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Datasheet for the decision of 22 November 2021

Case Number: T 2453/18 - 3.3.07

Application Number: 08725543.6

Publication Number: 2152315

IPC: A61K47/34, A61K31/519, A61P25/18, A61P25/00

Language of the proceedings: EN

Title of invention:
SUSTAINED DELIVERY FORMULATIONS OF RISPERIDONE COMPOUNDS

Patent Proprietor:
Indivior UK Limited

Opponent:
Lecomte & Partners

Headword:
Risperidone / INDIVIOR

Relevant legal provisions:
EPC Art. 113(1), 100(b), 100(c), 54, 56
EPC R. 103(1)(a)

Keyword:

Right to be heard - substantial procedural violation (no)
Reimbursement of appeal fee - (no)
Grounds for opposition - insufficiency of disclosure (no) - added subject-matter (no)
Novelty - (yes)
Inventive step - closest prior art

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Beschwerdekammern

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Case Number: T 2453/18 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 22 November 2021

Appellant: (Opponent)	Lecomte & Partners P.O. Box 1623 1016 Luxembourg (LU)
Representative:	Lecomte & Partners 76-78, rue de Merl 2146 Luxembourg (LU)
Respondent: (Patent Proprietor)	Indivior UK Limited 103-105 Bath Road Slough Berkshire SL1 3UH (GB)
Representative:	HGF 1 City Walk Leeds LS11 9DX (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 23 July 2018 rejecting the opposition filed against European patent No. 2152315 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	A. Jimenez

Summary of Facts and Submissions

I. European patent 2 152 315 (hereinafter: the patent) was granted on the basis of seven claims.

Independent claim 1 as granted related to:

"A flowable composition consisting of:
(a) a biodegradable thermoplastic polymer that is at least substantially insoluble in body fluid, wherein the polymer is a poly(DL-lactide-co-glycolide) with a carboxy terminal group in a weight ratio of lactide to glycolide of 75:25 or 85:15;
(b) N-methylpyrrolidone; and
(c) risperidone;
wherein the flowable composition is an injectible subcutaneous formulation."

Independent claim 5 as granted relates to:

"A method of forming a flowable composition for use as a solid controlled release implant, consisting of the step of mixing, in any order:
(a) a biodegradable thermoplastic polymer that is at least substantially insoluble in aqueous medium or body fluid, wherein the polymer is a poly(DL-lactide-co-glycolide) with a carboxy terminal group in a weight ratio of lactide to glycolide of 75:25 or 85:15;
(b) N-methylpyrrolidone; and
(c) risperidone;
wherein the mixing is performed for a sufficient period of time effective to form the flowable composition for use as a solid controlled release implant."

II. The patent was opposed on the grounds that its subject-matter lacked novelty and lacked an 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 opposition division decided to reject the opposition. The opponent (appellant) filed the appeal against this decision.

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

D1: WO2007/041410
D2: US6565874
D5: WO00/24374
D6: Packhaeuser et al. European Journal of Pharmaceutics and Biopharmaceutics 58 (2004) 445-455
D8: WO2006/041942
D9: US5780044
D10: US2004/0101557
D11: WO2006/063794
D15: Samadi et al. Journal of Controlled Release, 172 (2013) 436-443

The opposition division came to the following conclusions:

(a) The subject-matter of claim 1 as granted was derivable from claim 1 as originally filed in combination with the mention of NMP as preferred polar aprotic solvent, the reference to a risperidone sustained release system, the listing of the particular poly(DL-lactide-co-glycolide) polymers (PLGA) and the disclosure of the

composition as flowable and subcutaneously injectable in the description of the application as filed. The term "injectible" as used in claim 1 as granted evidently contained a spelling error.

The features of claim 5 as granted were derivable from original claim 30 in view of the same passages concerning the NMP, the risperidone and the PLGA as mentioned for claim 1 as granted in combination with references to the solid constitution of the implant in the application as filed.

(b) With the instructions in the patent at hand, including the specific guidance from the examples, the skilled person knew how to prepare a composition as defined in the claims as granted. A lack of sufficiency could not be concluded from a mere ambiguity. It had not been shown that without specific definition of the mixing time and suitable amounts of the components it required undue burden for the skilled person to identify the technical measures required for solving the problem underlying the patent.

(c) The subject-matter claimed in the patent was new over the prior art. Document D8 did not disclose a PLGA with a carboxy terminal group in a weight ratio of lactide to glyclolide of 75:25 or 85:15. Documents D9, D10 and D11 also failed to disclose a composition of risperidone with a polymer and a solvent as defined in the claims of the patent.

(d) Document D1 disclosed injectable subcutaneous formulations forming a depot gel comprising 50/50 PLGA, risperidone and triacetin, benzyl alcohol or benzoyl benzoate. Document D8 was concerned with

delivery of drugs in the ocular region. In view of the problem addressed in the patent, namely the provision of sustained delivery of risperidone, the closest prior art was represented by document D1 and not by document D8.

The subject-matter of claim 1 of the patent as granted differed from the formulations of document D1 in the PLGA having a lactide to glycolide ratio of 75:25 or 85:15 and a carboxy terminal group and the choice of NMP as solvent. In view of the data in the patent showing the effect of the defined ratio of lactide to glycolide in the polymer on the prolonged release of risperidone the problem to be solved was the provision of a composition presenting an improved release profile. The skilled person would not have expected that the PLGA with the defined ratios and a carboxy terminal group would solve this problem. Accordingly, the claimed subject-matter involved an inventive step.

III. In the statement setting out the grounds of appeal the appellant contested the findings in the decision under appeal and contended that the decision involved substantial procedural violations.

IV. With the reply to the appeal the patent proprietor (respondent) filed auxiliary requests 1 to 8. With the reply the respondent also filed the following documents:

D16: Wikipedia entry for triacetin
D17: Wikipedia entry for ethyl benzoate
D18: Brodbeck et al. Journal of Controlled Release 62 (1999) 333-344

Annex A: photographs of solid implants formed after subcutaneous injection of the flowable composition into rats
Annex B: data on the effects of capped vs uncapped poly(DL-lactide-co-glycolide) polymers.

V. The Board invited the parties to attend oral proceedings with the summons of 29 October 2020.

In a communication pursuant to Article 15(1) RPBA issued on 29 March 2021 the Board expressed the preliminary opinion that the appeal was to be dismissed.

Following the appellant's withdrawal of the request for oral proceedings the scheduled oral proceedings were cancelled.

VI. The arguments of the appellant are summerized as follows:

(a) Procedural violations

The reasoning in the decision under appeal regarding the relevance of ambiguity in the assessment of sufficiency of disclosure had not been mentioned during the oral proceedings. This reasoning was new to the appellant. The decision therefore contravened the appellant's right to be heard under Article 113(1) EPC.

The opposition division's preliminary opinion attached to the summons addressed a problem-solution approach based on document D8. However, during the oral proceedings the opposition division denied the appellant the possibility to present

arguments regarding the requirement of inventive step starting from document D8. The appellant was thereby denied the right to be heard on this relevant matter.

(b) Added matter

The application as filed described the implant as a solid or a gel, but failed to disclose any link between the particular components and the resulting solid consistency of the implant defined in claim 5 as granted.

(c) Sufficiency

Claims 1 and 5 covered compositions that are not workable. These claims did not specify the amounts of the defined components and thus included for example compositions with such a low liquid content that the compositions could not possibly be flowable or injectable. Moreover, the patent did not provide the necessary guidance how to achieve the solid consistency of the implant as defined in granted claim 5 as opposed to the gel consistency equally mentioned in the patent.

(d) Novelty

The subject-matter of claim 5 lacked novelty in view of documents D8, D9 , D10 and D11.

(e) Inventive step

Both documents D1 and D8 described sustained release formulations comprising risperidone for subcutaneous administration. Document D8 described

the use of ATRIGEL(R) type delivery systems that were also referred to in the examples of the patent. Documents D1 and D8 therefore represented at least equally valid starting points in the prior art. With respect to the subject-matter of claim 5 documents D8, D9, D10 or D11 represented further pertinent starting points in the prior art.

The difference between the teaching of document D1 and the claimed subject-matter concerned the feature of the carboxy terminal group of the defined PLGA.

No evidence showed any special technical effect associated with this difference. The claims as granted further included compositions with minimal amounts of solvent. Such compositions were unsuitable to achieve any technical effect. Moreover, the patent acknowledged that the PLGA defined in the claims did not allow for a 10% initial burst, which the patent required for a beneficial release profile. The problem to be solved could therefore only be seen in the provision of an alternative composition.

The skilled person would consult document D2, which described the suitability of PLGA with a 50:50 monomer ratio and a carboxy terminal group for providing a flowable composition for use in a controlled release implant. In view of this teaching in document D2 the composition as defined in the claims of the patent was obvious to the skilled person.

Moreover, the patent acknowledged that the PLGA/NMP type delivery systems used in the examples were

known in the prior art under the commercial name ATRIGEL(R). Such ATRIGEL(R) type delivery systems had in fact been used in document D8 for sustained release of risperidone. Document D5 further described PLGA with a content of 50-90% lactide and 50-10% glycolide as suitable for formulating compositions for sustained drug release. It therefore required no more than obvious trial and error to determine that the PLGA as defined in the claims was suitable for achieving the sustained release of risperidone.

VII. The arguments of the respondent are summerized as follows:

(a) Procedural violations

The opposition division heard the parties on the issue whether documents D1 and D8 represented equally valid starting points in the prior art. The decision under appeal, which was based on the correct conclusion that document D1 represented the closest prior art, did therefore not involve a procedural violation.

(b) Added matter

The application as filed stated that the matrix forming the implant is preferably solid and that the use of a water-miscible liquid results in a solid implant. Moreover, examples prepared in line with claim 5 resulted in firm and non-fragmenting implants. The application as filed thereby provided an adequate basis for the feature in claim 5 as granted defining the controlled release implant as solid.

(c) Sufficiency

The definition of the composition as flowable and injectable in claims 1 and 5 as granted functionally excluded compositions which would not be workable due to a low liquid content. The disclosure in the patent provided adequate instructions with ample exemplification for reproducing the claimed subject-matter.

Claim 5 related to a process for preparing a flowable composition. As illustrated by the examples of the patent and further confirmed in Annex A such composition forms a solid implant when contacted with a bodily fluid following injection or when placed in an aqueous medium due to diffusion of the water-miscible NMP.

(d) Novelty

The opposition division correctly concluded that documents D8, D9, D10 and D11 did not anticipate the claimed subject-matter.

(e) Inventive step

The claimed compositions enabled subcutaneous administration of risperidone and allowed to achieve sustained release with low initial burst release and minimal initial lag-phase. Document D1 represented the closest prior art as it also described sustained release compositions for risperidone with low initial burst release and minimal lag-phase. Document D8 did not represent an equally valid starting point because it was

concerned with ocular delivery of drugs and only mentioned risperidone in a list of potentially suitable active agents.

The claimed composition differed from the compositions exemplified in document D1 in the type of PGLA and solvent.

In view of the experimental results reported in the patent the problem to be solved was the provision of a sustained release risperidone composition which has low initial burst and provides release of risperidone over a period of at least 1 month following subcutaneous injection.

No prior art suggested that claimed compositions allowed to avoid an initial burst release and to sustain the prolonged release of risperidone.

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

The appellant further requested reimbursement of the appeal fee.

IX. The respondent requested that the appeal be dismissed. Subsidiarily, the respondent requested that the patent be maintained on the basis of auxiliary requests 1-8 as filed with the reply to the appeal.

Reasons for the Decision

Main request, patent as granted

1. Procedural violations

1.1 The decision under appeal presents in sections 23 and 24 considerations regarding the relevance of ambiguity in the assessment of sufficiency of disclosure. The Board observes that the opposition division mentioned these considerations in the annex to the summons of 8 September 2017, sections 16-17.

The argument that the decision contravened the appellant's right to be heard by including these considerations is therefore not convincing.

1.2 According to the minutes of the oral proceedings held on 23 July 2018 (see pages 4-5, section 2.4.1) the appellant intended to present arguments on the basis of document D1 as well as document D8 as closest prior art. The opposition division allowed the appellant the opportunity to discuss whether documents D1 and D8 were to be considered as equally suitable starting points in the prior art. The parties were subsequently informed that according to the opposition division document D1 represented the closest prior art.

The Board therefore concludes from the minutes that the opposition division heard the appellant on the argument of document D8 representing the closest prior art, but found this argument not convincing.

1.3 Accordingly, the Board considers that the decision under appeal does not suffer from a substantial procedural violation under Article 113(1) EPC.

2. Added subject-matter

The application as filed describes the solid consistency of the matrix forming the implant as preferred (see page 42 lines 18-19 and page 8 lines 23-24), explains that the use of a water-miscible liquid results in a solid implant (see page 23, lines 20-22) and reports that exemplified compositions prepared in line with claim 5 resulted in firm and non-fragmenting implants (see *inter alia* page 98, line 5).

The Board therefore concludes that the application as filed discloses the solid consistency of the implant in accordance with claim 5 as granted and that the patent does not comprise subject-matter extending beyond the content of the application as filed.

3. Sufficiency

The Board observes that claims 1 and 5 as granted define the composition as flowable. Claim 1 further qualifies the composition as injectable and claim 5 defines the composition for use as a solid controlled release implant. The independent claims 1 and 5 thereby exclude in a functional manner compositions which are not flowable or injectable, for instance due to a low liquid content. The patent provides guidance for reproducing the claimed subject-matter by indication of preferred amounts of the defined components (see paragraphs [0063], [0092],[0097]) and instructions for the actual preparation of the compositions (see paragraphs [0118] to [0120]) together with ample

exemplification. The patent further explains that the use of a water-miscible solvent results in a solid implant (see paragraph [0064]) and reports that exemplified compositions prepared in line with claim 5 resulted in firm and non-fragmenting implants (see *inter alia* paragraph [0064]).

In the absence of evidence that reproducing the claimed subject-matter requires undue burden the Board therefore considers that the patent sufficiently discloses the claimed invention.

4. Novelty

The decision under appeal (see page 8 section 26) explains, why documents D8, D9 , D10 and D11 were not considered to anticipate the subject-matter of claim 5 as granted. The appellant maintained on page 19 lines 26-39 of the statement of grounds of appeal that the subject-matter of claim 5 is not new over documents D8, D9 , D10 or D11. This passage in the grounds of appeal regarding the requirement of novelty corresponds literary to a passage in the notice of opposition (see section 2.5.2 on page 10 of the notice of opposition) and actually addresses the opposition division rather than the Board of Appeal. The appellant thus failed to address the reasons for acknowledging novelty in the decision under appeal. The Board finds therefore no reason to doubt the correctness of the finding in the decision under appeal that the subject-matter of the claims of the patent as granted is new over the prior art.

5. Inventive step

5.1 Closest prior art

According to the patent (see paragraphs [0052] and [0112]) the compositions of the claimed invention enable sustained release of risperidone following subcutaneous administration and allow to achieve particular beneficial release characteristics.

Document D1 describes injectable depot formulations with beneficial release characteristics (see paragraphs [0006] and [0013]), for instance following subcutaneous injection (see paragraph [0015]). Document D1 specifically exemplifies injectable depot formulations for administration of risperidone (see paragraphs [0027] and [0028]).

Document D8 is concerned with ocular delivery of drugs involving administration via the ocular region (see D8 page 3 lines 27-34) and describes in this context ATRIGEL$^{(R)}$ type delivery systems (see D8 pages 56-57), which are also referred to in the examples of the patent. Document D8 mentions risperidone (see D8 page 11 line 23 and claim 38) only in the context of a list of active agents which are potentially suitable for such delivery and without further exemplification or reference to a particular beneficial risperidone release profile. The Board acknowledges that document D8 mentions subcutaneous injection (see page 3 lines 7-10 and page 56 lines 11-18). However, taking account of the description of the ocular region (see D8 page 6 lines 14-22) in which the formulations are to be injected (see D8, claim 92) and the examples of ocular delivery by intra-ocular injection (see D8, page 57 onwards) the mention of subcutaneous injection in

document D8 appears to concern the prior known use of ATRIGEL(R) type delivery systems and not the ocular delivery specifically addressed in document D8. Having regard to the purpose of the compositions described in the patent and the prior art the Board therefore agrees with the decision under appeal that document D1 and not document D8 or the ATRIGEL(R) type delivery systems mentioned in document D8 represents the most promising starting point in the prior art.

The appellant argued on page 19 lines 26-39 of the statement of grounds of appeal that Documents D8, D9, D10 or D11 represented further pertinent starting points with respect to the subject-matter of claim 5. As observed in section 4 above this passage in the grounds of appeal addresses the opposition division and corresponds literary to a passage in the notice of opposition. The Board finds therefore no reason in the appellant's argument to further doubt the correctness of the finding in the decision under appeal that document D1 represents the most promising starting point in the prior art.

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.

5.2 Differences with the prior art

Document D1 mentions in paragraphs [0023] to [0025] PGLA with a lactide to glycolide ratio of 75:25 or 85:15 in a list of diverse polymers, the NMP amongst a variety of other solvents and risperidone amongst various other active agents.

The composition as defined in the claims as granted differs from the actual examples of risperidone formulations in document D1 (see paragraphs [0032] and [0037], compositions No. 63, 72 and 73 in tables 3 and 5) in

- the 75/25 or 85/15 PGLA having a carboxy terminal group instead of 50/50 PGLA without specification of a carboxy terminal group ("50/50 PLGA-502") and

- the solvent NMP instead of triacetin, benzyl benzoate or ethyl benzoate.

5.3 Problem to be solved

5.3.1 In example 1.10 and example 4 the patent presents results of *in vivo* experiments in rats and dogs involving risperidone formulations with 75/25 or 85/15 PGLA having a carboxy terminal group with NMP as solvent (see patent paragraphs [0148] and [194] to [0200]; see also Figure 18). These results indicate that formulations as claimed show a low initial burst and prolonged risperidone release. In contrast, the release profile of formulations with 50/50 PGLA reported in example 1.9 of the patent show an initial burst and failure to sustain release up to the end of a month (see conclusion in paragraph [0148]).

5.3.2 The appellant denied that any technical effect sought can be achieved over the whole scope of the claims, because the claims would include compositions with minimal amounts of solvent unsuitable for the use described in the patent. The Board notes that this argument corresponds to the appellant's argument concerning sufficiency of disclosure. For the same reasons as set out in section 3 above the Board is not convinced by this argument.

The appellant further suggested that according to the patent the PLGA defined in the claims did not demonstrate a 10% initial burst (see paragraph [0148]), although such 10% burst was required for a beneficial release profile (see paragraph [0136]). The Board observes that the patent mentions the requirement of approximately 10% burst only in the context of the preliminary experiments in rats of example 1. In contrast, the more advanced stage experiments with dogs reported in example 4 of the patent (see paragraph [0194]) explicitly aim at reducing initial release and increasing release duration using 75/25 PLGA with a free carboxy group. The Board does therefore not recognize that patent generally requires a 10% initial burst for the disclosed formulations to be beneficial.

5.3.3 In view of the results reported in the patent as discussed in section 5.3.1 the Board therefore formulates the technical problem to be solved as the provision of a sustained release risperidone composition which allows for a beneficial release profile involving a low initial burst and a prolonged release of at least 1 month following subcutaneous injection.

5.4 Assessment of the solution

Document D1 states that the solvent type used in the depot formulations can influence the release profile on the basis of the higher initial burst release found for formulations with the more water soluble triacetin in comparison to formulations with the less water soluble ethyl benzoate (see D1, paragraph [0033]). In this context the Board further observes that documents D6 and D18 indicate that the use of NMP in PLGA based depot formulations was actually known to be associated with a high drug burst release (see D6 page 449 column 1, see D18 page 338 figure 5). Document D1 itself does therefore not suggest the claimed solution.

Documents D2 describes flowable compositions for use as a controlled release implant for leuprolide on the basis of PLGA with NMP as solvent (see column 2 lines 35-63). Document D2 recommends 50/50 PLGA with a carboxy terminal group for a one month delivery system and 75/25 PGLA without a terminal carboxy group for a three month delivery system (see D2 column 2 lines 41-44 and column 5 lines 46-56). However, document D2 provides no suggestion that the defined 75/25 or 85/15 PGLA with terminal carboxy groups in combination with NMP as solvent would, in contrast to 50/50 PGLA, allow to avoid an initial burst release and to sustain the prolonged release of risperidone.

The patent describes the PLGA/NMP type delivery systems used in the examples as ATRIGEL$^{(R)}$ delivery systems (see paragraphs [0108] to [0110]). Document D8 specifically describes such ATRIGEL$^{(R)}$type delivery systems for ocular delivery (see D8 pages 56-57), in particular systems based on 50/50 PLGA with a terminal carboxy group or 75/25 PLGA without a terminal carboxy

group (see D8 claims 12-13). Document D5 further indicates that PLGA for sustained release of drugs may comprise 50-90% lactide with 50-10% glycolide (see D5, page 8 lines 15-18). However, this information does not provide the skilled person with any suggestion towards the claimed subject-matter as solution to the identified technical problem.

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

6. Accordingly, the Board considers the appeal not allowable.

Request for reimbursement of the appeal fee

7. 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