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Datasheet for the decision of 15 December 2020

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Title of invention:
COMPOSITIONS OF GLYCOPYRRONIUM SALT FOR INHALATION

Patent Proprietor:
Novartis AG

Opponent:
Teva UK Limited

Headword:
Compositions of glycopyrronium salt for inhalation / NOVARTIS

Relevant legal provisions:
EPC Art. 100(a), 56
RPBA 2020 Art. 13(1)

Keyword:
Inventive step - (no)
Late-filed document - admitted (no)

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Case Number: T 0916/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 15 December 2020

Appellant: (Opponent)	Teva UK Limited Ridings Point Whistler Drive Castleford WF10 5HX (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
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 16 February 2016 rejecting the opposition filed against European patent No. 2037879 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	C. Schmidt

Summary of Facts and Submissions

I. European Patent 2 037 879 ("the patent") was granted on the basis of 15 claims. Claim 1 of the patent as granted read as follows:

"A process for preparing a dry powder formulation of a glycopyrronium salt for inhalation that comprises the steps of (a) mixing a glycopyrronium salt and an anti-adherent agent to give a homogeneous blend; (b) micronising the blend; and (c) admixing carrier particles to form a dry powder formulation, wherein the process enhances the stability of the glycopyrronium salt."

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

III. The opposition division took the decision to reject the opposition filed against the patent.

The decision cited in particular the following documents:

D2: WO 2005/105043
D3: WO 02/43701

IV. In essence, the opposition division decided that:

(a) The patent met the requirements of Article 123(2) EPC and of sufficiency of disclosure.

(b) D2 was the closest prior art. The subject-matter of claim 1 of the patent differed from the disclosure of D2 (example 8) by the step (b) of micronising the blend. The patent did not show any technical effect of the invention over D2. The technical problem was the provision of an alternative glycopyrrolate dry powder formulation for inhalation having acceptable storage stability. Neither D2 alone nor its combination with any of the further cited prior art would incite the skilled person to include a co-micronisation step in the process according to D2. This conclusion would not be modified even if D3 were considered to be the closest prior art. Thus the requirements of Article 56 EPC were met.

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

VI. In reply to the appeal, the patent proprietor (respondent) defended its case on the basis of the patent as granted as sole request.

VII. By letter dated 23 December 2019, the appellant introduced the following document:

D7: P. Begat et al., KONA, 2005, 23, 109-121

VIII. The Board set out its preliminary opinion in a communication pursuant to Article 15(1) RPBA.

IX. Oral proceedings were held before the Board.

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

entirety. It further requested that document D7 be admitted into the proceedings.

XI. The respondent requests that the appeal be dismissed - i.e that the patent be maintained as granted - and that the late filed document D7 be not admitted into the proceedings.

XII. The appellant's arguments can be summarised as follows:

(a) D7 should be admitted into the proceedings on account of its *prima facie* relevance. In particular, D7 investigated the influence of force control agents on cohesive-adhesive balance in DPI formulations. Although it used salbutamol sulfate as a model drug, the teaching of D7 was not intended to be limited to this drug.

(b) D2 was concerned with the same or similar purpose/ effect as the patent and could be taken as the closest prior art.

D2 was directed to approaches for improving the stability of glycopyrrolate formulations over time. D2 identified the instability of the particles and their cohesion to be due to moisture absorption. In one option, this was addressed by the application of an additive, e.g. magnesium stearate, to the surface of the glycopyrrolate particles, using high-shear blending or other techniques.

Example 8 of D2 used mechanofusion for the blending step, and set out alternative milling processes at page 35, lines 18-20. Although in this example 8 the glycopyrrolate was already micronised, D2 stated that size reduction "may occur" (see page

35, lines 30-31). Page 36, lines 25-28 disclosed the mixing of the composite active/additive particles with a coarse carrier.

The mechanofusion step of example 8 achieved the effects of both the mixing step (a) and the micronising step (b) of claim 1. As the example only stated that size reduction "may occur", the distinguishing feature was the application of a size reduction step as part of the blending process.

It was plausible that both the claimed process and that of example 8 of D2 achieved the same end result, namely micronised glycopyrrolate with a coating of magnesium stearate prior to blending with the coarse carrier. The patent provided no comparative data.

The objective technical problem was therefore the provision of an alternative process. The addition to the objective technical problem that the formulation has an acceptable storage stability seemed superfluous, given that this was covered by the word "alternative".

Although example 8 chose to start with pre-micronised glycopyrrolate, this was not stated in D2 as a whole as being an essential feature of the method. Rather, in view of the suggestion in D2 that size reduction "may occur", it would have been obvious for the skilled person to start instead with a non-micronised material and incorporate the size-reduction step into the co-milling process.

XIII. The respondent's arguments can be summarised as follows:

(a) D7 was not *prima facie* relevant. In particular, in D7, the term "model" referred to representative formulations of salbutamol, but not to salbutamol as a "model" drug itself. Hence D7 neither referred to glycopyrrolate, nor could be interpreted as a general teaching having wider applicability beyond the specific drug salbutamol.

(b) D2 was the closest prior art.

In D2 (e.g. example 8), glycopyrrolate was pre-micronised prior to being blended with the anti-adherent agent in a mechanofusion machine.

The claimed invention differed from the process of D2 by the step (b) of co-micronisation, whereby glycopyrrolate and an anti-adherent agent were mixed prior to being micronised together. The mechanofusion process used in D2 could not be equated with the co-micronisation process of step (b) of claim 1.

The co-micronisation step (b) of claim 1 provided advantageous effects compared to the process of the closest prior art D2, as shown by example 2 of the patent: formulation 2 represented an example of a process such as that conducted in D2, where the particle size reduction was carried out separately before blending of the glycopyrronium salt and the anti-adherent agent. In contrast, formulation 3 represented an example of a process where particle size reduction was carried out together, via the co-micronisation process of step (b) of claim 1.

The comparison of formulation 3 and 2 showed that the process of the invention provided a dry powder formulation of a glycopyrrolate which was more stable over time upon storage.

Even if the formulation of the technical problem as an improvement over D2 could not be acknowledged, the technical problem had to be formulated, taking into account the effects exemplified in the patent and the explicit requirement of claim 1 itself that the stability of the glycopyrrolate be enhanced, as the provision of an alternative glycopyrrolate dry powder formulation for inhalation *having acceptable storage stability*.

The skilled person would have had no reasonable expectation that changing the process of D2 to one in which the glycopyrrolate and anti-adherent agent are co-micronised would have led to a process where the formulation has acceptable storage stability. D2 taught that micronized glycopyrrolate suffered from stability problems on storage, and sought to overcome these problems by various techniques, none of which was co-micronisation of the glycopyrrolate with the anti-adherent agent. Any size reduction contemplated for the mechanofusion of D2 meant a further refinement of particles that have already been micronised, e.g. from ~10 µm to ~5 µm. This was not the same as the "micronisation" of step (b) of claim 1, which referred to a reduction of the particle size of large particles down to the micronised range that is suitable for administration by inhalation. Considering how unpredictable the interactions between the different materials in dry powder formulations of drugs such as glycopyrrolate could be, the skilled

person looking to provide an alternative formulation that was “as good as” D2 in terms of stability would have been cautious of making any significant changes to the way that the materials were processed, especially in the absence of any guidance in the prior art that such modifications would be suitable for stabilising glycopyrrolate.

Accordingly, the claimed subject-matter involved an inventive step over D2.

Reasons for the Decision

1. Admittance of D7

D7 was submitted by the appellant after it had filed its grounds of appeal. This submission constitutes an amendment to the appellant's case, and its admittance into the proceedings is subject to the Board's discretion pursuant to Article 13(1) RPBA 2020.

According to the appellant, D7 should be admitted into the proceedings on account of its *prima facie* relevence. However, D7 does not mention any glycopyrrolate formulations, but only salbutamol formulations. The appellant argues that the use of the expression "model" shows that the teaching of D7 is not intended to be limited to salbutamol (see D7, abstract; page 111, four lines from the end of the first full paragraph; page 115, left-hand column, last paragraph, first sentence; page 118, first sentence of the conclusions). The Board does not agree. D7 never identifies salbutamol as a "model" drug, but only mentions that the formulations studied therein are “model” formulations of salbutamol. Consequently, D7 is

not *prima facie* relevant to the glycopyrrolate compositions of the invention and its admittance would be contrary to the principle of procedural economy.

Accordingly, document D7 is not admitted into the proceedings under Article 13(1) RPBA 2020.

2. Article 100(a) EPC, inventive step

2.1 The claimed invention relates to a process for preparing a dry powder formulation of a glycopyrronium salt for inhalation. This drug substance has a known tendency to agglomerate, particularly when stored in humid conditions or otherwise exposed to moisture (see paragraphs [0004] and [0010] of the patent).

The process of the invention reduces this tendency to agglomerate and therefore improves the stability of the resulting drug substance (see [0008]), both during handling and during storage, and enhances the dosing efficiency (see [0034]).

In accordance with claim 1 of the patent as granted (which is the respondent's sole request), these effects are achieved by a process comprising the steps of
(a) mixing a glycopyrronium salt and an anti-adherent agent to give a homogeneous blend;
(b) micronising the blend; and
(c) admixing carrier particles to form a dry powder formulation.

2.2 Both parties consider D2 to represent the closest prior art. The Board concurs.

D2 is directed to glycopyrronium salt formulations exhibiting improved stability over time, and methods

for producing the same (see page 1, first paragraph). D2 recognises that micronised glycopyrrolate suffers from an acute problem with respect to stability: micronisation induces the generation of amorphous material on the surface of the particles, which upon moisture absorption recrystallises and acts as a form of glue between the particles, thus significantly reducing the powder dispersability (see page 2 lines 16-17, 22; page 3, lines 14-16, 31-33; page 4, lines 14-15).

2.3 In example 8 of D2 (see page 34), micronised glycopyrrolate bromide is blended with magnesium stearate in a mechanofusion apparatus. Magnesium stearate is an anti-adherent agent in the sense of the patent (see e.g. claim 4 of the patent). D2 also explains that mechanofusion is a dry coating process designed to mechanically fuse a guest material onto a host material. The process is conducted in D2 in order to achieve a drug powder which is less susceptible to formation of solid bridges and related instability such as via re-crystallisation over time (see page 35 lines 5-9).

Thus D2 discloses a step (a) of mixing a glycopyrronium salt and an anti-adherent agent.

2.4 D2 further discloses that the blend resulting from this mechanofusion step is mixed with fine and coarse carrier lactose (see page 36, lines 25-28). Thus D2 discloses a step (c) of admixing carrier particles to form a dry powder formulation.

2.5 Claim 1 of the patent also specifies a micronisation step (b). According to the patent specification, step (b) of claim 1 covers the use of equipment similar to

example 8 of D2, mechanofusion being mentioned as an appropriate micronising equipment in paragraph [0035]. However, the parties agree that the expression "micronising" used in claim 1 further requires a particle size reduction, in line with paragraph [0033] of the patent. The Board sees no reason to differ.

Although D2 generally mentions (see page 35, last sentence) that a size reduction "may occur", it is not apparent that any particle size reduction takes place in the particular conditions of example 8 of D2. The claimed process thus differs from the process of D2 in that the size of the particles is reduced during the micronising step (b).

2.6 As evidence of a technical effect over D2 resulting from the above differentiating feature, the respondent relies on example 2 of the patent, showing a comparison between (comparative) formulation 2 and (inventive) formulation 3. In formulation 2, pre-micronised glycopyrronium salt particles are admixed with lactose carrier particles and magnesium stearate to give the inhalable dry powder. In formulation 3, glycopyrronium salt and magnesium stearate are co-micronised, and then admixed with lactose carrier particles and magnesium stearate.

However, the Board does not consider that this example 2 offers any meaningful comparison of the claimed process with the closest prior art D2. In D2, the pre-micronised glycopyrronium salt particles are first coated with magnesium stearate by mechanofusion and then admixed with the carrier particles. In contrast, in formulation 2 of example 2 of the patent, no mechanofusion step takes place. Thus formulation 2 of example 2 does not reflect the teaching of example 8 of

D2. Formulations 2 and 3 do not merely differ by the differentiating feature, namely the particle size reduction, but also in that step (b) is entirely omitted in formulation 2.

In the absence of comparable stability data for formulations resulting from the processes of the invention and of D2, it can neither be concluded that the claimed process achieves any improvement with respect to storage stability, nor that it leads to a stability which is "as good as" in D2. In light of example 2 of the patent, it can merely be accepted that the claimed process leads to a storage stability which is acceptable for a powder formulation for inhalation.

The functional feature of claim 1 according to which "the process enhances the stability of the glycopyrronium salt" does not lead to a different conclusion, because this feature does not specify that the enhancement should occur in comparison with a process as described in D2. In light of page 2 of the patent, the stated enhancement is rather understood as referring to the co-micronisation of glycopyrrolate together with the anti-adherent agent, in comparison with the mixing of separately micronised materials.

2.7 The objective technical problem is therefore to provide an alternative process for preparing a dry powder formulation of a glycopyrronium salt for inhalation having acceptable storage stability.

2.8 As noted above (see 2.5), the mechanofusion equipment used in example 8 of D2 is mentioned in paragraph [0035] as a suitable equipment for carrying out the micronising step (b) of claim 1. D2 further discloses alternative equipment for carrying out this step, such

as jet mills (see D2, page 35, line 20), which are also considered as suitable micronising equipment in the patent (see paragraph [0035]). The micronising step of the invention contributes, as in D2, to the stabilising effect by the formation of a layer of anti-adherent agent on the glycopyrronium salt particles (see [0034] of the patent and page 35, 2nd paragraph of D2).

It is not apparent that, in example 8 of D2, the pre-micronised glycopyrronium salt undergoes any (further) particle size reduction during the mechanofusion with magnesium stearate. However, D2 explicitly contemplates that such a size reduction "may occur" (see page 35, last sentence). Thus, contrary to the respondent's opinion, operating the mechanofusion equipment used in D2 in such conditions that a particle size reduction occurs does not represent any significant departure from its teaching. The Board shares the appellant's opinion that the skilled person would infer from this statement that he would not be prevented from achieving the goal of the invention described in D2 by including a size-reduction step. In other words he would not consider that the inclusion of such size-reduction step would be detrimental to the stability of the product.

2.9 In the mechanofusion step of D2, at least in the context of example 8, the starting glycopyrrolate has already been micronised. The respondent concludes that any size reduction contemplated in D2 for the mechanofusion means a further reduction within the micronised size range, such as from ~10 µm to ~5 µm, which is not the same as the micronisation of step (b) of claim 1. The respondent submits that the micronising step (b) should be interpreted in light of the description (see paragraphs [0024] and [0033]) as referring to a reduction of the particle size of large

particles down to the micronised range that is suitable for administration by inhalation.

The Board can however not follow the respondent's interpretation of claim 1. Claim 1 does not contain any limitation as to the particle size of the starting glycopyrrolate. Paragraphs [0024] and [0033] indicate that the micronising step should lead to a particulate material having an average particle size suitable for administration by inhalation. These paragraphs however do not impose any limitation as to the glycopyrrolate particle size before micronisation. Any interpretation of claim 1 in light of these paragraphs could in any case not go as far as reading into claim 1 limitations which do not arise from the wording of claim 1 itself. Since claim 1 contains no limitation as to the starting glycopyrrolate, it must be concluded that claim 1 allows for the use of pre-micronised glycopyrrolate. Thus, a size reduction within the micronised size range as suggested by D2 falls within the scope of step (b) of claim 1 of the patent.

2.10 As noted above, the Board considers that the mechanofusion of D2 fulfills the criteria of the mixing step (a) of claim 1, and renders the micronising step (b) of claim 1 obvious considering the suggested size reduction. Even if claim 1 was interpreted such that the two steps must be separate, the process of claim 1 would differ from the mechanofusion with size reduction suggested in D2, i.e. a micronising step (b), by the addition of the mixing step (a). The skilled person intending to subject glycopyrrolate and magnesium stearate together to mechanofusion would consider mixing the two materials without exercising any inventive skills. Thus even if this interpretation of

claim 1 was adopted, the conclusion as to inventive step would not be modified.

2.11 Accordingly, the patent does not meet the criteria of inventive step.

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:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated