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Datasheet for the decision of 6 December 2021

Case Number: T 1616/17 - 3.3.01

Application Number: 12196725.1

Publication Number: 2606891

IPC: A61K31/46, A61K9/00, A61K9/12, A61P11/00

Language of the proceedings: EN

Title of invention:
AN INHALABLE MEDICAMENT COMPRISING TIOTROPIUM

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

Opponent:
3M United Kingdom plc

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
Novelty - (yes)
Inventive step - (no)

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Beschwerdekammern

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Case Number: T 1616/17 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 6 December 2021

Appellant: (Patent Proprietor)	Teva Branded Pharmaceutical Products R&D, Inc. 41 Moores Road Frazer PA 19355 (US)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Appellant: (Opponent 2)	3M United Kingdom plc 3M Centre Cain Road Bracknell Berkshire RG12 8HT (GB)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 2 May 2017 concerning maintenance of the European Patent No. 2606891 in amended form.**

Composition of the Board:

Chairman	A. Lindner
Members:	R. Hauss
	L. Bühler

Summary of Facts and Submissions

I. European patent No 2 606 891 (patent in suit) was granted with a set of 17 claims.

II. Two notices of opposition were filed objecting to the patent in suit under Article 100(a) and (b) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step and was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

III. The patent proprietor requested that the oppositions be rejected and, with a submission dated 24 March 2016, filed three sets of claims according to its first, second and third auxiliary requests.

Claim 1 of the second auxiliary request, which is identical to claim 1 as granted, reads as follows:

1. A solution formulation comprising a tiotropium salt, 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.

Claim 1 of the third auxiliary request reads as follows (differences underlined by the board):

1. A solution formulation comprising a tiotropium salt, 12-<u>15</u>% ethanol, <u>0.30-0.60</u>% of water, 0.05-<u>0.08</u>% citric acid and an HFA propellant, wherein the percentages are percentages by weight based on the total weight of the formulation.

IV. The documents cited in the opposition proceedings included the following:

D1: WO 2011/061498 A2

D2: WO 2004/054580 A1

D3: WO 94/13262 A1

D10: Test report "API impurity profile analysis" (7 April 2014) filed by the patent proprietor

V. The decision under appeal is the opposition division's interlocutory decision, announced on 30 January 2017 and posted on 2 May 2017, rejecting the patent proprietor's main request and first auxiliary request and finding that the patent as amended in the form of the second auxiliary request met the requirements of the EPC.

According to the decision under appeal:

(a) The subject-matter of the claims as granted (main request) met the requirements of sufficiency of disclosure and novelty.

In particular, the formulations defined in claim 1 were novel as they differed from the formulations of examples II, III and V in D1 in the amount of citric acid used.

(b) However, the subject-matter of independent claim 11 as granted lacked an inventive step. This was also the case for claim 11 of the first auxiliary request.

(c) The second auxiliary request, in which claims 11 to 15 had been deleted, met the requirements of the EPC.

Inventive step was assessed starting from the teaching of document D1. The experimental data in document D10 showed that formulations conforming to claim 1 were more stable than those in D1. Even if, disregarding this data, the technical problem were to be formulated as the provision of further tiotropium solution formulations suitable for aerosol administration, the claimed subject-matter would not have been obvious. The person skilled in the art would have regarded the concentration range established for citric acid in D1 (expressed as a pH range) as favourable and would not have considered working outside that range.

The claimed subject-matter also involved an inventive step according to a second approach starting from the teaching of document D2.

VI. The patent proprietor and opponent 2 each filed an appeal against this decision. The patent proprietor requested that the patent be maintained as granted or, in the alternative, on the basis of the claims of one of the first to third auxiliary requests filed during the opposition proceedings (see point III above).

VII. Opponent 1 withdrew its opposition.

VIII. With its reply to opponent 2's grounds of appeal, the patent proprietor submitted a further test report:

D20: E09303F - Assessments of Patents on Tiotropium MDI Formulations (23 January 2018)

IX. In a further submission, the patent proprietor withdrew the main request and first auxiliary request and stated that the second auxiliary request became the new **main request** and that the third auxiliary request became the

new **first auxiliary request** (see point III above for the wording of claim 1 of each request). The patent proprietor also filed a further document:

D21: D. Brinkley: Commentary on the experimental data filed in support of EP2606891 (13 May 2021)

X. Oral proceedings before the board took place on 6 December 2021.

XI. The arguments of opponent 2 relevant to the present decision may be summarised as follows.

Novelty

The subject-matter of claim 1 of the main request was anticipated by example formulations II, III and V disclosed in document D1. The patent proprietor's experiments relating to this issue, presented in D10, had not been performed in line with the examples in D1, and the patent proprietor's calculations of citric acid concentrations were not correct. According to the opponent's own calculations based on data provided in D10, the concentrations of citric acid in the formulations of D1 were essentially the same as the concentration range of 0.05 to 0.10% by weight recited in claim 1.

Inventive step starting from the teaching in D1

Document D1 was the closest prior art as it described formulations very similar in their composition to those defined in claim 1 of the main request. The skilled person would have been well aware that citric acid was used in this type of formulation to ensure chemical stability.

Since the patent and the application as filed did not provide any data in support of the alleged technical

effect of improved stability, the patent proprietor's post-filed evidence (D10 and D20) should not be taken into account. D21, which contained a further analysis of the data in D20, could thus be disregarded as well. Moreover, the tests reported in D10 and D20 were flawed, as shown by discrepancies in their results relating to impurities levels. The tests were also inconclusive in that they did not focus on the technical feature distinguishing the claimed formulations from the relevant prior-art embodiments.

Without evidence of the alleged improvement in stability or of the criticality of the concentration ranges in claim 1, the objective technical problem was to provide alternative solution formulations of tiotropium.

The skilled person would have been guided by the teaching in documents D2 and D3 to optimise the concentrations of the organic acid and further components.

XII. The patent proprietor's arguments relevant to the present decision may be summarised as follows.

Novelty

The data provided in document D10 (Table 2) showed that the concentrations of citric acid required to adjust the pH in example formulations II, III and V of D1 were not within the range defined in claim 1.

Inventive step starting from the teaching of D1

As shown by the experimental data provided in documents D10 and D20, formulations conforming to claim 1 of the main request improved the stability of tiotropium in comparison with the formulations in D1. This technical effect was based on the combination of the specified

concentrations of water, co-solvent and acid. As confirmed by the statistical analysis presented in document D21, both water and, predominantly, citric acid played a critical role in providing stability to the tiotropium formulations.

It was not sensible to compare the results reported in D10 to those reported in D20. The experiments had been performed four years apart with different reagents and detection techniques. The data were comparable within each report, but not between reports.

The objective technical problem was to provide an MDI solution formulation of tiotropium with increased chemical stability of the active agent.

D1 was not about chemical stability and did not discuss citric acid concentrations. In fact, none of documents D1, D2 or D3 would have provided the skilled person seeking to improve the stability of tiotropium with any incentive to lower the concentration of citric acid while restraining the concentration of water present in the formulation within the claimed range.

The same reasoning applied to claim 1 of the first auxiliary request.

XIII. Appellant - opponent 2 requested that the decision under appeal be set aside and that the patent be revoked.

XIV. The appellant - patent proprietor requested that the patent be maintained on the basis of the claims of:

- the main request (filed as the second auxiliary request with the submission of 24 March 2016)

- in the alternative, the first auxiliary request (filed as the third auxiliary request with the submission of 24 March 2016)

Reasons for the Decision

1. Patent in suit and claim requests

1.1 The patent in suit concerns a propellant-based solution formulation of tiotropium intended for aerosol inhalation. Formulations of this type were known. It was also known that tiotropium is chemically unstable in the presence of co-solvents such as ethanol required to solubilise the drug in HFA propellants and that it can be stabilised by adding inorganic or organic acids. However, there were concerns about interactions with metallic container materials and the leaching of metal salts into the formulations (see paragraphs [0001], [0005], [0008] and [0009] of the patent in suit).

1.2 Thus, the patent in suit seeks to provide aerosol solution formulations of tiotropium salts, suitable for use with a pressurised metered-dose inhaler (pMDI), which are chemically stable and do not adversely react with the internal surfaces of the inhaler (see paragraph [0011] of the patent).

1.3 Claim 1 of the main request defines a HFA-based solution formulation of tiotropium with specified concentration ranges of ethanol, water and citric acid (see points IX and III above).

1.4 Claim 1 of the first auxiliary request corresponds to claim 1 of the main request but defines narrower concentration ranges (see points IX and III above).

2. Novelty - main request (Articles 100(a), 52(1), 54 EPC)

2.1 Document D1 concerns inhalation solutions comprising an anticholinergic, in particular tiotropium, for pMDI administration. Examples II, III and V of D1 disclose solution formulations containing:

- tiotropium bromide monohydrate
- 0.5% water
- 15% or (in the case of example III) 20% ethanol
- HFA 134a propellant
- "citric acid anhydrous q.s. to adjust pH between 2.7 to 3.1"

The formulation according to example II also contains:

- 1% glycerol

Document D1 also describes how the formulations were prepared (see page 14, lines 1 to 9 and 15 to 21 and page 15, line 14 to page 16, line 3):

- First, the ethanol was mixed with the water and glycerol (if included).
- Then, the pH was adjusted with citric acid to a value in the range of 2.7 to 3.1.
- Finally, tiotropium bromide and the propellant were added.

It was common ground that the percentages in D1 are by weight (see also D1: page 7, line 9 and page 8, lines 3 to 4).

2.2 The issue in dispute with regard to novelty was whether the amounts of citric acid required in the formulations of D1 must result in concentrations within the range of 0.05 to 0.10% by weight based on the total weight of the formulations, as defined in claim 1 of the main request.

2.3 The patent proprietor prepared solvent compositions (mixtures of ethanol, water and, if added, glycerol) using the same solvent ratios and preparation method as described in the examples of D1. The weights of citric acid used to adjust the pH to 2.7 and 3.1 (the endpoints of the pH range recited in D1) were recorded in each case (see D10: page 4, last paragraph and page 1 of the annex of D10 describing protocols: "Phase 1", with Table 1).

For instance, according to Table 2 reproduced below, a solvent mixture of 1 g water and 30 g ethanol (reproducing the solvent ratio in example V of D1), required 0.29 g citric acid to reach a pH of 3.1 and 1.57 g citric acid to reach a pH of 2.7.

On this basis, the resulting citric acid concentrations in the total formulations could then be calculated (see D10: page 5, Table 2).

Table 2: Phase 1 Studies (Patent ref. WO 2011/061498)

Example	pH	Solvent composition (g)			Weight (g)		Calculated %w/w citric acid anhydrous ((a/b)*100)
		Water	Glycerol	Ethanol	citric acid anhydrous (a)	Solvent mixture (b)	
II	2.7	1	2	30	2.35	200	1.18
	3.1	1	2	30	0.44	200	0.22
III	2.7	1	0	40	2.30	200	1.15
	3.1	1	0	40	0.40	200	0.20
V	2.7	1	0	30	1.57	200	0.79
	3.1	1	0	30	0.29	200	0.15

It is readily apparent from Table 2 that the concentration of citric acid was calculated in relation to a total weight of 200 g ("(a/b)·100"). This is in line with the following basic considerations:

- For calculating the concentration of citric acid in % by weight of the formulation, the weight of citric acid (determined experimentally) and the total weight of the final formulation are needed.
- The amounts (in grams) of solvents used in the solvent compositions according to Table 2 in D10, divided by 200 g, reproduce the solvent concentrations in examples II, III and V of D1, namely 0.5% water, 1% glycerol (where added) and 15% or 20% ethanol (see point 2.1 above). Accordingly, the reference weight (total weight of the formulation) is 200 g.
- According to D1, the difference to the total weight of the formulations would be made up by the propellant and the tiotropium salt. Within the framework of the experiment described in D10, it is of course not necessary to physically add the propellant and tiotropium to the compositions to make the final calculation.

2.4 As shown in Table 2, the concentrations of citric acid determined according to D10 were above 0.10% (the upper concentration limit defined in claim 1). This was also the case when the pH value was adjusted to 3.1, which would have required the lowest amount of acid.

2.5 The opponent understood the 200 g in Table 2 to relate to 200 g of the ethanol/water mixture and referred to its own calculations, which were based on that assumption. The following ranges were mentioned in this context (see the opponent's grounds of appeal, page 3):

- 0.0363 to 0.194 wt% citric acid for Example II
- 0.041 to 0.236 wt% citric acid for Example III
- 0.0225 to 0.122 wt% citric acid for Example V

2.6 The board believes the opponent's interpretation to be mistaken. The fact that the amounts of glycerol, water and ethanol indicated in Table 2, divided by 200 g, result in the concentrations used in examples II, III and V of D1 strongly suppports the patent proprietor's interpretation of Table 2, which is plausible even if the description in D10 does not set this out in detail. The sole purpose of the experiment of D10 was, after all, to reproduce the conditions in D1, to determine the amount of citric acid required.

2.7 In any case, the endpoints of the concentration ranges of citric acid, as calculated and indicated by the opponent, are outside the range of 0.05 to 0.10% by weight. Even assuming these calculations to be correct, they would, therefore, not permit the conclusion to be drawn that D1 provides an unambiguous disclosure of a citric acid concentration in the claimed range.

2.8 The opponent's further argument that the results in Table 2 of D10 should not be taken into account because the experiments were not performed in line with D1 cannot succeed either. Ignoring the results in D10 would still not lead to the conclusion that D1 directly and unambiguously anticipates the subject-matter of claim 1.

2.9 For these reasons, the subject-matter of claim 1 of the main request is novel in relation to the disclosure of document D1 (Articles 100(a), 52(1) and 54 EPC).

3. Inventive step - main request (Articles 100(a), 52(1) and 56 EPC)

3.1 The patent's objective and the technical features of claim 1 are as set out above in section 1.

Starting point in the prior art

3.2 It was common ground that document D1, specifically example formulations II, III and V in D1 (see point 2.1 above), provided a possible starting point for the assessment of inventive step. Example V may be used as a representative starting point.

3.3 While its technical teaching is mainly about the influence of constructional details of the inhaler on aerosol particle size, document D1 also mentions the issue of chemical stability. According to D1, it was known that organic or inorganic acids had been proposed as stabilisers preventing the chemical degradation of the active agent, e.g. ipratropium bromide, in aerosol formulations comprising HFAs (see D1: page 3, lines 5 to 9).

Distinguishing technical feature and technical effect

3.4 As set out in section 2 above, the claimed formulations differ from those of D1 solely in the concentration of citric acid.

3.5 The patent in suit does not contain experimental data providing a comparison between a formulation according to claim 1 and a formulation according to document D1.

3.6 In support of the alleged technical effect of increased stability of tiotropium, the patent proprietor relied instead on post-filed data provided in documents D10 and D20.

3.7 Regarding the question whether post-filed evidence may be used in this case, the following considerations apply.

3.7.1 It is the stated objective of the patent in suit to provide pMDI solution formulations of tiotropium salts with a high degree of chemical stability of the active ingredient which do not adversely affect the material of the inhaler (see paragraphs [0011] and [0013] of the patent). The patent reports that the formulations according to the invention were found to reduce or prevent the chemical degradation of the active ingredient (see paragraph [0028]) and that specific formulations conforming to claim 1 (Batches A, I, C, E and H in example 2) showed an acceptably low level of chemical degradation (see the patent in suit: example 2).

3.7.2 Stability is thus a principal issue in the patent. Furthermore, the stability data provided in example 2 also render it credible that the claimed formulations have acceptable stability. The alleged technical effect of the claimed formulations over the formulations of D1 (prior art newly cited during pre-grant proceedings) likewise relates to stability. In these circumstances, post-filed data can be used by the patent proprietor in support of the alleged technical effect of improved stability.

3.8 If comparative tests are chosen to demonstrate inventive step on the basis of an improved effect, the nature of the comparison must be such that the alleged advantage or effect is convincingly shown to have its origin in the distinguishing feature of the claimed subject-matter compared with the closest prior art (see Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, I.D.10.9).

3.9 This criterion is not met by the experiments described in documents D10 and D20, since:

- neither document describes a test in which only the concentration of citric acid was varied (see point 3.9.1 below)
- the results presented in D10 and D20 are inconsistent (see point 3.9.2)

3.9.1 The tests in both D10 and D20 concern the determination of API-related impurities before and after a storage interval. As set out in Table 3 in D10 and Table 3 in D20, formulations according to examples II, III and V of D1 were compared to formulations according to batches A, C and I in example 2 of the patent in suit.

This means, however, that the concentration of citric acid was not the only parameter which was varied in the experiments carried out. At the same time, the concentrations of either water or ethanol were also varied. This experimental set-up does not permit the technical effect linked to the concentration of citric acid to be observed.

The patent proprietor's argument that the concentrations of both citric acid and water play an important role in controlling degradation (see D21) does not overcome this difficulty. The concentration of water is not a distinguishing technical feature of the claimed subject-matter in comparison with example formulation V of D1. Moreover, as conceded by the patent proprietor, this feature may indeed have an influence on stability, and it was varied in the tests carried out in addition to varying the concentration of citric acid.

3.9.2 As correctly pointed out by the opponent, the level of impurities measured for formulations A, C and I according to example 2 of the patent in suit was in the

range of 5.99 to 6.82 in the experiments reported in D10, while the same formulations had impurities levels in the range of 0.97 to 1.21 in the experiments reported in D20 (Table 4). In contrast to this considerable shift, the impurities levels for the examples of D1 stayed in roughly the same range (D10: 9.49 to 11.04 and D20: 6.06 to 10.10, with example V having the highest impurities level in D10 and the lowest in D20).

According to the patent proprietor, the storage conditions were the same in the test protocols of D10 and D20, while the HPLC method employed for detection was different. Nevertheless, a change in the detection method does not explain why, between D10 and D20, a considerable shift was observed for the examples of the patent, while the results for the examples according to D1 remained in the same range (examples II and III) or decreased much less drastically (example V).

These inconsistencies cast doubt on the general reliability of the test method and the resulting comparative data.

Objective technical problem and solution

3.10 In the absence of conclusive evidence of the alleged technical effect of improved stability, the objective technical problem is to provide an alternative solution formulation of tiotropium suitable for pMDI administration.

3.11 It was not in dispute that this problem is solved by the claimed solution formulations.

Obviousness of the solution

3.12 To provide an alternative formulation, the person skilled in the art would routinely have contemplated

varying the concentrations of individual components. As set out in points 3.14 to 3.15.2 below, the prior art did not provide a reason for the skilled person not to consider varying the concentration of citric acid, as long as the known stabilising effect was still obtained.

3.13 The upper limit of 0.10% defined in claim 1 for the concentration of citric acid is slightly lower than the maximum concentration determined for example V in D1 (0.15% at pH 3.1, see point 2.3 above).

3.14 According to D1, citric acid is used as a pH-adjusting agent (page 8, lines 21 to 22). D1 also reports that it was known that acids may have a stabilising effect by preventing the degradation of the active agent in HFA-based aerosol solution formulations (page 3, lines 5 to 9). While D1 indicates a pH range of 2.7 to 3.1, the document does not give a rationale for the pH range chosen and does not present its endpoints as critical. Overall, there is no teaching in D1 which would prevent the person skilled in the art from modifying the citric acid concentration within certain limits, e.g. by lowering the concentration, to solve the objective technical problem of providing an alternative solution formulation.

3.15 Furthermore, lower citric acid concentrations were considered sufficiently effective according to other prior-art disclosures cited in these proceedings.

3.15.1 Document D2 discloses similar solution formulations of tiotropium bromide for aerosol administration, teaches that acids provide stability against degradation of the active agent (especially in a pH range of 2.5 to 4.5), and describes example formulations with a concentration of citric acid (present as the sole acid) of 0.003% and

0.004% by weight (see D2: claims, formulation examples A, C and E on pages 8-9; and page 1, first paragraph).

3.15.2 Document D3 (cited in the application as filed) also discloses solution formulations of the general type described in D1, in which the active agent is stabilised against degradation by the presence of an effective amount of acid. The selection of the acid depends on the active agent used and the acid concentration needed to effect an acceptably reduced rate of degradation of the active agent (D3: page 10, last paragraph). Citric acid is the most preferred acid because of MDI component compatibility. Formulations according to D3 may contain tiotropium bromide as the active agent, with a citric acid concentration as low as 0.002% by weight (see D3: claim 35 referring back to claims 1 and claims 32 to 34; and page 3, second paragraph).

3.16 In view of these considerations, the subject-matter of claim 1 of the main request does not involve an inventive step within the meaning of Article 56 EPC.

4. First auxiliary request

4.1 The composition of claim 1 according to auxiliary request 1 differs from the composition of claim 1 of the main request in that narrower concentration ranges are defined.

4.2 The formulation according to example V may still be considered a representative starting point in D1 which differs from the claimed formulations only in the concentration of citric acid. While in the case of auxiliary request 1, the upper limit for the concentration of citric acid is 0.08% rather than 0.10%, this difference does not change the assessment

of inventive step, which in all essential points remains the same as set out for the main request.

4.3 As a consequence, the subject-matter of claim 1 of the first auxiliary request does not involve an inventive step within the meaning of Article 56 EPC.

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:

M. Schalow A. Lindner

Decision electronically authenticated