. A hydrogel formulation comprising:

a) a gel phase, the gel phase including hydrogel particles comprising a substantially sericin-depleted silk fibroin and an amphiphilic peptide, wherein the particles have been milled to a particle size from 10 µm to 1000 µm in diameter; and

b) a carrier phase, wherein the carrier phase comprises saline, and wherein the amphiphilic peptide comprises a RGD motif. ."

Claim 1 of **auxiliary request 3** reads:

"1. A hydrogel formulation comprising:

a) a gel phase, the gel phase including hydrogel particles comprising a substantially sericin-depleted silk fibroin and an amphiphilic peptide, wherein the particles have been milled to a particle size from 10 µm to 1000 µm in diameter; and

b) a carrier phase, wherein the carrier phase comprises saline, and wherein the amphiphilic peptide is 23RGD, wherein the hydrogel particles comprise 1% (w/v) to 10% (w/v) of silk fibroin and wherein the amphiphilic peptide comprises of a tail region followed by a spacer region and finally the RGD motif."

Claim 1 of **auxiliary request 4** reads:

"1. A hydrogel formulation comprising:

a) a gel phase, the gel phase including hydrogel particles comprising a substantially sericin-depleted silk fibroin and an amphiphilic peptide, wherein the

particles have been milled to a particle size from 10 µm to 1000 µm in diameter; and

b) a carrier phase, wherein the carrier phase comprises saline, and wherein the amphiphilic peptide is 23RGD selected from the group of SEQ ID NOs: 1, and 2, wherein the hydrogel particles comprise 1% (w/v) to 10% (w/v) of silk fibroin."

Claim 1 of **auxiliary request 5** reads:

"1. A hydrogel formulation comprising:

a) a gel phase, the gel phase including hydrogel particles comprising a substantially sericin-depleted silk fibroin and an amphiphilic peptide, wherein the particles have been milled to a particle size from 10 µm to 1000 µm in diameter; wherein the silk is from *Bombyx mori* and wherein the substantially sericin-depleted silk fibroin has at most 4% (w/w) residual sericin, and wherein the amphiphilic peptide is 23RGD selected from the group of SEQ ID NOs: 1, and 2, wherein the hydrogel particles comprise 1% (w/v) to 10% (w/v) of silk fibroin;and

b) a carrier phase, wherein the carrier phase comprises saline".

VIII. The board appointed oral proceedings and in a communication pursuant to Article 15(1) RPBA, informed the parties of its preliminary opinion that, *inter alia*, it could not identify a substantial procedural violation by the opposition division, and with regard to the requirements of Article 123(2) EPC, the hydrogel formulation defined in claim 1 of the main request did not seem to find a basis in the application as filed in

the passage indicated by the respondent. The board stated "*In paragraph 117 of the description, the diameter range of the hydrogel particles is mentioned only in relation to a milling step which is followed by addition of the saline carrier to the resulting milled hydrogel, followed by a step of pulverisation. As such, the diameter range 10-1000 µm appears to be a value displayed by the particles at an intermediate step in the process leading to the preparation of the final product, i.e. the claimed hydrogel formulation. It therefore appears that, the diameter range in this paragraph does not reflect the particle diameter in the final product to which claim 1 is directed. Thus, paragraph 117 does not seem to provide a basis for the hydrogel formulation now claimed.*"

IX. The appellant, by a letter dated 9 April 2021, informed the board that they would not attend the oral proceedings. These proceedings duly took place in the absence of the appellant. They were held in the form of a video conference with the agreement of the represented party. At the end of the oral proceedings, the Chair announced the board's decision.

X. The following documents are referred to in this decision:

D2: Gil E.S. *et al.*, Macromol. Biosci., 2005, 5(8), 702-709.

D3: Gil E.S. *et al.*, Biomacromolecules, 2005, 6(6), 3079-3087.

D15: Collette A.L. *et al.*, Abstract No.719 of the 32nd annual meeting of the Society for Biomaterials, 2007.

D39: Declaration by Dr Daunch, February 2016.

XI. The appellant's arguments, as far as relevant to this decision, may be summarised as follows:

Main request
Amendments (Article 123(2) EPC) - Claim 1

The feature "*wherein the particles have a particle size from 10 µm to 1000 µm in diameter*" had been taken out of its context in paragraphs [0116] and [0117], which were to be read together. The particle size range in paragraph [0117] was not generally applicable and was not disclosed in the context of the particles as defined in claim 1. Instead, the teaching in paragraph [0117] was restricted by the process steps disclosed in paragraphs [0116] and [0117]. Paragraph [0116] related to gel which were leached of the gelation enhancers, including the amphiphilic peptide. Thus, the particles defined in claim 1, which included an amphiphilic peptide, were different from those disclosed in paragraph [0117]. The two paragraphs additionally taught that the particles had been milled in saline (to a diameter of 10 to 1000 µm), after which a desired volume of saline was to be added as carrier phase with vigorous pulverising of the hydrogel. Since these features were not present in claim 1, the claimed subject-matter was not directly and unambiguously disclosed in the application as filed.

Auxiliary requests 1 to 5
Amendments (Article 123(2) EPC) - Claim 1

No arguments were provided in respect of these requests.

Substantial procedural violation
Reimbursement of the appeal fee - (Article 113(1) EPC)

The decision was not sufficiently reasoned because it failed to take into account all of the appellant's submissions. Instead, the opposition division substituted its own unproven suppositions for the evidence in the file. This constituted a violation of the appellant's right to be heard pursuant to Article 113(1) EPC.

The decision was not sufficiently reasoned in three aspects. The first was the lack of evidence in the decision for interpreting the term "peptide" to mean amino acid chains of "up to 100" amino acids, although the decision was based on this meaning. The second was the absence of a logical position on the construction of the term "amphiphilic". Both aspects affected the opposition division's decision on sufficiency of disclosure. A third aspect was the lack of a decision on whether the silk fibroin disclosed in documents D2, D3 or D15 was "substantially sericin-depleted" and whether the "films" disclosed in documents D2 and D3 comprised a hydrogel.

XII. The respondent's arguments, as far as relevant to this decision, may be summarised as follows:

Main request
Amendments (Article 123(2) EPC) - Claim 1

Hydrogels with the particle size between 10 to 1000 µm in diameter were disclosed in paragraph [0117] of the application as filed. Each sentence in this paragraph defined an alternative embodiment of a hydrogel. As

such, the skilled person would have understood that a step of pulverising was not necessary after the milling step. This was also their understanding from reading claims 27 and 28, together with paragraphs [0020] and [0021]. Also paragraph [0151], which referred to milling the gel to a desired particle size, did not indicate a subsequent pulverising step.

Auxiliary request 1
Amendments (Article 123(2) EPC) - Claim 1

No arguments were presented in respect of this request.

Auxiliary request 2
Amendments (Article 123(2) EPC) - Claim 1

The subject-matter claimed was an allowable intermediate generalisation from the disclosure in paragraph [0117] because the claim now included saline as the carrier.

Auxiliary requests 3 to 5
Amendments (Article 123(2) EPC) - Claim 1

No arguments were provided in respect of these requests.

Reimbursement of the appeal fee - Substantial procedural violation- (Article 113(1) EPC)

No substantial procedural violation by the opposition division had taken place. All three points raised by the appellant had been addressed during the written procedure and additionally addressed and discussed at the oral proceedings before the opposition division.

The decision did not rely on grounds or evidence on which the parties had had no possibility to comment. Neither was the decision unclear such that it was not possible to understand it.

Regarding the term "peptide", the opposition division reasoned why the skilled person would have been able to provide a molecule falling within the definition of "peptide". The length of a peptide was used merely to clarify that there was a distinction between the terms "peptide" and "protein".

Regarding the term "amphiphilic", the opposition division referred in the decision to the definition of this term given in the patent in paragraphs [0013], [0079], [0083] and [0084].

Regarding "substantially sericin-depleted" and "films", no discussion was necessary with respect to documents D2 and D3 since they were not cited against novelty of the claims. No discussion with respect to document D15 was necessary either since novelty of the claimed subject-matter over that document was established by the feature "amphiphilic peptide". Thus, the absence of a decision on this aspect would not affect the entire proceedings.

XIII. The appellant requested in writing that the decision under appeal be set aside and the patent be revoked, alternatively, that the decision under appeal be set aside due to a substantial procedural violation and the case be remitted to the opposition division. Moreover, they requested that the appeal fee be reimbursed. Finally, they requested that documents D44 to D46 be admitted into the proceedings.

XIV. The respondent requested that the appeal be dismissed and that the patent be maintained on the basis of the claims of the main request, or of auxiliary requests 1 to 3, all filed on 20 October 2014, or, alternatively, on the basis of auxiliary requests 4 or 5, both filed on 19 February 2016. Furthermore, they requested that documents D44 to D46 and the opponent's three lines of argument on sufficiency of disclosure not be admitted into the proceedings.

Reasons for the Decision

1. The appeal complies with the requirements of Articles 106 to 108 EPC and the further provisions referred to in Rule 101(1) EPC and is admissible.

Main request
Amendments (Article 123(2) EPC) - Claim 1

2. Claim 1 includes the following feature which was not present in claim 1 of the application as filed: "*wherein the particles have a particle size from 10 µm to 1000 µm in diameter*".

3. As basis for this feature, the respondent indicated the following sentence in paragraph [0117] of the application as filed: "*In a particular example, the gel may be milled to a particle size from about 10 µm to about 1000 µm in diameter, such as 15 µm to 30 µm.*"

4. It is established case law of the boards of appeal of the EPO that any amendment to the parts of a European patent application or of a European patent relating to the disclosure (the description, claims and drawings) can only be made within the limits of what a skilled

person would derive directly and unambiguously, using common general knowledge and seen objectively and relative to the date of filing, from the whole of the application as filed (decision G 2/10, reasons 4.3).

5. Paragraph [0117] of the application follows a paragraph describing the removal of residual gelation enhancers from the hydrogel. The full paragraph reads as follows:

"*The hydrogel may then be further processed for cleaning, loading, and sterilizing for use. For example, the hydrogel may be pulverized and mixed with saline solution. In a particular example, the gel may be milled to a particle size from about 10 µm to about 1000 µm in diameter, such as 15 µm to 30 µm. Saline is then added to the hydrogel as a carrier phase by first determining the volume of a bulk of hydrogel, then vigorously pulverizing the hydrogel while incorporating an appropriate volume of saline to the hydrogel to achieve a desired carrier to hydrogel ratio. For example, hydrogel milling may be accomplished in one example by means of a forced sieving of bulk hydrogel material through a series of stainless steel cloth sieves of decreasing pore sizes. In another example, hydrogel may be loaded into a syringe and pulverized with a spatula to a fine paste with saline. The present hydrogel formulations are preferably sterile*."

6. This paragraph thus discloses a step of milling which results in a particle diameter as indicated in claim 1. The milling step is however followed by a pulverising step. The term "pulverizing" is generally understood to refer to the reduction of a material to a powder with an inherent reduction in size of the original material. Although in this paragraph it is applied to a gel and not to solid particles, the board has seen no evidence

that "pulverizing" would be understood differently in this context by the person skilled in the art. That the milling and pulverising steps must be carried out in the specified sequence is indicated by the use of "then" in the sentence "*Saline is then added* [...]" and "[...] *then vigorously pulverizing* [...]" (emphasis added by the board). Thus, contrary to the respondent's argument, the sentences in paragraph [0117] of the application do not relate to alternative embodiments, but in fact relate to a single embodiment including both steps. The board concludes that the diameter range 10 to 1000 µm refers to particles at an intermediate step of the method of preparation of the final product, i.e. the claimed hydrogel formulation, and does not reflect the particle diameter in the final product.

7. The respondent argued that the skilled person would have understood that the milling step was the last step carried out and no subsequent steps taking place to modify the particle size, as could be understood from the following passages:

Claims 27 and 28, which defined the method of preparing the hydrogel formulation, when read with paragraphs [0020] and [0021], confirmed that the milling step resulted in particles of the size set out in claim 1. Also paragraph [0149] of the application, and paragraph [0151] disclosed the milling step as being the final step in the preparation of the hydrogel.

8. However, claims 27 and 28 of the application as filed, while relating to a method of making a hydrogel formulation, do not define the order in which the steps (d) of adding the buffer and (e) of milling to a desired particle size are carried out. Thus, the

disclosure in these claims does not support the view that the milling step is necessarily the last step in the method which determines the final size of the hydrogel particles. Neither can it be concluded that the milling step is necessarily preceded by addition of the carrier solution. Moreover, according to paragraph [0117], the milling step is followed by the step of buffer (saline) addition.

9. Furthermore, the disclosure in paragraphs [0020] and [0021] of the application does not support the respondent's case either because, although it can be inferred from paragraph [0020] that a milling step determines the size of the hydrogel particles, in that embodiment the diameter of the resulting particles is not disclosed. A size is defined in the following paragraph [0021], which however differs from the particle diameter as set out in the claim because it refers to an "average size" without any reference to a diameter.

10. As regards the average size of 20 to 30 µm disclosed in paragraph [0021], it is not a direct and unambiguous disclosure of particles with sizes within the range of 10 to 1000 µm because the particle size distribution of the population used to calculate the average particle size is not known. Moreover, this paragraph does not disclose whether or not the particles are spherical, so that it cannot be inferred that a diameter is meant by "size".

11. In view of the above considerations, the board concludes that, even taking into account the disclosure in claims 27 and 28 and paragraphs [0020] and [0021] of the application as filed, the skilled person would not find a direct and unambiguous disclosure of a hydrogel

formulation comprising particles having a diameter in the 10 to 1000 µm range claimed.

12. The board is moreover not convinced that the skilled person would read the application as suggested by the respondent, because the reader is not directed from claims 27 and 28 to paragraphs [0020] and [0021]. Indeed, other passages defining the particle size could be read in combination with the claims 27 and 28, such as paragraph [0118] and following. Those paragraphs define yet further particle sizes, namely in terms of cross-sectional areas. These do not to correspond to the diameter range required in claim 1 of the main request.

13. Both paragraph [0151] and paragraph [0020], disclose processes for producing hydrogels in which the milling step is the last step modifying the particle size. However, they do not provide a particle size and there is nothing in these paragraphs that would convey to the skilled person that the milling step as last sizing step would apply to all processes of producing the hydrogel, so that the skilled person would disregard the reference to pulverisation in paragraph [0117].

14. In conclusion, the subject-matter of claim 1 extends beyond the content of the application as filed, contrary to the requirements of Article 123(2) EPC.

Auxiliary request 1
Amendments - Article 123(2) EPC - Claim 1

15. In this claim, the feature defining the diameter of the particles included in the gel phase of the hydrogel formulation reads "*wherein the particles have been milled to a particle size from 10 to 1000 µm*". However,

the reference to a milling step does not overcome the lack of a direct and unambiguous disclosure set out in the reasons above in respect of the main request.

Auxiliary request 2
Amendments - Article 123(2) EPC - Claim 1

16. The claimed hydrogel formulation differs from that of claim 1 of auxiliary request 1 by additional features of the carrier phase and the amphiphilic peptide. However, these additional features do not alter the conclusion reached for claim 1 of the main request because the issue of added matter resulting from the particle diameter affecting claim 1 of the main request remains.

Auxiliary requests 3 to 5
Amendments - Article 123(2) EPC - Claim 1

17. Claim 1 of each of auxiliary requests 3 to 5 is directed to a hydrogel formulation including the feature analysed above in the context of auxiliary request 1 (see point 15.) As set out above for auxiliary request 2 (see point 16.), the issues that led to the non-compliance of claim 1 of the main request apply equally to these claim requests. Thus, claim 1 of each request includes subject-matter which extends beyond the content of the application as filed (Article 123(2) EPC).

Reimbursement of the appeal fee and substantial procedural violation (Article 113(1) EPC)

18. One of the preconditions for reimbursement of the appeal fee according to Rule 103(1)(a) EPC is that a substantial procedural violation has taken place.

19. According to the appellant this was the case because their right to be heard was not respected and the decision was insufficiently reasoned. Three aspects were pointed to in this respect (see Section XI.).

20. The peptide length is mentioned in the decision of the opposition division in the context of sufficiency of disclosure with regard to the feature "amphiphilic peptide", on page 8, penultimate paragraph. This paragraph is immediately followed by the conclusion of the opposition division: "*Even though no unambiguous animo acid number can be said to define the limit between a protein and a peptide, it is considered that the skilled man would be able to select many compounds falling with the term "amphiphilic peptide", because the term is explained in the patent, and because various examples of hydrophilic and hydrophobic domains are described (see above)".* From this paragraph it can be understood that the peptide length was not decisive for the finding of the opposition division.

21. A second aspect contested by the appellant relates to the term "amphiphilic" within the feature "amphiphilic peptide". The board notes that, the opposition division in their assessment of sufficiency of disclosure decided that the description explains what is considered to be an amphiphilic peptide, giving examples of hydrophilic and hydrophobic domains and stating that the document D39 did not contradict that explanation (see decision under appeal point 7.6, second and fifth paragraphs on page 8 as well as first paragraph on page 9). It therefore cannot be concluded that the opposition division failed to decide on the alleged narrow interpretation of "amphiphilic", as this interpretation is clearly not endorsed.

22. The appellant referred to points 8.4 and 8.5 of the decision as presenting a discussion on novelty with regard to documents D2 and D3 and argued that the decision fails to discuss the parties' submissions concerning the "films" disclosed in these documents. However the board notes that no objection to lack of novelty had been raised based on documents D2 and D3. There was therefore no need for the opposition division to address these documents in this context.

23. As far as document D15 is concerned and the expression "substantially sericin-depleted" the opposition division decided that the claimed subject-matter was novel with regard to document D15 because this document did not disclose an amphiphilic peptide neither hydrogel particles (see decision under appeal, point 8.3, last paragraph). Therefore, novelty was established by the features "amphiphilic peptide" and "hydrogel particles" and there was no need for the opposition division to decide whether the document disclosed the feature "substantially sericin-depleted".

24. In view of the foregoing, the board cannot identify any insufficient reasoning or other procedural violation by the opposition division.

Admission of documents D44 to D46

25. The board did not decide on this issue as the contents of these documents were not of relevance for the decision.

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:

I. Aperribay A. Chakravarty

Decision electronically authenticated