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Datasheet for the decision of 29 June 2010

Case Number: T 0401/07 - 3.3.02

Application Number: 96906566.3

Publication Number: 0810853

IPC: A61K 9/12

Language of the proceedings: EN

Title of invention:
Aerosols containing nanoparticle dispersions

Patentee:
Elan Pharma International Limited

Opponent:
Pharma Concepts GmbH

Headword:
Aerosols/ELAN PHARMA INTERNATIONAL LIMITED

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Inventive step - no - claims alternative"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0401/07 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 29 June 2010

Appellant: (Opponent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 9 January 2007 rejecting the opposition filed against European patent No. 0810853 pursuant to Article 102(2) EPC.

Composition of the Board:

Chairman: A. Lindner
Members: J. Riolo
J. Van Moer

Summary of Facts and Submissions

I. European patent No. 0 810 853, based on European application No. 96906566.3, was granted on the basis of 18 claims.

Independent claims 1, 15 and 18 as granted read as follows:

1. A nebulized aerosol of a dispersion of liquid droplets, wherein:
(a) the aerosol is adapted for administration to the lung of a mammal; and
(b) the liquid droplets comprise:
(i) a liquid,
(ii) particles of a crystalline therapeutic agent which is poorly soluble in the liquid, wherein the agent particles have an effective average particle size of less than 1000 nm; and
(iii) at least one surface modifier adsorbed on the surface of the crystalline therapeutic agent particles.

15. The use of an aerosol according to any one of the preceding claims for the manufacture of a pharmaceutical composition for the treatment of respiratory illness.

18. A method of making the aerosol according to any one of claims 1 to 14 comprising forming a nebulized aerosol of a dispersion of the crystalline therapeutic agent particles.

II. Opposition was filed against the patent under Article 100(a) EPC for lack of novelty and inventive

step, Article 100(b) EPC for insufficiency of disclosure and Article 100(c) EPC because its subject-matter extended beyond the content of the application as filed.

The documents cited during the proceedings before the Opposition Division and/or the Board of Appeal included the following:

(1) WO-A-92/18105
(2) EP-A-602702
(3) US-A-5145684
(4) US-A-5091187
(6) R. Voigt: Pharmazeutische Technologie. 7th Edition, Ullstein Mosby, 1993
(7) H. Stricker (Ed:): Physikalische Pharmazie. 3rd Edition. Wissenschaftliche Verlagsgesellschaft Stuttgart. 1987
(15) Tiano, "Functionality Testing Used to Rationally Assess Performance of a Model Respiratory Solution or Suspension in a Nebulizer," UMI Dissertation Services, 1995, Chapter IV, pages 60-68.

III. By its decision pronounced on 26 October 2006, the Opposition Division rejected the opposition under Article 102(2) EPC.

Concerning the objections with respect to Article 123(2) EPC, the Opposition Division was of the opinion that the deletion of the term "discrete" in claim 1 did not infringe this article since this claim related to particles of crystalline therapeutic agent which were in fact "discrete". As to the wording "adapted for administration to the lungs" in claim 1,

it was of the opinion that it was disclosed in claims 5 and 6 of the application as originally filed.

It further held that the requirements of sufficiency were met because methods for preparing the claimed crystalline particles having a surface modifier adsorbed on their surface were described in the description. Moreover, the examples of the description were not contested.

As regards novelty, the Opposition Division acknowledged novelty vis-à-vis document (1) because this document did not disclose a therapeutic agent in crystalline form and vis-à-vis documents (2), (3) and (4) because these documents did not disclose a nebulised aerosol adapted for administration to the lungs of a mammal.

As for inventive step, document (1), which disclosed a nebulised aerosol dispersion wherein the therapeutic agent was present in an amorphous form, was considered to represent the closest prior art. The Opposition Division was of the view that it was not obvious to replace the amorphous form by a crystalline form because the amorphous form was required in document (1) and because the physical form might influence the therapeutic activity of the drug.

IV. The appellant (opponent) lodged an appeal against the said decision.

V. In a communication from the Board dated 1 June 2010, the Board expressed its preliminary opinion that the subject-matter of independent claim 1 of the patent in

suit seemed not to involve an inventive step vis-à-vis document (1) and (2) in combination.

VI. The respondent filed auxiliary requests 1 to 3 with its letter dated 21 June 2010.

Independent claim 1 of auxiliary request 1 reads as follows:

"1. A nebulized aerosol of a dispersion of liquid droplets, wherein:

(a) the aerosol is adapted for administration to the lung of a mammal; and
(b) the liquid droplets comprise:
(i) a liquid,
(ii) particles of a crystalline therapeutic agent which is poorly soluble in the liquid, wherein the agent particles have an effective average particle size of less than 1000 nm; and
(iii) at least one surface modifier adsorbed on the surface of the crystalline therapeutic agent particles, wherein the therapeutic agent is a corticosteroid."

Independent claim 1 of auxiliary request 2 reads as follows:

"1. A nebulized aerosol of a dispersion of liquid droplets, wherein:
(a) the aerosol is adapted for administration to the lung of a mammal; and
(b) the liquid droplets comprise:
(i) a liquid,

(ii) particles of a crystalline therapeutic agent which is poorly soluble in the liquid, wherein the agent particles have an effective average particle size of less than 1000 nm; and
(iii) at least one surface modifier adsorbed on the surface of the crystalline therapeutic agent particles, for use in delivery of the therapeutic agent to the lungs of a mammal via a nebulizer."

Independent claim 1 of auxiliary request 3 reads as follows:

"1. The use of a dispersion of crystalline therapeutic agent particles for the manufacture of a pharmaceutical composition for delivery of the therapeutic agent to the lungs of a mammal via a nebulizer, wherein the pharmaceutical composition is a nebulized aerosol of a dispersion of liquid droplets, wherein:
(a) the aerosol is adapted for administration to the lung of a mammal; and
(b) the liquid droplets comprise:
(i) a liquid,
(ii) particles of a crystalline therapeutic agent which is poorly soluble in the liquid, wherein the agent particles have an effective average particle size of less than 1000 nm; and
(iii) at least one surface modifier adsorbed on the surface of the crystalline therapeutic agent particles."

VII. Oral proceedings were held before the Board on 29 June 2010.

VIII. During the oral proceedings, the appellant essentially agreed with Board's preliminary opinion as to inventive step, that is, that the subject-matter of claim 1 appeared to be obvious vis-à-vis the disclosure in document (1).

It submitted that document (1), which disclosed the nebulisation and pulmonary delivery of an aerosol comprising a dispersion of surfactant-stabilised nanoparticles of a poorly soluble active compound which was amorphous, represented the closest prior art.

With respect to this prior art, the objective technical problem to be solved was the provision of an alternative.

Looking for a technical alternative, the skilled person would identify the crystalline form as a possible alternative without inventive skill as the crystalline form is the principal alternative state of solid materials, in particular since document (2), which disclosed similar formulations with a therapeutic agent in crystalline instead of amorphous form, did not mention any instability and/or activity problems.

IX. The respondent mainly argued during the oral proceedings that the skilled person would not consider document (1) for the following reasons:

- Document (1) did not deal with the problem according to the patent in suit, namely the delivery of agents to the lung, but with the problem of stabilising particles in a colloidal system.
- Pulmonary administration and nebulization were mentioned only "in passsing" in this document.

- Document (1) did not provide precise information on how to prepare nebulized aerosols.
- Document (1) referred to "solution" not to suspension.

It moreover held that the skilled person could but would not replace the amorphous form used in document (1) by a crystalline form because this document required the form to be amorphous and also having regard to the reduced solubility of the drugs in the crystalline compared to the amorphous form in general.

Finally, it submitted that the skilled person would not have expected a nebulized aerosol to be successful for pulmonary delivery.

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

The respondent requested that the appeal be dismissed or, in the alternative, that the decision under appeal be set aside and the patent be maintained on the basis of auxiliary requests 1 to 3 filed with letter dated 21 June 2010.

Reasons for the decision

1. The appeal is admissible.

2. *Main request*

2.1 Article 100(b) and (c) EPC

The Board agrees with the Opposition Division's favourable conclusions as to Article 100(b) and (c) EPC.

Having regard to the Board's conclusions in the assessment of inventive step (see below, point 3) and to the fact that the appellant did not put forward new substantial arguments compared with those submitted and dealt with before the Opposition Division, there would appear to be no need to devote further attention to this issue.

Accordingly, the Board concludes that the subject-matter of the main request fulfils the requirements of Article 100(b) and (c) EPC (see above under III, and the Opposition Division's decision, page 2, last sentence, to page 4, first line).

2.2 Novelty

The Board agrees with the Opposition Division's favourable conclusions regarding Article 54 EPC with respect to this subject-matter.

Having regard to the Board's conclusions in the assessment of inventive step (see below, point 3) and

to the fact that the appellant did not put forward new substantial arguments compared with those submitted and dealt with before the Opposition Division, there would appear to be no need to devote further attention to this issue.

Accordingly, the Board concludes that the subject-matter of the main request fulfils the requirements of Article 54 EPC (see above under III, and the Opposition Division's decision, page 4, first paragraph, to page 5, first paragraph).

3. *Inventive step*

3.1 The contested patent relates to a nebulized aerosol of a dispersion of liquid droplets adapted for administration to the lung of a mammal, wherein the liquid droplets comprise a liquid, particles of a crystalline therapeutic agent poorly soluble in the liquid, having an effective average particle size of less than 1000 nm, and at least one surface modifier adsorbed on the surface of the crystalline therapeutic agent particles (claim 1, paragraph 9).

Document (1) discloses a nebulized aerosol of a dispersion of liquid droplets adapted for administration to the lung of a mammal (page 14, last paragraph: "pulmonary inhalation", and page 19, third paragraph: "via nebulizers"), wherein the liquid droplets comprise a liquid (claim 31: "water"), particles of a therapeutic agent poorly soluble in the liquid (claim 1: "particle of a substantially water insoluble biologically active substance"; claim 4: "cyclosporin"), having an effective average particle

size of less than 1000 nm (claim 16: "1 nanometer to 10 micrometer"), and at least one surface modifier adsorbed on the surface of the therapeutic agent particles (claim 1: "the particles having on the surface a charged glyceryl ester").

Thus, this document discloses all features of claim 1 of the patent in suit except for the crystalline state of the active substance.

The Board considers that document (1) represents the closest prior art.

3.2 The problem to be solved by the subject-matter of claim 1 of the main request of the patent in suit as against document (1) can be seen in the provision of a further formulation of a nebulized aerosol for administration to the lung of a mammal.

3.3 This problem is solved by using particles of therapeutic substances in the crystalline state.

In the light of the description and examples in the patent in suit, and in the absence of any specific evidence to the contrary, the Board is satisfied that the problem has been solved.

3.4 Thus the question to be answered is whether the proposed solution would have been obvious to the skilled person in the light of the prior art.

In that respect, the Board observes that the crystalline state is only one of two principal solid states that dispersed particles can have, namely amorphous and crystalline.

Accordingly, the skilled person would immediately identify the crystalline form as a possible alternative without inventive activity and from its common general knowledge.

This is further confirmed by the available prior art such as documents (3) and (2).

Having regard to document (3), it does indeed appear that this feature is in fact a readily available alternative since this document, which does not mention a form of administration to the lung of a mammal, otherwise describes all the features of claim 1.

Thus, document (3) discloses the administration to mammals of nanoparticles of the same therapeutic agents as the ones disclosed in the patent in suit (column 3, line 53 to column 4, line 5) which also have surface modifiers adsorbed on their surface (column 5, lines 34 to 63), have a size of less than 400 nm (claim 1) and are in the crystalline form (column 3, lines 32 to 37). The forms of administration cited in this document are however oral or intravenous.

The same would apply with respect to document (2), which also discloses all the features of claim 1 of the contested patent but does not mention a form of administration to the lung of a mammal (column 7, lines 1 to 6: buccal or nasal spray).

Accordingly, the Board is convinced that the skilled person, faced with the problem defined under 3.2, would have considered the crystalline form of the therapeutic agent as an obvious solution from its common general knowledge as confirmed by documents (2) and (3) which illustrate that the crystalline form is a readily available alternative to the amorphous form in very similar formulations.

3.5 The Board does not agree with the respondent's first line of argument that the skilled person would not consider document (1) to be relevant.

It is correct that document (1) is concerned with the stabilisation of colloidal systems. This would not however dissuade the skilled person trying to find a nebulised aerosol formulation for administration to the lung from paying attention to this document since it discloses precisely also pulmonary application via nebulizers.

It is also true that pulmonary application via nebulizers is mentioned in document (1) among other modes of administration.

This does not however change the relevance of the disclosure the more so since this mode of administration is even recited again in the claims (claims 30, 31).

It is also correct that document (1) does not give precise information on how to prepare the nebulized aerosols. In that respect, the Board notes however that

according to the contested patent itself "aerosols of the invention are made by nebulizing the nanoparticule containing solution using a variety of known nebulizing techniques" (paragraph 15, first sentence), so that this argument cannot be succeed either.

As to the argument that the use of the term "solution" in document (1) gives rise to doubt as to whether the nebulized aerosol is a dispersion or not, the Board observes that the patent in suit itself uses both "solution" and "dispersion" (see e.g. paragraph 15, first sentence). Moreover, the disclosure in document (1) on page 19, paragraph 3 refers unambiguously to a dispersion, i.e. "re-dispersement in water and pulmonary application via nebulizers".

The Board disagrees also with the respondent's submissions that the skilled person would not replace the amorphous form used in document (1) by a crystalline form because this document required the form to be amorphous and also having regard to the reduced solubility of the drugs in the crystalline compared to the amorphous form in general.

It is first not correct that document (1) is restricted to amorphous form. Document (1) merely recites on page 1, paragraph 3 that "these colloidal compositions in the present invention are believed to consist only of active substances in amorphous form". There is no other mention of the amorphous form in the document. Accordingly, there is no reason to believe that the amorphous form has a particular importance in document (1) or even that the process of preparation leads to this solid form.

The Board agrees that, as a rule and as illustrated by various documents cited by the respondent, the amorphous form is more soluble than the crystalline form and this could lead to activity problems in case of poorly soluble drugs (see e.g. documents (6) and (7)).

In that respect, the Board notes however that the claim is not restricted to a particular drug and that, on the contrary, it concerns the same drugs (patent in suit, paragraph 20) as those disclosed in document (3) (column 3, line 53 to column 4, line 5), which are used precisely in the cristalline form. This argument too must therefore fail.

Finally, although it is true that the conclusion of the dissertation of Mrs Tiano is that an ultrasonic nebuliser could not efficiently aerosolise a respiratory suspension (page 65), it is also true that the disclosure in document (1) discloses the contrary, so that the Board can also not follow the last line of argumentation submitted by the respondent that there was no reasonable expectation of success.

The more so since the crystalline formulation was already available in the prior art (see documents (3) and (2)), so that the skilled person just needed to make a simple test to check the teachings of documents (1) and (2)/(3).

3.6 In the light of these facts, the Board can only conclude that the subject-matter of claim 1 of the main request does not involve an inventive step as required by Article 56 EPC.

Under these circumstances, there is no need to consider the remaining claims.

4. *Auxiliary requests 1 to 3*

During the oral proceedings, with regard to auxiliary requests the parties relied on their submissions with respect to the main request.

Since there are no additional distinguishing features in these requests which appear to be non-obvious vis-à-vis the combination of document (1) with the skilled person's common general knowledge, the conclusion as to lack of inventive step for the subject-matter of claim 1 of the main request applies equally to claim 1 of these requests.

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. Maslin A. Lindner