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Datasheet for the decision of 20 March 2018

Case Number: T 0899/15 - 3.3.07

Application Number: 08859423.9

Publication Number: 2234595

IPC: A61K9/00, A61K9/14, A61K31/4015

Language of the proceedings: EN

Title of invention:
Process for reducing the tendency of a glycopyyronium salt to aggegate during storage.

Patent Proprietor:
Novartis AG

Opponents:
Teva UK Limited
I P S Intellectual Property Services

Headword:
Glycopyrronium salt/NOVARTIS

Relevant legal provisions:
EPC Art. 123(2), 56, 100(b)

Keyword:

Amendments - allowable (yes)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

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Beschwerdekammern

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Case Number: T 0899/15 - 3.3.07

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

Appellant: (Opponent 1)	Teva UK Limited Ridings Point Whistler Drive Castleford WF10 5HX (GB)
Representative:	Gillard, Richard Edward Elkington and Fife LLP Thavies Inn House 3-4 Holborn Circus London EC1N 2HA (GB)
(Opponent 2)	I P S Intellectual Property Services 11 Rue La Fayette 75009 Paris (FR)
Representative:	Casalonga, Axel Casalonga & Partners Bayerstrasse 71-73 80335 München (DE)
Respondent: (Patent Proprietor)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Warner, James Alexander Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 5 March 2015 rejecting the opposition filed against European patent No. 2234595 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	A. Usuelli
	C. Schmidt

Summary of Facts and Submissions

I. European patent No. 2 234 595, based on European patent application No. 08859423.9, was granted on the basis of 7 claims.

Independent claim 1 read as follows:

"1. A process for reducing the tendency of a glycopyrronium salt to aggregate and/or agglomerate during storage, the process comprising the steps of:
(a) micronising the glycopyrronium salt to give a mean particle size of less than about 10 µm; and
(b) exposing the micronised glycopyrronium salt to a dry environment at a temperature between 40°C and 120°C for at least six hours, said environment being substantially devoid of any solvent or solvent vapour".

II. Two oppositions were filed against the patent on the grounds that its subject-matter lacked inventive step, was not sufficiently disclosed and it extended beyond the content of the application as filed.

The documents cited during the opposition proceedings included the following:

D5: WO 2005/105043
D9: International journal of pharmaceutics, 193 (2000), 247-259
D10: Particulate interactions in dry powder formulations for inhalation, Taylor & Francis, (2001), 133-138 and 172.
D11: Drug Development and industrial pharmacy, 29, 10, 1077-1084, 2003

III. By decision posted on 5 March 2015 the opposition division rejected the opposition. In the decision, the opposition division came *inter alia* to the following conclusions:

(a) The process of claim 1 had a basis in original claim 5 in combination with page 6 of the description. The requirements of Article 123(2) EPC were therefore met.

(b) The patent was sufficiently disclosed.

(c) Document D5 was the closest prior art for the assessment of inventive step. The process defined in claim 1 of the opposed patent differed from the process of D5 on account of step (b). The technical problem was to be seen in the provision of an alternative process for increasing the stability of micronized glycopyrrolate powders. None of the other prior art documents including D9 and D10 suggested a step of drying at elevated temperature as defined in step (b) of claim 1. The requirements of Article 56 EPC were therefore met.

IV. Opponent 1 (hereinafter: the appellant) appealed the decision of the opposition division. An appeal was formed also by opponent 2 but it was withdrawn by letter of 8 July 2015.

V. In its reply to the appeal submitted on 30 November 2015 the patent proprietor (hereinafter: the respondent) requested that the appeal be dismissed.

VI. In a communication pursuant to Article 15(1) RPBA issued on 5 February 2018, the Board expressed the opinion that the patent was sufficiently disclosed and

met the requirements of Article 123(2) EPC. In relation to Article 56 EPC, it observed that one of the points of discussion during the oral proceedings was whether the skilled person would have regarded the teaching of D9 as specific to the revatropate hydrobromate or whether he would have considered this teaching also when confronted with the problem of increasing the stability of micronised glycopyrrolate powders.

VII. Oral proceedings before the Board were held on 20 March 2018. Regarding the course of the oral proceedings, reference is made to the minutes.

VIII. The appellant's arguments, as far as they are relevant for the present decision, can be summarised as follows:

(a) Article 123(2) EPC

In claim 1 both the definition of the drug substance and the definition of the drying environment were limited. This amendment did not comply with the requirements of Article 123(2) EPC.

(b) Sufficiency of disclosure

Claim 1 related to the preparation of a micronised powder of a glycopyrronium salt, i.e. a pharmaceutical product. However, the patent did not contain any teaching on how to prepare a pharmaceutical composition.

(c) Inventive step

Document D5, representing the closest prior art for the assessment of inventive step, referred to alternative methods for improving the stability of glycopyrrolate

formulation. These included a conditioning process which involved exposing glycopyrrolate to humid conditions of 30 to 100% relative humidity, for 10 minutes to 48 hours, at 5° to 90°C. The process of the patent differed from the disclosure of D5 in the specific combination of drying condition, temperature and duration of the drying treatment defined in step (b). The technical problem was the provision of an alternative process for conditioning a glycopyrrolate powder. Document D9 addressed the problem of stabilizing revatropate hydrobromide in micronised form and suggested to perform a drying process after the micronisation. The teaching of D9 was in line with the indication of D10, which explained that temperature and humidity affected the stability of micronised powders. Document D11 suggested to treat the micronised powders of salbutamol under humid conditions. However, the skilled person would have not considered the teaching of this document since salbutamol had a very different chemical structure and a different biological activity than glycopyrrolate.

IX. In relation to the requirement of inventive step, the respondent essentially argued as follows:

Document D5 gave a clear teaching to treat the dry powder formulation of glycopyrrolate under conditions of high humidity. For instance in example 7 the conditioning step was carried out at 60% of relative humidity. The solution proposed in claim 1 of the patent, namely to expose the micronised glycopirrinium salt to a dry environment, was inventive even if the technical problem was formulated as the provision of an alternative process for conditioning glycopyrrolate. Document D9, considered by the appellant in combination with D5, concerned a different compound, namely

revatropate hydrobromide. The skilled person had no reason to combine the teachings of D5 and D9 since these documents disclosed two different methods for treating two different products.

X. The appellant requested that the decision under appeal be set aside and that European patent No. 2 234 695 be revoked.

XI. The respondent requested that the appeal be dismissed.

Reasons for the Decision

Main request (patent as granted)

1. Article 123(2) EPC

1.1 Claim 1 of the patent derives from the introduction in claim 5 as filed of the feature disclosed in page 6 (third complete paragraph) indicating that the environment is substantially devoid of any solvent or solvent vapour. In claim 5 as filed the drug substance is defined as a glycopyrronium salt.

The sentence of page 6 relates in general to the process of the invention and is not restricted to any particular active ingredient. Thus, it relates also to the process of original claim 5 wherein the drug substance is a glycopyrronium salt.

Thus, the limitations introduced in claim 1 do not result in an addition of subject-matter. The requirement of Article 123(2) EPC is therefore met.

2. Sufficiency of disclosure

2.1 The appellant's objection in relation to the requirement of sufficiency of disclosure is based upon the observation that the patent provides the skilled person with no teaching of how to prepare a medicinal product. However, as noted by the opposition division, claim 1 does not refer to a medicinal product. The appellant's objection is therefore irrelevant.

2.2 Hence, the opposition ground pursuant to Article 100(b) EPC does not prejudice the maintenance of the patent as granted.

3. Inventive step

3.1 Closest prior art

3.1.1 The Board concurs with the parties and with the opposition division that document D5 represents the closest prior art.

3.1.2 This document relates to stable dry powder compositions containing a glycopyrrolate salt, such as glycopyrronium bromide (page 1, lines 1 to 4). Starting from the last paragraph of page 5, document D5 discloses various measures for increasing the stability of the powder formulation. One of the measures is a method of conditioning the micronised powder which involves exposing the micronised glycopyrrolate to humid conditions of 30 to 100% relative humidity (RH), preferably 40 to 95% RH, for at least 10 minutes, at a temperature in the range 5°C to 90°C, preferably 10°C to 50°C (pages 37 line 8 to page 38 line 5). Example 7 discloses the conditioning of different batches of

glycopyrrolate. The procedures are carried out at 25°C and 60% RH.

3.1.3 In the process according to the opposed patent, the stabilisation of the glycopyrrolate is achieved by exposing the micronised product to a dry environment, at a temperature between 40°C and 120°C for at least six hours (step (b)). A dry environment is defined as an ambient which is devoid or at least substantially devoid of any solvent or solvent vapour, including any organic solvents or water (see claim 1 and [0031]). The Board considers that this definition of "dry environment" clearly excludes the range of humidities defined in D5 (30 to 100% RH).

3.1.4 Thus, the process defined in claim 1 of the patent differs from the disclosure of D5 in the conditioning step (step (b)) and in particular in the requirement that this step is carried out in a dry environment.

3.2 Technical problem

3.2.1 According to example 1 of the patent, if fresh micronised glycopyrrolate is exposed to increased humidity, a particle aggregation and a smoothening of the particle surface is observed. In contrast, if it is dried in the conditions defined in paragraph [0044] of example 1 (storage in a drying chamber at 70°C for 48 hours), no particle aggregation is observed if the material is exposed to increased humidity afterwards, and also the surface remains rough (see [0049]). On the basis of this example, the technical problem can be formulated as proposed by the opposition division, namely the provision of an alternative process for increasing the stability of micronised glycopyrrolate powders.

3.3 Obviousness

3.3.1 The appellant argues that the subject-matter of claim 1 is not inventive since the skilled person would find in document D9 an incentive to solve the technical problem defined in point 3.2.1 above by performing a conditioning step in a dry environment.

3.3.2 Document D9 relates to revatropate hydrobromate, a substance that is reported to agglomerate on storage after micronisation (page 247, right column).

The authors of D9 consider *inter alia* the effect of storing the micronised powders over phosphorous pentoxide or activated clay, to protect them from moisture (page 249, left column). Figure 11, refers to a sample of micronised revatropate hydrobromate dried over phosphorous pentoxide for 39 days. In the conclusions (page 259 left column), it is observed that the samples of micronised revatropate hydrobromate need to be stored at less than 25% RH immediately after micronisation to prevent agglomeration.

3.3.3 Document D9 therefore suggests that the tendency of revatropate hydrobromate to agglomerate after micronisation can be reduced by treating the substance in an environment of low humidity for long periods.

3.3.4 On the other hand documents D10 and D11 suggest, in relation to salbutamol, to adopt different measures in order to stabilize the micronised powder.

In particular, both documents suggest conditions of high relative humidity in order to reduce the presence of amorphous regions which can cause problem of

stability of the powders (D10, paragraph 5.2.1 lines 14 to 22; D11 sections "Conditioning with elevated temperature" and "Conditioning with moisture" starting from page 1079).

3.3.5 In the Board's view, a person skilled in the art would conclude, on the basis of the teaching of documents D5 and D9 to D11, that the technical measures for stabilizing a micronised substance are very much dependent on the nature of this substance. Hence, when confronted with the problem of stabilizing micronised glycopyrronium salts he would give more weight to the teaching of documents concerning the same compound.

In the present case, among the relevant prior art documents only D5 relates to glycopyrronium salts. As discussed above this document suggests exposing the micronised glycopyrrolate salt to humid conditions in order to increase its stability. In the Board's view, the skilled person would have no reason to modify the teaching of this document in the light of the disclosure of D9, which concerns a different compound and propose a radically different approach to stabilise a micronised powder, namely to treat the substance in an environment of low humidity.

4. For the above reasons the Board considers that the subject-matter of the patent meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated