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Datasheet for the decision of 14 October 2014

Case Number: T 0205/11 - 3.3.07

Application Number: 02075905.6

Publication Number: 1210942

IPC: A61K9/16, A61K9/50, A61K31/517

Language of the proceedings: EN

Title of invention:
Microparticles

Patent Proprietor:
Alkermes, Inc.
Janssen Pharmaceutica NV

Opponent:
Ratiopharm GmbH

Relevant legal provisions:
EPC Art. 54, 123(2)
RPBA Art. 13

Keyword:
Novelty - implicit disclosure (yes)
Amendments - allowable (no)
Late-filed auxiliary requests - justification for late filing

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Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0205/11 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 14 October 2014

Appellant: (Patent Proprietor 1)	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 (US)
Appellant: (Patent Proprietor 2)	Janssen Pharmaceutica NV Turnhoutseweg 30 2340 Beerse (BE)
Representative:	Chapman, Paul William Kilburn & Strode LLP 20 Red Lion Street London WC1R 4PJ (GB)
Appellant: (Opponent)	Ratiopharm GmbH Graf-Arco-Strasse 3 89079 Ulm (DE)
Representative:	Hollatz, Christian Ter Meer Steinmeister & Partner Patentanwälte Mauerkircherstrasse 45 81679 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 23 December 2010 concerning maintenance of the European Patent No. 1210942 in amended form.**

Composition of the Board:

Chairman J. Riolo
Members: D. Semino
W. Ungler

Summary of Facts and Submissions

I. The appeals by the patent proprietors and by the opponent lie against the decision of the opposition division announced at the oral proceedings on 16 November 2010 concerning maintenance of the European Patent No. 1 210 942 in amended form. The patent as granted included 13 claims, claim 1 reading as follows:

"1. Microparticles of a biodegradable biocompatible polymeric matrix containing an active agent and an organic solvent free from halogenated hydrocarbons, said residual organic solvent being present in said microparticles at 2% or less of the total weight of said microparticles wherein the active agent is selected from the group of risperidone, 9-hydroxy-risperidone, and pharmaceutically acceptable salts thereof."

II. A notice of opposition was filed against the granted patent requesting revocation of the patent in its entirety on the grounds of added subject-matter, insufficiency of disclosure, lack of novelty and lack of inventive step in accordance with Article 100(a), (b) and (c) EPC.

III. During opposition proceedings the following documents *inter alia* were cited:

D1: WO-A-95/13799
D5: J.C. Leroux et al., Eur. J. Pharm. and Biopharm., Volume 41(1), 1995, pages 14 to 18
D8: Declaration by J. Michael Ramstack dated 26 September 2007 (filed by the patent-proprietors with their reply to the notice of opposition)

IV. The decision was based on a set of claims filed with letter of 26 June 2008 as main request and on two sets of claims filed during the oral proceedings before the opposition division on 16 November 2010 as first and second auxiliary requests.

Claim 1 of the main request corresponded to claim 1 as granted with the addition of the feature "wherein said microparticles are prepared by a process comprising contacting said microparticles with an aqueous solvent system comprising water and a water-miscible solvent for said organic solvent" at the end of the claim. Additionally claim 1 of the first auxiliary request included the specification at the end of the product-by-process feature "whereby the content of said organic solvent in said microparticles is reduced to 2% or less of the weight of said microparticles". Claim 1 of the second auxiliary request corresponded to claim 1 of the first auxiliary request with the replacement of the expression "organic solvent" with "organic solvent system", the specification "said organic solvent system being a blend of at least two solvents" and the reformulation of the condition on the organic solvent as a condition on the blend of at least two solvents.

V. The decision of the opposition division can be summarised as follows:

a) Claim 1 according to the main request did not meet the requirements of Article 123(2) EPC, as the added product-by-process feature was always linked to the associated effect (reduction to 2% of the residual organic solvent) in the application as filed.

b) The addition of the effect in claim 1 of the first auxiliary request solved this issue. Claim 1 of the first auxiliary request was not new over D1, as the condition on an organic solvent being present at 2% or less by weight was met in view of the results in D8.

c) Claim 1 of the second auxiliary request met the requirements of Article 123(2) EPC and also of Article 84 EPC, as the repetition of a product characteristic did not introduce a lack of clarity. The product of claim 1 of the second auxiliary request was inventive over D1 as the closest prior art, from which it differed in the lower content of the solvent system, as there was no hint in the prior art to use this measure in order to solve the problem of improving the stability and shelf life of the claimed microparticles. In particular D5 was silent on the relevance of a solvent quantity below 2% and D8 did not form part of the state of the art. As to sufficiency of disclosure, the objections of the opponent were not supported by convincing evidence, so that they had to be rejected.

VI. Both appellants lodged an appeal against that decision, and filed a statement of grounds in due time.

With their statement setting out the grounds of appeal the appellants-patent proprietors filed two sets of claims as main request and auxiliary request.

Claim 1 of the main request corresponded to claim 1 of the first auxiliary request on which the decision was based with the deletion of the word "said" with

reference to the residual organic solvent and had therefore the following wording:

"1. Microparticles of a biodegradable biocompatible polymeric matrix containing an active agent and an organic solvent free from halogenated hydrocarbons, residual organic solvent being present in said microparticles at 2% or less of the total weight of said microparticles wherein the active agent is selected from the group of risperidone, 9-hydroxy-risperidone, and pharmaceutically acceptable salts thereof, wherein said microparticles are prepared by a process comprising contacting said microparticles with an aqueous solvent system comprising water and a water-miscible solvent for said organic solvent, whereby the content of said organic solvent in said microparticles is reduced to 2% or less of the weight of said microparticles."

In claim 1 of the auxiliary request the term "organic solvent" was replaced by "organic solvent system", so that also the limitation on the quantity of the residual organic solvent referred to the "organic solvent system".

VII. In a communication sent in preparation for oral proceedings, the Board reviewed the submissions of the parties and in particular indicated with reference to the main request that "the Board has doubts that the deletion of the term "said" with reference to the residual organic solvent succeeds in expressing a condition on the total amount of solvent, as also the amended wording can be understood as a condition of the (single) organic solved mentioned in claim 1" (point 2.4) with a consequent lack of novelty over D1 (point 5.1). With regard to the requirements of Article 123(2)

EPC it was said that "a reformulation which successfully expresses the condition that the total amount of solvents must be 2% by weight or less would contravene the requirements of Article 123(2) EPC" (point 2.4) in particular with reference to the embodiment in which a blend of ethyl acetate and benzyl alcohol is used as solvent, where "the condition on the residual is given only for benzyl alcohol" (point 2.3).

VIII. With letter dated 12 September 2014 the appellants-patent proprietors filed a further set of claims as second auxiliary request, which corresponded to claim 1 of the main request with the addition in claim 1 of a definition of the organic solvent as "a blend of ethyl acetate and benzyl alcohol" and of a condition on the residual benzyl alcohol, which "is present in a range of from 0.5 to 1.5% by weight".

IX. Oral proceedings were held on 14 October 2014.

After novelty of the main request over document D1 had been discussed and the Board had announced its opinion on the matter, the appellants-patent proprietors withdrew their auxiliary requests and filed as auxiliary request a slightly amended version of the previous second auxiliary request, whose claim 1 read as follows (deletion with respect to claim 1 of the previous second auxiliary request in strike through):

"1. Microparticles of a biodegradable biocompatible polymeric matrix containing an active agent and an organic solvent free from halogenated hydrocarbons, wherein said organic solvent is a blend of ethyl acetate and benzyl alcohol, ~~residual organic solvent being~~ present in said microparticles at 2% or less of the total weight of said microparticles, wherein said

~~residual~~ benzyl alcohol is present in the range of from 0.5 to 1.5% by weight, wherein the active agent is selected from the group of risperidone, 9-hydroxy-risperidone, and pharmaceutically acceptable salts thereof, wherein said microparticles are prepared by a process comprising contacting said microparticles with an aqueous solvent system comprising water and a water-miscible solvent for said organic solvent, whereby the content of said organic solvent in said microparticles is reduced to 2% or less of the weight of said microparticles."

After the fulfillment of the requirements of Article 123(2) for the auxiliary request had been discussed and the Board had announced its opinion on the matter, the appellants-patent proprietors requested time for the purpose of reconsideration of their requests and then filed a second auxiliary request, whose claim 1 read as follows:

"1. A pharmaceutical composition comprising microparticles of a biodegradable biocompatible polymeric matrix containing an active agent and an organic solvent free from halogenated hydrocarbons, residual organic solvent being present in said microparticles at 2% or less of the total weight of said microparticles wherein the active agent is selected from the group of risperidone, 9-hydroxy-risperidone, and pharmaceutically acceptable salts thereof, wherein said microparticles are prepared by a process comprising contacting said microparticles with an aqueous solvent system comprising water and a water-miscible solvent for said organic solvent, whereby the content of said organic solvent in said microparticles is reduced to 2% or less of the weight of said microparticles, wherein the microparticles have a

diameter ranging in size from 25 to 180 microns comprising: a copolymer of poly(glycolic acid) and poly(d,l-lactic acid) wherein the molar ratio of lactide to glycolide is in the range of from 85:15 to 50:50 and having dispersed or dissolved therein from 35 to 40wt% of an active agent selected from risperidone, 9-hydroxy-risperidone and pharmaceutically acceptable salts thereof, and from 0.5 to 1.5% by weight of benzyl alcohol."

X. The arguments of the appellants-patent proprietors, as far as relevant to the present decision, may be summarised as follows:

Main request - novelty

a) By means of the deletion of the term "said" with reference to the residual organic solvent it was clear that the limitation of 2% or less by weight referred to the total amount of all solvents present and not to a single solvent. This was in agreement with the disclosure of the patent which consistently referred to the total amount of residual solvent. D1 did not provide in its examples any information on the quantity of residual solvent, so that the disputed feature was not directly and unambiguously disclosed therein. Document D8 did not form part of the state of the art and could not be used to complement the disclosure of D1. In any case the total amount of solvents disclosed in D8 with reference to the reproduction of the examples of D1 was always above 2% by weight. The burden of proof that D1 directly and unambiguously disclosed the disputed feature lay with the appellant-opponent, who had provided no evidence in this respect.

Auxiliary request - admittance and amendments

b) The auxiliary request was almost identical to the second auxiliary request previously filed and should be admitted on that basis.

c) The description of the application as originally filed disclosed in its introductory part (paragraphs [0007] and [0009] of the A publication in particular) that the core of the invention concerned the reduction of the level of the residual organic solvent and that its quantity should be kept at less than 2%. It specified thereafter that the organic solvent could be a blend of solvents, that the preferred blend was a blend of ethyl acetate and benzyl alcohol and that the reduction referred to the residual solvent(s) (paragraphs [0034], [0037], [0044], [0045], [0073], [0075]). Therefore a clear basis could be found in the application as filed that the blend of ethyl acetate and benzyl alcohol was present in the microparticles at 2% or less by weight. The fact that a specific embodiment indicated a similar condition for benzyl alcohol alone was not sufficient to invalidate the general disclosure.

Second auxiliary request - admittance

d) The second auxiliary request was a fair attempt to deal with the objections against the previous requests which had been found valid by the Board. It overcame the objections and reformulated the claimed subject-matter in a much narrower form. While the issues raised for the previous requests were known before, the appellants-patent

proprietors did not agree with the argument of the appellant-opponent, nor with the preliminary opinion of the Board.

XI. The arguments of the appellant-opponent, as far as relevant to the present decision, may be summarised as follows:

Main request - novelty

a) The deletion of the term "said" with reference to the limitation of the residual organic solvent being 2% or less by weight did not have any bearing on the scope of the claim. As no total solvent was mentioned, the claim still covered the situation in which the condition applied to a single solvent. On that basis lack of novelty with respect to D1 still applied on the basis of the analysis made in the appealed decision with reference to the first auxiliary request. The crucial point was that the reproduction of the examples of D8 provided by the appellants-patent proprietors with D8 showed that the quantity of residual ethyl acetate was at 1.5 or 1.6% by weight and therefore well below the limit of 2% by weight. D8 showed that the quantity of residual ethyl acetate in the desired range was an intrinsic feature of the product disclosed in D1, which the skilled person would inevitably obtain when repeating the examples of D1.

Auxiliary request - admittance and amendments

b) The auxiliary request was late filed and should therefore not be admitted into the proceedings.

c) The condition on the residual organic solvent related in the original application to a single solvent and there was no basis for extending that condition to a blend of ethyl acetate and benzyl alcohol. The citations given by the appellants-patent proprietors did not make it clear that it was the whole blend which had to be at 2% by weight or less. When the embodiment relating to the process which made use of the specific blend was disclosed (paragraph [0026] of the A publication), it was clear that the condition was valid for the residual quantity of benzyl alcohol. Indeed in the application it was repeatedly stated that the crucial issue was the residue of benzyl alcohol. Therefore the feature of claim 1 of the auxiliary request related to the blend of ethyl acetate and benzyl alcohol being present at 2% or less by weight was not directly and unambiguously derivable from the application as originally filed.

Second auxiliary request - admittance

d) There was no justification for the late filing of the second auxiliary request, as no new objection was raised during the oral proceedings and no new argument was presented. The appellant-opponent could not tackle the second auxiliary request without being given time to analyse it in detail. On that basis the request should not be admitted into the proceedings.

XII. The appellants-patent proprietors requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims of the main request filed with the statement of grounds of appeal,

or on the basis of the claims filed as auxiliary request and as second auxiliary request during the oral proceedings of 14 October 2014.

XIII. The appellant-opponent requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Main request - novelty

1. Example 3 of D1 (page 36) discloses the preparation of microparticles of polylactide-co-glycolide (the preferred biocompatible polymer according to the patent in suit, paragraph [0051]) loaded with risperidone (see title of example and the composition of the organic phase on page 36, lines 7 to 12) wherein benzyl alcohol and ethyl acetate are used as organic solvents in the preparation of the particles (see page 36, lines 3 to 10). The microparticles of example 3 are indicated as "40% Theoretically Loaded Risperidone Microparticles" (page 36, title). A similar disclosure is available in example 2 of D1 (page 35) for particles indicated as "35% Theoretically Loaded Risperidone Microparticles" (page 35, title).

1.1 It was not disputed by the parties that this amounts to a disclosure of microparticles according to claim 1 of the main request, the only disputed feature being whether the residual organic solvent present in the microparticles is at 2% or less of the total weight of said microparticles. Indeed no value for the residual content of benzyl alcohol and ethyl acetate is given in D1.

1.2 Document D8 filed by the appellants-patent proprietors with their reply to the notice of opposition contained a reworking of examples 2 and 3 of D1. While D8 refers to examples 2 and 3 of a US patent (US 5 650 173), it was stated in that letter that it was the US equivalent of D1, which was never disputed by the parties. The residual content of ethyl acetate and benzyl alcohol for the microparticles of examples 2 and 3 of D1 is indicated in the table in the middle of page 6 of D8. In particular as far as example 3 is concerned (40% theoretical load) the residual content is 1.5% by weight for ethyl acetate and 3.8% by weight benzyl alcohol.

1.3 Such experiments show that the given contents are the result of a reproduction of example 3 of D1. In this respect it is of no weight that document D8 is late published, as long as it is used only to show that by running the example of D1 as fully disclosed at its publication date a specific result is inevitably obtained. It is also not relevant that the data were not filed by the appellant-opponent. While it is true that in a case as the present one the burden of proof is on the opponent to show that a non explicitly disclosed feature is to be considered as implicitly disclosed as being the inevitable result of a disclosed process, this may well be discharged by referring to data contained in a reproduction of the relevant process which is on file, even if provided by the opposing party.

1.4 Claim 1 of the main request requires that the microparticles contain "an organic solvent free from halogenated hydrocarbons, residual organic solvent being present in said microparticles at 2% or less of the total weight of said microparticles". In patent

language this clearly means that the microparticles contain "at least" one such organic solvent and that this solvent (the singular is used with reference to the residual organic solvent) is present at 2% or less by weight. In this respect the absence of the word "said" before the expression "residual organic solvent" does not make any difference, as no other solvent can be understood than the one just mentioned in the claim.

1.5 Ethylene acetate is such an organic solvent and is present in the microparticles of example 3 of D1 at 1.5% by weight. By means of that the disputed feature is disclosed independently of the fact that another solvent is present in the microparticles (benzyl alcohol) and that its content or the total solvent content are above 2% by weight.

1.6 The product-by-process feature at the end of claim 1 of the main request can also not constitute a difference for the claimed product, as the only product feature which it defines is still a "content of said organic solvent in said microparticles [*which*] is reduced to 2% or less of the weight of said microparticles".

1.7 For these reasons claim 1 of the main request lacks novelty over the disclosure of document D1.

Auxiliary request - admittance and amendments

2. The claims of the auxiliary request correspond to the claims of the previous second auxiliary request filed with letter of 12 September 2014 with the deletion in claim 1 of a few superfluous words, which do not change the meaning of the corresponding features, namely the content of the blend of ethyl acetate and benzyl alcohol and the content of benzyl alcohol in the

microparticles (see point IX, above). The auxiliary request corresponds therefore in substance to that previously filed request.

2.1 The second auxiliary request filed with letter of 12 September 2014 can be seen as a reasonable reaction to the communication of the Board in which it came clear for the appellants-patent proprietors that the requests on file did not succeed in solving the issues of novelty and extension of subject-matter. It was filed sufficiently in advance of oral proceedings not to put the appellant-opponent and the Board in the position of being unable to tackle it during the oral proceedings. The same holds due to the previously observed correspondence for the auxiliary request currently on file.

2.2 On that basis the Board finds it appropriate to exercise its discretion according to Article 13 (1) of the Rules of Procedure of the Boards of Appeal by admitting the auxiliary request into the proceedings.

2.3 With regard to the proposed amendments, the critical point is whether the original application provides a basis for the condition on the content of residual solvent at 2% or less by weight for a blend of ethyl acetate and benzyl alcohol, in view of the amended feature now reading "wherein said organic solvent is a blend of ethyl acetate and benzyl alcohol, present in said microparticles at 2% or less of the total weight of said microparticles".

2.4 The condition on the content of organic solvent is formulated for the first time and in the most general form on page 3, lines 14 to 29 of the original application (including paragraph [0009] of the A

publication cited by the appellants-patent proprietors), which reads as follows (emphasis by the Board):

"In the process of the invention, the initial content of organic solvent in the particles will generally be above 3.5%, more generally above 4.0% of the total weight of the particles. Advantageously, the process will reduce this content to less than 2%, preferably to less than 1.5% and most preferably less than 1%. The organic solvent in question preferably contains a hydrophobic group containing at least 5 carbons, e.g. an aryl group such as a naphthyl or more especially a phenyl group.
The organic solvent in the particles will generally be present as a result of a particle formation process where the particles have been produced from a solution of the matrix forming polymer material in the organic solvent or in a solvent mixture or blend containing the organic solvent."

2.5 The underlined wording clearly shows that the expression "organic solvent" for which conditions are given in the previous paragraph is in the case of a solvent mixture or blend a single solvent contained in the blend. The whole cited section therefore does not provide a basis for a quantitative condition on the total amount of solvents in case a blend of solvents is used.

2.6 While ample sections of the detailed description relate to the usage of solvent blends comprising at least two solvents (page 12, lines 26 to 32 and page 14, line 9 to page 15, line 20, which include paragraphs [0037], [0044] and [0045] of the A publication cited by the appellants-patent proprietors), no condition is given

on the total content of the solvents included in the blend in the produced microparticles.

2.7 However, when a preferred process for the production of microparticles is disclosed which makes use of the specific blend of ethyl acetate and benzyl alcohol, the condition on the level of residual solvent is given for a single solvent, namely benzyl alcohol (see page 8, line 16 to page 9, line 7, in particular point F) which reads "washing said discontinuous first phase with an aqueous solution comprising water and ethanol, thereby reducing the level of benzyl alcohol to less than about 2% by weight of said microparticles").

2.8 These disclosures alone and in combination provide the skilled reader with a clear teaching that the condition of a quantity at 2% or less by weight applies in a case of a blend to an individual organic solvent of the blend.

2.9 Such a clear teaching cannot be changed by the further passages cited by the appellants-patent proprietors in which the term "solvent(s)" is used (page 11, lines 18 to 26 and page 27, line 35 to page 28, line 2 corresponding to paragraphs [0034] and [0075] of the A publication). In these passages, in spite of the possibility of the plural, a disclosure of a total residual solvent content of 2% or less by weight is not available neither for the general case of multiple organic solvents, nor for the specific one of a blend of ethyl acetate and benzyl alcohol. Also the passage on page 27, lines 14 to 26 (corresponding to paragraph [0073] of the A publication) does not provide that disclosure, but even mentions the possibility of an ethyl acetate content higher than the benzyl alcohol content (see page 27, lines 20 to 23: "At high ethyl

acetate contents in the quench liquid, more ethyl acetate may be retained by the microparticles than benzyl alcohol").

2.10 Therefore the introduction of the feature "wherein said organic solvent is a blend of ethyl acetate and benzyl alcohol, present in said microparticles at 2% or less of the total weight of said microparticles" in claim 1 of the auxiliary request is not directly and unambiguously derivable from the application as originally filed, so that the auxiliary request does not meet the requirements of Article 123(2) EPC.

Second auxiliary request - admittance

3. The second auxiliary request was filed at the oral proceedings before the Board after a discussion on novelty of the main request over document D1 and on the requirements of Article 123(2) EPC for the auxiliary request had taken place and the Board had given an opinion on the matters. In the second auxiliary request a number of features were introduced for the first time in claim 1, including the redefinition of the claimed object as a "pharmaceutical composition comprising microparticles" and the specification that the microparticles have "a diameter ranging in size from 25 to 180 microns" and comprise "a copolymer of poly(glycolic acid) and poly(d,l-lactic acid) wherein the molar ratio of lactide to glycolide is in the range of from 85:15 to 50:50 and having dispersed or dissolved therein from 35 to 40wt% of an active agent selected from risperidone, 9-hydroxy-risperidone and pharmaceutically acceptable salts thereof, and from 0.5 to 1.5% by weight of benzyl alcohol".

3.1 The second auxiliary request cannot be seen as a reaction to a new situation which arose during oral proceedings before the Board, where the main request and the auxiliary request were objected to on the basis of issues which had been present in the submissions in writing of the appellant-opponent and in the communication of the Board. No justification is present therefore for the late filing. In this respect the fact that the appellants-patent proprietors did not agree with the objections has no bearing, as long as the objections were known to them.

3.2 Moreover, claim 1 of that request introduces for the first time a completely new combination of features which requires a new analysis both for the requirements of Article 123(2) EPC and as far as novelty and inventive step are concerned, which the Board and the opposing party cannot reasonably be expected to undertake without adjournment of the oral proceedings.

3.3 On that basis the Board finds it appropriate to exercise its discretion according to Article 13 (1) of the Rules of Procedure of the Boards of Appeal (see also Article 13 (3) of those Rules) by not admitting the second auxiliary request into the proceedings.

Conclusion

4. As none of the requests admitted into the proceedings meets the requirements of the EPC, the patent is to be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

N. Schneider J. Riolo

Decision electronically authenticated