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**Datasheet for the decision of 22 October 2020**

**Case Number:** T 1025/18 - 3.3.07

**Application Number:** 02709742.7

**Publication Number:** 1381346

**IPC:** A61K9/12, A61K9/72, A61K9/08, A61P11/08, A61K31/167

**Language of the proceedings:** EN

**Title of invention:**
PHARMACEUTICAL COMPOSITIONS CONTAINING FORMOTEROL

**Patent Proprietor:**
Mylan Specialty L.P.

**Opponent:**
Teva Pharmaceutical Industries Ltd

**Headword:**
Pharmaceutical compositions containing Formoterol/MYLAN

**Relevant legal provisions:**
EPC Art. 56
RPBA Art. 12(4), 13(1)

**Keyword:**
Main request and auxiliary requests 1-11 - Inventive step (No)
Admission of auxiliary requests 12-25 into the proceedings (No)

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**Case Number: T 1025/18 - 3.3.07**

# D E C I S I O N
# of Technical Board of Appeal 3.3.07
# of 22 October 2020

| | |
|---|---|
| **Appellant:** (Patent Proprietor) | Mylan Specialty L.P.<br>2751 Napa Valley Corporate Drive<br>Napa, CA 94558 (US) |
| **Representative:** | Boult Wade Tennant LLP<br>Salisbury Square House<br>8 Salisbury Square<br>London EC4Y 8AP (GB) |
| **Respondent:** (Opponent) | Teva Pharmaceutical Industries Ltd<br>5 Basel Street<br>P.O. Box 3190<br>49131 Petah Tiqva (IL) |
| **Representative:** | D Young & Co LLP<br>120 Holborn<br>London EC1N 2DY (GB) |
| **Decision under appeal:** | **Decision of the Opposition Division of the European Patent Office posted on 12 February 2018 revoking European patent No. 1381346 pursuant to Article 101(3)(b) EPC.** |

**Composition of the Board:**

| | |
|---|---|
| **Chairman** | A. Usuelli |
| **Members:** | D. Boulois |
| | Y. Podbielski |

## Summary of Facts and Submissions

I. European patent No. 1 381 346 was granted on the basis of a set of 40 claims.

Independent claim 1 as granted read as follows:

"1. A pharmaceutical composition, comprising formoterol free base at a concentration of 5 µg/ml to 50 µg/ml, or a derivative thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, and the composition is suitable for direct administration to a subject in need thereof."

II. An opposition was filed under Article 100 (a) and (c) EPC against the granted patent on the grounds that the subject-matter of the granted patent lacked inventive step and extended beyond the content of the application as filed.

III. The appeal lies from the decision of the opposition division to revoke the patent. The decision was based on 30 sets of claims, namely the claims as granted as main request, auxiliary requests 1, 2, 4-6, 8-10, 12-14, 16-18, 20-22, 24-29 filed with letter of 6 September 2017 and auxiliary requests 3, 7, 11, 15, 19 and 23 filed with letter of 26 October 2017.

IV. The documents cited during the opposition proceedings included the following:
D1: US 6.040,344
D2: PERFOROMIST® product label and prescribing information

D3: Pérez Puigbo et at., Revista Venezolana de Atergia, Asma e Immunologia (2000) 2(2):73-76
D5: Reddi, int. J. Med. Sci. (2013) 10:747-750
D7: Labeling of Foradil® Aerolizer® as approved on 16 February 2001 by the Center for Drug Evaluation and Research (CDER) as part of the U.S. Food and Drug Administration (FDA)
D11: US 6,150,418
D12: CIVIL ACTION NO. 1:09CV87 in the United States District Court for the Northern District of West Virginia (21 March 2014)
D13: Brovana® (arformoterol tartrate) Inhalation Solution Medication Guide and Prescribing information
D21: Howard C. Ansel et. al,, Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th ed., (1999), pages 75-82

V. According to the decision under appeal, claim 1 of the main request did not meet the requirements of Article 123(2) EPC. The same applied to auxiliary requests 4, 8, 12, 16 and 20.

Auxiliary request 1 did not meet the requirements of Article 123(3) EPC, and the same applied to claim 1 of auxiliary requests 2, 3, 5-7, 9-11, 13-15, 17-19 and 21-23.

Novelty was admitted as a new ground of opposition after expiry of the opposition period, in view of the prima facie relevance of document D3. The disclosure of document D3 anticipated the novelty of claim 1 of auxiliary requests 24 and 25.

D3 was seen as the closest prior art for assessing inventive step of auxiliary request 26. Claim 1 of auxiliary request 26 was restricted by the features

"the composition comprises a buffer at a concentration from 1 mM to 20 mM, and the pH of the composition is from 4.0 to 6.0". The subject-matter of claim 1 differed from D3 in the use of a buffer at a concentration from 1 mM to 20 mM. An alleged stabilisation effect of the buffer had not been demonstrated and the technical problem was seen as the provision of an alternative formoterol composition. The subject-matter of claim 1 was not inventive for this reason.

Claim 1 of auxiliary requests 27-29 did not provide a further difference over D3 and also lacked inventive step for the same reason.

VI. The patent proprietor (hereinafter the appellant) filed an appeal against said decision. With the statement setting out the grounds of appeal dated 22 June 2018, the appellant filed a main request and 47 auxiliary requests, and submitted five new documents D23-D27, among them the following:
D25: Ionic strength calculations assuming addition of 5 mM citrate buffer to composition of D3

VII. With its reply dated 2 November 2018 the opponent (hereinafter the respondent) requested that auxiliary requests 10-15 and 21-47 as well as documents D25-D27 not be admitted into the proceedings.

VIII. The parties were summoned to oral proceedings with letter dated 4 June 2019. In its communication pursuant to Article 15(1) RPBA 2020 dated 17 January 2020 the Board expressed its preliminary opinion that the main request and all the auxiliary requests did not appear inventive over D1 as closest prior art and that

auxiliary requests 24-47 should not be admitted into the appeal proceedings.

IX. With letter dated 6 March 2020, the appellant filed a new main request and auxiliary requests 1-23 and a replacement copy of D25.

The subject-matter of the independent claims 1 of the requests read as follows, the difference(s) compared with the main request, or the request as otherwise indicated, shown in bold:

Main request

"1. A pharmaceutical composition, comprising formoterol free base at a concentration of 5 µg/ml to 50 µg/ml, or a derivative thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, the composition is suitable for direct administration to a subject in need thereof, the composition comprises a buffer at a concentration from 1 mM to 20 mM, and the pH of the composition is from 4.0 to 6.0."

Auxiliary request 1

1. A pharmaceutical composition, comprising **formoterol fumarate, formoterol fumarate dihydrate or formoterol tartrate**, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, the composition is suitable for direct administration to a subject in need thereof, the composition comprises a buffer at a concentration from 1 mN to 20 mM, the pH of the composition is from 4.0 to 6.0 and the formoterol free

base concentration in the composition is 5 µg/ml to 50 µg/ml.

Auxiliary request 2

Claim 1 corresponded to claim 1 of the main request with the additional feature "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C".**

Auxiliary request 3

Claim 1 corresponded to claim 1 of auxiliary request 1 with the additional feature "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C".**

Auxiliary request 4

Claim 1 corresponded to claim 1 of the main request with the additional amendment "the composition comprises a buffer at a concentration from **5 mM to 20 mM, the ionic strength of the composition is 0.05 to 0.16,...".**

Auxiliary request 5

Claim 1 corresponded to claim 1 of auxiliary request 1 with the additional amendment "the composition comprises a buffer at a concentration from **5 mM to 20 mM, the ionic strength of the composition is 0.05 to 0.16,...".**

Auxiliary request 6

Claim 1 corresponded to claim 1 of the main request with the additional amendments "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C**" and "the composition comprises a buffer at a concentration from **5 mM to 20 mM, the ionic strength of the composition is 0.05 to 0.16,...**".

Auxiliary request 7

Claim 1 corresponded to claim 1 of auxiliary request 1 with the additional amendments "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C**" and "the composition comprises a buffer at a concentration from **5 mM to 20 mM, the ionic strength of the composition is 0.05 to 0.16,...**".

Auxiliary request 8

"1. A pharmaceutical composition, comprising formoterol free base at a concentration of 5 µg/ml to 50 µg/ml, ~~**or a derivative thereof**~~, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, the composition is suitable for direct administration to a subject in need thereof, the composition comprises a buffer at a concentration from 1 mM to 20 mM, and the pH of the composition is from 4.0 to 6.0."

Auxiliary request 9

Claim 1 corresponded to claim 1 of auxiliary request 8 with the additional feature "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C".**

Auxiliary request 10

Claim 1 corresponded to claim 1 of auxiliary request 8 with the additional amendment "the composition comprises a buffer at a concentration from **5 mM to 20 mM, the ionic strength of the composition is 0.05 to 0.16,...".**

Auxiliary request 11

Claim 1 corresponded to claim 1 of auxiliary request 8 with the additional amendments "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C"** and "the composition comprises a buffer at a concentration from **5 mM to 20 mM, the ionic strength of the composition is 0.05 to 0.16,...".**

Auxiliary request 12

1. A pharmaceutical composition, comprising formoterol free base at a concentration of 5 µg/ml to 50 µg/ml, or a derivative thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, **the composition is suitable for use in treating, preventing, or ameliorating one or more symptoms of**

**bronchoconstrictive disorders, wherein the bronchoconstrictive disorders are chronic obstructive pulmonary disorders, by direct administration via nebulization to a subject in need thereof,** the composition comprises a buffer at a concentration from 1 mM to 20 mM, and the pH of the composition is from 4.0 to 6.0.

Auxiliary request 13

1. A pharmaceutical composition, **comprising formoterol fumarate, formoterol fumarate dihydrate or formoterol tartrate,** in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, **the composition is suitable for use in treating, preventing, or ameliorating one or more symptoms of bronchoconstrictive disorders, wherein the bronchoconstrictive disorders are chronic obstructive pulmonary disorders, by direct administration via nebulization to a subject in need thereof,** the composition comprises a buffer at a concentration from 1 mM to 20 mH, the pH of the composition is from 4.0 to 6.0 and the formoterol free base concentration in the composition is 5 µg/ml to 50 µg/ml.

Auxiliary request 14

Claim 1 corresponded to claim 1 of auxiliary request 12 with the additional feature "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C".**

Auxiliary request 15

Claim 1 corresponded to claim 1 of auxiliary request 13 with the additional feature "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C".**

Auxiliary request 16

Claim 1 corresponded to claim 1 of auxiliary request 12 with the additional amendment "the composition comprises a buffer at a concentration from **5 mM to 20 mM, the ionic strength of the composition is 0.05 to 0.16,...".**

Auxiliary request 17

Claim 1 corresponded to claim 1 of auxiliary request 13 with the additional amendment "the composition comprises a buffer at a concentration from **5 mM to 20 mM, the ionic strength of the composition is 0.05 to 0.16,...".**

Auxiliary request 18

Claim 1 corresponded to claim 1 of auxiliary request 12 with the additional amendments "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C"** and "the composition comprises a buffer at a concentration from **5 mM to 20 mM, the ionic strength of the composition is 0.05 to 0.16,...".**

Auxiliary request 19

Claim 1 corresponded to claim 1 of auxiliary request 13 with the additional amendments "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C**" and "the composition comprises a buffer at a concentration from **5 mM to 20 mM, the ionic strength of the composition is 0.05 to 0.16,...**".

Auxiliary request 20

1. A pharmaceutical composition, comprising formoterol free base at a concentration of 5 µg/ml to 50 µg/ml, ~~**or a derivative thereof,**~~ in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, **the composition is suitable for use in treating, preventing, or ameliorating one or more symptoms of bronchoconstrictive disorders, wherein the bronchoconstrictive disorders are chronic obstructive pulmonary disorders, by direct administration via nebulization to a subject in need thereof**, the composition comprises a buffer at a concentration from 1 mM to 20 mM, and the pH of the composition is from 4.0 to 6.0.

Auxiliary request 21

Claim 1 corresponds to claim 1 of auxiliary request 20 with the additional feature "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C".**

Auxiliary request 22

Claim 1 corresponded to claim 1 of auxiliary request 20 with the additional amendment "the composition comprises a buffer at a concentration from **5 mM to 20 mM, the ionic strength of the composition is 0.05 to 0.16,...**".

Auxiliary request 23

Claim 1 corresponded to claim 1 of auxiliary request 20 with the additional amendments "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C**" and "the composition comprises a buffer at a concentration from **5 mM to 20 mM, the ionic strength of the composition is 0.05 to 0.16,...**".
feature

X. With a letter dated 28 September 2020, the appellant filed new auxiliary requests 24 and 25

Independent claim 1 of the new auxiliary requests read as follows, with the differences compared to the main request in bold:

Auxiliary request 24

"1. A pharmaceutical composition, comprising ~~**formoterol free base at a concentration of 5 µg/ml to 50 µg/ml, or a derivative thereof**~~ **a pharmaceutically acceptable salt of formoterol** in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, the composition is suitable for direct administration to a subject in need

thereof, the composition comprises a buffer at a concentration from **5 mM to 20 mM**, and the pH of the composition is from **4.5 to 5.5**."

Auxiliary request 25

"1. A pharmaceutical composition, comprising ~~**formoterol free base at a concentration of 5 µg/ml to 50 µg/ml, or a derivative thereof**~~ **formoterol fumarate** in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, the composition is suitable for direct administration to a subject in need thereof, the composition comprises a buffer at a concentration from **5 mM to 20 mM**, and the pH of the composition is from **4.5 to 5.5**."

XI. After several postponements, the oral proceedings took place on 22 October 2020 and were conducted by videoconference.

XII. The arguments of the appellant may be summarised as follows:

Main request and auxiliary request 1 - Inventive step

The claimed composition needed to demonstrate a long-term storage stability, a suitability for direct administration to a subject, and a suitability for nebulisation. Neither D3 nor D1 had as aim the development of a formulation with long-term storage stability. The composition of D3 was administered immediately after it was prepared and the composition of D1 was stated to be "not attractive for long term storage".

The claimed subject matter differed from the composition of D1 in that the concentration of the buffer included in the composition was unknown. The buffer concentration and pH had an influence on long-term stability of aqueous formoterol containing compositions, while the concentration of formoterol did not directly influence the stability of the formulation. This was demonstrated in the patent using formulations containing 61 and 122 µg/mL of formoterol free base in the examples. The stability studies described in the Patent were therefore clearly relevant to the claimed subject-matter. A composition that provided long-term stability using formulations containing 61 and 122 µg/mL of formoterol free base would also provide long term storage stability at other concentrations of formoterol. Moreover, the examples employed formoterol fumarate dihydrate, a formoterol derivative for which the concentration was not limited according to the claim interpretation provided by the Board.

The inventors performed extensive stability testing and the results of formulation testing were reported in the patent. Firstly, page 16 from lines 15-26 of the application (corresponding to paragraph [0048] of the patent) described the effect of pH on decomposition of aqueous solutions of formoterol. These studies confirmed that a pH from 4 to 6 minimised decomposition of aqueous solutions of formoterol. This observation was not derivable from any of the cited prior art documents.

Moreover, buffer concentration affected the stability of the claimed compositions. This was discussed in paragraph [0051] of the patent. As a consequence of

this testing, relatively low buffer concentrations were selected.

PH and buffer concentration had interrelated effects on stability and higher concentrations of buffer increased the rate constant of decomposition significantly al low and neutral pH conditions (cf. par. [0055]). Compositions comprising higher buffer concentrations were less stable, in particular above 20 mM. This was also expressed by the ionic strength, which was lower.

Moreover, D1 indicated that its formulation was unsuitable for long-term storage, this implying that the buffer concentration was higher than 20 mM. A stabilising effect was therefore demonstrated compared to D1.

The problem to be solved had to be considered as the provision of an improved aqueous formoterol composition.

D1 did not provide any motivation to modify the formoterol compositions they formulated. The formulation of D1 was explicitly described as "not attractive for long term storage" (col. 20 lines 5-6). Instead, reference was made to a co-pending US application. Based on the disclosure of D1 there was no motivation whatsoever for the skilled person to develop an improved aqueous formoterol composition. The only motivation from D1 would therefore be for the skilled person to use an alternative approach, such as one involving keeping the formoterol dry until shortly before it is administered. The reliance by the respondent on D8 and D21 was entirety misplaced because it was based on the fundamentally incorrect assumption

that the skilled person would perform stability testing of the aqueous formulations disclosed in D1.

The claimed subject matter was inventive. The same reasoning applied to auxiliary request 1.

Admission of auxiliary requests 2-7 and 9-11 into the proceedings

These requests corresponded to requests filed with the statement of grounds of appeal, and were a direct response to the decision of the opposition division.

Admission of D25 into the appeal proceedings

Document D25 was filed as evidence of the effect of adding a citrate buffer in the compositions of D3 on the overall ionic strength.

Auxiliary requests 2-11 - Inventive step

The arguments were essentially the same as for the main request. The ionic strength had a positive influence on stability as shown in paragraph [0052] of the patent. D1 did not provide any incentive to the selection of a particular ionic strength or buffer concentration.

Admission of auxiliary requests 12-23 into the proceedings

These requests should be admitted under Article 13(1) RPBA. The Board's interpretation of claim 1 raised new issues to which the patentee has previously not had an opportunity to respond.

Moreover, the requests corresponded to requests 24-47 filed with the statement setting out the grounds of appeal, with claim 1 drafted as a product for use in a treatment, and the claims were now reverted to product claims and thus they were of the same type as those decided upon by the opposition division. The amendment was consistent with the procedure to date and did not constitute a fresh case, the claim scope was narrowed by the added feature and no unclear terms were introduced.

The amended claims should be allowed for all the reasons discussed in relation to the higher ranking requests, in particular because the composition of D1 was not suitable for direct administration via nebulization to treat COPD.

Admission of auxiliary requests 24 and 25 into the proceedings

The respondent brought two new lines of argument, which caused the filing of these requests. These requests were filed in good faith at the earliest possible opportunity having only become aware of the respondent's further submission on Friday 25 September 2020. They did not add significant procedural complexity as they merely further limited existing claim requests to render moot the respondent's newly raised objections.

XIII. The arguments of the respondent may be summarised as follows:

Main request and auxiliary request 1 - Inventive step

D1 could be seen as the closest prior art and disclosed a formulation buffered to a pH of 5, wherein the concentration of the buffer was not provided. There was, however, no evidence at all in the patent that the buffer concentration range recited in the claims had an advantageous effect on storage stability.

Example 3 of the patent provided only an incomplete protocol for testing the stability of the exemplified formulations and no results were provided, and paragraph [0051], lines 49-51, of the patent stated, without any supporting evidence, that "the buffer concentration has been found herein to affect the stability of the composition". The patent reported that suitable buffer concentrations range broadly from as little as 0.01 mM up to 150 mM, and no link was provided in the patent between the claimed buffer concentration range (1-20 mM) and an improved stability.

The patent reported that for compositions having a low or neutral pH, increasing the buffer concentration from 5 mM to 20 mM increased the rate constant of decomposition; but for compositions having a pH in the region of about 4.5 to 5.5, such as disclosed in D1, increasing the buffer concentration from 5 mM to 20 mM did not result in any increase in the rate of decomposition (see col. 10, line 58 to col. 11, line 6).

Whilst paragraph [0051] of the patent indicated that pH played a role in stability, it could not be inferred from this that there was any increased decomposition at buffer concentrations above 20 mM, provided the pH was between 4.5 and 5.5, as was the case in D1.

The technical problem had to be formulated as the provision of an alternative aqueous formoterol composition.

It was quite clear from D1 that the instability being discussed related to R,R-formoterol L-tartrate, and that when reviewing the whole of D1 the skilled person would have concluded that this instability was not associated with the racemic form of formoterol. As such, the skilled person would have been motivated to investigate the aqueous formulation described in D1 at least with racemic forms of formoterol and its derivatives.
In any case, the stabilisation of a formulation was a routine problem for a skilled person, and the determination of a specific buffer concentration was the result of routine experimentation. This was shown by D21.

Admission of auxiliary requests 2-7 and 9-11 into the proceedings

None of the newly filed requests should be admitted into the appeal proceedings. Claim 1 of each of auxiliary requests 4-7, 10 and 11 provided a new, narrower range for the concentration of the buffer (namely 5-20 mM). According to the appellant, the effect of this new buffer concentration range on ionic strength was to allegedly distinguish the claimed subject matter from the prior art. However, this point had never been discussed during first instance proceedings and played no part in the decision of the opposition division. Moreover, the appellant had ample opportunity during the first instance proceedings to address this point, and it could and should have filed

these requests, and made the corresponding factual argumentation, during first instance proceedings.

Moreover, these claims raised issues under Art. 123(2) EPC, since claim 1 of these requests involved two separate selections for which there is no pointer in the application as filed.

Admission of document D25 into the proceedings

This document was filed to support some arguments in relation to auxiliary requests 4-7,10-11,16-19 and 22-23. As these auxiliary requests should not be admitted into these proceedings, nor should this new document.

Auxiliary requests 2-11 - Inventive step

The modifications made to claim 1 of these request did not change anything with regard to inventive step. The stability requirements added in some requests did not provide any particular effect, and there was no evidence in the contested patent that a restriction with regard to the buffer concentration and the ionic strength provided an effect.

Admission of auxiliary requests 12-23 into the proceedings

These requests were new and had been filed very late. There was no justification for filing these requests so late in the proceedings and they should not be admitted.

Firstly, these new requests did not directly address the claim features that were at issue in the Board's

communication. The appellant was using this issue as a "cover" for the introduction of new claims at a very late stage.

Secondly, these requests raised new issues, such as, for the first time, that although the formulation disclosed in D1 was for use with a nebulizer the formulation would not be suitable for treating COPD (chronic obstructive pulmonary disorders).

Admission of auxiliary requests 24 and 25 into the proceedings

These requests had been filed very late and were not in response to an objection of the Board. They related to new subject-matter resulting from a combination of features originating from the description, in particular the examples and other features present in the claims; the description and the claims should not serve as a reservoir to bring new subject-matter. Moreover, these requests raised new questions as regards inventive step and Article 123(2) EPC. The combination of such features at such late stage of the appeal proceedings could not be accepted, and these requests should not be admitted.

XIV. Requests

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The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed with letter dated 6 March 2020 or one of auxiliary requests 1-25, wherein auxiliary requests 1-23 were filed with letter dated 6 March 2020 and auxiliary requests 24 and 25 were filed with letter dated 28 September 2020.

The respondent requested that the appeal be dismissed. The respondent also requested that documents D25-D27 and auxiliary requests 2-7 and 9-23 not be admitted into the proceedings.

## Reasons for the Decision

1. Main request - Inventive step

The invention relates to compositions of formoterol in a pharmacologically suitable fluid that contains water, that are stable during long term storage. The compositions are suitable for direct administration to a subject in need thereof.

1.1 Interpretation of the subject-matter of claim 1

Claim 1 of the main request pertains to "a pharmaceutical composition, comprising formoterol free base at a concentration of 5 µg/ml to 50 µg/ml, or a derivative thereof...".

During the opposition proceedings, the issue of the interpretation of this feature arose in the context of the discussion under Article 123(2) EPC, in particular the issue whether the concentration range of the derivative of formoterol should also be within the concentration range of 5 µg/ml to 50 µg/ml that was explicitly claimed for formoterol in free base form.

The opposition division did not follow the appellant's interpretation that the concentration range of any derivative was the equivalent concentration range resulting from the calculation and conversion of the claimed concentration range of 5 µg/ml to 50 µg/ml of the formoterol free base to the corresponding

derivative. Instead of that, this wording was interpreted by the opposition division as relating to a composition comprising any derivative of formoterol within the same concentration range of 5 µg/ml to 50 µg/ml as claimed for the free base form. This interpretation led to the finding in the opposition proceedings that this feature did not meet the requirements of Article 123(2) EPC.

The Board's view is, by contrast, that the claim wording suggests that the concentration of formoterol free base is comprised between 5 µg/ml to 50 µg/ml, but that the concentration of any derivatives of formoterol is undefined and unlimited. This interpretation is furthermore in line with the teaching of the description, which discloses formulations of derivatives of formoterol at a concentration higher than the claimed 50 µg/ml (see the examples and page 15, lines 17-25 of the application as filed).

This reading of the feature has an effect on the assessment of Article 123(2) EPC, but not on the assessment of inventive step. Indeed, the problem of storage stability of the derivative of formoterol remains the same whatever the concentration of the derivative or the free base is. This was confirmed by the appellant who argued that the concentration of formoterol did not directly influence the stability of the formulation, since the formulation was developed such that the formoterol, at whatever concentration it was included, did not degrade appreciably under long-term storage and usage conditions. According to the appellant, this was demonstrated in the patent using formulations containing 61 and 122 µg/mL of formoterol free base, under the form of 85 and 170 µg/mL of formoterol fumarate dihydrate, and was clearly

applicable to formulations containing lower or indeed higher concentrations of formoterol.

1.2 The Board agrees with the appellant that D1 is the closest prior art.

D1 discloses in the first paragraph of column 20 an aerosol composition for use in a nebulizer comprising 2 mg of formoterol tartrate in 10 mL buffered to pH 5 with a citrate buffered saline. Said passage states further that "because of the problematic stability of R,R-formoterol L-tartrate in aqueous solution, this formulation is not attractive for long term storage, but it is quite suitable for short term use". The formulation disclosed in D1 is suitable for direct administration, since it is presented as a solution to be nebulized directly. The buffer amount is however not disclosed in D1.

1.3 According to the appellant, the objective technical problem is the provision of an improved aqueous formulation of formoterol for direct administration to a subject.

The respondent defined the problem as the provision of an alternative aqueous formulation of formoterol.

1.4 As a solution to any of these alleged problems, claim 1 of the main request proposes a formulation comprising a buffer in particular within the concentration range of 1 to 20 mM.

1.5 The next step in the problem solution approach consists of investigating whether there is sufficient evidence supporting the alleged effect.

The appellant argues that the technical effect observed is an improvement with regard to the long term stability and the suitability for administration to a subject (see patent, par. [0055]). The improvement in long term storage of the claimed formulation is linked to the pH and the buffer concentration (see patent, par. [0051]).

The pH and buffer concentrations have interrelated effects on stability and higher concentrations of buffer increase the rate constant of decomposition significantly at low and neutral pH conditions. Compositions comprising higher buffer concentrations are less stable, in particular above 20 mM. The claims reflect these technical effects by specifying that the buffer concentration is no more than 20 mM and by defining the pH of the composition as between 4.0 and 6.0 (see par. [0048]).

According to the respondent, there is no evidence in the patent that might render credible the allegation of an improvement in long term storage stability for the claimed formulations. The passages in the patent relied on by the appellant are only statements and do not constitute credible disclosure for evidencing the existence of such effect.

1.6 The assessment of the credibility of a technical effect as to the storage stability does however not appear to be necessary in the present case. The claimed solution, namely the adaptation of the buffer concentration appears to be in any case an obvious solution, irrespective of the definition of the problem to be solved, whether as defined by the appellant or by the respondent. In the Board's view, in the present case, the adaptation of common variables such as the amount

or nature of a buffer of a liquid formulation, belongs to the field of the routine tasks for the person skilled in the art.

The Board's view is confirmed by the teaching of document D21. D21 is a textbook on pharmaceutical dosage forms and drug delivery systems and the relevant extracts therefrom are evidence of the common general knowledge of the person skilled in the art. D21 teaches that one of the most important activities of preformulation work is the evaluation of the physical and chemical stability of the drug substance (see page 75). While D21 states that alternative solutions for long term storage are the use of dry forms or non-aqueous solutions, the document also highlights that, in the case of aqueous solutions, temperature and pH are the major determinants for the stability of a drug prone to hydrolytic decomposition, and that the concentration of hydroxyl and hydronium ions and the optimal pH for stability can easily be determined by the skilled person. Said optimal pH value is commonly between pH 5 and 6 for most drugs, and the use of buffering agents to maintain the optimal pH increases the stability of the drug substance (see D21, pages 79 -80).

This general teaching suggests that the person skilled in the art, in view of the disclosure of D1, in particular of the satisfactory short-term stability, would inevitably test the long-term stability of the disclosed formulation and, in the case of an insufficient stability, would work initially and inevitably on the pH of the formulation and the linked ionic concentration, as well as on the concentration of the buffer to effectively maintain the pH of the formulation.

Consequently, the adaptation of the buffer concentration to the claimed range of 1 to 20 mM, said buffer concentration being the only variable constituting a distinguishing technical feature between the subject-matter of claim 1 and the formulation disclosed by D1, is obvious and cannot confer an inventive step on the claimed subject-matter.

1.7 The Board could not follow the appellant's argument that the skilled person would not consider the formulation disclosed in D1 in view of its unsuitability for long term storage. This argument is based on the statement given in D1 as to the stability of the disclosed formulation in column 20, namely "because of the problematic stability of R,R-formoterol L-tartrate in aqueous solution, this formulation is not attractive for long term storage, but it is quite suitable for short term use".

Whilst the Board accepts that the skilled person would regard storage in dry form as easier than storage in liquid form, the latter would nevertheless remain a possible alternative, especially as the term "long term storage" has neither been defined in claim 1 of the main request nor in D1. More importantly, the statement in column 20 of D1 can also be seen as an incentive for improving the disclosed formulation, or, as argued by the respondent, for adapting it to the racemic form of formoterol, which is presented in D1 as more stable than R,R-formoterol L-tartrate in aqueous solution (see D1, col. 18, l. 11-27).

1.8 The citation of further documents by the appellant does not change this conclusion as these documents are no more relevant than the documents cited above.

D2 is the prescribing information of the product Perforomist® comprising 10 µg/mL of formoterol fumarate, saline solution and a pH adjusted to 5.0 with a citrate buffer in an unspecified concentration (see point 11). According to the appellant, this product corresponds to the product of the claimed invention and is said to be stable up to three months after opening at 2 to 25°C (see point 16). This document confirms the stability of the claimed product.

D7 relates to the dry powder form of Foradil® (formoterol fumarate) and discloses the sensitivity of the product to moisture (see page 12 or 18). However, for the reasons explained above, the Board considers that having regard to the teaching of D1 and D21, the skilled person would be able to provide aqueous formulations of formoterol.

D11 discloses a composition of formoterol in a saline solution at pH5 for inhalation, and shows that formoterol breaks down to 10% at 40°C within three months. A comparable test was disclosed in D12, and shows that 91% by weight of formoterol remains in water after six months of storage at 5°C. This teaching highlights the necessity to use a buffer to stabilize the compositions.

D12 refers furthermore to D1 and a co-pending application mentioned in D1, which discloses that an approach to a long-term storage product was a kit with a powder comprising formoterol and an aqueous vehicle to dissolve the powder before use. However, the fact that other solutions may exist to provide stable aqueous formulations of formoterol does not imply that

the solution adopted in the present case involves an inventive step.

1.9 Consequently, the subject-matter of claim 1 of the main request is not inventive.

2. Auxiliary request 1 - Inventive step

Claim 1 has been restricted to specific salts of formoterol namely "formoterol fumarate, formoterol fumarate dihydrate or formoterol tartrate". Since D1 discloses a formulation with formoterol tartrate, this amendment does not constitute a further distinguishing feature over D1 and has therefore no impact on the assessment of inventive step. Auxiliary request 1 does not meet the requirements of Article 56 EPC for the same reasons as the main request.

3. Admission of auxiliary requests 2-7 and 9-11 into the proceedings

The appeal was filed before 1 January 2020, and therefore Article 12(4) RPBA 2007 applies (Article 25(2) RPBA 2020, OJ 2019, A63).

Auxiliary requests 2-7 and 9-11 correspond to requests filed with the statement of grounds of appeal, namely to auxiliary requests 8-11, 14, 15, 20, 21 and 23 filed on 22 June 2018.

Claim 1 of auxiliary requests 2-7 and 9-11 has been amended by one or more of the following features relating to the salts of formoterol, the stability requirements, the buffer concentration and the ionic strength:

**a) "formoterol fumarate, formoterol fumarate dihydrate or formoterol tartrate",**
b) "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C",**
**c)** "the composition comprises a buffer at a concentration from **5 mM to 20 mM",**
**d) "the ionic strength of the composition is 0.05 to 0.16".**

Features a) and d) were already present in some requests presented during the opposition proceedings, while features b) and c) are of the same nature but more restricted than other amendments also present in auxiliary requests filed during the opposition proceedings, namely "wherein the composition is stable during long term storage such that greater than **80%** of the initial formoterol is present after **1** month usage time at 25°C and **1** year storage time at 5°C" and "the composition comprises a buffer at a concentration from **1** mM to 20 mM" (emphasis added by the Board).

Said amendments therefore address the same issues as, and are a further limitations of, the requests filed during the opposition proceedings. They relate to the opposition division's findings on the late-filed ground of lack of novelty over D3 and on inventive step.

The introduction of auxiliary requests 2-7 and 9-11 is therefore a direct response to the decision of the opposition division, and the Board is not convinced that the appellant should have filed these requests already before the opposition division. Therefore, the Board sees no reason to exercise its discretion not to admit auxiliary requests 2-7 and 9-11 into the

proceedings. These requests therefore form part of the appeal proceedings (Article 12(4) RPBA 2007).

4. Admission of D25 into the appeal proceedings

D25 has been filed with the statement of grounds of appeal and relates to the calculation of ionic strength of formulations stabilised by a citrate buffer. This document is intended to support the auxiliary requests which contain an ionic strength limitation, among them auxiliary requests 4-7, 10 and 11 filed with the grounds of appeal. The Board, having decided to admit these auxiliary requests, sees no reason for exercising its discretion not to admit D25. D25 thus forms part of the appeal proceedings (Article 12(4) RPBA 2007).

5. Auxiliary requests 2 and 3 - Inventive step

In comparison to claim 1 of respectively the main request and auxiliary request 1, claim 1 of auxiliary requests 2 and 3 has been restricted through the additional feature "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C**".

As for the main request, the adaptation of common variables such as the amount or nature of a buffer of a liquid formulation, with the aim of an improved stability as now explicitly claimed in claim 1 of auxiliary requests 2 and 3, belongs to the field of the routine tasks for the person skilled in the art. The fact of providing a definition of the concept of long term storage stability, does not provide any inventive contribution to the subject-matter of the claim.

Accordingly, the subject-matter of claim 1 of auxiliary requests 2 and 3 is not inventive.

Consequently, auxiliary requests 2 and 3 do not meet the requirements of Article 56 EPC for the same reasons as the main request.

6. Auxiliary request 4 - Inventive step

Claim 1 of auxiliary request 4 corresponds to claim 1 of the main request with the additional amendment "the composition comprises a buffer at a concentration from **5 mM to 20 mM, the ionic strength of the composition is 0.05 to 0.16**".

The appellant referred to document D25 to show that at the lowest claimed buffer concentration of 5 mM, the addition of sufficient buffer components to maintain a pH of 5 or 5.5 to a saline liquid formulation as disclosed in D3, would take the ionic strength above that of claim 1. This calculation is however not relevant, since the closest prior art is D1, wherein the buffer concentration is not disclosed; D25 proves however that the buffer concentration and the ionic strength are closely linked.

As stated in paragraph 1.6 above for the main request, document D21 teaches that the ionic concentration and the optimal pH for stability can easily be determined by the skilled person using his common general knowledge, said parameters being both impacted by the buffer concentration which is a routine variable to be adapted by the skilled person. Thus, the specification of the ionic strength of the composition has no impact on the assessment of inventive step, and auxiliary request 4 does not meet the requirements of Article 56

EPC essentially for the same reasons as the main request.

7. Auxiliary requests 5-7 - Inventive step

Claim 1 of these requests corresponds to claim 1 of the main request or of auxiliary request 1 amended with at least one of the features "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C**" and /or "the composition comprises a buffer at a concentration from **5 mM to 20 mM, the ionic strength of the composition is 0.05 to 0.16**".

Since these features do not have any effect on the assessment of inventive step, auxiliary requests 5-7 do not meet the requirements of Article 56 EPC for the same reasons as set out above for the main request or auxiliary requests 1 or 4.

8. Auxiliary requests 8 - Inventive step

Claim 1 of this request differs from claim 1 of the main request in the deletion of the term "or a derivative thereof". In addition to the buffer concentration, the difference between the claimed subject-matter and the disclosure of D1 is therefore that the active ingredient is used as free base and that a lower concentration of active ingredient is present in the claimed formulations, namely 5 to 50 µg/mL instead of 139 µg/mL in the formulation of D1. Auxiliary request 8 corresponds to auxiliary request 18 filed by the appellant with the statement setting out the grounds of appeal. This request was filed in response to some objections raised by the opposition

division under Article 123(2) EPC (see paragraph 15 of the statement setting out the grounds of appeal). The appellant did not present any specific argument as to the relevance of the modifications introduced in this request to the assessment of inventive step.

In the absence of any unexpected effect, the Board considers that using the free base instead of a salt and lowering the amount of active ingredient does not provide any inventive contribution to the subject-matter of the claim. Furthermore, as explained under point 1.1 above, the concentration of formoterol does not influence the stability of the formulation.
The reasoning and conclusion as to inventive step reached above for the main request apply therefore mutatis mutandis to auxiliary request 8 which does not meet the requirements of Article 56 EPC.

9. Auxiliary requests 9-11 - Inventive step

Claim 1 of these requests corresponds to claim 1 of auxiliary request 8 amended with at least one of the features "wherein the composition is stable during long term storage **such that greater than 90% of the initial formoterol is present after 3 months usage time at 25°C and 3 years storage time at 5°C**" and/or "the composition comprises a buffer at a concentration from **5 mM to 20 mM, the ionic strength of the composition is 0.05 to 0.16**".

Since these features do not have any effect on the assessment of inventive step, auxiliary requests 9-11 do not meet the requirements of Article 56 EPC essentially for the same reasons as set out above for auxiliary request 8.

10. Admission of auxiliary requests 12-23 into the proceedings

10.1 Auxiliary requests 12-23 have been filed with letter dated 6 March 2020, after the summons to oral proceedings dated 4 June 2019 had been notified to the parties. Article 13 RPBA 2007 continues to apply to such submissions filed after the statement of grounds of appeal and the reply to the appeal (Article 25(3) RPBA 2020).

Article 13(1) RPBA 2007 gives discretion to the Board for the consideration of any amendment to a party's case. This discretion is exercised with a view of inter alia the current state of the proceedings, the complexity of the new subject-matter, and the need for procedural economy. The latter criteria has been repeatedly interpreted by the Boards to mean that an amendment should only be admitted if, *prima facie*, it overcomes the issues raised and does not give rise to new issues.

10.2 Auxiliary requests 12-23 have been filed after the Board has issued a preliminary opinion and shortly before the oral proceedings initially scheduled for 7 April 2020, and thus at a late stage of the appeal proceedings.

The subject-mater of claim 1 of all auxiliary requests 12-23 comprises the following new terms originating from the description, namely "the composition is suitable for use in treating, preventing, or ameliorating one or more symptoms of bronchoconstrictive disorders, wherein the bronchoconstrictive disorders are chronic obstructive

pulmonary disorders" and "**by** direct administration **via nebulization** to a subject in need thereof".

None of these new terms was present in the claims as granted, in particular not in the medical use claims 37-39 as granted, which pertained to the "treatment, prevention or amelioration one or more symptoms of bronchoconstrictive disorders" in general, and not to the specific treatment of chronic obstructive pulmonary disorders. In addition, claims 37-39 as granted did not claim the mode of administration via nebulization.

Auxiliary requests 12-23 also do not correspond to any request filed with the statement of grounds of appeal, or discussed during the opposition proceedings, in particular not to any of auxiliary requests 24-47 filed with the statement of grounds of appeal which claimed in claim 1 "a pharmaceutical composition for use in treating" and did not mention the administration via nebulization.

In its communication in preparation of the oral proceedings the Board had expressed its preliminary opinion that said auxiliary requests 24-47 appeared to constitute a fresh case which would have to be discussed for the first time in the appeal proceedings, and should not be admitted into the the appeal proceedings for this reason.

10.3 The modifications introduced in auxiliary requests 12-23 raise new and complex issues.

While the main issue in the discussion about inventive step was presented in the appeal proceedings as being a problem of long term storage stability, as was the case during the opposition proceedings, the filing of

auxiliary requests 12-23 shifts this problem to one of the suitability for direct administration via nebulization to treat a specific disease. Not only has this way of administration never been a subject of discussion, but the combination of the administration via nebulization and of the treatment of a specific disease puts the focus now on a discussion about the concentration of formoterol. However, that concentration had been presented as a non-essential feature for the assessment of inventive step with regard to the previous requests.

The concentration disclosed in D1 is indeed now presented by the appellant as too high to be safely administered via nebulization in the treatment of COPD (see page 13 of appellant's letter of 6 March 2020). As argued by the respondent in its submissions of 31 March 2020 (see pages 2 and 3), this appears however not clearly to be the case in view of the description of the contested patent, since the description and the examples of the contested patent have the same concentration level as that disclosed in D1, and do not specify the concentration suitable for treating COPD via nebulization. Hence, this new issue renders the discussion more complex.

Therefore, the introduction of these features represents a fresh case and adds considerable complexity at a late stage of the proceedings. Admitting these requests into the appeal proceedings would be contrary to the principle of procedural economy.

10.4 The Board could not follow the appellant's argument that these requests were filed in response to new

issues raised by the Board's interpretation of the claim wording.

The new requests contain amendments which do not address the claim feature that is at issue. There is for example no link between the term "via nebulization" and the issue of whether the amount of the derivative of the formoterol free base is limited or not.

Moreover, the Board's interpretation of the claim wording has an effect on the assessment of the objections under Article 123(2) EPC. Given that the claim interpretation renders the objections under Article 123(2) EPC unconvincing, the Board can see no reason why it should have given rise to the filing of new auxiliary requests.

10.5 Consequently, auxiliary requests 12-23 are not admitted into the appeal proceedings Article 13(1) RPBA 2007.

11. Admission of auxiliary requests 24 and 25 into the proceedings

Auxiliary requests 24 and 25 have been filed with letter dated 28 September 2020 very shortly before the oral proceedings postponed initially to 1st October 2020, and then further to 22 October 2020. Article 13 RPBA 2007 also applies to these submissions (Article 25(3) RPBA 2020).

11.1 The subject-matter of claim 1 of auxiliary request 24 has been restricted by a new feature originating from the description, namely **"a pharmaceutically acceptable salt of formoterol"**, by a feature originating from a dependent claim as granted, namely "the pH of the composition is from **4.5** to **5.5**", and by a feature

resulting from the combination of dependent claims as granted, namely "a buffer at a concentration from **5 mM** to **20 mM**" (emphasis added by the Board).

11.2 The subject-matter of claim 1 of auxiliary request 25 has been restricted to "**formoterol fumarate**". In none of the previous requests was the active ingredient limited to formoterol fumarate. Furthermore, claim 1 specifies that the buffer is present in "a concentration from **5 mM to 20 mM**", a feature resulting from a combination of dependent claims, and that "the pH of the composition is from **4.5 to 5.5**", a feature taken from a dependent claim (emphasize added by the Board).

11.3 The Board notes that the amendments made to either request do not appear to be *prima facie* suitable to solve the problems posed as regards inventive step having regard to the considerations made in relation to the main request and auxiliary requests 1 to 11. Furthermore, the Board agrees with the respondent that the amendments give rise to additional issues to be assessed under Article 123(2) EPC. It is therefore not immediately apparent to the Board that the modified requests solve the problems posed without creating new ones.

Hence, the Board finds it appropriate to exercise its discretion by not admitting auxiliary requests 24 and 25 into the proceedings (Article 13(1) RPBA 2007).

11.4 According to the appellant, these requests were filed in response to two new lines of arguments raised by the respondent, and were filed in good faith at the earliest possible opportunity, since the appellant only

become aware of the respondent's further submission on 25 September 2020.

The Board notes that the respondent objected that the subject-matter of claim 1 of most requests on file involved two separate selections as regards the claimed value range of 5 to 50 µg/mL and the buffer concentration of 5-20 mM under Article 123(2) EPC. A further objection related to the previously claimed pH range of 4 to 6, since data were provided only for a pH range of 4.5 to 5.5 in paragraph [0051] of the patent.

A patent proprietor does not have a right to have newly filed requests admitted every time a new or a more specific objection is made under Article 123(2) EPC. Instead, the Board has discretion whether to admit them.

Moreover, there is no link between said objection and the amendments made to claim 1 of auxiliary request 24 and 25 with regard to at least the nature of the active substance. Consequently, the Board cannot follow the appellant's line of argument.

## Order

## For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated