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Datasheet for the decision of 29 July 2022

Case Number: T 0133/20 - 3.3.09

Application Number: 14733524.4

Publication Number: 3010962

IPC: C08J3/12, A61K9/16, B01J13/02, C08J3/14

Language of the proceedings: EN

Title of invention:
PREPARATION OF POLYLACTIDE-POLYGLYCOLIDE MICROPARTICLES HAVING A SIGMOIDAL RELEASE PROFILE

Patent Proprietor:
Pharmathen S.A.

Opponent:
Alkermes Pharma Ireland Limited

Headword:
MICROPARTICLES HAVING A SIGMOIDAL RELEASE PROFILE/PHARMATHEN

Relevant legal provisions:
EPC Art. 56, 83, 84, 123(2)
RPBA 2020 Art. 12(4), 12(6)

Keyword:

Sufficiency of disclosure - (yes)
Inventive step - (yes)
Amendment to case - evidence
Amendments - added subject-matter (no)
Claims - support in the description (yes)

Decisions cited:

G 0007/93, T 0640/91, T 0304/08, T 0075/11, T 0544/12

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Case Number: T 0133/20 - 3.3.09

D E C I S I O N
of Technical Board of Appeal 3.3.09
of 29 July 2022

Appellant: (Opponent)	Alkermes Pharma Ireland Limited Connaught House 1 Burlington Road Dublin 4 (IE)
Representative:	Lee, Nicholas John Kilburn & Strode LLP Lacon London 84 Theobalds Road London WC1X 8NL (GB)
Respondent: (Patent Proprietor)	Pharmathen S.A. 6, Dervenakion Str. 15351 Pallini Attikis (GR)
Representative:	Appleyard Lees IP LLP 15 Clare Road Halifax HX1 2HY (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 15 November 2019 concerning maintenance of the European Patent No. 3010962 in amended form.**

Composition of the Board:

Chairman	A. Haderlein
Members:	C. Meiners
	W. Sekretaruk

Summary of Facts and Submissions

I. This decision concerns the appeal filed by the opponent (appellant) against the opposition division's interlocutory decision finding that the patent in suit (hereinafter "the patent"), as amended in accordance with the first auxiliary request filed in the oral proceedings before the opposition division, met the requirements of the EPC.

II. In its notice of opposition, the opponent had requested that the patent be revoked in its entirety, *inter alia*, on the grounds for opposition under Article 100(a) EPC in combination with Article 56 EPC (lack of inventive step) and Article 100(b) EPC (insufficiency of disclosure).

III. The opposition division found that the subject-matter of the then-main request (patent as granted) was directly and unambiguously derivable from the application as filed (Article 100(c) EPC) but held that the claimed invention was insufficiently disclosed (Article 100(b) EPC). The then-auxiliary request 1 (granted set of claims but with claim 8 cancelled), filed during the oral proceedings, was admitted into the proceedings and was found to meet the requirements of Rule 80 EPC and Articles 123(2) and (3) EPC. The claimed subject-matter was found to be sufficiently disclosed and novel and to involve an inventive step.

IV. The following documents, filed in the opposition or appeal proceedings, are relevant to the present decision:

D1 WO 00/40221 A1

D3 "Principles of encapsulating hydrophobic drugs in PLA/PLGA microparticles", C. Wischke et al., International Journal of Pharmaceutics, **2008**, *364*, 298-327

D9 "A detailed view of microparticle formation by in-process monitoring of the glass transition temperature", K. Vay et al., European Journal of Pharmaceutics and Biopharmaceutics, **2012**, *81*, 399-408

D10 "Solvent selection in the preparation of poly(DL-lactide) microspheres prepared by the solvent evaporation method", R. Bodmeier et al., International Journal of Pharmaceutics, **1988**, *43*, 179-186

D11 "Control of Encapsulation Efficiency and Initial Burst in Polymeric Microparticle Systems", Y. Yeo et al., Arch. Pharm. Res., **2004**, *27(1)*, 1-12

D12 Experimental report, filed with the appellant's grounds of appeal, including appendices 1-4

V. With its statement setting out the grounds of appeal, the appellant argued, *inter alia,* why the request the opposition division had allowed was not allowable. It filed documents D10 to D12.

VI. In its reply to the statement setting out the grounds of appeal, the patent proprietor (respondent) requested that the appeal be dismissed and filed an auxiliary request. This request is the same as auxiliary request 2 filed together with the patent proprietor's response to the opposition, but with dependent claim 8 cancelled.

VII. The board summoned the parties to oral proceedings and issued a communication pursuant to Article 15(1) RPBA

2020 ("the board's communication") in which it set out its preliminary opinion. Its preliminary finding was, *inter alia*, that the claimed subject-matter of the main request (request held allowable by the opposition division) was not allowable, but that the auxiliary request was.

VIII. In response to the board's communication, the respondent withdrew its main request, its auxiliary request becoming the sole request. It also filed a description adapted to the sole request.

IX. Independent claim 1 of the sole request reads:

"1. A process for the preparation of biodegradable microparticles of poly(D,L lactide-co-glycolide) (PLGA) polymer, having a sigmoidal release profile of Risperidone, contained within the microparticles, comprising the following steps:
a. preparing an inner oil phase by dissolving the PLGA polymer and Risperidone in an organic solvent which is dichloromethane, wherein the polymer concentration in the inner oil phase is in the range of 5-8% w/w;
b. preparing an outer aqueous phase consisting of water, polyvinyl alcohol (PVA), optionally an aqueous buffer solution to adjust the pH to a value that Risperidone appears the lower solubility, and the same organic solvent used in oil phase, wherein the amount of organic solvent added in the outer phase is sufficient to saturate the outer phase;
c. emulsifying the inner phase into the outer phase either by mechanical stirring or using a high shear homogenizer;
d. transferring the emulsion into a quench media having a temperature set at 5°C and thermostatically controlled;

e. separating the resulting hardened microparticles and, optionally washing of the microparticles, and
f. drying the microparticles in a single drying step with no further washing and/or drying step."

Independent claim 2 differs from the process of claim 1 in that steps a. and d. are characterised as follows:
"a. preparing an inner oil phase having a viscosity of 10-1000cP by dissolving PLGA polymer and Risperidone in an organic solvent which is dichloromethane, wherein the polymer concentration in the inner oil phase is in the range of 5-40% w/w;" and
"d. transferring the emulsion into a quench media having a temperature set in the range of 30-40°C and thermostatically controlled;"

Independent claim 3 differs from the process of claim 1 in that steps a. and b. are characterised as follows:
"a. preparing an inner oil phase having a viscosity of 10-1000cP by dissolving PLGA polymer and Risperidone in an organic solvent which is dichloromethane, wherein the polymer concentration in the inner oil phase is in the range of 5-40% w/w;" and
"b. [...], wherein the amount of organic solvent is added in an amount 2-10 times above the saturation point;"

X. The appellant advised the board that it would not be attending the scheduled oral proceedings, and requested that a decision be taken on the basis of the written submissions.

XI. The board cancelled the oral proceedings.

XII. The appellant's arguments, where relevant to the decision, may be summarised as follows:

(a) Documents D10 to D12 had been submitted in response to the opposition division's decision in order to support the assertion that the claimed subject-matter would not work over the entire range covered by the claims. D10 and D11 reflected common general knowledge in the field concerned.

(b) With regard to sufficiency of disclosure, the patent did not disclose how to select suitable solvents or solvent combinations for producing particles resulting in a sigmoidal release profile under the process conditions of the claims. This meant having to undertake a research programme. When using dichloromethane as a solvent in D12, a nitrogen flush was required in order to achieve sufficient solvent removal to form solid microparticles. This step was essential to form solid microspheres, but was not disclosed in example 3 of the patent. Furthermore, none of the experiments described in D12 using dichloromethane resulted in particles exhibiting a sigmoidal release profile of Risperidone.

What was more, the patent did not make it plausible that a PLGA polymer concentration of up to 40% would bring about the desired technical effect. It was extremely doubtful that a process having for example a high polymer concentration, a high quench temperature and a high degree of pre-saturation at the upper end of the ranges defined by claim 2 could achieve microspheres having a sigmoidal release profile.

In addition, the drying step markedly influenced the properties of the microparticles obtained,

including the drug release profile and the residual solvent content. There was no guidance in the patent as to how the single drying step should be modified when other process parameters were varied. However, if the drying conditions were not effective, more than one drying step might be required to achieve the required release profile. D11 and D12 showed that drying time and conditions had a bearing on drug distribution in the particles formed and on the release profile.

It also followed from paragraph [0042] of the patent that embodiments encompassed by claim 2 as granted relating to oversaturated outer phases resulted in high early release and almost-linear release profiles.

(c) Example 2 of D1 represented an equally valid starting point to example 6 for assessing inventive step. D1 did not teach away from using a single drying step. The purpose of the additional washing and drying step was merely to further reduce the level of residual solvent, which was a greater problem when employing an ethyl acetate/benzyl alcohol solvent mixture, since it was more difficult to remove than dichloromethane. Hence, a skilled person would be aware that fewer washing steps might be required when using dichloromethane. As also taught in D1, the amount of residual solvent had an impact on controlling the release profile of the microspheres formed.

The mere optimisation of the process parameters of claims 1 to 3 (i.e. polymer concentration, quench temperature and degree of saturation) did not confer inventive merit. A skilled person would be

familiar with the impact of the process parameters for the microsphere preparation on drug release profile at the priority date of the patent in suit. Moreover, a skilled person would be unable to know whether they were working within or outside the scope of the claimed invention. This lack of clarity had implications beyond Article 84 EPC. A comparison between the drug release curves for comparative example 2c and example 2d in the patent showed that obtaining a sigmoidal release profile was not uniquely linked to the claimed combination of process parameters. A skilled person would be at a loss as to what the invention was, given that combinations other than those claimed did not fail (to provide a sigmoidal release profile).

What was more, the sigmoidal release characteristics of the microparticles produced according to the claimed process were not a feature of the process itself.

In addition, it followed from the results described in D12 that the choice of solvent and drying conditions influenced the release profile of the microparticles formed, and that not substantially all the claimed processes covered by claims 1 to 3 (as granted) exhibited the technical effect of producing microspheres having a sigmoidal release profile. As regards claims 2 and 3, it had not been demonstrated that by raising the quench media temperature to 30-40°C or the degree of solvent saturation in the outer phase to 2-10 times above saturation point the polymer concentration could be extended to up to 40% w/w. The greater polymer concentration working range in claims 2 and 3 (as granted) as a further parameter gave rise to the

conclusion that an even greater number of embodiments would not exhibit the technical effect sought.

Consequently, the technical effect had to be disregarded in determining the objective technical problem, which was thus to provide a microsphere preparation process having a single drying step and an unspecified release profile of the microspheres.

XIII. The respondent's arguments, where relevant to the decision, may be summarised as follows:

(a) Documents D9 to D12 should not be admitted into the appeal proceedings as they had been late-filed.

(b) In respect of sufficiency of disclosure, the appellant had failed to provide convincing evidence that there would be an undue burden on the skilled person aiming at reducing the claimed subject-matter into practice. D12 could not support insufficiency of disclosure since the processes applied therein did not fall within the scope of the claims (of the former main request).

Finally, a distinction between the terms "saturated" and "oversaturated" had been made in paragraph [0042] of the patent, and the expression "sufficient to saturate" in claim 2 did not include "oversaturation".

(c) In view of example 2 of D1, the objective technical problem had to be defined as how to modify D1 in order to obtain an initial lag phase and therefore a sigmoidal release profile. D1 taught using a near-complete intermediate drying step in order to

provide a sigmoidal release profile for Risperidone. Hence, nothing in D1 would incite the skilled person to keep the single drying step of example 2 and to consider instead modifying some other process features in that example.

As was held in the opposition division's decision, generic teachings from the secondary prior art would not incite the person skilled in the art to go against the direct teaching of D1.

For a claim directed towards a method for making a product, the fact that the method results in the product had to be treated as an integral method step.

Moreover, the appellant had failed to provide any evidence supporting the assertion that the technical effect (sigmoidal release profile) was not obtained over the claimed scope. The data provided in D12 only related to the subject-matter of claim 1 (as granted) and was flawed. The opposition division was correct in assessing that a technical benefit had been achieved over the entire ranges claimed and that the claimed subject-matter involved an inventive step.

XIV. Requests

The appellant (opponent) requests that the decision under appeal be set aside and that the patent be revoked.

The respondent (patent proprietor) requests that the patent be maintained in amended form based on the new sole request (claims of the former auxiliary

request), the amended description filed together with said claim request and Figures 1 to 4 of the patent as granted.

Reasons for the Decision

1. Admissibility of documents D9 to D12

1.1 The respondent requests that the opposition division's decision to introduce document D9 into the proceedings be reversed ("deemed inadmissible") and that likewise documents D10 to D12 not be admitted into the proceedings.

It is established case law that a board of appeal should only overrule the way in which a department of first instance has exercised its discretion when deciding on a particular case if it concludes that the department has done so according to the wrong principles, or without taking into account the right principles, or in an unreasonable way, and has thus exceeded the proper limits of its discretion (Case Law Book, 9th edition, chapter IV.C.4.5.2; T 640/91, OJ 1994, 918; G 7/93, OJ 1994, 775; see also Case Law chapter V.A.3.5.). It is not the function of a board of appeal to review all the facts and circumstances of the case as if it were in the place of the department of first instance in order to decide whether or not it would have exercised such discretion in the same way (T 75/11; see, however, T 544/12, where the opposition division did not give sufficient reasons for its decision). The board considers that the opposition division, after having heard the parties in the matter, has applied the correct criteria in a reasonable way

and has given the reasons for this decision in writing. There is thus no reason to reverse the relevant decision. Therefore, D9 forms part of the appeal proceedings.

1.2 With regard to document D10, the board takes the view that it is not necessary for assessing the case. As stated in the impugned decision, a skilled person would choose solvents that allow for saturation of the continuous phase. Solvents or solvent systems which are completely soluble in the continuous phase would be disregarded by a skilled person wishing to carry out the subject-matter of claims 1 to 3 of the former main request on which the impugned decision is based. D10 is thus not *prima facie* relevant to the discussion of sufficiency of disclosure and does not address contentious issues which would arise from the impugned decision; the unsuitability of such solvents was not called into question by the opposition division. It is plausible that an entirely water-soluble solvent cannot saturate or oversaturate an aqueous phase. Hence it is not clear to the board how D10 could contribute to a better understanding of the art in relation to the reasoning provided in the opposition division's decision (see paragraph bridging pages 5/6 of the decision). It should also be noted that D10 is directed to a different drug than that specified in claims 1 to 3 of the request on file. What is more, in the sole request on file, the organic solvent is limited to dichloromethane in the inner oil phase and the outer aqueous phase.

Consequently, the board does not admit document D10 into the appeal proceedings (Article 12(4) and (6) RPBA 2020).

1.3 Document D11, however, addresses the opposition division's conclusion that it was plausible that the conditions imposed by claims 2 and 3 as granted might lead to greater flexibility in the choice of polymer concentration (see page 6, second paragraph, lines 4 to 10 of the impugned decision). Furthermore, the filing of D11 is plausibly occasioned by the opposition division's assessment that the drying step in the patent in suit had nothing special or inventive about it. The appellant cited the paragraph bridging the left-hand and right-hand columns on page 9 and figure 6 as relevant passages of D11. In this text section, the influence of the drying conditions on drug diffusion/ migration in microparticles is explained. Hence, this passage of D11 is *prima facie* relevant to the question of sufficiency of disclosure and deals with issues raised previously. Consequently, the board admits document D11 into the appeal proceedings (Article 12(4) and (6) RPBA 2020).

1.4 Regarding D12, the board notes that, in the opposition proceedings, the appellant relied in particular on document D3 to support its line of argument that the subject-matter of claims 1 to 3 as granted could not be carried out without imposing an undue burden on a skilled practitioner wishing to do so. In its grounds of appeal, the appellant referred to the corresponding conclusions of the opposition division on page 6 of its decision regarding the choice of suitable solvents and drying conditions.

The board notes that the opposition division had already stated in its preliminary opinion that the evidentiary burden in respect of the choice of solvents in relation to sufficiency of disclosure had not been met by the opponent. The opponent could thus have

reacted to this criticism by filing pertinent experimental data to support its corresponding objections at that stage.

However, the opposition division's conclusion in its decision that the drying conditions in the claimed processes were trivial justifies the filing of the additional experiments described in D12.

The data presented in D12 address the core of the objections raised by the appellant in the first-instance proceedings, i.e. the impact of the solvent and drying conditions on the question of sufficiency of disclosure, and do not appear to give rise to new issues. The filing of D12 can thus be considered as a legitimate and appropriate reaction to the impugned decision.

Despite the fact that the experiments in D12 were carried out using a static mixer, the document shows that the drying conditions of the microparticles have an impact on particle morphology. D12 is thus also *prima facie* relevant to the outcome of the case.

The board therefore admits document D12 into the appeal proceedings (Article 12(4) and (6) RPBA 2020).

2. Amendments

The appellant has not raised objections under Article 123(2) EPC in its grounds of appeal over the respondent's former, withdrawn, main request (corresponding to the first auxiliary request held allowable by the opposition division). The only additional limitation, i.e. restricting the solvent in claims 1 to 3 to dichloromethane, finds its basis on

e.g. page 10, lines 27 to 28 of the description as originally filed. The board sees no contravention of the requirement of Article 123(2) EPC by the claimed subject-matter of the sole request.

3. Sufficiency of disclosure

3.1 Solvent selection

The board observes that the examples provided in D12 are not representative of the examples described in the patent. *Inter alia*, a nitrogen gas flush was used in D12 to drive off the evaporating solvent dichloromethane, and a static mixer instead of an in-line homogeniser was used in the in-line mixing device. Furthermore, different pump speeds were used in the emulsification step, and the stirring speed applied in the quench vessel and the scale of the experiment differed from the examples of the patent.

Therefore, while the experiments of D12 support the serious doubts substantiated by D3 with respect to choosing an appropriate organic solvent or solvent systems in granted claims 1 to 3, they cannot call into doubt the reproducibility of the examples of the impugned patent using only dichloromethane as an organic solvent. The examples of the patent describe the preparation of PLGA microparticles having the sigmoidal release profile sought.

3.2 Polymer concentration ranges in claims 2 and 3

3.2.1 Firstly, the board observes that claims 2 and 3 contain (apart from the viscosity of the inner oil phase) different distinguishing features vis-à-vis claim 1, namely either i) oversaturation of the organic solvent

contained in the aqueous phase of step b. in claim 3 or ii) quench media having a temperature set in the range of 30-40°C in claim 2. Both measures may plausibly impinge on the morphology of the microspheres formed.

3.2.2 As to i), this impact can plausibly be attributed to the suppression of too-fast microsphere solidification ascribable to quick solvent extraction (see scenarios a to c on page 7 of D11) due to the oversaturation of the aqueous phase with organic solvent. Such oversaturation could potentially compensate for the accelerated hardening at higher polymer concentrations. Such compensation would mean slowing down solvent extraction from the microparticles, with solvent acting as a plasticiser.

3.2.3 As to ii), this measure would effect the annealing/tempering, of the microparticles being formed, in the quench medium at temperatures exceeding the glass transition temperature of the matrix resin (still plasticised by residual solvent), i.e. at a temperature of 30°C to 40°C. Such annealing/tempering of PLGA above its glass transition temperature could reduce the porosity of the microparticles formed (see e.g. abstract of D9). This is reflected in paragraph [0001] of the patent, where it is stated that the release profile can be controlled by adjusting the degree of saturation of the outer phase/water phase with the organic solvent used in the inner phase and the temperature at the quenching step.

3.2.4 Secondly, the comparison of the Risperidone release rate profiles of example 2a in figure 3 and of example 3 in figure 4 demonstrates that example 2a also already comes close to a sigmoidal release rate profile.

3.2.5 As regards the exact meaning of the term "sigmoidal", the board concurs with the opposition division's finding that the definition of the term in the patent is ambiguous as to its exact limits. However, claim 7 defines this term by an initial lag phase, a steep intermediate release phase and a flat final release phase. This definition is mirrored in paragraph [0031] of the patent. Moreover, as found in the decision of the opposition division, the term "sigmoidal release profile" had an established meaning in the art of delayed-release drug-loaded particles at the priority date of the patent in suit.

Hence, the board concurs with the opposition division's conclusion that a skilled person could establish whether or not a given prepared microparticle population exhibits a sigmoidal release profile (see third paragraph on page 5 of the impugned decision). Any remaining ambiguity as to the exact scope of claims 1 to 3 would have to be subsumed under the provisions of Article 84 EPC, which are not open to review in opposition (appeal) proceedings for unamended features in the light of the principles established in decision G 3/14.

3.2.6 The appellant argued that the feature "wherein the amount of organic solvent added in the outer phase is sufficient to saturate the outer phase" in step b. of claim 2 covered both saturated and oversaturated outer phases. The comparison between example 1a and example 1b made by the appellant appears to be based on the assumption that claim 2 encompasses embodiments of oversaturation of the aqueous phase with organic solvent. Such an interpretation of claim 2 is, however, ruled out by the board. Giving the expressions "sufficient to saturate" and "amount 2-10 times above

the saturation point" (as used in claim 3) their ordinary meaning, a skilled person would rule out interpretations of claim 2 that include oversaturation. This is also reflected in the patent, where a distinction is made between saturated and oversaturated scenarios in paragraph [0037] and the examples. Embodiments constructed in the last three paragraphs of point 3.1.2 of the grounds of appeal, including high polymer concentration, high quench temperature and a high degree of pre-saturation, do not fall within the scope of claim 2 (or claim 3), in line with the explanations provided in paragraph [0042] of the patent, to which the appellant referred in its grounds of appeal under item 3.1.4.

3.2.7 Consequently, the board notes that the appellant has not put forward plausible reasons or even evidence which would undermine the assumption that, even when using higher concentrations of matrix polymers, the desired sigmoidal distribution profile can be achieved without undue burden when reducing such variants of claims 2 and 3 to practice.

3.3 Drying conditions

Likewise, the board sees no reason to assume that, departing from the examples of the patent, a skilled person would be faced with an undue burden in having to select suitable drying conditions, since the claims of the sole request are limited to dichloromethane as a solvent to be employed in steps a. and b. The examples, also being limited to the use of dichloromethane, can thus serve as a reasonable starting point for implementing further variants of claims 1 to 3, varying a single parameter at a time.

4. Inventive step

4.1 Closest prior art

4.1.1 There is apparently no dispute between the parties that document D1 represents the closest prior art for the subject-matter of claims 1 to 3. The board also holds that document D1 is a suitable starting point for assessing inventive step when applying the problem-solution approach.

4.1.2 The appellant starts from example 2 of D1 and specifically chooses the runs prepared without an intermediate drying step as a starting point for assessing inventive merit (see samples 813 and 826 of example 2).

4.1.3 The technical problem as formulated in the patent is to provide a simpler process for the preparation of Risperidone-containing PLGA microspheres exhibiting a sigmoidal release profile (see paragraphs [0017] and [0026] of the patent). In this light, the board concurs with the appellant that the runs of example 2 lacking an intermediate drying step (samples 813 and 826) are a suitable starting point.

4.2 Distinguishing features

4.2.1 The appellant argues, contrary to its own submissions in opposition proceedings (in respect of the same feature in claim 1 as granted, see page 4, first full paragraph of the minutes), that a sigmoidal release profile was not a technical feature of claims 1 to 3 (as granted).

4.2.2 The board does not share this view. Claims 1 to 3 categorically require the process to result in the preparation of a *specific product*, i.e. microspheres having a *sigmoidal release profile* of Risperidone (a functional feature), as argued by the respondent. Hence, the present case differs from the scenario underlying decision T 304/08 cited by the appellant. In that decision, it was held by the entrusted board that all the structural and process features of the claimed method (a method for reducing malodour associated with a disposable absorbent product intended for the absorption of body fluids) were disclosed in the prior art. The fact that a sought technical effect may inevitably be obtained when carrying out specific method steps called for in a claim does not mean that the required effect does not form part of the features of the claim. It would in this case simply be inherently satisfied by the method steps of the claim bringing about the effect claimed.

4.2.3 Should the view indeed be taken that a sigmoidal release profile is not a technical feature of claims 1 to 3 (a position which is not endorsed by the board), the appellant's objections in relation to sufficiency of disclosure would be pointless, as the remaining technical features of claims 1 to 3 could most likely be carried out without undue experimentation.

4.2.4 As can be derived from the teaching of D1, the microcapsules obtained in example 2 without an intermediate drying step show a linear release profile, lacking an initial lag phase. D1 teaches that "if the degree of intermediate drying performed is no intermediate drying, then the resulting microparticles have an initial burst and a substantially linear release profile". However, an initial burst and a

linear release profile would not be associated with a "sigmoidal release profile" (see above). The board concurs with the opposition division that, *inter alia*, "having a sigmoidal release profile of Risperidone" is one of the differences between the subject-matter of claims 1 to 3 and the microparticles of example 2 prepared without an intermediate drying step.

4.2.5 Consequently, starting in example 2 from the runs accomplished without an intermediate drying step, the following distinguishing features can be identified:

(a) Claim 1: i) dichloromethane as a solvent, ii) sigmoidal release profile, iii) PLGA concentration in the inner oil phase 5-8% w/w, iv) saturation of the outer phase with the same solvent (system) as employed in the inner phase, v) emulsification accomplished by mechanical stirring or using a high shear homogeniser, vi) thermostatic control of the temperature of the quench media (at 5°C),

(b) Claim 2: i), ii), iv), v) as for claim 1, iii) a viscosity of the oil phase in step a. of 10-1000 cP, vi) thermostatic control of the temperature of the quench media, set at 30°C to 40°C, and

(c) Claim 3: i), ii), v), vi) as for claim 1, iii) a viscosity of the oil phase in step a. of 10-1000 cP, iv) oversaturation of the outer phase with the same solvent (system) as employed in the inner phase, added in an amount 2-10 times above the saturation point.

4.3 Problem to be solved

4.3.1 The objective technical problem underlying the subject-matter of claims 1 to 3 in view of example 2 of D1 could be formulated as being to provide PLGA microparticles having an alternative, i.e. a sigmoidal, release profile of Risperidone.

4.3.2 There is no information at hand that this problem would not have been solved across the full breadth of claims 1 to 3, involving the respective distinguishing features mentioned above. These include, *inter alia*, a limitation of the solvent to dichloromethane in steps a. and b. of the process. The experiments of D12 differ in various aspects from the experiments conducted in the patent and the subject-matter of claim 1. The scenario depicted by the appellant described above that claim 2 encompassed embodiments including high polymer concentration, high quench temperature and a high degree of oversaturation of the outer aqueous phase with organic solvent (see point 3.2.6) does not fall within the scope of claim 2. Thus, the technical problem posed does not need to be reformulated.

4.4 Obviousness

4.4.1 D1 does not disclose the use of dichloromethane as a solvent for the preparation of PLGA microparticles. Assuming that a skilled person would have considered substituting the solvent system employed in example 2 of D1 with dichloromethane, they would have departed from variants of example 2 lacking an intermediate drying step. This modification of the process would have included an intermediate drying step to obtain the required sigmoidal release profile. D1 teaches unequivocally that such an intermediate drying step is

essential for obtaining a sigmoidal release profile of Risperidone.

4.4.2 The appellant argued that a skilled person would be aware that an intermediate drying step would not be necessary if ethyl acetate/benzyl alcohol were replaced by the (more volatile) solvent dichloromethane.

4.4.3 The board, however, does not see that D1 teaches or suggests that the intermediate drying step could be omitted if solvents with lower boiling points than e.g. benzyl alcohol and/or ethyl acetate were used. The text passage on page 6, lines 6 to 8 of D1 mentions that the duration of action (not any specific drug distribution profile such as a sigmoidal drug release profile) can, *inter alia,* be controlled by manipulating the concentration of residual solvent remaining in the microparticle.

Moreover, whilst page 14, lines 7 to 8 of D1 suggests that, after an intermediate drying step 130, the microparticles are washed to remove or extract residual solvent, it follows from the examples that D1 focuses on the residual water/moisture content of the microspheres after intermediate drying in this context. This residual moisture content after this step should be lower than 0.2% (see example 3 and e.g. claim 4; see corresponding indications for the final drying step on page 14, lines 9 to 11).

Hence, there is no support for the argument that D1 would link the necessity of an intermediate drying step, categorically required in D1 for obtaining a sigmoidal distribution profile, to the degree of volatility of the organic solvent, and that a skilled person would infer from D1 that an intermediate drying

step could thus be omitted in D1 when using more-volatile organic solvents.

4.4.4 Therefore, starting from embodiments of D1 which do not include an intermediate drying step (see the corresponding samples in example 2), a skilled person would not realistically be prompted to depart from the general teaching of D1 by omitting the intermediate drying step and to adduce secondary literature for compensating for this omitted step.

4.4.5 Moreover, the presence of six technical features that distinguish the subject-matter of claims 1 to 3 from the samples of example 2 which are conducted without an intermediate drying step is indicative of non-obviousness and hence of an inventive step. This consideration holds even more true since a skilled person departing from those samples of example 2 of D1 would have been faced with a high probability of failure, meaning arriving at non-working embodiments.

4.5 Consequently, the subject-matter of independent claims 1 to 3 is not obvious to a skilled person and therefore involves an inventive step (Article 56 EPC). This finding applies *mutatis mutandis* to the dependent claims 4 to 7, comprising the feature combinations of claims 1, 2 or 3, held to involve an inventive step.

5. Adaptation of the description

The appellant did not put forward any objections regarding the amendments undertaken in the adapted description, and requested a decision based on the written submissions after the filing of the adapted description by the proprietor. The board does not have any objections either and takes the view that the

claims of the sole request are supported by the amended description (Article 84 EPC).

Order

For these reasons it is decided that:

1. The appealed decision is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent as amended in the following version:

Description:
Paragraphs [0001] to [0021] and [0023] to [0057] filed by letter of 23 March 2022

Claims:
No. 1 to 7 in accordance with the auxiliary request filed with the reply to the grounds of appeal

Drawings:
Sheets 1 to 3 of the patent specification.

The Registrar: The Chairman:

S. Sánchez Chiquero A. Haderlein

Decision electronically authenticated