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Datasheet for the decision of 2 November 2022

Case Number: T 0951/20 - 3.3.07

Application Number: 10181899.5

Publication Number: 2283817

IPC: A61K9/14, A61K9/72, A61K9/00

Language of the proceedings: EN

Title of invention:
Method of making particles for use in a pharmaceutical composition

Patent Proprietor:
Vectura Limited

Opponent:
Glaxo Group Limited

Headword:
Fused composite particles/VECTURA

Relevant legal provisions:
EPC Art. 87(1), 56

Keyword:
Priority - basis in priority document (no)
Inventive step - obvious alternative

Decisions cited:

G 0003/93

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Case Number: T 0951/20 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 2 November 2022

Appellant: (Opponent)	Glaxo Group Limited 980 Great West Road Brentford Middlesex TW8 9GS (GB)
Representative:	J A Kemp LLP 80 Turnmill Street London EC1M 5QU (GB)
Respondent: (Patent Proprietor)	Vectura Limited 1 Prospect West Chippenham, Wiltshire SN14 6FH (GB)
Representative:	CMS Cameron McKenna Nabarro Olswang LLP Cannon Place 78 Cannon Street London EC4N 6AF (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 26 March 2020 rejecting the opposition filed against European patent No. 2283817 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	Y. Podbielski

Summary of Facts and Submissions

I. European patent 2 283 817 ("the patent") was granted on the basis of fifteen claims.

Claim 1 as granted related to:

"A method for making composite active particles for use in a pharmaceutical composition for pulmonary administration, the method comprising a milling step in which particles of active material are milled in the presence of particles of an additive material which is suitable for the promotion of the dispersal of the composite active particles upon actuation of an inhaler, wherein the composite active particles have, smeared over or fused on their surfaces an amount of additive material in the form of particles adhering to the surfaces of the particles of active material, wherein after the milling step the mass median aerodynamic diameter of the composite active particle is not more than 10 µm as determined using a multi stage liquid impinger, and wherein the additive material comprises magnesium stearate."

Claim 8 as granted defined:

"Composite active particles made according to claim 1-7 for use in a pharmaceutical composition for pulmonary administration, each composite active particle comprising a particle of active material and a particle of additive material smeared over or fused on the surface of that particle of active material, the composite active particles having a mass median aerodynamic diameter of not more than 10 µm as determined using a multi stage liquid impinger and the

additive material being suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device, and wherein the additive material comprises magnesium stearate."

II. The patent was opposed on the grounds that its subject-matter lacked novelty and lacked inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the (earlier) application as filed.

The opponent filed the appeal against the decision of the opposition division to reject the opposition.

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

P1: Priority document GB 0029261.5
P2: Priority document GB0 030946.8
P3: Priority document PCT/GB01/01606
P4: Priority document GB 0124010.0
D1: WO 00/027363
D6: WO 01/76575
D15: Handbook of Pharmaceutical Excipients (2nd edition, 1994), p. 280-281
D16: Handbook of Pharmaceutical Excipients (3rd edition, 2000), p. 305-306
D30: Colombo et al., Surface smoothing of lactose particles for dry powder inhalers. Respiratory Drug Delivery VII, 2000

The opposition division arrived at the following conclusions:

(a) The claims as granted did not comprise subject-matter extending beyond the original disclosure.

(b) The patent was considered to provide sufficient guidance for the skilled person to carry out the claimed invention.

(c) The priority documents P1, P2, P3 and P4 provided no basis for the feature "smeared over or fused" defined in the claims as granted. Partial priority was recognized for Example 4b), which was disclosed in priority document P4.

(d) The subject-matter of claim 1 as granted was new in view of the available prior art.

(e) Document D1, which described surface-modified active particles for pulmonary administration with improved inhalation properties represented the closest prior art. The claimed subject-matter differed from the teaching in document D1 in the definition of the surface modifying additive material.

The patent demonstrated in example 4 that blends of salbutamol sulphate and magnesium stearate provided high Fine Particle Fraction (FPF) values compared to salbutamol sulphate alone. The problem to be solved was the provision of a method for the preparation of composite particles for pulmonary administration with an alternative surface modifier. The claimed subject-matter was not obvious to the skilled person, because no prior art suggested the use of magnesium stearate as a solution, especially when considering the

toxicological concerns regarding the use of magnesium stearate expressed in document D30.

The subject-matter of the claims as granted therefore involved an inventive step.

III. With the statement of grounds of appeal the appellant (opponent) maintained *inter alia* that the subject-matter of the patent lacked an inventive step starting from document D1.

IV. With the reply to the appeal the respondent (patent proprietor) filed auxiliary requests 1-11.

Claim 1 of auxiliary request 1 differs from claim 1 as granted by the additional feature that the milling step involves compressing a mixture of active particles and additive particles in a gap of a predetermined width not more than 10 mm wide.

Claim 1 of auxiliary request 2 differs from claim 1 as granted by the additional feature that the milling step is performed in the absence of liquid.

Claim 1 of auxiliary request 3 differs from claim 1 as granted by the additional feature that the active particles have the additive material on their surfaces in the form of a discontinuous coating of adhering particles.

Claim 1 of auxiliary request 4 differs from claim 1 as granted by the additional feature that the active particles have the additive material on their surfaces in the form of a coating of adhering particles which is on average less than 1 µm thick.

Claim 1 of auxiliary request 5 differs from claim 1 as granted by the definition that the additive material consists of magnesium stearate.

Claim 1 of auxiliary request 6 includes the additional features defined in accordance with auxiliary requests 1 and 2.

Claim 1 of auxiliary request 7 includes the additional features defined in accordance with auxiliary requests 1, 2 and 3.

Claim 1 of auxiliary request 8 includes the additional features defined in accordance with auxiliary requests 1, 2, 3 and 4.

Claim 1 of auxiliary request 9 includes the features defined in accordance with auxiliary requests 1, 2 and 5.

Claim 1 of auxiliary request 10 includes the features defined in accordance with auxiliary requests 1, 2, 3 and 5.

Claim 1 of auxiliary request 11 includes the features defined in accordance with auxiliary requests 1, 2, 3, 4 and 5.

V. The Board invited the parties to attend oral proceedings on 8 December 2022.

In its communication pursuant to Article 15(1) RPBA the Board questioned the validity of the claimed priority and expressed *inter alia* the preliminary opinion that document D1 represented a suitable starting point for the assessment of an inventive step and that document

D6 seemed to confirm that magnesium stearate was suitable for inhalation and delivery of drugs via the lung.

VI. With the letter of 22 September 2022 the respondent withdrew its request for oral proceedings and announced not to attend the oral proceedings scheduled for 8 December 2022.

VII. The oral proceedings were cancelled with the Boards communication of 14 October 2022.

VIII. The arguments of the appellant relevant to the present decision are summarized as follows:

Priority

The claimed subject-matter was not entitled to any of the claimed priorities. Documents P1 and P2 did not disclose the feature concerning the "smeared over or fused" arrangement. This feature was not the inevitable result of the defined milling procedure. Documents P3 and P4 also failed to provide any relevant teaching in this regard.

Inventive step

Document D1 described surface modified drug particles for delivery to the respiratory tract and thus concerned the same problem as addressed in the patent. The subject-matter of the claims as granted differed from the teaching of document D1 in the definition of magnesium stearate as the surface modifier. As no comparative data demonstrated any advantage over the surface modifiers described in document D1, the problem to be solved concerned the provision of an alternative

method for preparing particles for pulmonary administration. Document D1 already described surfactants in general as suitable surface modifiers and mentioned calcium stearate as an example. At the same time magnesium stearate was, as evidenced by documents D15 and D16, a well known alternative surfactant for pharmaceutical application. Documents D15, D16 and D30 did not raise any relevant toxicity concern regarding the use of magnesium stearate in pharmaceutical compositions for inhalation. Moreover document D6 specifically described the use of magnesium stearate for coating an active agent for delivery via the lung. The claimed subject-matter therefore lacked an inventive step.

As regards the auxiliary requests, no data indicated any technical significance associated with

- the milling involving the compression of the active and additive particles in a gap of a predetermined width not more than 10 mm wide,

- the milling being performed in the absence of liquid,

- the additive material being in the form of a discontinuous coating, or

- the additive material being in the form of a coating which is on average less than 1 µm thick

The objection regarding the main request therefore equally applied to the auxiliary requests which additionally required these features. Moreover, magnesium stearate was routinely used as a

pharmaceutical excipient both in admixture with other surfactants and as a pure compound.

IX. The arguments of the respondent relevant to the present decision are summarized as follows:

Priority

The feature concerning the "smeared over or fused" arrangement was an inevitable result of the milling procedure using the soft magnesium stearate as additive material as described in priority documents P1 and P2. The claimed subject-matter was therefore entitled to the priority of P1 and P2.

Inventive step

Document D1 related to the provision of surface-modified drug particles with improved inhalation properties. The claimed subject-matter differed from the teaching in document D1 by the choice of magnesium stearate as the surface modifying additive material. The objective technical problem was the provision of an alternative method for making composite active particles for inhalation. Document D1 described calcium stearate as part of an extensive list of surface modifiers, but failed to provide any general teaching suggesting magnesium stearate as a suitable alternative surface modifier. Moreover, document D1 referred to document D15, a handbook on pharmaceutical excipients, which explicitly warned against the harmful inhalation of magnesium stearate.

Document D6 did not represent relevant prior art in view of the validly claimed priority. Moreover, document D6 aimed at providing a controlled release

formulation. It did not disclose composite active particles having an MMAD of less than 10 µm and presented in its example a formulation tested for dissolution, not for inhalation.

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

XI. The respondent requested that the appeal be dismissed.

As an auxiliary measure, the respondent requested that the patent be maintained on the basis of one of auxiliary requests 1-11 as filed with the reply to the appeal.

Reasons for the Decision

1. Main request

1.1 Priority

1.1.1 In its communication under Article 15(1) RPBA the Board expressed its preliminary opinion that the feature of the "smeared over or fused" arrangement defined in the claims as granted is not entitled to the claimed priorities in view of the following considerations.

As acknowledged by the respondent the "smeared over or fused" arrangement defined in the claims as granted was not explicitly mentioned in the priority documents. The application as filed (see page 6 lines 4-11) further tought that the required adhesion of the additive particles may be achieved without deformation of the particles in case very small particles of additive material, which are sufficiently adhered by Van der

Waals forces alone. No evidence on file indicated that this teaching does not apply in case the additive material is magnesium stearate. The "smeared over or fused" arrangement could therefore not be regarded as the inevitable result of the defined milling procedure. As concluded in the decision under appeal (see section 8.2) the defined "smeared over or fused" arrangement thus presented with respect to the disclosure in the priority documents new technical information regarding the constitution of the defined product.

No substantive arguments were submitted by the appellant in response to the Board's communication. Accordingly, the Board confirms its preliminary opinion that claimed invention is not entitled to the claimed priorities (Article 87(1) EPC).

1.1.2 Document D6, which corresponds to priority document P3, was published before the relevant filing date for the patent. Having regard to the above conclusion regarding the validity of the claimed priority and in line with the principles laid out in G 3/93 document D6 qualifies as prior art for the purpose of Article 56 EPC.

1.2 Inventive step

1.2.1 Starting point in the prior art

1.2.2 Document D1 describes the provision of surface modified drug particles. Document D1 qualifies as a suitable starting point in the prior art, as this document relates to the same purpose and effect as the patent, namely the provision of surface modified drug particles with improved inhalation properties. Document D1 describes surfactants as preferred surface modifiers (see D1 page 26 lines 13-14), mentions calcium stearate

in a list of surface modifiers (see page 26 line 18) and presents actual preparative examples involving milling using polyvinylpovidone (PVP) as surface modifier (see in particular D1 page 32 example 3).

The claimed subject-matter differs from the teaching of document D1 in the choice of magnesium stearate as the surface modifier.

The suitability of document D1 as a starting point in the prior art and the difference between the claimed subject-matter and the teaching in document D1 was not in dispute.

1.2.3 Problem to be solved

The respondent did not rely on a particular advantage of the use of magnesium stearate with respect to the teaching of document D1. The problem to be solved in view of document D1 is therefore formulated as the provision of an alternative method of preparing composite active particles for inhalation. This formulation of the problem to be solved was not in dispute.

1.2.4 Assessment of the solution

Document D1 describes surfactants in general as suitable surface modifiers and mentions calcium stearate as an example of a suitable surface modifier (see D1, page 26, line 18).

The document refers in this context specifically to the handbook on pharmaceutical excipients from which document D15 represents an excerpt (see D1, page 27, lines 23-26). Document D15 as well as document D16,

which represents the corresponding section of the subsequent edition of the handbook, mention calcium stearate as a pharmaceutical excipient related to magnesium stearate (see D15, page 281, right column, under "18. Related Substances"; see D16, page 306, right column, under "18. Related Substances").

The Board considers that in the absence of convincing indications to the contrary the skilled person had therefore good reason to expect that magnesium stearate would be suitable as an alternative to the surface modifier calcium stearate mentioned in document D1.

The respondent referred in this context to the warning mentioned in document D15 regarding harmful inhalation of magnesium stearate. Moreover, the opposition division noted in its decision (see page 17, lines 11-13) that document D30 mentions toxicological concerns regarding the deposition of magnesium stearate in the lung (see D30, page 630, paragraph 3).

The Board observes, however, that document D15 and its update in document D16 (see D15, page 281, right column, under "14. Safety" and "15. Handling Precautions"; see D16, page 306, right column, under "15. Handling Precautions") evidently refer to precautions aimed at avoiding harm from excessive inhalation of magnesium dust when handling the bulk substance. As pointed out by the appellant and not contested by the respondent, the claimed subject-matter relates to pharmaceutical compositions for pulmonary administration in which only limited amounts of magnesium stearate are inhaled. The mentioned handling precautions against excessive inhalation are therefore not considered to affect the skilled person's expectation regarding the suitability of magnesium

stearate for use as an alternative to the surface modifiers described in document D1. In this context the concern mentioned in document D30 reflects in the Board's view the general desirability to minimize the amount of low soluble excipients introduced in the lung, but does not discourage the skilled person from using magnesium stearate as an alternative to the surface modifiers mentioned in document D1.

In fact document D6 (see page 5 lines 1-12) explicitly confirms that magnesium stearate was suitable for inhalation and delivery of drugs via the lung.

Accordingly, the Board concludes that the subject-matter of claim 1 of the main request does not involve an inventive step.

2. Auxiliary requests 1-11, inventive step

As pointed out by the appellant and not contested by the respondent, no data indicate any technical significance associated with the features that the milling involves compressing the active and additive particles in a gap of a predetermined width not more than 10 mm wide, that the milling is performed in the absence of liquid, that the additive material is in the form of a discontinuous coating, or that the additive material is in the form of a coating which is on average less than 1 µm thick. As further pointed out by the appellant and not contested by the respondent, magnesium stearate was routinely used as a pharmaceutical excipient both in admixture with other surfactants and as a pure compound.

The respondent did in fact not argue that any of the additional features required according to auxiliary

requests 1-11 supported an inventive step and merely referred with respect to the issue of inventive step regarding the auxiliary requests to its argumentation with respect to the main request.

Accordingly, the Board concludes that auxiliary requests 1-11 do not comply with the requirement of inventive step for the same reason as presented for the main request.

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:

S. Sánchez Chiquero A. Usuelli

Decision electronically authenticated