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Datasheet for the decision of 14 June 2018

Case Number: T 2321/15 - 3.3.07

Application Number: 07786813.1

Publication Number: 2034951

IPC: A61K9/00, A61K9/16, A61K47/30, A61K47/48

Language of the proceedings: EN

Title of invention:
REHYDRATABLE PHARMACEUTICAL PRODUCT

Patent Proprietor:
Biocompatibles UK Limited

Opponent:

Headword:
REHYDRATABLE PHARMACEUTICAL PRODUCT/Biocompatibles UK Limited

Relevant legal provisions:
EPC Art. 56

Keyword:
Main request - Inventive step (yes)
Unrecognized problem

Decisions cited:
T 1895/15, G 0003/14

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 2321/15 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 14 June 2018

Appellant: (Patent Proprietor)	Biocompatibles UK Limited Chapman House Farnham Business Park Weydon Lane Farnham Surrey GU9 8QL (GB)
Representative:	Wynne-Jones, Lainé and James LLP Essex Place 22 Rodney Road Cheltenham Gloucestershire GL50 1JJ (GB)
Respondent: (Opponent)	
Representative:	Stewart, Hazel Cleveland 10 Fetter Lane London EC4A 1BR (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 19 October 2015 revoking European patent No. 2034951 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	D. Boulois
	Y. Podbielski

Summary of Facts and Submissions

I. European patent No. 2 034 951 was granted on the basis of a set of 17 claims.

Independent claim 1 as granted read as follows:

"1. A method for formulating a dried product suitable for direct administration to an animal after rehydration to form a suspension comprising:
i) a freezing step in which particles of polymer matrix swollen with water and having absorbed therein a non-volatile biologically active compound cooled to a temperature below the freezing point for water;
ii) a lyophilisation step in which the cooled particles from step i) are subjected to a reduced pressure at which ice sublimes for a period during which at least a portion of the absorbed ice sublimes and water vapour is removed; and
iii) a packaging step in which the dried particles are packaged;
characterised in that the packaging step is carried out under reduced pressure and the package containing the particles is substantially airtight and has an interior under vacuum."

II. An opposition was filed under Article 100 (a), (b), (c) EPC on the grounds that its subject-matter lacked novelty and inventive step, was not sufficiently disclosed, and extended beyond the content of the application as filed.

III. The appeal by the patent proprietor lies from the decision of the opposition division to revoke the patent. The decision was based on 4 sets of claims filed as main request and auxiliary requests 1-3 during

the oral proceedings before the opposition division on 1 October 2015.

Claim 1 of the main request read as following, the difference with claim 1 as granted shown in bold:

Main request

"1. A method for formulating a dried product suitable for direct administration to an animal as an embolic agent after rehydration to form a suspension comprising:
i) a freezing step in which particles of polymer matrix swollen with water and having absorbed therein a non-volatile biologically active compound are cooled to a temperature below the freezing point for water;
ii) a lyophilisation step in which the cooled particles from step i) are subjected to a reduced pressure at which ice sublimes for a period during which at least a portion of the absorbed ice sublimes and water vapour is removed; and
iii) a packaging step in which the dried particles are packaged;
characterised in that the packaging step is carried out under reduced pressure and the package containing the particles is substantially airtight and has an interior under vacuum; and
the particles are substantially spherical in shape and the particle sizes are selected such that upon rehydration in 0.9wt% saline at room temperature, the average particle size is in the range 40 to 2000 µm."

IV. The documents cited during the opposition proceedings included the following:
D4: WO 2004/071495
D8: A guide to freeze Drying for the Laboratory; An

Industry service Publication (2004)
D9: Remington, The Science and Practice of Pharmacy, 21st Ed.
D11: Buckley et al., PDA J. Pharm. Sci. and Tech., 1994, 48, 189-196
D13: US 5 393 527
D17: Lin et al.: J. Pharm. Sci. and Tech., 2004, 58, 106-115
D22: US 6 349 850

V. According to the decision under appeal, a person skilled in the art would not have had any difficulties in carrying out the claimed method steps. The skilled person was also in a position to select the suitable average particle sizes and the suitable starting materials. The main request therefore met the requirements of sufficiency of disclosure.

Since D4 did not disclose a sealing under vacuum, the claimed invention was novel over this document.

As regards inventive step, D4 represented the closest prior art. It disclosed the preparation of anthracyclin loaded particles for use as embolic agents. The lyophilisation procedure involved two drying steps and the vials were sealed in situ, under a protective atmosphere if required (see D4, page 9, line 28 to page 10, line 9). The difference with the claimed process was that the sealing step was carried out under vacuum. The technical problem was the provision of a preparation process that improved the rehydration properties of the particles known from D4. The opposition division considered that the problem was solved in view of example 1 of the patent which provided a comparison between two processes, namely one with and one without vacuum. The solution was seen as

obvious, since it was commonly known that residual air in lyophilized microspheres inhibited the rehydration process, and it was an obvious measure to overcome this problem by applying a vacuum. The storage under vacuum was also known from D11 and D17. For these reasons, the main request did not meet the requirements of Article 56 EPC.

The additional features brought to claim 1 of auxiliary request 1 did not change the analysis of inventive step made for the main request, since the defined pressure range and the single dose packaging steps were seen as routine steps.

The same conclusion as regards inventive step was reached for auxiliary requests 2 and 3, since the definition of the polymer used for the microspheres corresponded also to the PVA polymers disclosed in D4.

VI. The proprietor (hereinafter appellant) filed an appeal against said decision.

VII. With the statement setting out the grounds of appeal dated 29 February 2016 the appellant submitted a main request and auxiliary requests 1-4. The main request and auxiliary requests 1-3 corresponded to the requests on file on which the decision of the opposition division was based. It also submitted following documents:
L1: letter from patentee dated 5 June 2014
L2: Letter from patentee dated 1 September 2015.

VIII. With a letter dated 4 May 2016, the opponent withdrew its opposition without having submitted any argument or request in the course of the appeal proceedings.

IX. A communication from the Board was sent to the appellant.

X. Oral proceedings took place on 14 June 2018.

XI. The arguments of the appellant may be summarised as follows:

Main request - Inventive step

As regards inventive step, the problem to be solved by the contested patent was the improvement of the rehydration of the particles and the resolution of the buoyancy problem, which was due to the presence of air pockets in the particles. The invention was in particular the recognition of an unknown problem linked with said air pockets. It was not known before that air penetrated the pores of the particles and involved a high buoyancy when rehydrated.

D4 was the closest prior art. This document was silent about a packaging and storing step under vacuum and also did not address the problem caused by the presence of air pockets in the particles. The objective technical problem was seen as how to prepare non buoyant particles, which would allow a fast rehydration. To solve this problem, it was necessary to pack and store the microsphere composition under vacuum.

Other documents suggested a packaging under vacuum, and that vacuum facilitated the resuspension of particles, but none of them concerned embolic particles. In D11, the nature of the product was not comparable with the microspheres of the invention. In D13, the rehydration step related to an emulsion and D22 was about a pre-

filled syringe. It was true that rehydration of a vacuum stored product was generally known, but not in relationship with the problem of the present invention.

XII. Requests

The appellant (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request or, in the alternative, one of auxiliary requests 1-4, all filed with letter dated 29 February 2016.

Reasons for the Decision

1. Main request - Article 100(b) EPC

The Board does not see any reason to deviate from the decision of the opposition division on this point. A person skilled in the art would indeed not have any difficulty in carrying out the claimed process; the claimed invention is therefore sufficiently disclosed.

As to the point relating to the "average particle size" in claim 1 as discussed by the opposition division in its decision, it appears that this term gives rise to a clarity problem under Article 84 EPC, rather than to a problem relating to sufficiency of disclosure (see for instance T 1895/15, point 2). Since the term was present in dependent claim 11 as granted, it is however not open to examination under Article 84 EPC (cf. G 3/14).

2. Main request - Article 54 EPC

D4 does not disclose directly and unambiguously a sealing step under vacuum, but mentions a sealing "under a protective atmosphere" (see page 10, lines 8-9). The claimed subject-matter is therefore novel over D4.

3. Main request - Article 56 EPC

3.1 The invention relates to methods for formulating easily rehydratable dried pharmaceutical compositions made from swelling particles, which are used as chemo-embolic compositions. One problem with freeze drying gels, such as porous microspheres is that air pockets develop within the microspheres as the water is removed during the drying process, which is problematic when the dry beads are rehydrated.

3.2 The closest prior art is D4, which discloses the preparation of PVA porous microspheres comprising an active agent for embolization, by a method involving a freeze-drying step (see pages 8-9 and examples 23-26). This document does not disclose a sealing step under vacuum, but mentions that "the vials can be sealed, in situ, under a protective atmosphere if required" (see page 10, lines 8-9). Examples 25 and 26 of D4 mentions the rehydration of microspheres.

3.3 According to the appellant, the presence of air pockets within the microspheres has two main detriments to the subsequent use of the particles as a suspension in a liquid. The first problem is that they prevent rehydration of the polymer; the second problem is that retained air pockets also affect the buoyancy of the particle, in turn preventing proper dispersion of the particles in the suspending liquid even when the polymer is re-hydrated (see par. [0007] of the patent

specification). The present invention overcomes these problems of speed of hydration and ineffective suspension and avoids the addition of additional excipients to the particles.

The problem is therefore seen as the provision of a preparation method improving the rehydration properties and also the dispersion properties of the particles.

3.4 As a solution to this problem, claim 1 of the main request proposes a packaging step carried out under reduced pressure and that the package containing the particles is substantially airtight and has an interior under vacuum.

3.5 Example 1 of the patent provides a comparison between a process involving a sealing step under vacuum, and a sealing step performed at atmospheric pressure. According to example 1, the method of the invention allows faster rehydration and easier handling, and the control microspheres include a fraction which float on the surface even after a longer period of shaking.

Said experimental result of example 1 is confirmed by the tests provided by the appellant in document L1 (cf Annex 1 of L1), which provide the same results with the help of comparative pictures.

Consequently, there is sufficient evidence supporting the alleged effect, namely that said step(s) performed under vacuum suppresses the unwanted air pockets, and improves the rehydration properties and also the dispersion properties of the particles.

3.6 The question remaining is whether the skilled person, starting from the disclosure of D4 would arrive at the

subject-matter of claim 1 of the main request in an obvious manner in order to solve the problem posed.

3.6.1 A known solution of the problem would be to use a specific existing freeze-dryer, as disclosed in D8 or D9, which allows as an option special stopper sealing conditions, such as under vacuum, under inert gas or alternatively under filtered dry air (see D8, page 7, "Batch Method"; see D9, page 828, right hand column "secondary drying stage" and Table 41-7 on page 829). The choice of a sealing step under vacuum represents therefore one of the standard options the skilled person has at its disposal when performing a lyophilization.

3.6.2 In the present case, D4 does however not mention the presence of air pockets in the porous microspheres and any of the problems linked thereto. Examples 25 and 26 of D4 show the rehydration of the microspheres composition and do not mention any problem linked with said rehydration.

D4 suggests on page 10 of the description the use of a protective atmosphere during the lyophilisation step and the sealing, which demonstrate rather a concern about stability and protection against degradation due to atmosphere. Hence, said passage on page 10 also suggests that the problem linked with the presence of air pockets in the porous microsphere was not identified in D4, since the use of a protective atmosphere during the sealing step would not allow to suppress the air pockets.

Consequently, the Board considers that the problem posed by the contested patent is an unrecognized problem in D4. The discovery of a yet unrecognised

problem may give rise to patentable subject-matter in spite of the fact that the claimed solution is retrospectively trivial and in itself obvious ("problem inventions"). The question regarding the inventive step, in relation to the modification of the process of D4, is not whether the skilled man could have added a sealing and storage step under vacuum, but whether he would have done so in expectation of some improvement or advantage. Since the process disclosed in D4 appears to be satisfactory, the addition of a further process step would have appeared superfluous, wasteful and devoid of any technical effect. In view of the recognition that a sealing and storage step under vacuum has a substantial proven effect, the outcome was not predictable and the claimed modification involves an inventive step on this basis. There is therefore no indication, incentive or suggestion, when starting from D4, to make a sealing and storage under vacuum.

The Board can therefore not follow the decision of the opposition division, which made an *ex post facto* analysis of the situation.

3.6.3 As to the disclosure of documents D11, D13, D17 and D22, they all mention the rehydration facilitation when a product is stored under vacuum. However, none of these documents relates to porous microspheres and their re-hydration and re-suspension, and none of said documents deals with the problems linked specifically to the presence of air pockets within the microspheres and also the linked buoyancy problem of the particles, which prevents a proper dispersion of the particles in the suspending liquid:

(a) D11 and D17 are general documents relating to respectively lyophilized pharmaceuticals or lyophilized biological products as such, and

mention that storage under reduced pressure facilitates the dissolution of solid products before use.

(b) D13 discloses that the rehydration of microparticles forming a microemulsion is facilitated when the samples have been closed under vacuum (see D13, col. 8, l. 14-26).

(c) D17 shows a packaging step in a syringe under vacuum of sustained-release microspheres as "safety mechanism" and to "facilitate monitoring of the integrity of the packaging prior to use" (see Col. 5, lines 4-10 ad 23-34).

The problem(s) linked with the presence of air pockets in porous microspheres has therefore not been identified in any of the cited prior art.

3.7 The solution according to the subject-matter of claim 1 is therefore not obvious and it follows that the process of claim 1 involves an inventive step.

The main request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of the main request and a description to be adapted.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated