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Datasheet for the decision of 12 October 2021

Case Number: T 2921/18 - 3.3.07

Application Number: 12777430.5

Publication Number: 2701687

IPC: A61K9/16, A61K31/519, A61K47/34, A61P25/18, A61K9/14, A61K9/19

Language of the proceedings: EN

Title of invention:
RISPERIDONE SUSTAINED RELEASE MICROSPHERE COMPOSITION

Patent Proprietor:
SHANDONG LUYE PHARMACEUTICAL CO., LTD.

Opponent:
Lecomte & Partners

Headword:
Risperidone microsphere compositions/SHANDONG-LUYE

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - closest prior art - non-obvious alternative - unexpected improvement shown

Decisions cited:
T 0892/08, T 0197/86

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Beschwerdekammern

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Case Number: T 2921/18 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 12 October 2021

Appellant: (Opponent)	Lecomte & Partners P.O. Box 1623 1016 Luxembourg (LU)
Representative:	Aera A/S Niels Hemmingsens Gade 10, 5th Floor 1153 Copenhagen (DK)
Respondent: (Patent Proprietor)	SHANDONG LUYE PHARMACEUTICAL CO., LTD. No. 9 Baoyuan Road Laishan District Yantai, Shandong 264003 (CN)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 31 October 2018 rejecting the opposition filed against European patent No. 2701687 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	C. Schmidt

Summary of Facts and Submissions

I. European patent 2 701 687 (hereinafter "the patent") was granted on the basis of fifteen claims.

The independent claim 1 as granted related to:

"A pharmaceutical composition, comprising:
an active component selected from risperidone or a salt thereof, 9-hydroxy risperidone or a salt thereof; and
a polymer blend consisting of a first uncapped poly(lactide-co-glycolide) and a second uncapped poly(lactide-co-glycolide),
wherein a weight ratio of the first uncapped poly(lactide-co-glycolide) and the second uncapped poly(lactide-co-glycolide) is (50-95):(5-50);
the first uncapped poly(lactide-co-glycolide) has an intrinsic viscosity of 0.4-0.9 dl/g, a weight average molecular weight of 50,000-145,000, a molar ratio of lactide to glycolide of 65:35 to 90:10;
the second uncapped poly(lactide-co-glycolide) has an intrinsic viscosity of 0.1-0.35 dl/g, a weight average molecular weight of 4,000-45,000, a molar ratio of lactide to glycolide of 50:50 to 75:25;
a weight content of the active ingredient in the pharmaceutical composition is within a range from 10% to 60%;
a weight content of the polymer blend in the pharmaceutical composition is within a range from 40% to 90%;
and the pharmaceutical composition is present in the form of microspheres."

II. The patent was opposed on the grounds that its subject-matter lacked inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as filed.

The appeal was filed by the opponent (hereinafter: appellant) against the decision of the opposition division to reject the opposition.

In its decision the opposition division cited *inter alia* the following documents:

D1 : Zheng-Xing Su et al., Pharmaceutical Development and Technology, (2011), vol. 16, no. 4, 377-384;
D6: CN101653422;
D6a/D6b: English translations of CN101653422;
D9: Lewis D. H., "Controlled Release of Bioactive Agents from Lactide/Glycolide Polymers" pages 1 to 41 in: Biodegradable Polymers as Drug Delivery Systems, Drugs and the Pharmaceutical Sciences, Volume 45, 1990
D10: Anderson J. M. and Shive M. S., Advanced Drug Delivery Reviews 28 (1997) 5-24;
D12: Su, Z. et al., Chem. Pharm. Bull., 57, 2009, 1251-1256.

The opposition division came to the following conclusions:

(a) Late filed document D12 was prima facie relevant and admitted into the proceedings.

(b) The patent as granted did not contain subject-matter extending beyond the content of the

application as filed and the claimed invention was sufficiently disclosed.

(c) Document D1 represented the closest prior art describing the preparation of risperidone containing microspheres using blends of poly(lactide-co-glycolide) (PLGA) polymers. The subject-matter of the claims of the patent differed from this prior art in:

- the higher lactide to glycolide ratio for the high molecular weight polymer, and

- the uncapped state of both PLGA polymers of the blend.

The problem to be solved was defined as how to provide an alternative formulation of microspheres for sustained release comprising risperidone showing stability, a satisfactory release profile and *in vivo* release.

The solution defined in the claims of the patent was not obvious, as none of documents D1, D6, D9, D10 or D12 relied upon by the opponent motivated the skilled person to provide a sustained release formulation with the defined combination of features.

(d) As explained in the decision under a heading "OBITER DICTUM" no different conclusion would result starting from the formulations described in document D12.

III. In the statement setting out the grounds of appeal the appellant contested the finding in the decision under

appeal that the subject-matter defined in the claims as granted involved an inventive step.

IV. With its reply to the appeal the patent proprietor (hereinafter: respondent) filed auxiliary requests 1 to 4 as well as the following documents:

D17: FDA's Guidance for Industry, Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations, September 1997

D18: J. Control Release, 72(2001), 127-32 (Uppoor)

V. The Board issued its communication pursuant to Article 15(1) RPBA on 16 September 2020.

Further arguments were filed by the appellant with its letter of 13 October 2020 and by the respondent with its letter of 6 November 2020.

VI. Oral proceedings were held on 12 October 2021.

VII. The arguments of the appellant relevant to the present decision can be summerized as follows:

Documents D17 and D18 should not be admitted into the appeal proceedings, because these documents lacked relevance and were filed with the reply to the appeal without justification.

The submission filed with the letter of 13 October 2020 merely further developed the arguments already presented in the statement of grounds of appeal and should therefore not be disregarded.

Documents D1 and D12 both described formulations of risperidone encapsulated in PLGA based microspheres aimed at providing zero-order sustained release of risperidone. Each of these documents therefore qualified as feasible starting point in the prior art.

The claimed subject-matter differed from the microsphere compositions described in document D12 in the feature of the defined blend of a high and a low molecular weight PLGA polymer instead of a single polymer. The comparative results reported in the patent concerning formulations using a single polymer as described in document D6 did not allow for any conclusion as to an effect of the claimed formulations with respect to the formulations of document D12. The preparation of the microspheres described in documents D6 and D12 was carried out under different process parameters, which influenced the characteristics of the resulting microspheres. Moreover, the patent did not identify the supplier of the PLGA used for the described experiments, whereas it was evident from the prior art that the use of PLGA polymers from different suppliers resulted in microspheres with different release characteristics. The results reported in the patent further concerned microspheres as described in document D6 using a PLGA polymer with a relatively high molecular weight, whilst document D12 additionally disclosed microspheres with single PLGA polymers having a relatively low molecular weight. The problem to be solved in view of document D12 could therefore only concern the provision of an alternative composition. As solution to this problem it would have been obvious to the skilled person that a blend of PLGA polymers, which were already known from document D12 to be individually suitable for achieving zero-order release of

risperidone, would also be suitable to achieve such desirable risperidone release profile.

The claimed subject-matter differed from the teaching in document D1 in the feature of the defined high lactide to glycolide ratio of the high molecular weight PLGA polymer of the blend and the feature of the defined uncapped state of both the PLGA polymers in the blend. No particular effect had been shown to result from these differences and the problem to be solved in view of document D1 was therefore to be seen in the provision of an alternative composition. The influence of the capped state of the PLGA polymer on the risperidone release depended on the supplier of the polymer and was in case of the heavy weight polymer actually used in the blend of document D1 only marginal. Document D12 further indicated that uncapped PLGA polymers with a high lactide to glycolide ratio as defined in the patent showed suitable risperidone release characteristics. As document D1 showed that the risperidone release characteristics of blends could be predicted from the properties of the individual polymers the claimed subject-matter was obvious to the skilled person as solution to the stated problem.

VIII. The arguments of the respondent relevant to the present decision can be summerized as follows:

Documents D17 and D18 addressed the problem of *in vitro - in vivo* correlations and were relevant to the appeal in which the appellant relied on *in vitro* data from the prior art, whereas the patent presented *in vivo* results.

The appellant's arguments relying on microspheres with a single low molecular weight polymer as closest prior

art and the arguments referring to different properties of PLGA polymers depending on the supplier of the polymers were first presented in the the letter of 13 October 2020 and should not be admitted in to the appeal proceedings for being late filed.

Document D1 described microsphere compositions for sustained release of risperidone comprising a blend of PLGA polymers with distinct molecular weights, which differed from the blend defined in the claims of the patent by the capped state and the lower lactide to glycolide ratio of the PLGA with the higher molecular weight. Having regard to the experimental results reported in the patent the problem solved by the claimed subject-matter starting from document D1 concerned the provision of a "working" alternative formulation of microspheres for sustained release comprising risperidone and a blend of PLGA polymers that is characterized by stability, a satisfactory release profile without lag phase and initial burst and *in vivo* release. The prior art provided the skilled person with no suggestion that the high molecular weight PLGA polymer in the blend of document D1 could be replaced by an uncapped PLGA polymer with the defined higher lactide to glycolide ratio in order to solve the stated problem. Document D1 itself indicated that the release properties of PLGA based microspheres could be affected by a multitude of factors, including the capped state of the PlGA polymer. The teaching of document D12 was of no relevance as it only concerned the optimization of the risperidone release profile of microspheres comprising a single PLGA polymer in stead of a blend.

The teaching of document D12 was more remote from the claimed invention than the teaching of document D1.

Document D12 could therefore not qualify as closest prior art. Moreover, as demonstrated by the results reported in the experimental section of the patent the claimed microsphere composition comprising the defined blend of PLGA polymers allowed, in contrast to comparative compositions comprising a single type of PLGA polymer, up-scaling of production without formation of drug crystals, 6-month storage without affecting *in vivo* drug release and avoidance of a lag phase also in case of low drug-loading. With respect to document D12 the problem solved concerned the provision of improved microsphere compositions. The prior art provided no suggestion towards the claimed compositions comprising the defined blend of PLGA polymers as solution to that problem.

IX. The appellant requested that the decision under appeal be set aside and that the patent be revoked.

The appellant further requested that the appeal fee be reimbursed and that documents D17 and D18 and auxiliary requests 1 to 4 not be admitted into the proceedings.

X. The respondent requested that the appeal be dismissed. Subsidiarily, it requested to maintain the patent on the basis of one of auxiliary requests 1 to 4, filed with the response to the grounds of appeal.

The respondent further requested that the appellant's objections against the admission of documents D17 and D18 not be admitted and that the appellant's new arguments in the submission of 13 October 2020 be disregarded.

Reasons for the Decision

1. Admission of new evidence and further arguments

In view of the respondent's explanation regarding the relevance of documents D17 and D18 the Board finds no grounds for not admitting these documents filed with the respondent's reply to the appeal (Article 12(4) RPBA 2007). The Board therefore rejects the appellant's request not to admit these documents, which leaves the respondent's request not to admit the appellant's request without consequence.

The Board further considers the submissions in the appellant's letter of 13 October 2020 to represent a mere development of the arguments already presented in the statement of grounds of appeal, which did not confront the respondent with a fresh case to answer. Accordingly, the Board does not recognize any ground for disregarding these submissions (Articles 12(3) and 13(2) RPBA 2020).

Main request, patent as granted

2. Inventive step

2.1 The patent discusses in paragraphs [0006]-[0009] known microsphere compositions in which risperidone is encapsulated in PLGA polymers to achieve sustained release. Problems encountered with known formulations concerned an initial drug release lag phase when high molecular weight (150 kD) PLGA was used, as observed with the market-product Riperidal Consta™, and low drug-loading and initial burst-release when a low molecular weight (30 kD) polymer with a 50:50 lactide

to glycolide ratio was used (50/50 PLGA). Improved formulations described in document D6 increased the drug-loading rate and resolved drug release lag phase and burst-release problems, but suffered from crystal formation upon up-scaling the production process and changes of *in vivo* release upon long-term storage.

In paragraph [0010] the patent mentions the need for the provision of a risperidone microsphere formulation which is stable in quality and suitable for large scale production. The patent indicates in paragraph [0030] that the claimed microspheres provide the advantages of sustained drug-release without a lag phase in case of high as well as low drug-loading, production in a scaled-up process without precipitation of drug crystals during production and high stability such that the *in vivo* release profile does not change after long-term storage.

The patent presents experimental results showing that examples of microspheres comprising blends of PLGA as defined in the claims (see embodiments 1-13, paragraphs [0040]-[0052]), including blends comprising uncapped 75/25 PLGA with a molecular weight of 74 kD (see embodiments 1, 4, 5, 9, 12 and 13), may be prepared on large scale (kettles with >75 L liquids) without crystal precipitation, whereas formation of drug crystals is observed in microspheres prepared by up-scaling a process of document D6 using 74 kD 75/25 PLGA (comparative test 1, paragraphs [0054]-[0057]).

The patent further describes experimental results demonstrating that the *in vivo* sustained release from microspheres comprising blends of PLGA as defined in the claims (embodiments 1, 3, 4, 6, 7 and 9) does not change substantially after 6 month storage, whereas the

release profile of the microspheres of embodiment 3 of document D6 comprising 74 kD 75/25 PLGA shifts substantially following such storage (comparative test 2, paragraphs [0058]-[0064], Table 1, figures 2-8).

The patent finally reports experimental results indicating that microspheres comprising PLGA blends as defined in the claims (embodiments 2, 5, 8, and 10) allow for release without lag phase even with low drug-loading, whereas a drug release lag phase occurs with microspheres produced according to document D6 having a drug loading below 45% (comparative test 3, paragraphs [0065]-[0072], Table 2, figure 9).

2.2 The parties disagree whether document D12 is to be considered, in addition to document D1, as an alternative suitable starting point in the prior art in the assessment of inventive step in accordance with the problem solution approach.

The Board recalls in this context that, in line with the jurisprudence as summerized in sections I.D.3.1 to I.D.3.4 of the Case Law of the Boards of Appeal of the EPO, 9th Edition 2019, the problem solution approach implies that in case an inventive step can be recognized starting from a particular item of prior art which is convincingly identified as most promising starting point and thus represents the closest prior art, attempts to argue a lack of inventive step starting from less promising starting points are bound to fail. However, in case an inventive step is apparently convincingly denied starting from a promising particular item of prior art, the mere argument that the claimed subject-matter nevertheless involves an inventive step in view of an allegedly closer prior art, will generally not be persuasive,

because in such case the allegedly closest prior art may well turn out to represent a starting point that is in fact not more promising.

In the present case only two items of prior art have been presented as potential starting points for the assessment of inventive step, document D1 and document D12. The appellant maintains on the basis of these documents two complementary rather than repetitive lines of argument, which do not appear *prima facie* unsuitable to deny the claimed subject-matter an inventive step. In its analysis of the issue of inventive step in accordance with the problem solution approach the Board considers it therefore in the present case purposeful to take account of documents D1 and D12 as alternative starting points in the prior art without attempting to determine from the outset which of documents D1 and D12 would effectively represent the closer prior art.

2.3 Starting from document D1

2.3.1 Document D1 describes the preparation of microspheres containing risperidone using various types of 50/50 PLGA polymers as well as blends of such polymers (see page 378 Table 1). The preparation of the microspheres was aimed at optimizing the release profile, in particular at achieving zero-order sustained release behaviour with appropriate initial release (see page 378 bridging paragraph between left and right column).

The *in vitro* release experiments reported in document D1 indicate that zero-order kinetics could be approached with microspheres comprising a single uncapped PLGA polymer with a molecular weight of 51 kD, designated as formulation 50504A (see page 383,

conclusions) as well as microspheres from a blend of low molecular weight uncapped PLGA polymer with a capped higher molecular weight PLGA polymer, designated as 502H:50505E(3:7)/batch 9 (see page 382, figure 5 and table 2 and page 383, conclusions).

2.3.2 The difference between the microspheres of the patent and the microspheres of document D1 is not in dispute. The patent requires that the PLGA polymer with the higher molecular weight in the blend is uncapped and has a lactide-glycolide ratio of 65:35 to 90:10, whereas document D1 describes its optimal blend (502H: 50505E(3:7)/batch 9) as comprising a high molecular weight polymer which is capped and has a lactide-glycolide ratio of 50:50.

The experiments presented in the patent (see discussion in section 2.1 above) do not concern a comparison between the microspheres as defined in the claims of the patent and the microspheres from the blend of polymers described in document D1. Having regard to the experimental results reported in the patent the Board therefore identifies the problem underlying the claimed invention with respect to document D1 as the provision of an alternative microsphere formulation useful for sustained release of risperidone.

2.3.3 The rationale in document D1 for preparing microspheres using blends of PLGA polymers is illustrated in figure 4 (see D1 page 381). This figure 4 shows how in the predicted release profiles from blends the initial burst release from a low molecular weight polymer (502H) combines with the initial lag phase from a capped high molecular weight polymer (50505E) to approach zero-order kinetics for the optimum blend of these polymers (502H:50505E(3:7)/batch 9).

Faced with the identified problem the skilled person is informed in document D1 that the drug-release profile from microspheres may be influenced by a multitude of factors (see page 380, left column paragraph 3). The document refers specifically to the reduction of the initial burst and the extended risperidone release with the use of PLGA polymers with higher molecular weight as well as the lag phase prolonging effect of end-capping of the used PLGA polymer, be it that the extend of the effects appears to depend on the supplier of the PLGA (see D1 page 381, left column lines 2 to right column line 15). Thereby document D1 indicates that that the capped state of the high molecular weight PLGA polymer (50505E) in its blends contributes to the release desired profile of the blends, in which the initial lag phase from the capped high molecular weight polymer (50505E) compensates the initial burst release from the low molecular weight polymer (502H).

Document D1 further associates the problematic characteristics of the market product Risperidal Consta™ with the high molecular weight (>100 kD) and high monomer ratio (75/25) of the used PLGA polymer (see page 378, left-hand column) and thereby teaches away from the use of 75/25 PLGA polymers. In this context the skilled person may have appreciated from document D12 that uncapped 75/25 PLGA polymers may still be suitable to prepare microspheres for sustained release of risperidone without a lag phase, which may approach zero-order release kinetics in case polymers with a molecular weight of 28 kD or 67 kD are used (see document D12 Abstract, page 1252 Table 1, page 1254 Figure 2). However, such 75/25 PLGA polymers as described in document D2 would not seem suitable for replacing the capped polymers in the blends of document

D1 precisely because they lack the lag phase that compensates the initial burst release from the low molecular weight PLGA polymer in the blends in the rationale of document D1.

The Board thus distinguishes the situation of the present case, in which only a particular type of blends of polymers had been described in the prior art, from the circumstances considered in decision T 892/08 (see section 1.7), in which a combination of already conventional features was considered obvious as solution to the problem of providing a mere alternative.

Therefore, the cited prior art provides the skilled person with no suggestion towards the claimed subject-matter as solution to the problem of providing an alternative microsphere formulation useful for sustained release of risperidone with respect to the composition of document D1.

2.4 Starting from document D12

2.4.1 Document D12 describes the preparation of a series of microsphere formulations for sustained release of risperidone comprising a 75/25 PLGA polymer, wherein the molecular weight of the polymer ranges from 18-110 kD and wherein the polymer is uncapped or capped (see page 1252, tables 1-2). The use of uncapped PLGA with a molecular weight of 28 kD or 67 kD is reported to allow for the preparation of formulations with an *in vitro* release profile characterized by a low initial burst phase and a subsequent zero-order release phase (see page 1254, right-hand column). Higher drug loading is reported to lead to faster release (see page 1254, figure 3).

2.4.2 The difference between the microspheres of the patent and the microspheres according to document D12 is not in dispute. The microspheres of the patent differ from the microspheres of document D12 in comprising a blend of a PLGA polymer of a lower molecular weight and a PLGA polymer of a higher molecular weight in stead of a single PLGA polymer.

The experiments presented in the patent do not provide a direct comparison between microspheres as defined in the claims of the patent and microspheres as prepared according to document D12. However, as discussed in section 2.1 above, the experimental results reported in the patent do substantiate that microspheres as defined in the claims allow in contrast to the microspheres of document D6, which like those of document D12 comprise a single PLGA polymer, for large scale production of the microspheres without crystal precipitation and preservation of the *in vivo* sustained release profile without a lag phase after 6 month storage.

In this context the Board acknowledges that the method of preparation of the microspheres described in document D6 differs from the method described for the preparation of the microspheres in document D12 in process parameters which are known to influence the resulting risperidone release profile, including the concentration of the PLGA polymer used for the organic phase and the homogenisation speed to prepare an initial emulsion (see for instance D12 page 1255 right column under "Conclusion"). Moreover, document D6 does not mention the supplier of the PLGA polymer, whereas document D1 observes significant differences in the release behaviour of microspheres prepared with polymers from different suppliers (see page 383 under

"Conclusions"). Notwithstanding the differences between the microspheres of document D6 and document D12, the experiments described in the patent show advantages properties for tested microspheres in accordance with the claims which essentially differ from the tested microspheres as described in document D6 only in the feature of the blend of PLGA polymers forming the microspheres. In the Board's view it is therefore justified to conclude that the advantageous properties reported in the experimental section of the patent for the composition in accordance with the claims are associated with the distinguishing feature in relation to the teaching of document D6, namely microspheres comprising the defined blend of polymers. As the distinguishing feature between the claimed composition and the compositions of document D12 equally resides in the microspheres comprising the defined blend of polymers the Board considers it, in the absence of evidence to the contrary and in line with the principle applied in T 197/86 (see section 6.1.3), reasonable to assume that the advantages associated with microspheres comprising a blend of PLGA polymers as defined in the claims also persist in relation to the microspheres comprising a single PLGA polymer in accordance with document D12.

The Board therefore identifies the problem underlying the claimed invention with respect to document D12 as the provision of an improved microsphere formulation useful for sustained release of risperidone.

2.4.3 Document D12 itself only describes microspheres comprising single PLGA polymers without any reference to blends of polymers. Document D1 describes microspheres comprising blends of capped high-molecular weight and uncapped low molecular weight 50/50 PLGA

polymers showing zero-order release kinetics, but does not mention of any effect of the use of blends on the prevention of crystallisation in large scale production or the stability of the sustained release profile without a lag phase after long term storage.

Accordingly, the cited prior art fails to provide the skilled person with any suggestion towards the claimed subject-matter as solution to the problem of providing compositions with starting from document D12.

2.5 The Board therefore concludes that having regard to the state of the art the subject-matter defined in the claims of the patent as granted would not have been obvious to the skilled person and thus meets the requirement of inventive step.

3. The appellant contested the decision under appeal only with respect to the issue of inventive step. Following the conclusion concerning the requirement of inventive step in section 2.5 the Board considers the appeal therefore not allowable.

Request for reimbursement of the appeal fee

4. As the appeal is not considered allowable the appellant's request for reimbursement of the appeal fee lacks a legal basis (Rule 103(1)(a) EPC) and is therefore rejected.

Order

For these reasons it is decided that:

1. The appeal is dismissed

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated