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Datasheet for the decision of 20 November 2018

Case Number: T 0143/15 - 3.3.07

Application Number: 05738040.4

Publication Number: 1755555

IPC: A61K9/00, A61K31/40

Language of the proceedings: EN

Title of invention:
METHODS FOR PREPARING DRY POWDER COMPOSITIONS OF GLYCOPYRROLATE

Patent Proprietor:
Vectura Limited

Opponent:
Teva UK Limited

Headword:
Glycopyrrolate / VECTURA

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Decisions cited:
T 0439/92

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Case Number: T 0143/15 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 20 November 2018

Appellant: (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)
Respondent: (Opponent)	Teva UK Limited Ridings Point Whistler Drive Castleford WF10 5HX (GB)
Representative:	Elkington & Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 30 October 2014 revoking European patent No. 1755555 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	Y. Podbielski

Summary of Facts and Submissions

I. European Patent 1 755 555 B1 was granted on the basis of European patent application 05 738 040.4. Claim 1 of the patent as granted read as follows:

"A method for preparing a dry powder formulation suitable for inhalation comprising glycopyrrolate and magnesium stearate, wherein the glycopyrrolate is micronised and then undergoes a conditioning step, which step includes exposure to humid conditions of 30-100% RH at temperatures between 5°C to 90°C for at least 48 hours".

II. The patent was opposed on the grounds that its subject-matter lacked novelty and inventive step (Article 100(a) EPC), was not sufficiently disclosed (Article 100(b) EPC) and extended beyond the content of the application as filed (Article 100(c) EPC).

The following documents were among those cited during the first-instance proceedings:

D7: WO 02/43701

D8: WO 95/05805

D9: Excerpt from Chapter 5 of the textbook X-M. Zeng et al. *Particle interactions in dry powder formulations for inhalation*, Taylor & Francis, London and New York, 2001

D10: G.H. Ward and R.K. Schultz, Pharmaceut. Res. 1995, 12, 773-779

D11: B.C. Hancock and G. Zografi, J. Pharrn. Sci. 1997, 86, 1-12

D12: Experimental data filed by the proprietor by letter dated 12.09.2014

D13: Experimental data filed by the proprietor by letter dated 25.10.2013

III. The appeal of the patent proprietor (hereinafter: the appellant) lies against the decision of the opposition division to revoke the patent. The decision was based on the patent as granted as main request and on three auxiliary requests filed by letter dated 12 September 2014.

Concerning the assessment of inventive step for the main request, the opposition division considered that starting from D7 as the closest prior art, the claimed process differed by a conditioning step of exposure to defined humid conditions. No improved stability was shown to result therefrom. Hence the technical problem was seen as the provision of an alternative method for preparing a stable dry powder formulation suitable for inhalation comprising micronised glycopyrrolate and magnesium stearate. The claimed solution was found to be obvious in light of D8.

The opposition division likewise found that none of the auxiliary requests 1-3 met the requirements of Article 56 EPC.

IV. In the statement setting out the grounds of appeal, the appellant contested the opposition division's finding of lack of inventive step over D7 in respect of the main request (i.e. the patent as granted), relying

additionally on the following documents submitted with this statement:

D14: Technical experimental report

D15: Declaration from Mr Matthew Green

D16: Declaration from Dr David Morton

The appellant submitted that auxiliary requests 1-3 (filed in the proceedings before the opposition division) met the requirements of inventive step for the same reasons. Claim 1 of auxiliary requests 1-3 differed from the main request in respect of the following features:

Auxiliary request 1: "[...], which step includes exposure to humid conditions of ~~30~~50-~~100~~90% RH at temperatures between ~~5~~10°C to ~~90~~50°C for at least 48 hours".

Auxiliary request 2: "[...], which step includes exposure to humid conditions of ~~30~~50-~~100~~90% RH at temperatures between ~~5~~10°C to ~~90~~50°C for at least 48 hours, and wherein the powder is agitated or turned during conditioning to ensure that all of the particles are equally exposed to the humid atmosphere".

Auxiliary request 3: "[...], which step includes exposure to humid conditions of ~~30~~50-~~100~~90% RH at temperatures between ~~5~~10°C to ~~90~~50°C for at least 48 hours, wherein the magnesium stearate is predominantly present on the surface of the glycopyrrolate particles".

V. With the reply to the appeal of the patent proprietor, the opponent (hereinafter: the respondent) expressed *inter alia* the view that none of the requests fulfilled the requirements of Article 56 EPC.

VI. By letter dated 26 July 2016, the appellant presented further arguments regarding inventive step and submitted the following evidence in the form of photographs, hereinafter referred to as:

D17: photographs

VII. On 2 October 2018, the Board issued a communication pursuant to Article 15(1) RPBA.

With regard to inventive step, the Board observed that the method claimed in the patent in suit differed from the method shown in D7 in that the glycopyrrolate underwent a conditioning step in conditions as defined in claim 1. The stability of the resulting formulations did not appear to be thereby improved in comparison with the magnesium stearate - coated particles of D7. The problem to be solved was seen in the provision of an alternative method for preparing stable formulations of glycopyrrolate suitable for inhalation. D8 disclosed the use of a conditioning step, under the same conditions as in claim 1, to improve stability on storage of formulations for inhalation. The skilled person, presumed to be seeking a solution to the problem of providing an alternative preparative method, would consider that the addition of this step to the process known from D7 would still lead to stable formulations of glycopyrrolate, irrespective of any expected benefit.

VIII. By letter dated 11 October 2018, the appellant filed two further claim sets as auxiliary requests 4 and 5. Both auxiliary requests 4 and 5 differed from the main request by the deletion of dependent claims, but comprised the same claim 1 as in the main request.

IX. Oral proceedings took place on 20 November 2018 in the presence of both parties.

X. The appellant's arguments, as far as relevant for the present decision, may be summarised as follows:

The closest prior art D7 described the production of composite particles made by mechanofusing pre-micronized glycopyrrolate particles in the presence of magnesium stearate, resulting in fully coated, completely stable particles. The problem was seen as the provision of an alternative method for preparing a stable formulation of glycopyrrolate suitable for inhalation. The skilled person would not have combined the teaching of D7 with that of D8 because glycopyrrolate was highly hygroscopic and would not obviously have been stabilised by exposure to humid conditions. Moreover, the skilled person would not condition the glycopyrrolate before coating with magnesium stearate because [s]he would know that the conditioning process would have no effect on a completely coated active, and because the mechanofusion step would re-introduce amorphous material. The application of a conditioning step after coating with magnesium stearate was outside the scope of the claims because the complete coating would prevent the exposure of glycopyrrolate to humid conditions required by claim 1.

XI. The respondent's arguments, as far as relevant for the present decision, may be summarised as follows:

The claimed method differed from the disclosure of D7 in that a conditioning step was provided, under the conditions of 30-100% RH at 5-90°C for at least 48 hours. As there were no data showing any advantage for the distinguishing feature, the objective technical problem was the provision of an alternative method for preparing a formulation. D8 provided a clear pointer to conditioning the active ingredient under humid conditions as in the present invention in order to reduce the amorphous content and thereby improve storage stability. Contrary to the appellant's position, the teaching of D7 was not limited to a continuous, non-porous coating around the active ingredient; lastly the appellant's argument that, the composition of D7 being already stable, there was no motivation to modify it according to D8 was not persuasive. Alternatively a combination with the teaching of D9, D10 or D11 would equally lead to the claimed invention.

XII. The appellant requested that the decision under appeal be set aside and the opposition be rejected (i.e. that the patent be maintained as granted) or alternatively, that the patent be maintained on the basis of one of auxiliary requests 1-3 (filed in the proceedings before the opposition division) or on the basis of one of auxiliary requests 4 or 5 (submitted by letter dated 11 October 2018).

XIII. The respondent requested that the appeal be dismissed.

Reasons for the Decision

Main request (patent as granted)

1. Article 100(a) EPC, Inventive step

The problem underlying the claimed invention is the provision of dry powder formulations comprising glycopyrrolate and exhibiting greater stability on storage. These dry powder formulations are to be administered using dry powder inhalers (see patent in suit, page 2). Known micronized glycopyrrolate comprises surface hygroscopic amorphous material leading to formation of hard agglomerates upon moisture absorption (see [0015]). To address this problem, the claimed invention relies on a conditioning step, whereby exposure to moisture leads to re-crystallisation of the amorphous material (see [0035]), and on the addition of a force control agent (magnesium stearate) which reduces the cohesion between fine particles (see [0047]).

1.1 Both parties agree on the choice of document D7 as the closest prior art. The Board sees no reason to differ.

D7 (see the abstract) generally relates to a method of making composite active particles for inhalation, comprising the steps of milling particles of the active material with particles of an additive material, such as magnesium stearate. In D7, it is recognised that small particles of active material have a tendency to agglomerate and that milling increases the level of amorphous material on the surface of the milled particles, making them more cohesive (see pages 1-2; page 4 lines 13-15). The additive material promotes

dispersion of the particles and avoids the formation of agglomerates (e.g. page 4, lines 13-18). The method of D7 will in general produce composite active particles bearing the additive material in the form of a coating on their surface, which coating may be continuous or discontinuous (see page 3, lines 9-19; page 12, lines 5-16; page 6 lines 18-20).

A disclosure of glycopyrrolate as active material can be found in example 5 of D7, where micronised glycopyrrolate and magnesium stearate (in a ratio of 75:25 or 95:5) are milled together in a mechanofusion machine.

1.2 According to the appellant, the process shown in example 5 of D7 leads to a complete and coherent coating of magnesium stearate onto the glycopyrrolate particles, with both ratios of 75:25 and 95:5. A reproduction of example 5 of D7 (i.e. D14) and two declarations (D15 and D16) were submitted as evidence. The Board sees no reason to depart from these conclusions.

1.3 In the process of claim 1, the glycopyrrolate undergoes a conditioning step, "which step includes exposure to humid conditions [...]". According to the appellant, since claim 1 requires the glycopyrrolate to be exposed to these humid conditions, a process in which the conditioning step takes place after complete coating of the glycopyrrolate particle (as in D7) is outside the scope of the claims, because the coating will prevent the exposure of glycopyrrolate.

Even if following *arguendo* this interpretation, it remains the case that claim 1 requires the glycopyrrolate to be micronised and conditioned, and

the final formulation to comprise magnesium stearate, without limitation as to how this magnesium stearate is to be incorporated. Accordingly, the magnesium stearate may be incorporated as a coating after conditioning; indeed, a coating step is explicitly considered in the patent in suit in example 8 (which is not identified as a reference example), where a glycopyrrolate is coated with 5% magnesium stearate in a manner similar to that of D7.

Thus the claims cover embodiments in which glycopyrrolate is milled and then undergoes a conditioning step before being finally coated with magnesium stearate in the conditions of D7. Such an embodiment differs from the method shown in D7 by, and only by, the addition of the conditioning step as an intermediate step before coating.

1.4 It is undebated that the particles resulting from the claimed process do not exhibit any improved stability over those of D7 as a result of the conditioning step. The process of D7 was stated by the appellant (e.g. in D15) to result in an inhalable glycopyrrolate formulation with excellent stability. Neither example 7 of the patent in suit, nor any of D12-D16 allow for any proper comparison between conditioned and unconditioned formulations of magnesium stearate - coated glycopyrrolate. Accordingly no effect is shown to arise as a result of this additional step.

1.5 The Board thus concurs with the appellant's definition of the technical problem as the provision of an *alternative* method for preparing stable formulations of glycopyrrolate suitable for inhalation. Considering the evidence on file, this technical problem is regarded as solved by the subject-matter of claim 1.

1.6 Turning to the obviousness of the claimed solution, document D8 relates to a process for providing a stable crystalline form of a fine-grained substance or substance mixture which can be produced, stored and used while maintaining the aerodynamic properties required for inhalation (see the abstract). D8 thus belongs to the same technical field and addresses the same problem of stability on storage as D7 or the patent in suit. D8 explains on page 2, lines 10-21 that during micronisation of solids, disruption or activation of the crystalline structures often leads to varying degrees of disorder through the formation of defects or amorphous regions. Such regions are often more sensitive to moisture. D8 further states that it is necessary to convert the amorphous form to the more stable crystalline state. This is achieved using a conditioning step in which the micronised material is treated with a water containing vapour phase in a controlled fashion, under the same conditions as those defined in claim 1 of the patent in suit, namely a temperature between 0 and 100°C, preferably between 10 and 50°C, a relative humidity above 35%, preferably above 50%, for a time ranging from minutes to days (see page 5, line 15 to page 6, line 1). Thus D8 suggests to apply the claimed conditioning step as a solution to the same problem of stability on storage.

Regarding the order of steps, D8 also considers mixing the substances after conditioning (see page 10, lines 9-11) and recommends that the conditioning step be performed directly after micronisation (see paragraph bridging pages 10-11).

Accordingly, the Board considers that, in light of D8, the skilled person would anticipate that the addition

of a conditioning step prior to coating as taught in D7 would still lead to stable particles.

1.7 The appellant submits that the stability issue is already solved in D7, such that the skilled person would not subject the already stable glycopyrrolate particles to an unnecessary, long and hence inconvenient extra processing step when there was no expectation of a benefit in doing so. The appellant further argues that the skilled person would not consider recrystallising the amorphous surface of the particles using a conditioning step if this crystalline layer was subsequently to be destroyed by the coating step. In this respect, the appellant, referring to T 439/92, considered the modification to go beyond the limits imposed by the choice of D7 as the closest prior art.

For the Board, the addition of the conditioning step as an intermediate step between milling of glycopyrrolate and coating with magnesium stearate remains within the scope of the potential developments the skilled person would consider starting from D7: it is firstly to be noted that, although the specific conditions of example 5 of D7 lead to a complete coating, the general disclosure of D7 allows for partial, discontinuous or porous coating (see page 6, lines 18-20). Furthermore, the starting material in example 5 of D7 is micronized glycopyrrolate; according to D7 (see page 4, lines 13-15), it is known that milling generates amorphous material on the surface of the particles, making them more cohesive. Thus D7 would prompt the skilled person to address the presence of amorphous material in the starting material of D7 by adding a conditioning step as taught in D8 before coating with magnesium stearate. Thus, contrary to the appellant's position, a

combination with the teaching of D8 does not amount to a departure from the disclosure or framework of D7 (as in case T 439/92), but represents a further development which the skilled person would consider based on the information in D7.

It may be possible that a complete coating in the conditions taught in D7 will damage the crystalline state induced by the conditioning step of D8 on the surface of the particles. This however does not mean that the skilled person would, when combining these steps, thereby modify the closest prior art in a manner contrary to its purpose: the addition of the conditioning step does not jeopardize the properties of the (stable, coated) final formulation, is not detrimental to the coating step of D7, nor does it require any modification thereof.

As part of the problem-solution approach, the skilled person is assumed to seek a solution to the objective technical problem. As a consequence, in the context of the present invention, the modification of the known process by addition of the otherwise known conditioning step, without thereby achieving any benefit, cannot derive an inventive step from the very fact that the skilled person would expect no benefit from this modification.

The appellant also argues that the skilled person would not look to stabilise the highly hygroscopic glycopyrrolate by exposure to moisture as taught in D8; the evidence D17, comparing the physical state of micronised drugs after 4 days in vials, is cited to show the increased difficulty of working with glycopyrrolate as compared with other substances. However D17 does not appear relevant, as the skilled

person would not wait 4 days between micronisation and conditioning in light of the teaching of D8. Furthermore, if glycopyrrolate is so hygroscopic as to render the conditioning of D8 technically impracticable, then it must be observed that no such special precautions during conditioning are defined in claim 1.

Accordingly the main request does not comply with the requirements of Article 56 EPC.

Auxiliary request 1

2. Article 56 EPC

The more narrowly defined temperature (10-50°C) and relative humidity (50-90%) parameters do not depart from those explicitly mentioned in D8 (namely a temperature preferably between 10 and 50°C and a relative humidity preferably above 50%, see page 5, lines 15-36). Consequently the conclusion of lack of inventive step equally applies to auxiliary request 1.

Auxiliary request 2

3. Article 56 EPC

3.1 Starting from D7 as the closest prior art, the claimed process now differs in that the glycopyrrolate undergoes a conditioning step including exposure to humid conditions of 50-90% RH at temperatures between 10°C to 50°C for at least 48 hours, wherein "the powder is agitated or turned during conditioning to ensure that all of the particles are equally exposed to the humid atmosphere".

3.2 The added feature of agitation or turning of the powder is not shown to be associated with any additional effect on stability. The evidence cited regarding an effect of the conditioning step remains unconvincing, even taking this additional feature into account, for the reasons already given above (see point 1.5).

3.3 The objective technical problem thus remains the provision of an alternative method for preparing stable formulations of glycopyrrolate suitable for inhalation.

3.4 Considering that the way D8 addresses the stability problem is by provoking a phase transition from amorphous to crystalline state by contact with a water containing vapour phase, it follows that the skilled person would naturally seek to guarantee a proper contact when implementing the teaching of D8. An agitation or turning of the particles therefore represent a trivial addition to the teaching of D8, which the skilled person would consider as a matter of evidence. Accordingly, the subject-matter of auxiliary request 2 does not comply with the requirements of Article 56 EPC.

Auxiliary request 3

4. Article 56 EPC

The process disclosed in D7 leads to glycopyrrolate particles bearing a coating of magnesium stearate. The feature introduced in claim 1 of auxiliary request 3, according to which the magnesium stearate is predominantly present on the surface of the glycopyrrolate particles, is consequently fulfilled by the particles produced in the closest prior art D7, and

does not modify the above conclusions on inventive step.

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

Auxiliary requests 4 and 5

5. Article 56 EPC

Claim 1 of each of auxiliary requests 4 and 5 is identical to claim 1 of the main request. These requests thus do not comply with the requirements of Article 56 EPC either.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Fabiani A. Usuelli

Decision electronically authenticated