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Datasheet for the decision of 18 November 2014

Case Number: T 0457/11 - 3.3.07

Application Number: 01921631.6

Publication Number: 1276474

IPC: A61K9/72, A61K9/14

Language of the proceedings: EN

Title of invention:
FORMULATIONS FOR USE IN INHALER DEVICES

Patent Proprietor:
Vectura Limited

Opponent:
NORTON HEALTHCARE LIMITED

Headword:

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - main request (no)
Inventive step - auxiliary requests 1 to 4 (no)

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Catchword:

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Case Number: T 0457/11 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 18 November 2014

Appellant: (Patent Proprietor)	Vectura Limited 1 Prospect West Chippenham, Wiltshire SN14 6FH (GB)
Representative:	Jump, Timothy John Simon Venner Shipley LLP 200 Aldersgate London EC1A 4HD (GB)
Appellant: (Opponent)	NORTON HEALTHCARE LIMITED Regent House 5-7 Broadhurst Gardens Swiss Cottage London NW6 3RZ (GB)
Representative:	Gillard, Richard Edward Elkington and Fife LLP Thavies Inn House 3-4 Holborn Circus London EC1N 2HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 21 December 2010 concerning maintenance of the European Patent No. 1276474 in amended form.**

Composition of the Board:

Chairman	J. Riolo
Members:	A. Usuelli
	D. T. Keeling

Summary of Facts and Submissions

I. The appeals of the patent proprietor and of the opponent lie from the decision of the opposition division, announced at the oral proceedings on 15 October 2010, concerning the maintenance of European patent No 1 276 474 in amended form.

II. The patent was opposed under Article 100 (a) and (b) EPC on the grounds that its subject-matter lacked inventive step and the patent was not sufficiently disclosed. The following documents were among those cited during the opposition proceedings:

D1: International Journal of Pharmaceutics, 172, 1-2, 179-188
D2: WO96/23485
D7: Kona, 16, 1998, 7-44

III. The decision of the opposition division was based on the granted patent as main request and on a set of claims submitted as an auxiliary request during the oral proceedings.

Claim 1 of the granted patent (main request) read as follows:

"1. A formulation for use in an inhaler device, comprising:
carrier particles in the form of an agglomerate consisting of a plurality of crystals fused to one another, wherein the carrier particles have a diameter of at least 50µm, a mass median aerodynamic diameter of at least 175µm and a fissured surface in which the fissures are at least 5µm wide and at least 5µm deep; fine particles of an excipient material having a mass

median aerodynamic diameter of not more than 20µm; and active particles."

Claim 1 of the auxiliary request differed from claim 1 of the granted patent in the indication that the carrier particles had a mass median diameter of at least 200µm and in the indication that the fine excipient particles were of the same material as the carrier particles.

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

a) Document D2 was selected as the closest prior art. The difference between the subject-matter of claim 1 of the patent and the disclosure of document D2 was found to reside in the width and depth of the fissures. The objective technical problem was formulated as "the provision of a composition having a higher drug load without imparting the amount of fine particle fraction". The skilled person having in mind to improve the drug load of dry powder inhaler would have learned from D1 that the carrier with the highest specific surface area, namely the fluidized bed granulated (FBG) lactose, carried the highest amount of drug. From the figures disclosed in D1, FGB lactose appeared to have fissures of the dimensions required by the claims of the opposed patent. Hence, the subject-matter of claim 1 of the main request was obvious in view of the combination of the teachings of documents D1 and D2.

b) Concerning the auxiliary request, document D2 represented again the closest prior art and the problem to be solved was the same as for the main

request. The solution was characterized in that the excipient was of the same material as the carrier. The provision of a formulation which consisted of less distinct chemical compounds had the benefit of reducing potential interactions with the patient's body. The prior art did not suggest a formulation in which the carrier particles and the particles of the fine excipient were of the same material. The requirements of Article 56 EPC were therefore met.

c) The subject-matter of the auxiliary request was considered to comply with the requirements of the convention.

V. Both parties lodged an appeal against that decision. With the statement setting out the grounds of appeal the appellant-opponent submitted the following document:

D10: International Journal of Pharmaceutics 182, (1999), 133-144.

VI. In the statement setting out the grounds of appeal dated 28 April 2011, the appellant-patent proprietor requested that the patent be maintained on the basis of the main request or auxiliary requests 1 to 4 filed therewith.

Claim 1 of the main request and claim 1 of the first auxiliary request were identical to the corresponding claims of the main request and of the auxiliary request underlying the impugned decision.

Claim 1 of the second auxiliary request differed from claim 1 of the main request in the addition of the following feature at the end of the claim:

"...; said formulation having a fines content of at least 20% by weight of the fines and carrier particles."

Claim 1 of auxiliary request 3 differed from claim 1 of auxiliary request 2 in the indication that the carrier particles had a mass median diameter of at least 200µm.

Claim 1 of auxiliary request 4 differed from claim 1 of auxiliary request 3 in the indication that the fine excipient particles were of the same material as the carrier particles.

VII. On 18 October 2014 oral proceedings were held before the Board in the absence of the appellant-patent proprietor, as announced by letter dated 1 April 2014.

VIII. As far as relevant for the present decision, the arguments of the appellant-opponent can be summarised as follows:

Main request - Inventive step

The closest prior art D2 disclosed a powder for a dry powder inhaler containing a coarse carrier, an excipient and an active ingredient. The particles of the carrier contained asperities and clefts. The excipient had a particle size falling within the scope of claim 1 of the patent. Its presence had the effect of promoting the release of the active particles from the surface of the carrier thereby increasing the fine particle fraction. The carrier's particles claimed in

the opposed patent differed from those disclosed in document D2 in that they were in the form of an agglomerate having a fissured surface in which the fissures are at least 5µm wide and at least 5µm deep. The objective technical problem was the provision of a composition having a higher drug load. Document D1 related to the effects of the surface morphology of lactose carrier particles on the inhalation's properties of dry powders. One of the carriers studied was the fluidised bed granulated lactose (FGB) which was characterised by the presence of deep fissures in its surface. The results shown in D1 demonstrated that the FGB lactose was able to carry more drug on account of the grater surface area. Accordingly, the skilled person would have considered using this kind of lactose in order to increase the amount of drug loaded. D1 discussed also the problem associated with the use of FGB lactose as carrier, namely the fact that it hold more firmly the drug thereby causing a reduction of the drug release. However, D2 already provided the solution to this problem, which was to include an additive material to facilitate the release of the active ingredient from the carrier. Hence, the skilled person would have combined the teachings of documents D1 and D2 to arrive at a formulation which balances the ability of a fissured carrier to hold larger amounts of drug and the ability of an additive to promote release from the carrier.

First auxiliary request - Inventive step

Claim 1 of this request was limited to specify the mass median diameter of the carrier particles and to state that the fine excipient particles were of the same material as the carrier particles. There were no effects associated with the specific mass median

diameter of the carrier particles. The advantage of the fine excipient and carrier being of the same material was a reduced number of substances entering the body. Document D10 suggested the use of micronised lactose as excipient for powders employing coarse lactose as carrier. Moreover D10 underlined the advantage of combining coarse and fine lactose, namely that fewer materials were used. Hence, the use of an excipient of the same material of the carrier was suggested by the teaching of D10.

Auxiliary requests 2 to 4 - Inventive step

The arguments submitted in respect to the main request and the first auxiliary request applied also to the remaining requests. Accordingly, also these requests did not comply with the requirements of Article 56 EPC.

IX. As far as relevant for the present decision, the arguments of the appellant-patent proprietor can be summarised as follows:

Main request - Inventive step

The carrier particles of the invention had an extremely rugged surface with large fissures which allowed them to carry more fine particles. Unexpectedly, the presence of fine excipient particles ensured that the active ingredient was dispersed upon actuation of the inhaler. The carrier particles disclosed in D2 had a surface with asperities and clefts. The particles of the active ingredient adhered more strongly to these sites of high energy. D2 recommended that additive material be used to control the adhesion of the fine drug to the carrier and promote its dispersion. Furthermore, D2 suggested to treat the carrier particle

in a milling process in order to remove the asperities. Said treatment provided a marked improvement in the dispersion of the active ingredient. D1 discussed the properties of various carrier particles with different surface morphologies. According to the results disclosed in Table 3, the active particles adhered most strongly to the FGB lactose which was characterised by the presence of large valleys or clefts. These represented sites where the active particles tended to adhere firmly. FGB carrier had therefore a bad performance in terms of delivering the drug to the lungs. The skilled person might have expected that carrier particles with extremely rough surface could accommodate a greater amount of active particles. However, he would have also recognised that with such particles, it would have been very difficult to control the adhesion. Thus, the teaching of the prior art documents did not direct the skilled person to use FGB lactose as carrier in order to provide a formulation having a higher drug load.

According to an alternative approach, it was noted that the powders disclosed in D2 did not exhibit particularly good flowability. The technical problem over D2 was the provision of a powder showing improved flowability. This problem was solved by the provision of carrier particles having a highly fissured surface and a mass median aerodynamic diameter of at least 175µm. Such carrier enabled the formulation to incorporate a high content of fine particles. It was known in the art that powders with a high content of fine particles had poor flow properties. Hence, the improved flowability of the carrier particles of the invention was a surprising property which was not suggested in the prior art documents.

Auxiliary requests 1 to 4 - Inventive step

Auxiliary request 1 was based upon the claims of the request which was found by the opposition division to meet the requirements of the EPC.

Claim 1 of auxiliary requests 2 to 4 included the additional feature that the fines content was at least 20%. None of the prior art documents relied upon by the appellant-opponent disclosed formulations with this feature. Thus, the subject-matter of auxiliary requests 2 to 4 met the requirements of Article 56 EPC.

X. The appellant-patent proprietor requested in writing that the decision under appeal be set aside and the patent maintained on the basis of the main request or of one of the auxiliary requests 1 to 4, all filed with the grounds of appeal.

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

Reasons for the Decision

Main request

1. *Inventive step*

1.1 The invention underlying the patent in suit relates to carrier materials for use in inhaler devices and to formulations comprising these materials ([0001]).

1.2 Closest prior art

1.2.1 The Board agrees with the parties and with the opposition division that document D2 represents the closest prior art. This document relates to carrier particles for use in dry powder inhalers, which are characterised *inter alia* by the presence of an additive material on their surface (see page 5, lines 8 to 21)., The aerodynamic diameter of the carrier particles lies preferably between 20µm and 250µm (page 10, lines 10 to 26) and the particles of the additive have a mass median aerodynamic diameter which is not more than about 10µm (page 15, lines 11 to 15).

1.2.2 The Board agrees with the appellant-opponent that the carrier particles defined in claim 1 differ from those disclosed in D2 in that they are in the form of an agglomerate having a fissured surface in which the fissures are at least 5µm wide and at least 5µm deep.

Moreover, with regard to the size of the carrier particles, claim 1 recites in addition to the mass median aerodynamic diameter also the diameter which is of at least 50µm. In document D2 the size of the particles is described only in terms of aerodynamic diameter (see page 10, lines 24-26).

1.3 Technical problem

1.3.1 According to the description, the formulation of the opposed patent has an excellent flowability and permits good dispersion of the active particles from the carrier ([0010]). Furthermore, the presence of fissures on the surface of the particles offers the advantage that higher amounts of fine materials, including the active ingredient, can be retained on the carrier ([0019]).

1.3.2 There are no experimental data permitting a comparison of the properties of the carrier particles of the opposed patent with the properties of the carriers disclosed in D2. The patent discloses nevertheless some technical data concerning a formulation according to the invention containing salbutamol as active ingredient (see Table 1 of example 1). These data indicate that the formulation tested provides good results in terms of inhalation efficiency (40% of fine particle fraction). It can be furthermore observed from Table 1 that the carrier particles represent 80% of the total weight of the formulation, while salbutamol and the excipient (microfine lactose) are present in an amount of 10% each. Confronted with the information disclosed in D2, according to which the amount of the carrier is preferably at least 90% and more preferably at least 95% of the formulation (page 16), the data of Table 1 of the patent suggest that the carrier particles of the invention may indeed contain more fine materials and in particular more active ingredient, than the carrier particles of D2.

As to the flow properties, the patent does not provide any experimental data which could be used for a comparison with the carrier particles disclosed in D2.

1.3.3 In the light of the above, the Board considers that the technical problem solved by the subject-matter of claim 1 is the provision of a composition for use in an inhaler device having a higher drug load.

1.4 *Obviousness*

1.4.1 Document D1 relates to an experimental study in which the inhalation properties of different carrier particles are investigated. The particles tested are

made of the same material, i.e. lactose, but they are characterised by different surface morphologies. One of the types of lactose studied is fluidized bed granulated (FGB) lactose which is characterised by a high specific surface area and a high surface roughness (see table 1). The microphotographs disclosed in Figure 1, show that FGB lactose has an irregular surface with asperities and clefts.

1.4.2 One of the observations made by the authors of D1 in their conclusions, is that lactose particles having larger surface area can carry higher amounts of drug particles because of higher capacity of depositing (page 185, second sentence of section 3.3). This applies in particular to FGB lactose (see page 184, right column). The skilled person would therefore learn from document D1, that carrier particles having a high surface roughness characterised by the presence of clefts and asperities, such as FGB lactose, can load a higher amount of active ingredient. This would give a clear hint to solve the problem of increasing the amount of drug transported by the carrier, by providing particles having deep fissures.

1.4.3 Document D1 also discusses the effects of the surface morphology of the carrier particles on the separation of the active ingredient. With regard to FGB lactose, it is noted that the adhesion of the drug on the surface of the carrier particles is particularly strong. This results in a reduction of the inhalation efficiency (see abstracts and paragraph 3.2).

The finding of the authors of D1 as to the poor separation properties of FBG lactose is in line with the teaching of D2, which reports that the active particles are preferentially attracted to and adhere

most strongly to the sites of high surface energy, which are the asperities and the clefts (see page 7, line 21 to 22). Document D2 provides however a solution to this problem, namely the addition of an additive material. The particles of this substance adhere to the sites of high energy on the surface of the carrier. This forces the particles of the active ingredient to occupy the sites of low energy from which they can be easily released. The final result is a more efficient separation of the active ingredient in the airstream created on inhalation (page 7, line 23 to page 8 line 6).

The carrier particles tested in document D1, including FGB lactose, do not contain any additive material on their surface. Thus, in the Board's view the skilled person would regard the drawbacks associated with the use of FGB lactose as foreseeable behaviour for a carrier material having a surface with many asperities and clefts. However, since document D2 already provides the means for overcoming these drawbacks, namely the addition of an excipient, the skilled person would not disregard the teaching of document D1 as to the ability of the FGB lactose to transport a higher amount of active ingredient in view of the rugosity of its surface.

1.4.4 The appellant-patent proprietor observed that D2 suggests carrying out a treatment of the carrier particles in order to reduce the asperities on their surface (page 21, lines 5 to 20). In view of this indication, the skilled person would avoid modifying the surface of the carrier particles of D2 by enhancing their rugosity.

The Board observes in this respect that the surface treatment described in D2 has the function of reducing the number of high energy sites associated with the asperities as they cause too strong an adhesion of the active ingredient to the carrier (page 21, lines 10-20). The description of the general method for preparing the carrier particles which starts from the last paragraph of page 19 does not include said surface treatment which is described only as an optional step starting from page 21. As discussed in point 1.4.3 above, document D2 suggests the addition of an excipient as the principal method for avoiding too strong an adhesion of the drug to the carrier. The treatment of the carrier particles for reducing the number of the asperities therefore represents an optional procedure which has substantially the same purpose of the addition of the excipient.

In the Board's opinion, a skilled person seeking to enhance the amount of drug transported by the carrier would know from D1 that the particles should preferably have a high rugosity. He would therefore avoid carrying out the surface treatment disclosed in D2 because this is only an optional step and because the drawbacks associated with a high rugosity can be minimised even without said surface treatment, i.e. by adding an excipient.

1.4.5 In the light of these considerations, the Board concludes that the skilled person faced with the problem defined in point 1.3.3 above would follow the teaching of D1 to provide carrier particles having a highly fissured surface.

1.4.6 It is noted that D1 does not provide any information as to the width and depth of the fissures on the surface

of the FGB lactose. However, the specific dimensions recited in claim 1 of the patent in suit ("at least 5µm wide and at least 5µm deep") do not appear to have any particular significance because there are no data showing the criticality of the value 5µm. Hence, the indication in claim 1 of specific figures for the minimal width and depth cannot contribute to the inventiveness of the claim.

1.4.7 As discussed in point 1.2.2 above, in document D2 the size of the particles is described only in terms of aerodynamic diameter while claim 1 of the opposed patent recites also the diameter of the particles. However, it is stated in paragraph [0045] of the patent that the "diameter as measured with laser diffraction approximates the aerodynamic diameter". Considering that the carrier particles disclosed in D2 have preferably an aerodynamic diameter between 20µm and 250µm, it is very doubtful whether the indication in claim 1 of a diameter of "at least 50µm" could be regarded as a distinguishing feature over the disclosure of D2. In any case, there is no proof of effects associated with the specific dimension of the particle's diameter recited in claim 1. Hence, this feature does not provide any inventive contribution to the subject-matter of the claim.

1.5 In view of the above reasons, the Board concludes that the subject-matter of the main request does not comply with the requirements of Article 56 EPC.

Auxiliary request 1

2. *Inventive step*

2.1 Compared to claim 1 of the main request claim 1 of this request contains two additional features, namely the indication that the carrier particles have a mass median diameter of at least 200µm and the indication that the fine excipient particles are of the same material as the carrier particles.

2.2 The mass median diameter is a further parameter characterising the size of the carrier particles. The patent does not contain any data useful for assessing whether the selection of particles with a mass median diameter of at least 200µm results in some additional effect different from those considered for the carrier particles of the main request (see point 1.3.2 above). Nor has the appellant-patent proprietor submitted any argument in this respect. Accordingly, the Board concludes that this additional characterisation of the particle size does not provide any inventive contribution to the subject-matter of the claim.

2.3 As to the requirement that the fine excipient must be of the same material as the carrier, the Board observes that also in this case the patent does not provide any data useful for the appreciation of the effects associated with this feature. In its decision the opposition division considered that providing a formulation with less distinct chemical compounds has the advantage of reducing potential unfavourable interactions with the patient's body. To the benefit of the appellant-patent proprietor, the Board concurs with the observation made by the opposition division as to the effect associated with the choice of an excipient which is of the same material as the carrier.

2.3.1 In the Board's opinion, the skilled person working in the pharmaceutical field will always try to reduce the

number of different chemical substances to be used in the formulation of a medicament in order to minimize the risk of adverse drug reactions. At the same time he knows that formulations for use in inhaler devices comprising a carrier and an excipient which are of the same material, are commonly used in the prior art. This appears to be acknowledged in paragraph [0008] of the patent in suit where it is explained that it is known to improve the proportion of the drug reaching the lungs by adding an excipient which is "normally of the same material as the carrier". A specific example is provided by document D10 in which it is reported that the addition of micronised lactose to a carrier of coarse lactose improves the dispersion of the active ingredient (page 134, second paragraph of left column). Furthermore, the possibility of using an additive which is of the same material as the carrier is contemplated also in document D7, in which lactose is mentioned both as a suitable carrier material and as excipient (page 24 paragraph 3.3.2).

2.3.2 From the above, it is concluded that using an excipient which is of the same material as the carrier is a common measure in the field of formulations for inhalers. Hence, for the skilled person faced with the problem of providing a formulation for use in an inhaler device which is as safe as possible it would be obvious to adopt this measure.

2.4 On that basis it is concluded that claim 1 of auxiliary request 1 does not comply with the requirements of Article 56 EPC.

Auxiliary request 2

3. *Inventive step*

3.1 Claim 1 of auxiliary request 1 differs from claim 1 of the main request in the indication that the formulation has a "fines content of at least 20% by weight of the fines and carrier particles."

3.2 The feature added in claim 1 of this request expresses the effect associated with the presence of fissures on the surface of the carrier particles, namely the capacity of the carrier to transport a higher amount of fine materials, i.e. active ingredient and excipient.

This effect was already considered in the assessment of inventive step of the main request (see point 1.3 above). Accordingly, the arguments developed in respect to the inventive step of the main request apply also to this request.

3.3 In the light of the above, it is concluded that the subject-matter of auxiliary request 2 does not comply with the requirements of Article 56 EPC.

Auxiliary request 3

4. *Inventive step*

4.1 Claim 1 of this request differs from claim 1 of auxiliary request 2 in the indication that the carrier particles have a mass median diameter of at least 200µm.

For the reasons discussed in point 2.2 above, this additional feature does not provide any inventive contribution to the subject-matter claimed.

4.2 Accordingly, auxiliary request 3 does not comply with the requirements of Article 56 EPC.

Auxiliary request 4

5. *Inventive step*

5.1 Compared to claim 1 of auxiliary request 3, claim 1 of auxiliary request 4 differs in the indication that the fine excipient particles are of the same material as the carrier particles.

As discussed in points 2.3 to 2.4 above, the use of excipient particles which are of the same material as the carrier particles is regarded as an obvious technical measure.

5.2 It follows that also the subject-matter of auxiliary request 4 does not comply with the requirements of Article 56 EPC.

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. Fabiani J. Riolo

Decision electronically authenticated