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Datasheet for the decision of 19 July 2021

Case Number: T 2783/18 - 3.3.07

Application Number: 15000500.7

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Language of the proceedings: EN

Title of invention:
Sustained delivery formulations of risperidone compounds

Applicant:
Indivior UK Limited

Headword:
Risperidone sustained delivery/INDIVIOR

Relevant legal provisions:
EPC Art. 76(1), 123(2)
RPBA 2020 Art. 13(2)

Keyword:
Amendments - intermediate generalisation

Decisions cited:
T 1067/97, T 0025/03, T 0714/00

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Case Number: T 2783/18 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 19 July 2021

Appellant: (Applicant)	Indivior UK Limited The Chapleo Building Henry Boot Way Priory Park Hull HU4 7DY (GB)
Representative:	HGF 1 City Walk Leeds LS11 9DX (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 10 July 2018 refusing European patent application No. 15000500.7 pursuant to Article 97(2) EPC.**

Composition of the Board:

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

Summary of Facts and Submissions

I. The appeal was filed by the applicant (hereinafter: "appellant") against the decision of the examining division to refuse the European patent application EP15000500.7. This application had been filed as divisional application from the earlier application EP08725543.6 originally published as international application WO2008/153611 (hereinafter: "parent application").

II. The decision was based on a main request filed on 26 April 2018 and auxiliary requests 1 and 2 both filed during the oral proceedings held before the examining division on 26 June 2018.

Claim 1 of the main request related to:

"A flowable injectable composition comprising:
15 weight % risperidone in;

(i) 45 weight % of a biodegradable thermoplastic polymer that is at least substantially insoluble in body fluid, wherein the polymer is a 80/20 poly (Dl lactide-co-glycolide) with a terminal carboxy group; and
(ii) 55 weight % of N-methyl-2-pyrrolidone;

wherein the biodegradable thermoplastic polymer has a molecular weight of 10,000 Daltons to 45,000 Daltons, optionally 15,000 Daltons to 40,000 Daltons;

wherein the composition has a volume from 0.3 ml to 1.0 ml."

In the decision under appeal the examining division arrived at the following conclusions:

(a) The amended definition of the flowable injectable composition in claim 1 of the main request included the features of the relative amounts of risperidone in combination with the relative amounts of a 80/20 poly (Dl lactide-co-glycolide) with a terminal carboxy group (PLGH) and the N-methylpyrrolidone (NMP) as described for tested compositions originally disclosed in examples 4 and 5. The amended claim involved an intermediate generalisation with respect to the state of purification and the molecular weight of the polymer described for the composition of examples 4 and 5 which did not meet the requirements of Articles 76(1) and 123(2) EPC.

(b) Claim 1 of auxiliary request 1 involved the same objectionable intermediate generalisation as claim 1 of the main request. Moreover, contrary to the requirements of Article 84 EPC the formulation for administration about once per month was imprecise and defined the invention in terms of the problem to be solved.

(c) Auxiliary request 2 was not admitted in the proceedings under Rule 116(2) and Rule 137(3) EPC, because it did not address all the objections held against the preceding requests.

III. With the statement setting out the grounds of appeal the appellant submitted a main request as well as auxiliary requests 1-4.

The claims of the main request are identical to the claims of the main request underlying the decision under appeal.

Claim 1 of auxiliary request 1 corresponds to claim 1 of the main request except for the replacement of the feature defining the volumes by the feature: "wherein the flowable composition is formulated for administration once per month".

Claim 1 of auxiliary request 2 corresponds to claim 1 of the main request except for the additional definition "and where the polymer has been purified by solvent/non-solvent precipitation method".

Claim 1 of auxiliary request 3 corresponds to claim 1 of auxiliary request 1, in which the definition of the range for the molecular weight is omitted and in which the following feature is added: "and wherein the composition provides a steady state plasma concentration (Css) of risperidone in plasma from day 3 until day 42 following subcutaneous injection of the composition in a dose of 60, 90 or 120 mg risperidone".

Claim 1 of auxiliary request 4 corresponds to claim 1 of auxiliary request 3 in which the definition of the range for the molecular weight is reintroduced.

IV. With the summons of 29 July 2020 the Board invited the appellant to attend oral proceedings. A communication pursuant to Article 15(1) RPBA was issued on 12 January 2021, in which the Board expressed its concerns that the main request and auxiliary requests 1-4 did not comply with the requirements of Articles 76(1) and 123(2) EPC.

V. With the appellant's consent oral proceedings were held on 19 July 2021 by means of a video conference.

During the oral proceedings the appellant filed a further auxiliary request. Claim 1 of this auxiliary request 5 corresponds to claim 1 of the main request, except that the definition of the ranges for the molecular weight and the volume are replaced by the following definitions: "...wherein the biodegradable thermoplastic polymer has a molecular weight of 42,000 Daltons; wherein the polymer has been purified by solvent/non-solvent precipitation method; and wherein the risperidone is present in an amount of 60 mg, 90 mg or 120 mg."

Claim 3 of auxiliary request 5 corresponds to the wording of claim 3 of the main request defining such composition "for use in the treatment of delusional psychosis, schizophrenia, bipolar disorder, psychotic depression, obsessive-compulsion disorder, Tourette syndrome, autistic spectrum disorders, or any combination thereof."

At the end of the proceedings the Board announced its decision.

VI. The appellant's arguments can be summarized as follows:

The definition of the composition in claim 1 of the main request was derived from examples 4 and 5 of the parent application, which described experiments using an injectable composition comprising 15 weight % risperidone in 45 weight % of 80/20 PLGH and 55 weight % of NMP. The experiments concerned compositions intended for once per month administration in which the effect of minor variations in the polymer

were tested. The results of example 4 reported in figure 18 revealed the 80/20 PLGH as advantageous and the use of PLGH with this preferred monomer ratio was further explored in example 5.

The parent application described on page 145 the amount of 15 weight % risperidone with 45 weight % of PLGH as generally advantageous and mentioned on page 6 line 7 volumes of 0.3 to 1.0 ml as generally preferred, which supported together with the advantageous monomer ratio the definition of the combination of features in claim 1 of the main request.

It was not required to include in claim 1 of the main request the purified state and the specific molecular weight of the 80/20 PLGH or the particular volumes of the compositions of examples 4 and 5, because these features were not inextricably linked to the relative amounts of the components and the 80/20 monomer ratio of the composition of examples 4 and 5.

The parent application described a one-month sustained release system without any indication that the purified state of the 80/20 PLGHp or the volumes used in examples 4 and 5 were essential and the use of purified PLGHp was only specifically mentioned for formulating a three-month sustained delivery system (see page 28). As confirmed by results relating to experiments with 65/35 PLGH reported on page 119 any effect of the state of purification of the PLGH as mentioned on pages 23-24 did not affect the one-month sustained release. Furthermore, the passage on page 28 relating to the one-month sustained release formulations indicated that the molecular weight of the polymer could range from 10,000 to 45,000 Dalton. This implied that the specific molecular weight of 42.000 Dalton of the polymer in the

relevant composition of examples 4 and 5 was also not essential.

Claim 1 of auxiliary request 1 included the feature of formulation for once per month administration to explicitly align the claims with the embodiment of examples 4 and 5 and page 28 of the description.

Claim 1 of auxiliary request 2 included the feature of the purified state of the polymer to specifically address the finding in the decision under appeal regarding the generalisation with respect to this feature in claim 1 of the main request.

The independent claims of auxiliary requests 3 and 4 included the feature of formulation for once per month administration and the definition of steady state plasma concentrations following subcutaneous injection of a defined dose to further explicitly align the claims with the embodiment of examples 4 and 5 and page 28 of the description.

Claim 1 of auxiliary request 5 explicitly included all the features of the relevant compositions of examples 4 and 5. No instructions from the appellant had allowed the representative to file this request earlier. The request should be admissible as a predictable response which was evidently suitable to overcome any maintained objection against the preceding requests.

VII. The appellant requested that the decision under appeal be set aside and that the application be remitted to the first instance for grant or further prosecution on the basis of the claims of the main request or auxiliary request 1, 2, 3 or 4, all filed with the

statement of the grounds of appeal, or on the basis of auxiliary request 5 filed during the oral proceedings.

Reasons for the Decision

Main request

1. Articles 76(1) and 123(2) EPC

1.1 The description of the present divisional application as filed is identical to the description of the parent application as filed except for the presentation of the list of embodiments on pages 251-256, which correspond in wording to the original claims of the parent application. The references in the reasons for this decision to passages and examples in the original disclosure apply therefore equally to the parent application in the context of Article 76(1) EPC and the present divisional application in the context of Article 123(2) EPC.

1.2 Claim 1 of the main request defines a flowable injectable composition comprising 15 weight % risperidone in 45 weight % 80/20 PLGH and 55 weight % NMP, wherein the PGLH has a molecular weight of 10,000-45,000 Dalton and the composition has a volume of 0.3 ml to 1.0 ml.

The original disclosure relates to a flowable injectable composition including a biodegradable thermoplastic polymer, a biocompatible, polar, aprotic liquid and risperidone (see for instance page 3, lines 14-16). The polymer is preferably 50/50, 75/25 or 85/15 PLGH (see page 4, lines 7-13) and present in 30-60

weight % of the composition (see page 4, lines 30-34) having preferably an average molecular weight of 10,000 to 45,000 Dalton (see page 4, line 34 - page 5, line 3). The solvent is preferably NMP pyrrolidone and preferably present in 30 to 70 weight % of the composition (see page 5, lines 24-27). The risperidone is preferably present in 1-30 weight % of the composition (see page 5, lines 31-33). The composition has preferably a volume of 0.30-1,0 mL (see page 6, lines 6-7).

On page 28 the original disclosure specifically addresses the embodiment in which the compositions are used for a one-month sustained release delivery system for risperidone, wherein the polymer can be 50/50, 55/45, 75/25, 85/15, 90/10, or 95/5 PLGH, preferably 50/50 PLGH, which can be present in about 20 to about 70 weight % of the composition and have an average molecular weight of about 10,000 Dalton to about 45,000 Dalton, preferably about 15,000 Daltons to about 40,000 Dalton.

As acknowledged by the appellant the original disclosure mentions the particular feature-combination involving 15 weight % risperidone with 45 weight % of 80/20 PGLH and 55 weight % of NMP only in the context of examples 4 and 5, in which the 80/20 PLGH used is in a purified state (PLGHp) and has a molecular weight of 42,000 Dalton and in which the compositions have volumes of 0.4, 0.6 and 0.8 ml.

Claim 1 of the main request thus involves an intermediate generalisation of the compositions of examples 4 and 5 with respect to the purified status and molecular weight of the comprised polymer as well as the volumes of the compositions.

1.3 According to established jurisprudence of the Boards of Appeal of the EPO it is normally not admissible under Articles 76(1) and 123(2) to extract isolated features from a set of features which have originally only been disclosed in combination. According to T 1067/97 (point 2.1.3) and T 25/03 (point 3.3) such kind of amendment , would only be justified in the absence of any clearly recognisable functional or structural relationship among the features of the combination. In the wording of T 714/00 (points 3.3-3.4) extracting an isolated feature from an originally disclosed combination and using it for delimiting claimed subject-matter can only be allowable under the concept of Article 123(2) EPC if that feature is not inextricably linked with further features of that combination and thus not so closely associated with the other features of the combination as to determine the properties of this embodiment as a whole to a significant degree.

1.4 In the present case the original disclosure explains in the introductory section to the examples that the ATRIGEL(R)/Risperidone formulations used in the examples concern compositions of risperidone with poly(lactide-co-glycolide) (PLG), which may carry a carboxylic acid end group (PLGH) and which may be purified (PLGHp), in N-methyl-2-pyrrolidone(NMP) (see page 44, line 29 to page 45, line 1; see also list of abbreviations pages 48-49). The original disclosure further describes the PLGHp material as PLG low-burst copolymer, which is obtainable by solvent precipitation starting from non-hydrolysed PLG (see page 23, line 23 to page 24, line 9).

On the basis of the results from experiments in rats reported in example 1 the original disclosure concludes

that a 15% risperidone loading in the formulation in total and 45% polymer loadings in the ATRIGEL(R) delivery system seemed an optimum formulation choice (see page 145).

Example 3 (starting on page 169) presents a study of pharmacokinetics and anti-emetic effect in dogs involving a Risperidone /ATRIGEL(R) formulation of 15 weight % risperidone in 45 weight % of 65/35 PLGHp (37K)/ NMP for subcutaneous injection of 30 mg or 60 mg risperidone (see "Group III" on page 174 and "Group IV" on page 176).

Example 4 (starting on page 181) relates to a follow up study with respect to example 3. In order to verify if slight modifications could reduce initial release and increase duration of release, various different Risperidone /ATRIGEL(R) formulations were used in this dog study, including a formulation of 15 weight % risperidone in 45 weight % of 80/20 PLGHp (42K) / NMP in a composition of 0.4 ml (60 mg) for subcutaneous injection (see Group II: page 182, lines 4-10; table 36, page 185; table 37, page 190; table 38, page 191; see also the reference to Figure 18 on page 182, lines 30-31).

Example 5 (starting on page 191) describes a further study of pharmacokinetics and pharmacodynamics in dogs. The formulation of 15 weight % risperidone in 45 wt of 80/20 PLGHp (42K) / NMP administered by subcutaneous injection in volumes of 0.4, 0.6 or 0.8 ml (60, 90, 120 mg) was compared to a composition for oral administration in order to verify dosing in humans (see Groups IV, V and VI: page 191, line 10 to page 192, line 2; table 39, pages 202/206/209; table 37, page 190; table 38, page 191).

1.5 As observed in the decision under appeal (see sections 1.3-1.3.3) the original disclosure presents PLGHp as a distinctive biodegradable polymer material with low-burst qualities (see paragraph bridging pages 23-24 and the table of definitions on page 49) and indicates the relevance of such low-burst qualities in risperidone formulations (see page 5, lines 4-9 and page 19, lines 29-31). As further observed in the decision under appeal (see section 1.4.1) the original disclosure also indicates that the molecular weight inversely affects the rate of risperidone release (see page 25, lines 21-34).

The Board agrees with the decision under appeal that in these passages the original disclosure actually underlines the functional relevance of the purified state of the polymer used as well as its particular molecular weight for the risperidone release, which was the focus of the experiments in examples 4 and 5. Accordingly, the original disclosure itself indicates that the purified state and the molecular weight of the PLGHp used in examples 4 and 5 significantly determined the properties of the described embodiments as a whole. The original disclosure does therefore not provide any appropriate justification for the generalisation of the compositions of examples 4 and 5 with respect to the purified status and molecular weight as defined in claim 1 of the main request.

In addition, the Board considers that the disclosure of formulations with 15 weight % risperidone in 45 wt of 80/20 PLGHp (42K) / NMP having a volume of 0.40, 0.60 and 0.80 ml in examples 4 and 5 does not provide a suitable basis for the general definition of the formulations for injection having a volume of 0.3-1.0

ml as defined in claim 1. The particular volumes disclosed in examples 4 and 5 determine together with the defined relative amount of risperidone the specific dosing of the risperidone (60 mg, 90 mg and 120 mg) in the context of a pharmacokinetic and pharmacodynamic study in dogs. These specific volumes are therefore closely associated with and cannot be abstracted from the relative amounts of risperidone described for the compositions in examples 4 and 5.

In line with the principles as established in the jurisprudence of the Boards of Appeal of the EPO as cited above in section 1.3 the Board therefore concludes that the subject-matter of claim 1 of the main request involves an intermediate generalisation which cannot be directly and unambiguously derived from the original disclosure.

1.6 The Board is not convinced by the appellant's argument that the skilled person would recognize from the comments and the presented results in example 4 (see pages 181-182, see also Figure 18), that a 80/20 monomer ratio in PLGH was disclosed as preferred irrespective of its purified state and its molecular weight. The original disclosure mentions that the purpose of the study of example 4 was to determine if slight modifications could reduce initial release and increase release duration (see page 181, line 19 to page 182 line 4). The slight modifications in the 3 compositions tested in example 4 included the PLGH ratio (75/25, 80/20 and 65/35), the molecular weight (37,000, 42,000 and 19,000) and the form of the PLG (purified PLGHp and PLG-Dod). In view of the explicit reference in the generic part of the original disclosure to the influence of the molecular weight and the purified form on risperidone release (see page 25,

lines 21-25 and pages 23-24, bridging paragraph) the skilled person could not directly and unambiguously derive from the original disclosure the information that the 80/20 ratio of the 80/20 PLGHp (42K) polymer determined the favourable properties reported in examples 4 and 5 independently from the molecular weight and the purified form.

1.7 The Board is further not convinced by the appellant's argument that the original disclosure did not generally require the purified state and the precise molecular weight of the polymer or particular volumes for compositions used in one-month sustained release systems (see page 28) and that experimental results confirmed that the purified state did not affect the sustained release of risperidone over a one month period (see page 119).

The focus of the experiments in examples 4 and 5 was the performance of the compositions in terms of the reduction of the initial risperidone release and the increase of duration of the risperidone release (see pages 181-182, bridging paragraph). According to the explicit teaching in the original disclosure the purified form and the molecular weight of the polymer influence specifically these aspects of the risperidone release (see section 1.5 above). The original disclosure thereby teaches that these features of the compositions of examples 4 and 5 significantly determine, in association with the monomer ratio and the relative amounts of the components, the performance of the compositions of examples 4 and 5 as a whole. This conclusion regarding the functional relevance of the features of the compositions of examples 4 and 5 is not affected by the argument that according to the original disclosure one-month delivery may still be

achieved using PLGH which is not necessarily in the purified state and which has a molecular weight in the range of 15,000 to 45,000 Dalton. In fact, examples 4 and 5 do not describe once per month administration as discussed on page 28 of the original disclosure. Instead these examples relate to studies in dogs and mention a study-duration of 45 and 56 days (see page 182, lines 23-24; see page 192, lines 6-8) with example 4 reporting a minimum efficacy of 29 days (see page 190, lines 18-20) and example 5 reporting steady state plasma levels until day 42 (see page 215, lines 3-6).

1.8 Accordingly, the Board concludes that claim 1 of the main request does not meet the requirements of Articles 76(1) and 123(2) EPC

Auxiliary requests 1-4

2. Auxiliary requests 1, 3 and 4

Claim 1 of auxiliary request 1 differs from claim 1 of the main request in the replacement of the feature defining the volumes by the feature defining that the flowable composition is formulated for administration once per month.

Claim 1 of auxiliary request 3 corresponds to claim 1 of auxiliary request 1 except for the omission of the range for the molecular weight and the addition of the feature that the composition provides a steady state plasma concentration of risperidone over a defined period following subcutaneous injection in a dose of 60, 90 or 120 mg.

Claim 1 of auxiliary request 4 corresponds to claim 1 of auxiliary request 3 in which the definition of the range for the molecular weight is reintroduced.

The independent claims of each of these requests thus define a similar generalisation with respect to the compositions of examples 4 and 5 regarding the purified state of the 80/20 PLGH and its molecular weight as claim 1 of the main request, which the Board considers not directly and unambiguously derivable from the original disclosure for the reasons as set out in section 1 above.

The appellant's argument that the amendments in accordance with auxiliary requests 1, 3 and 4 further align the claims with with the embodiments of examples 4 and 5 and page 28 of the original disclosure does not affect the Board's conclusions concerning this generalisation. As explained in section 1.7 examples 4 and 5 do in the Board's view not describe compositions for once per month administration as discussed on page 28 and thus do not provide any basis for the intended alignment.

The independent claims of auxiliary requests 1, 3 and 4 do therefore not comply with the requirements of Articles 76(1) and 123(2) EPC.

3. Auxiliary request 2

Claim 1 of auxiliary request 2 corresponds to claim 1 of the main request except for the additional definition that the polymer has been purified by solvent/non-solvent precipitation method.

Claim 1 of this request thus defines the same generalisation with respect to the compositions of examples 4 and 5 regarding the molecular weight of the 80/20 PLGH and the volumes as claim 1 of the main request, which the Board considers not directly and unambiguously derivable from the original disclosure for the reasons as set out in section 1 above.

Claim 1 of auxiliary request 2 does therefore not comply with the requirements of Articles 76(1) and 123(2) EPC.

Auxiliary request 5

4. Admission of the request

Auxiliary request 5 was filed during the oral proceedings arranged by the Board. Claim 1 of this request additionally defines with respect to claim 1 of the main request the specific molecular weight of 42,000 Daltons for the polymer, its purified state from solvent/non-solvent precipitation and the risperidone amounts of 60 mg, 90 mg or 120 mg. The wording of claim 3 of this request remained unamended with respect to claim 3 of the main request, which defined the flowable injectable composition for use in the treatment of various specific human disorders, including delusional psychosis.

According to Article 13(2) RPBA (2020)any amendment to a party's appeal case made after after notification of a summons to oral proceedings shall, in principle, not be taken into account, unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

The appellant's representative justified the filing of auxiliary request 5 as late as during the oral proceedings by the absence of relevant instructions from the appellant and argued that auxiliary request 5 introduced predictable amendments which evidently overcame the objection concerning the generalisations with respect to the purified state, the molecular weight and volume of the compositions.

In this context the Board observes that auxiliary request 5, which according to the representative' own argument introduced predictable amendments, was only filed during the oral proceedings after the Board had concluded that the main request and auxiliary requests 1-4 did not comply with the requirements of Articles 76(1) and 123(2) EPC, although this conclusion was in line with the finding in the decision under appeal as well as the concerns already expressed in the preliminary opinion pursuant to Article 15(1) RPBA. The Board further notes that auxiliary request 5 does not *prima facie* comply with the requirements of Articles 76(1) and 123(2) EPC, as it may be questioned whether the utility of the specific compositions in treatment the human disorders as defined in claim 3 of auxiliary request 5 may be directly and unambiguously derived from the original disclosure describing these specific compositions only in the context of a study involving administration to dogs.

In the present case the Board does therefore not recognize any exceptional circumstance justified by cogent reasons for admitting auxiliary request 5 in the representative's submission that no timely instructions from the appellant to file the amendments had been received.

The Board has therefore decided not to admit auxiliary request 5 into the proceedings.

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