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Datasheet for the decision of 28 May 2024

Case Number: T 0669/22 - 3.3.04

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Language of the proceedings: EN

Title of invention:
AN INHALABLE MEDICAMENT COMPRISING TIOTROPIUM

Patent Proprietor:
Teva Branded Pharmaceutical Products R & D, Inc.

Opponent:
3M Innovative Properties Company

Headword:
Inhalable tiotropium / TEVA

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - all requests (no) - obvious alternative

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Case Number: T 0669/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 28 May 2024

Appellant: (Opponent)	3M Innovative Properties Company 3M Center P.O. Box 33427 St. Paul MN 55133-3427 (US)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Respondent: (Patent Proprietor)	Teva Branded Pharmaceutical Products R & D, Inc. 41 Moores Road Frazer, Pennsylvania 19355 (US)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 3 January 2022 concerning maintenance of the European Patent No. 3143998 in amended form.**

Composition of the Board:

Chair	M. Pregetter
Members:	S. Albrecht
	A. Bacchin

Summary of Facts and Submissions

I. European patent 3 143 998 ("the patent") was granted with seven claims.

II. Opposition proceedings were based on the grounds for opposition under Article 100(a) EPC for lack of novelty and lack of inventive step, under Article 100(b) and (c) EPC.

III. The following documents, cited during the opposition proceedings, are referred to below:

D1: WO 2011/061498 A2
D2: WO 2004/054580 A1
D5: A. Bakle, Study report "API impurity profile analysis", 7 April 2014, eleven pages in total
D9: A. Bakle, B. Nyambura, "E09303F: Assessments of Patents on Tiotropium MDI Formulations", eight pages in total
D11: D. Brinkley, Commentary on the experimental data filed in support of EP3143998, 13 May 2021, four pages in total

IV. The opposition division decided that the patent in amended form in the version of auxiliary request 3 and the invention to which it relates met the requirements of the EPC.

Independent claims 1 and 7 of auxiliary request 3 read as follows:

"1. A process for preparing a formulation in a pMDI canister comprising the steps of:
providing a concentrate sub-batch comprising tiotropium bromide, ethanol, water and citric acid in a container, wherein the tiotropium bromide and the citric acid are dissolved in the concentrate sub-batch;
dispensing the concentrate sub-batch into aluminium canisters;
placing a pMDI metering value on each filled canister;
crimping the valve to the canister using a pMDI valve crimper;
and adding an HFA propellant into the canisters through the valve using pressure fill equipment,
wherein the formulation is a solution formulation comprising tiotropium bromide, 12-20% ethanol, 0.1-1.5% of water, 0.05-0.10% citric acid and an HFA propellant, wherein the percentages are percentages by weight based on the total weight of the formulation.

"7. A formulation in a canister obtainable by the process of any preceding claim."

In its decision, the opposition division held, *inter alia*, that the claimed subject-matter of auxiliary request 3 would not have been obvious starting from document D2.

V. The opponent ("appellant") lodged an appeal against the opposition division's decision.

VI. In its statement of grounds of appeal, the appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

VII. With its reply to the statement of grounds of appeal, the patent proprietor ("respondent") filed a set of six claims labelled as auxiliary request 1.

Claims 1 and 6 of auxiliary request 1 are identical to claims 1 and 7 of the main request, respectively, except that the HFA propellant has been limited to HFA 134a.

VIII. Oral proceedings before the board were arranged, as requested by the parties, and were scheduled for 16 April 2024.

IX. In a communication under Article 15(1) RPBA ("communication"), the board informed the parties of its preliminary opinion that the subject-matter of claim 7 of the main request and that of claim 6 of auxiliary request 1 would have been obvious starting from document D1 as the closest prior art.

X. In a letter dated 2 April 2024, the respondent withdrew its request for oral proceedings and informed the board that it would not be attending the oral proceedings.

XI. In a letter dated 3 April 2024, the appellant withdrew its request for oral proceedings on condition that the board adopt its preliminary opinion and decide to revoke the contested patent in its entirety.

XII. Subsequently, the board cancelled the oral proceedings and informed the parties that it would issue the decision in writing.

XIII. The appellant's written submissions relevant to the present decision may be summarised as follows.

Main request - claim 7 - inventive step

Example V of document D1 could be considered the closest prior art. The subject-matter of claim 7 differed from this example in terms of the citric acid content. The patent's examples did not illustrate any advantage compared with the closest prior art. As for the respondent's post-filed data (documents D5, D9 and D11), these should be disregarded because they contained inherent flaws and were not credible. Consequently, the objective technical problem to be solved was solely to provide an alternative solution formulation. It was well known from the cited prior art (e.g. document D2) that degradation of tiotropium which was caused by ethanol and/or water could be avoided by addition of an acid. Since no surprising effect had been shown to be connected to the claimed citric acid concentration range, the skilled person would have arrived at the claimed range without an inventive step.

Auxiliary request 1 - claim 6 - inventive step

This claim included the additional feature according to which the propellant was HFA 134a. All the examples of document D1 already disclosed this propellant. Hence claim 6 of auxiliary request 1 lacked inventive step for the same reasons as claim 7 of the main request.

XIV. The respondent's written submissions relevant to the present decision may be summarised as follows.

Main request (claim 7) and auxiliary request 1 (claim 6) - inventive step

In contrast to document D2, document D1 was not a credible candidate for closest prior art because it was not directed to the same purpose or effect as the patent, i.e. to provide chemical stability to tiotropium (or any active pharmaceutical ingredient).

If document D1 were nevertheless taken as the closest prior art, the subject-matter of claim 7 differed from Example V of this document in that it used 0.05-0.10% of citric acid instead of 0.15-0.70% of citric acid. As evidenced by Table 3 of document D5 and confirmed in Table 4 of document D9, Example V of document D1 demonstrated a significantly higher amount of impurities after 1 month under accelerated conditions. The objective technical problem was thus to provide an MDI solution formulation of tiotropium with increased chemical stability of the active pharmaceutical ingredient. The solution of using 0.05-0.10% citric acid would not have been obvious. It was known from document D2 that the use of either an inorganic acid or an organic acid provided stability against degradation of the medicament. In terms of the amount of citric acid used, however, document D2 (Examples A, C, D and E) used much lower amounts than those claimed.

XV. The parties' requests relevant to the present decision and as understood by the board are as follows:

The appellant requested in writing that the decision under appeal be set aside and that the patent be revoked in its entirety.

The appellant further requested that auxiliary request 1 not be admitted into the proceedings.

The respondent requested in writing as its main request that the appeal be dismissed, implying that the patent be maintained as amended on the basis of auxiliary request 3 held allowable by the opposition division.

As an auxiliary measure, the respondent requested that the patent be maintained in amended form on the basis of the set of claims filed as auxiliary request 1 with the reply to the statement of grounds of appeal.

Reasons for the Decision

1. The appeal is admissible.

Decision in written proceedings

2. This decision is taken in written proceedings without holding oral proceedings.

2.1 Pursuant to Article 12(8) RPBA, subject to Articles 113 and 116 EPC, the board may decide on the case at any time after filing of the statement of grounds of appeal.

2.2 The findings of this decision correspond to those indicated in the board's preliminary opinion,

contained in the communication under Article 15(1) RPBA dated 18 March 2024, in which the parties' submissions were taken into account and to which the parties had the opportunity to react.

2.3 The order of this decision complies with the appellant's main request. The respondent unambiguously withdrew its request for oral proceedings (see point X.) based on the board's preliminary opinion that the claimed subject-matter of the main request and auxiliary request 1 would have been obvious starting from document D1 as the closest prior art.

2.4 The issuance of the decision in written proceedings without oral proceedings being held thus complies with the requirements of Articles 113(1) and 116(1) EPC (see also Case Law of the Boards of Appeal, 10th edn., 2022, in the following "Case Law", III.B.2.7.3).

Main request

3. Claim 7 - inventive step (Article 56 EPC)

Closest prior art

3.1 In the respondent's view, document D1 did not constitute a credible candidate for closest prior art (see point XIV. above).

3.2 The board does not concur.

3.2.1 A promising starting point is typically a prior-art document that relates to the claimed invention, in the sense that it discloses subject-matter conceived for the same purpose or aiming at the same objective, corresponding to a similar use, or relating to the same

or a similar technical problem, or at least to the same or a closely related technical field. As a further criterion, the closest prior art should disclose subject-matter having the greatest number of relevant technical features in common with the claimed invention.

3.2.2 However, this does not mean that another prior-art document can be immediately ruled out as a possibly suitable starting point merely because it has a different purpose from the invention or fewer technical features in common with the invention than other, seemingly "closer", prior art (see Case Law, I.D.3.1). Any consideration of "how close" the prior-art starting document is judged to be to the claimed invention is not something which should exclude it from being the closest prior art. In fact, claimed subject-matter can only be considered inventive if it would not have been obvious starting from any piece of prior art.

3.2.3 As a consequence, the board accepts the appellant's choice of document D1, in particular Example V thereof, as the closest prior art.

Distinguishing features vis-à-vis Example V of document D1

3.3 Example V of document D1 (see page 15, line 10 to page 16, line 3) discloses a solution formulation containing tiotropium bromide monohydrate, 15% ethanol, 0.5% water, HFA 134a propellant (q.s.), and citric acid (q.s. to adjust pH between 2.7 to 3.1) in a can equipped with a metering valve ("formulation of Example V").

3.4 In the respondent's favour, the board assumes that the resulting citric acid concentrations in the formulation of Example V are 0.15% for a pH of 3.1 and 0.79% for a pH of 2.7 (see paragraph (74) of the reply to the statement of grounds of appeal).

3.5 The subject-matter of claim 7 thus differs from the formulation of Example V in terms of the amount of citric acid, i.e. 0.05 to 0.10% by weight based on the total weight of the formulation. What is more, claim 7 requires the can to be an aluminium canister.

Objective technical problem and solution

3.6 The objective technical problem is to be formulated on the basis of the technical effects that the distinguishing features provide over the closest prior art.

3.7 As conceded by the respondent, the patent does not contain any experimental data providing a comparison between a formulation according to claim 7 and the formulation of Example V.

3.8 The respondent submitted that the latter had a significantly higher amount of impurities after 1 month under accelerated conditions than any of Examples A, C and I of the patent, as evidenced by the experimental data disclosed in post-published documents D5 (see Table 3) and D9 (see Table 4). Moreover, document D11 carried out a statistical analysis confirming the role of citric acid in stabilising the tiotropium bromide. The objective technical problem was thus to be formulated as the provision of an MDI solution formulation of tiotropium with increased chemical stability of the active pharmaceutical ingredient.

3.9 The board does not concur. As correctly pointed out by the appellant, the amount of impurities measured for Examples A, C and I of the patent was in the range of 5.99 to 6.82 in the experiments reported in document D5 (see Table 3), while the same examples had impurity levels in the range of 0.970 to 1.205 in the experiments reported in document D9 (see Table 4). In contrast to this considerable shift, the impurity levels for the formulation of Example V in documents D5 (11.04) and D9 (6.060) are relatively close.

3.10 These inconsistencies cast doubt on the general reliability of the experimental data reported in Table 3 of document D5 and Table 4 of document D9. As a consequence, the data in documents D5 and D9 and, by the same token, those of document D11, are not suitable to demonstrate the alleged increase in chemical stability of tiotropium bromide.

3.11 In the respondent's view, noting differences between separate experimental reports carried out by different workers under different situations at different times is not enough to cast doubt on their concurring conclusions, particularly in the absence of any other data. In a situation like the current one, where the respondent had provided considerable evidence, but no counter-experiments had been performed by the appellant, the benefit of the doubt should be given to the respondent.

3.12 The board does not agree. In view of the considerable discrepancies reported in point 3.9 above, it is unlikely that the claimed formulations exhibit the alleged technical effect of increased chemical stability over the formulation of Example V. In the

absence of any evidence from the respondent to dispel the aforementioned doubts about the general reliability of the experimental data reported in Table 3 of document D5 and Table 4 of document D9, the alleged technical effect of increased chemical stability cannot be taken into account in formulating the objective technical problem.

3.13 The latter is thus to be worded as the provision of an alternative solution formulation suitable for pMDI administration.

3.14 The solution proposed to this problem is a formulation according to claim 7.

Obviousness of the proposed solution

3.15 The proposed solution would have been obvious having regard to the state of the art.

3.16 As set out in the decision under appeal (see point 4.7.3, first paragraph), it was known from the art that acids stabilise tiotropium salts against degradation.

3.16.1 Specifically, document D2 (see page 1, lines 3 to 9) pertains to aerosol solution formulations containing a tiotropium salt (medicament), an environmentally safe hydrofluorocarbon (HFC) as a propellant, an organic compound as a cosolvent, and an acid (organic or inorganic). The latter provides stability against degradation or decomposition of the medicament resulting largely from interaction of the medicament with the cosolvent and/or water present in the solution formulation (see page 1, lines 9 to 11).

3.16.2 In line with this disclosure, Examples A and C of document D2 (see page 8) describe aerosol solution formulations containing tiotropium bromide monohydrate, ethanol as cosolvent (25% and 15% w/w, respectively), water (1% and 2% w/w, respectively), citric acid (0.003% and 0.004% w/w, respectively) and an HFC propellant (HFC-134a and HFC-227, respectively).

3.17 In view of the foregoing, the skilled person would immediately have recognised that amounts of citric acid as low as 0.003% and 0.004% w/w are sufficient to stabilise tiotropium bromide against its degradation or decomposition resulting from its interaction with ethanol and water at the concentrations specified in Examples A and C of document D2.

3.18 Noting that the formulation of Example V has similar ethanol and water concentrations (see point 3.3 above), the skilled person would have expected citric acid amounts of 0.003% w/w or more to be suitable to stabilise the tiotropium contained in this formulation. Since the claimed range (0.05 to 0.10% w/w of citric acid) falls within this broader range (i.e. from 0.003% w/w up to 0.79%), the selection of the claimed sub-range amounts to an arbitrary choice devoid of inventive merit.

3.19 For the sake of completeness, the board notes that the further distinguishing feature of the aluminium canister (see point 3.5 above) cannot contribute to an inventive step either. As submitted by the appellant and not disputed by the respondent, aluminium canisters are among the types of canister commonly employed in pMDIs.

3.20 It follows that the claimed invention amounts to a mere aggregation of obvious features which is devoid of any inventive merit.

Overall conclusion on inventive step of the main request

3.21 The board concludes that the appellant's objection of lack of inventive step under Article 56 EPC prejudices maintenance of the patent as amended in accordance with the main request.

Auxiliary request 1

4. Claim 6 - inventive step (Article 56 EPC)

4.1 Claim 6 of this request differs from claim 7 of the main request solely in that the HFA propellant is HFA 134a.

4.2 Since the formulation representing the closest prior art already contains HFA 134a (see point 3.3 above), limiting the HFA propellant to HFA 134a has no impact on the assessment of inventive step.

4.3 Accordingly, the subject-matter of claim 6 of auxiliary request 1 does not meet the requirements of Article 56 EPC for the same reasons as set out for claim 7 of the main request.

Further points raised by the appellant

5. Since none of the claim requests to be considered by the board meet the requirements of Article 56 EPC, it is not necessary for the board to deal with the further

objections raised by the appellant against these requests.

6. The appellant has requested that auxiliary request 1 not be admitted into the appeal proceedings. In view of the outcome of the assessment of inventive step in relation to this request (see point 4 above), the board sees no need to provide reasons for its decision to admit the request into the proceedings.

Overall conclusion

7. Since none of the claim requests are allowable, the patent has to be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

I. Aperribay M. Pregetter

Decision electronically authenticated