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Datasheet for the decision of 30 November 2021

Case Number: T 2289/17 - 3.3.07

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Language of the proceedings: EN

Title of invention:

DRY POWDER FORMULATIONS OF PARTICLES THAT CONTAIN TWO OR MORE ACTIVE INGREDIENTS FOR TREATING OBSTRUCTIVE OR INFLAMMATORY AIRWAYS DISEASES

Patent Proprietor:

Novartis AG

Opponent:

Vectura Limited

Headword:

Dry powder formulations / NOVARTIS

Relevant legal provisions:

EPC Art. 100(a), 56

This datasheet is not part of the Decision
It can be changed at any time and without notice

Keyword:
Inventive step - (yes)

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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 2289/17 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 30 November 2021

Appellant: (Opponent)	Vectura Limited 1 Prospect West Chippenham, Wiltshire SN14 6FH (GB)
Representative:	Clarke, Christopher John Vectura Limited Intellectual Property Department One Prospect West Chippenham Wiltshire SN14 6FH (GB)
Respondent: (Patent Proprietor)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Frigola Deulofeu, Maria Carmen Novartis Pharma AG Patent Department 4002 Basel (CH)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 31 July 2017 rejecting the opposition filed against European patent No. 2670395 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	D. Boulois
Members:	E. Duval
	Y. Podbielski

Summary of Facts and Submissions

I. European Patent EP 2 670 395 (hereinafter the patent) was granted on the basis of 15 claims.

Claim 1 of the patent read as follows:

"A dry powder formulation for inhalation comprising spray-dried particles that comprise a core of a first active ingredient in substantially crystalline form that is coated with a layer of a second active ingredient in substantially amorphous form that is dispersed in a pharmaceutically acceptable hydrophobic excipient."

Claim 13 of the patent read as follows:

"A process for preparing a dry powder formulation of spray-dried particles that contain a first active ingredient and a second active ingredient, the process comprising the steps of: (a) preparing a feedstock comprising the second active ingredient dissolved in a solvent phase, a hydrophobic excipient, and crystalline particles of the first active ingredient, said crystalline particles being substantially insoluble in said solvent phase; and (b) spray-drying said feedstock to provide the formulation, wherein said particles comprise a core of the first active ingredient in substantially crystalline form that is coated with a layer of the second active ingredient in substantially amorphous form that is dispersed in a pharmaceutically acceptable hydrophobic excipient."

II. The patent was opposed on the grounds that its subject-matter lacked novelty and inventive step and it was not sufficiently disclosed.

III. The opposition division decided to reject the opposition.

The decision cited in particular the following documents:

D6: US 2005/0003004 A1
D7: US 2009/0004282 A1
D8: US 2004/0052732 A1
D9: US 2004/0028619 A1
D10: US 2009/0181100 A1

IV. According to the decision under appeal,

(a) The claimed subject-matter was sufficiently disclosed and was novel over D6 and D7.

(b) D7 was the closest prior art, because it had more technical features in common with the opposed patent than D8 or D9. The claimed subject-matter differed from D7 in that it required a spray-drying process, in that the second active agent must be in amorphous form and in that the second active agent is dispersed in a pharmaceutically acceptable hydrophobic excipient. With regard to the amorphous form of the second active ingredient, the objective technical problem was the provision of an alternative dry powder formulation having a blend of multiple active ingredients. D7 did not provide any incentive to consider any amorphous form, in particular of the second active agent. With regard to the dispersion in a hydrophobic excipient, the

problem was the provision of particles with reduced cohesiveness between adjacent particles. There were no pointers to the claimed solution. The criteria of inventive step were accordingly met.

V. The opponent (appellant) lodged an appeal against the decision of the opposition division.

VI. In its reply to the appeal, the patent proprietor (respondent) defended its case on the basis of the patent as granted, auxiliary requests 1-2 filed on 11 August 2016 and auxiliary request 3 filed on 12 May 2017.

VII. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA dated 20 December 2019.

VIII. Oral proceedings were held before the Board on 30 November 2021 by means of videoconference.

IX. The appellant acknowledged, during the oral proceedings before the Board, that the subject-matter of the main request was novel over D6. The appellant's arguments regarding inventive step may be summarised as follows:

Inventive step was to be assessed starting from each of D7, D8 and D9, because all of these documents were plausible starting points.

In some embodiments, D7 disclosed dry powder formulations comprising particles having a core of a crystalline active ingredient and a coating of an amorphous second active ingredient, made by a precipitation process, optionally in the presence of a surfactant or hydrophobic excipient such as oleates or

stearates (see paragraphs [0038], [0063], [0023] and [0052]-[0053]). The subject-matter of claim 1 of the main request only differed from D7 in that the second active ingredient was dispersed in the pharmaceutically acceptable hydrophobic excipient. The product-by process feature of claim 1 requiring the particles to be spray-dried did not impart any further feature to the claimed formulation and hence did not represent a differentiating feature over D7. Furthermore, the amorphous state of the second active ingredient was also disclosed in D7.

No comparison had been adduced to show an effect resulting from the differentiating feature. The problem was accordingly to provide alternative dry powder formulations containing particles having a core of a crystalline active ingredient and a coating of an amorphous second active ingredient.

The claimed solution was obvious in light of D6 or D10. D6 disclosed dry powder formulations comprising particles in which a crystalline active ingredient was encapsulated in a coating which could include a second active agent (see paragraph [0050] and figure 1c). D6 mentioned phospholipids (see paragraph [0037]) and allowed for large amounts of coating (see paragraphs [0042]-[0043]). It was also known that hydrophobic excipients, such as phospholipids, could be used in dry powder formulations to improve their stability or dispersibility (see paragraph [0024] of D6) and to control the particle size and shape (see paragraph [0023]-[0025] and [0052]-[0053] of D7). Similarly, D10 described the production of particles for inhalation comprising an active ingredient and a surface modifier (see paragraph [0022]), which may be a hydrophobic material such as a phospholipid (see paragraphs [0105]-

[0106]). The amount of surface modifier indicated in paragraph [0109] of D10 would result in a dispersion of the drug in a continuous excipient phase.

D8 and D9 were also suitable starting points for the assessment of inventive step. D8 disclosed inhalation particles incorporating a combination of two or more different active ingredients, and optionally additives (see paragraphs [0001] and [0049]). Example 1 disclosed particles comprising a first active ingredient in crystalline form and a second partly or totally in the amorphous state ([0067]). Figure 6 of D8 showed a particle with a rounded structure, hence the crystalline component having sharp edges had to be coated with the amorphous second active ingredient. The disclosure of D9 was similar to that of D8. The only differentiating feature of claim 1 of the main request was the second active being dispersed in a pharmaceutically acceptable hydrophobic excipient.

There was no evidence of any technical effect resulting from the hydrophobic excipient. Consequently, the problem was to provide an alternative formulation.

The claimed solution did not involve an inventive step considering the teaching D6 or D10 discussed above.

X. The respondent's arguments may be summarised as follows:

D7 represented the closest prior art, because it had more features in common with the invention than D8 or D9. The claimed invention differed from D7 in that (i) the invention required a spray-drying process, (ii) the second active had to be in amorphous form, and (iii) the second active was dispersed in a hydrophobic

excipient. Feature (iii) led to an enhanced surface rugosity which resulted in enhanced aerosol performance (see paragraphs [0020], [0064], [0154] and [0161] of the patent), as compared with the particles of D7 (see Figures 3, 7 and 9).

Even if the problem was seen as the provision of alternative formulations of two or more active ingredients in fixed dose combination for inhalation, the claimed solution involved an inventive step. There was nothing in D7 or in any of the other cited documents to motivate the skilled person to modify the particle surface and use hydrophobic excipients to establish a dispersion. D6 focused primarily on formulations comprising one active ingredient, obtained using a technology (spray-drying) which was unrelated to the precipitation method used in D7, and made only one brief mention of a second active ingredient. D10 merely disclosed the presence of one active ingredient, only mentioned some hydrophobic excipients in a long list of surfactants (see [0105]-[0106]) without exemplifying any, and provided no meaningful disclosure of a high amount of surfactant. There was no expectation that the claimed formulations would have sufficient stability to be used in inhalation. The mention of a coating in D6 or D10, even with larger amounts of excipient, did not amount to a disclosure that the second active ingredient be dispersed therein.

The claimed subject-matter also involved an inventive step starting from D8 and D9 as closest prior art. D8 did not show the feature pertaining to the dispersion in the hydrophobic excipient. Furthermore, no information regarding the morphology of the particles could be inferred from figure 6 of D8. Lastly,

paragraph [0049] of D8 provided no incentive to add additives in such amounts as to coat the particles.

XI. The appellant requests that the decision under appeal be set aside and that the patent be revoked.

XII. The respondent requests that the appeal be dismissed, or, alternatively, that the patent be maintained in amended form on the basis of one of auxiliary requests 1-2 filed on 11 August 2016 or auxiliary request 3 filed on 12 May 2017.

Reasons for the Decision

1. Main request (patent as granted), inventive step

1.1 The problem underlying the claimed invention is, according to paragraphs [0009] and [0011] of the patent, to provide improved formulations of two or more active ingredients in fixed dose combination for inhalation, to overcome the dosing issues associated with blends of multiple active ingredients, and to provide for improvements in dose consistency and lung targeting.

Each of D7 (see paragraphs [0001] and [0010]), D8 (see paragraphs [0006]-[0009]) and D9 (see paragraphs [0004]-[0007]) shares these objectives.

1.2 Inventive step starting from D7

1.2.1 In D7, a suspension of a first active compound and a solution of a second active compound are contacted with a dense fluid such that the second active compound precipitates in the presence of the first active

compound (see paragraphs [0013]-[0015]). The process may result in the first active compound being encased in the second active compound (see paragraph [0033]). In particular the resulting particles may comprise a core of the first active compound coated with the second active compound (see paragraph [0038]). In the decision under appeal (see paragraph 24), it is deduced from paragraphs [0015] and [0063] of D7 that the first active ingredient may be in crystalline form while the second active ingredient is in amorphous form. The Board shares this opinion.

The presence of a hydrophobic excipient, such as a phospholipid (which is used as hydrophobic excipient in the examples of the patent), is mentioned in paragraphs [0023]-[0026] of D7. However, D7 does not disclose the feature relating to the second active ingredient being dispersed in a pharmaceutically acceptable hydrophobic excipient.

For the purposes of the present decision, it is not necessary to assess whether claim 1 contains further features differentiating its subject-matter from D7, such as the feature that the particles result from spray-drying.

1.2.2 According to the respondent, the feature pertaining to the second active ingredient being dispersed in a hydrophobic excipient leads to an enhanced surface rugosity which results in enhanced aerosol performance. Beyond the statements of paragraphs [0064] and [0020] of the patent, the respondent relies in this respect on a comparison of the particles of D7 (see figures 3, 7 and 9) with those of the patent (see examples 1 and 2, paragraphs [0154] and [0161]). However, this comparison does not demonstrate that the alleged effect results

from the differentiating feature, considering that the particles differ in numerous further respects.

Nonetheless, it is shown in the patent, and it is not contested by the appellant, that the claimed formulations are suitable for inhalation.

1.2.3 Consequently, the Board agrees with the technical problem proposed by the respondent, namely the provision of alternative formulations of two or more active ingredients in fixed dose combination for inhalation. Specifying in the problem, as the appellant proposed, that the first active ingredient should be crystalline and the second active ingredient amorphous would in any case not lead to a different conclusion, these features being already known from D7.

1.2.4 For the following reasons, the Board finds that none of the documents cited by the appellant give any incentive to modify the coating of the particles of D7 in the way defined by claim 1 of the main request.

D6 discloses (see paragraph [0050] and figure 1c) a particle morphology in which an active agent (10), which may be in crystalline or non-crystalline or amorphous form, is encapsulated with a coating material (12). The coating layer (12) may optionally include the active agent or a second active agent. However, D6 is silent about the optional second active agent being amorphous, the manner in which it should be included in the coating or the nature of this coating in such a case. D6 does not disclose any dispersion. The appellant's objection supposes that the skilled person select the highest amounts of coating material generally permitted by D6 (see the wide range for the ratio of active agent to coating material in paragraph

[0043]), despite the statements pointing to the opposite in paragraph [0042], and choose as coating a hydrophobic excipient such as phospholipids, which are mentioned among many excipients or dispersibility enhancing agent in D6 (see paragraphs [0024] and [0037]). But, contrary to the appellant's view, making these choices would not lead to particles as defined in claim 1 of the main request, because the skilled person would additionally have to include, in the excipient coating, the second active ingredient specifically in amorphous form as a dispersion. There is no teaching to that effect in D6, and no indication that modifying the particles in such a way would still afford a dry powder suitable for inhalation.

D10 does not come closer to the differentiating feature. D10 discloses dry powder formulations made by spray-drying aqueous dispersions of a nanoparticulate drug and a surface modifier (see paragraph [0022]). D10 mentions hydrophobic excipients such as phospholipids among numerous surface modifiers (see paragraphs [0105]-[0106]), and discloses unspecific ranges for the ratio of drug to surface modifiers (see paragraph [0109]). D10 is entirely silent about the possible presence of an amorphous second active ingredient dispersed in the surface modifier.

Thus, even if the skilled person were to combine the teachings of D7 with those of D6 or D10, they would not arrive at the subject-matter of claim 1 of the main request.

1.3 The appellant's alternative objections starting from D8 or D9 do not modify this conclusion.

D8 and D9 (which have similar contents) also fail to disclose the feature relating to the second active ingredient being dispersed in a pharmaceutically acceptable hydrophobic excipient. In addition, neither D8 nor D9 disclose a particle morphology comprising a core of the first active ingredient coated with a layer of the second active ingredient. In D8 and D9, dry powder formulations are prepared using an aerosol flow reactor or spray drying (see figure 1 and paragraph [0034] of D8). The particles may contain two active ingredients, one of which is crystalline and the other amorphous (see example 1, especially paragraph [0067]). However it is not derivable from D8 that the preparation process shown therein, in which both active ingredients are dissolved in the feedstock, must lead to particles having the crystalline active agent as the core and the amorphous second active agent as a coating. Figure 6 merely shows a rounded particle shape, from which no conclusion as to such a morphology can be inferred.

1.4 Thus, the subject-matter of claim 1 of the main request meets the requirements of inventive step.

1.5 Claim 13 relates to a process for preparing a dry powder formulation of spray-dried particles defined by the same features as the particles of claim 1. Accordingly, this process involves an inventive step for the same reasons.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos D. Boulois

Decision electronically authenticated