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Datasheet for the decision of 12 March 2007

Case Number: T 0940/04 - 3.3.02

Application Number: 01112230.6

Publication Number: 1157689

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Language of the proceedings: EN

Title of invention:
Stable pharmaceutical solution formulations for pressurised metered dose inhalers

Applicant:
CHIESI FARMACEUTICI S.p.A.

Opponent:
-

Headword:
Stable aerosol composition of formoterol fumarate/CHIESI FARMACEUTICI

Relevant legal provisions:
EPC Art. 123(2), 54, 56

Keyword:
"Main request, first and second auxiliary requests: the subject-matter of claim 1 lacks inventive step"
"Third auxiliary request: novelty (yes); inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0940/04 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 12 March 2007

Appellant: CHIESI FARMACEUTICI S.p.A
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 12 December 2003 refusing European application No. 01112230.6 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: M. C. Ortega Plaza
P. Mühlens

Summary of Facts and Submissions

I. European patent application No. EP-A-1 157 689 based on European application No. 01 112 230.6 was filed with 12 claims.

Claim 1 read as follows:

"1. An aerosol composition which comprises a ß$_2$-agonist drug of the phenylalkylamino class bearing a functional group sensitive to oxidative and/or hydrolytic reaction in a solution of a liquefied HFA propellant, a co-solvent selected from pharmaceutically acceptable alcohols, wherein the pH of the solution is comprised between 2.5 and 5.0 by addition of small amounts of a mineral acid such as hydrochloric, nitric or phosphoric acid."

II. The following documents were cited *inter alia* during the examination proceedings:

(1) WO 94/13262

(7) WO 99/65460

III. The present appeal lies from the decision of the examining division refusing the application under Article 97(1) EPC, pursuant to the requirements of Articles 54 and 56 EPC.

IV. The examining division considered that the subject-matter of claim 1 of the main request lacked novelty with respect to the disclosure of document (1). In the examining division's opinion, the only feature not

explicitly mentioned in document (1) was the pH interval of 2.5 to 5.0, which could not be seen as a purposive selection of the range of 1-7 disclosed in document (1).

The examining division further considered that, even had novelty been acknowledged, the subject-matter of claim 1 of the main request could not be regarded as being an inventive solution to the problem of providing an aerosol composition containing β_2-agonists characterised by adequate shelf-life, since document (1) unambiguously taught that the stability of medicaments which degrade or decompose by the interaction with the co-solvent or water or other mechanism, including β_2-agonists, can be reduced to acceptable levels by the addition of either an inorganic or organic acid.

V. The appellant (applicant) lodged an appeal against the decision of the examining division. The appellant filed, with the grounds of appeal, a main request and a first and second auxiliary request.

VI. The board stated in its communication of 19 July 2006 that none of the sets of claims on file met the requirements of Article 123(2) EPC.

VII. In a response to the board's above-mentioned communication, the appellant filed a letter dated 4 October 2006 with further requests.

VIII. The board sent a communication as an annex to the summons to oral proceedings in which further objections re Articles 123(2) and 84 EPC were raised.

IX. The appellant filed by fax a letter dated 12 February 2007 in response to the board's communication sent as an annex to the summons to oral proceedings. The appellant withdrew the sets of claims filed with its letter of 4 October 2006 and filed auxiliary requests 3 to 6.

Claim 1 of auxiliary request 5 read as follows:

"1. An aerosol composition which comprises as active ingredient formoterol fumarate in a solution of a liquefied HFA propellant selected from the group consisting of HFA 134a, HFA 227, and mixtures thereof, and ethanol as a co-solvent, and hydrochloric acid in an amount such that the solution has an apparent pH between 3.0 and 3.5."

Dependent claim 2 of auxiliary request 5 read as follows:

"2. An aerosol composition according to claim 1 which comprises as active ingredient formoterol fumarate in a solution of a liquefied HFA propellant selected from the group consisting of HFA 134a, HFA 227, and mixtures thereof, and ethanol as a co-solvent, and 1.0 M hydrochloric acid in an amount between 3 and 3.5 μl per 1.44 mg formoterol fumarate in 12 mL of the composition."

Dependent claim 3 of auxiliary request 5 read as follows:

"3. A composition according to any one of claims 1 or 2, comprising formoterol fumarate in combination with beclomethasone dipropionate."

X. The board sent a communication by fax on 28 February 2007 in which the appellant was informed that, as the facts on file stood, none of the sets of claims met the requirements of Article 123(2) EPC. Although claim 1 of auxiliary request 5 was considered to meet the requirements of Article 123(2) EPC, claims 2 and 3 of that set of claims were objected to.

The board also expressed in said communication a preliminary opinion concerning the novelty of the subject-matter of claim 1 of auxiliary request 5 and reminded the appellant that the assessment of inventive step had to be made during the oral proceedings. In this respect the board mentioned document (7), which had been cited and commented on in the description of the patent in suit, as a more realistic starting point for formoterol fumarate formulations than document (1).

XI. Oral proceedings took place on 12 March 2007.

XII. During the oral proceedings the appellant filed four sets of claims (main request and auxiliary requests 1 to 3) replacing the seven sets of claims previously on file.

Claim 1 of the main request is identical to claim 1 of the (previous) auxiliary request 5 filed with the letter of 12 February 2007.

Claim 2 of the main request differs from claim 2 of the previous auxiliary request 5 in that the propellant has been specified as "a liquefied HFA 134a propellant", with deletion of the other options. Furthermore, when compared to the previous auxiliary request 5, claim 3 and claims 5 to 7 have been deleted, and the references to previous claims in renumbered claims 3 and 4 have been corrected.

Claim 1 of the first auxiliary request is identical to claim 1 of the main request and claim 2 reads as follows:

"2. An aerosol composition according to claim 1 which comprises as active ingredient 1.44 mg (12 μg/100μl) formoterol fumarate in a solution of a liquefied HFA 134a propellant containing 12% w/w ethanol in respect to the total weight of the composition as a co-solvent, and 3.1-3.4μl 1.0M hydrochloric acid in 12mL composition."

Furthermore, when compared to the previous auxiliary request 5, claims 3 and 5 to 7 have been deleted, and the references to previous claims in renumbered claims 3 and 4 have been corrected.

Claim 1 of the second auxiliary request is identical to claim 1 of the main request. Furthermore, when compared to the previous auxiliary request 5, claims 2 and 3 have been deleted and the references to previous claims in renumbered claims 2 to 6 have been corrected.

Claim 1 of the third auxiliary request differs from claim 1 of the main request merely in that the

propellant has been specified as "a liquefied HFA 134a propellant" and the other options have been deleted.

Claims 2 to 4 of the third auxiliary request are identical to claims 2 to 4 of the main request.

XIII. The appellant's arguments may be summarised as follows:

As regards admissibility, the main request and the first and second auxiliary requests were filed as a direct and clear response to the board's communication of 28 February 2007, since they were based on previously filed auxiliary request 5.

The third auxiliary request was filed during the oral proceedings before the board as a direct response to the previous discussion on inventive step. The amendment introduced was clear and easy to handle since it merely related to the specification of the propellant by deletion of the other options.

As regards the main request, the amendments were in accordance with the requirements of Article 123(2) EPC since claim 1 was based on originally filed claims 1, 5, 10 and 11, with the deletion of the options nitric and phosphoric acid from the list of mineral acids. Moreover, the specifications undertaken in claim 2 found as their basis the description on page 11 and the examples, in particular examples 2, 5 and 6. The volume of the formulations corresponded to that of the cans (or vials) employed in the examples, i.e. 12 ml (examples 1, 3 and 4). The examples further showed that the most preferred propellant system was HFA 134a/ ethanol and that 1.44 mg was the most preferred amount

of formoterol fumarate to be employed. Additionally, the description disclosed that an amount comprised between 3 and 3.5 μl of 1.0 M hydrochloric acid should preferably be added to the preferred formoterol formulations. This was further illustrated in examples 5 and 6. As regards the actual concentration of ethanol in the formulations according to claim 2, it proved to be 12% w/w when considering all the parameters specified in that claim, i.e. the same value as specified in examples 5 and 6. The claimed formulations concerned formoterol fumarate in a solution, ethanol being the co-solvent. It was unusual to add more solvent than necessary to dissolve the active ingredient and too high amounts of co-solvent were to be avoided.

Claim 1 of the third auxiliary request differed from claim 1 of the main request merely in that the propellant was specified to be the most preferred propellant as shown by the examples.

As regards the requirements of novelty, they were clearly met by the subject-matter now claimed in all requests.

In relation to the inventive step issue, document (7) represented the closest prior art since it disclosed formoterol fumarate formulations in the propellant system HFA 134a/ethanol, whereas document (1) disclosed ipratropium bromide formulations, which had a very different chemical structure to formoterol fumarate. The difference between the formulations claimed in claim 1 of the main request and the formulations disclosed in document (7) was the presence of

hydrochloric acid and the value of the apparent pH, defined in the claim.

Although document (7) addressed the problem of providing stable aerosol formulations, it wrongly assumed that there was no chemical deterioration of the active drug and attributed the losses to drug adsorption onto the valve gasket material.

Moreover, there was chemical degradation during storage in the formulations according to document (7), as determined by HPLC in the stability experiments of example 2 of the application in suit, which had nothing to do with the adsorption onto the valve gasket material. In the experiments of example 2 the pressurised metered dose inhalers were stored upright.

The problem to be solved lay in the provision of aerosol formulations of formoterol fumarate, in the form of solution in the propellant system HFA/ethanol, with better stability.

The solution related to the addition of hydrochloric acid and the choice of the specific apparent pH of between 3.0 and 3.5.

The problem had been solved in the light of the examples 2, 5 and 6.

The application in suit provided a general teaching for solving the problem of chemical stability in systems with high polarity HFA propellants, in particular HFA 134a. The dielectric constant played an important role.

The application in suit disclosed a model in example 3 which served to determine the amount of hydrochloric acid to be added to the HFA/ethanol system. This teaching could be generalised to other HFA propellants.

The reason for the preference of HFA 134a over other HFA relied on practical aspects such as those concerning the availability of toxicological data and the fact that it was considered by the EU as a safe propellant.

The solution to stability problems proposed by document (7) merely related to the use of ethanol, in amounts of about 15% by weight. However, the authors of document (7) did not recognise the problem of chemical deterioration of the active drug in the particular propellant system and only addressed the physical stability of the formulation.

Therefore, when starting from document (1), the skilled person would have first tried with further gasket materials rather than look to adding other ingredients to the formulation. Additionally, even if document (1) was considered, this document did not render the proposed solution obvious since it taught the use of either organic or mineral acids and broad pH ranges of about 1.0 to 7.0. However, low concentrations of hydrochloric acid were not sufficient for stabilising formoterol (in this context the appellant referred to the submissions made with the grounds of appeal). The aerosol formulations of the application in suit were sensitive to variations of dielectric constant of the medium and hence the teaching of document (1) was not

enough to solve the technical problem as previously defined. Furthermore, the "optimal pH range of 2.0-4.7" was given in document (1) as optimal **aqueous** pH range for **ipratropium bromide** and was attained with the addition of an organic acid such as citric acid.

The same arguments applied to the first and second auxiliary requests and to the third auxiliary request in which the propellant had been restricted to HFA 134a.

XIV. The appellant had requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed in the oral proceedings or on the basis of one of the first, second or third auxiliary requests filed in the oral proceedings.

Reasons for the Decision

1. *Admissibility*

1.1 The present appeal is admissible.

1.2 The main request and the first and second auxiliary requests were indeed filed as a direct and clear response to the board's communication of 28 February 2007, since they were clearly based on previously filed auxiliary request 5, and were intended to overcome the objections raised by the board.

The third auxiliary request was filed during the oral proceedings before the board as a direct response to the previous discussion on inventive step. The amendment was a clear restriction to the preferred

propellant. This limitation was easy to handle and did not require a new discussion.

Therefore, all these requests were admitted into the proceedings.

2. *Main request*

2.1 Claim 1 of the main request is based on claims 1, 5, 10 and 11 as originally filed with a mono-dimensional restriction by deletion of other options for mineral acid than hydrochloric acid.

Dependent claim 2 is directly and unambiguously derivable from the description (including the examples) as originally filed. The basis stated and explanations given by the appellant are accepted.

The generic claims 3 and 4 were already present as dependent claims in the set of claims as originally filed and their combination with restricted claims 1 and 2 does not generate subject-matter beyond that of the application as originally filed.

Therefore, the set of claims of the main request meets the requirements of Article 123(2) EPC.

2.2 For the assessment of novelty of the subject-matter claimed documents (1) and (7) have to be investigated.

2.2.1 Document (1) discloses generically "aerosol solution formulations comprising a medicament, an HFC propellant, a cosolvent, and an inorganic acid or an organic acid" (page 4, second paragraph from the bottom).

However, in order to arrive at the subject-matter claimed in claim 1 of the main request it is necessary to perform selections in several directions.

In particular, the active drug, the propellant, the co-solvent, the acid and the apparent pH of the solution have to be selected.

Although 1,1,1,2-tetrafluoroethane (HFC-134(a)) and 1,1,1,2,3,3,3-heptafluoropropane (HFC-227), i.e. the two hydrofluoroalcanes appearing in claim 1 of the main request, were disclosed in document (1) as particularly preferred HFC (hydrofluorocarbon) propellants, document (1) also teaches that other non-halogenated propellants may be used instead (page 5, first paragraph).

However, document (1) also discloses that a "substantially non-aqueous HFC propellant/cosolvent system is preferred" (page 5, last paragraph).

As regards the active drug (called in document (1) "the medicament"), it "may be any substance which is suitable for aerosol administration from an MDI or similar device. The medicament must be soluble in the HFC propellant/cosolvent system and, characteristically exhibit significant degradation or decomposition in the HFC propellant/cosolvent system. The degradation or decomposition of the medicament must be acid sensitive in that the rate of degradation or decomposition can be effectively reduced by the addition of an acid" (page 6, second paragraph).

A list of possible active drugs is given on pages 7 and 8 of document (1). Formoterol appears on page 8 among other options for sympathomimetic bronchodilators. Document (1) also discloses on page 8 that the medicaments "may be in the form of either the free base or a pharmaceutically acceptable, non-toxic salt thereof".

The option "fumarate" appears on page 9 among a long list of possible salts. Moreover, document (1) clearly states that "(t)he selection of a particular salt will depend upon the chemical nature of the base and the chemical stability and solubility of the salt in the formulation" (end of page 8), but it gives no hint on the use of formoterol fumarate. Indeed, all the formulations specifically disclosed in document (1) relate to ipratropium bromide, which is very different in its chemical structure to formoterol fumarate.

A list of possible co-solvents is given on pages 9 and 10. Among the options listed in document (1) are alcohols, for example ethyl alcohol. Although ethanol is also mentioned as "a preferred cosolvent" according to the "invention", document (1) clearly states that "(t)he chemical nature of the medicament defines the nature of the cosolvent, which may be any one of a number of organic solvents that are toxicologically safe and amenable to MDI solution formulations" (page 10, third paragraph, and page 9, last paragraph).

Document (1) further discloses that "(t)he selection of the acid in the aerosol solution formulations of this invention depends on the medicament used and the acid concentration needed to effect an acceptable rate of

degradation of the medicament". Indeed, the acid may be any inorganic or organic acid (page 10, last paragraph).

Hence, there is no specific teaching in the whole document (1) on the choice of HFA 134a/ethanol as the propellant system in the case of formoterol fumarate, nor on the choice of hydrochloric acid as a further essential ingredient.

2.2.2 As regards document (7), the claimed subject-matter is novel over the formoterol fumarate aerosol formulations disclosed therein at least in view of the presence of the acid.

Further documents cited during the procedure are not relevant for the novelty assessment.

2.2.3 Consequently, the subject-matter claimed is novel over the cited prior art documents (Articles 52 and 54 EPC).

2.3 Document (7), which specifically discloses pharmaceutical aerosol formulations of formoterol fumarate in the propellant system HFA 134a/ethanol, represents the closest prior art. This has not been disputed by the appellant.

2.3.1 In particular, document (7) states that "(a)nother objective of the present invention is to provide a stable formulation of a ß-agonist drug that is suitable for use as an aerosol, which does not require the use of refrigeration" (page 2, lines 17 to 19).

Document (7) discloses "a (novel) aerosol formulation adapted for use in a pressurized aerosol container,

said aerosol formulation being formulated from a composition comprising:

> a ß-agonist drug;
> at least one fluoroalkane propellant; and
> greater than 5% by weight, based on the total weight of the aerosol formulation, of a solvent that is capable of solubilizing or dissolving the ß-agonist drug" (page 3, lines 9 to 16).

Document (7) also states: "The aerosol formulations are surprisingly stable under conditions up to about 40°C and about 75% relative humidity for at least about four weeks" (page 3, lines 24, 25).

Document (7) further discloses: "It has been unexpectedly discovered that the stability of aerosol formulations of solutions of a ß-agonist drug can be significantly improved by utilizing more than 5% by weight of a solvent capable of solubilizing or dissolving the ß-agonist drug" (page 4, lines 11 to 14).

The preferred ß-agonist drug according to the description and illustrated by the examples of document (7) is formoterol, which is preferably in its "weak acid form" as formoterol fumarate (page 4, lines 16 to 20).

"For formoterol fumarate, the concentration utilized is usually about 1% by weight or less, preferably about 0.01% to about 0.02% by weight, based on the total weight of the aerosol formulation" (page 4, lines 22 to 25).

According to document (7), the solvent is usually present in an amount of from about 6% to about 30% by weight. Moreover, the most preferred solvent is ethanol (page 5, lines 2, 8 and 9).

Furthermore, "(a)ny fluoroalkane propellant that is suitable for inhalation can be used. Examples of suitable fluoroalkanes include HFA-134a, HFA-227ea,..." (page 5, lines 14, 15).

"A particularly preferred aerosol formulation comprises about 85% by weight of HFA-134a, about 15% by weight of ethanol, and about 0.01% by weight of formoterol fumarate" (page 5, lines 26 to 28).

Examples 8 and 9 illustrate two solutions as aerosol formulations comprising formoterol fumarate in the propellant system HFA 134a/ethanol (ethanol about 15% by weight) (pages 9, 10 and Table 3).

The results of the stability study for the aerosol formulations of examples 8 and 9 are shown in Table 3. Document (7) states that "(e)xample 9 was maintained for 1 month (28 days) at 40°C and 75% relative humidity, which are considered herein as accelerated conditions..." (page 9, paragraph below the heading "Examples 8 and 9"), and that "(t)he drug could not be recovered from the gasket materials during this study, which resulted in a loss of about 15% by weight. However, the solution aerosol formulations showed no signs of chemical deterioration" (last two lines on page 9, first line on page 10).

These findings are expressed in Table 3 on page 14 as 85% of recovery of "drug per canister" for the 28 days data.

2.3.2 In the light of this prior art, the problem to be solved lies in the provision of further aerosol formulations comprising formoterol fumarate.

The solution as defined in claim 1 of the main request relates to the propellant system HFA 227/ethanol, in which hydrochloric acid is added, and wherein the solution has an apparent pH between 3 and 3.5.

The board is satisfied that the problem has been plausibly solved in the light of the description.

2.3.3 Therefore it has to be assessed whether the proposed solution is obvious in the light of the prior art.

As becomes evident from the analysis made in point 2.3.1 above, document (7) specifically discloses aerosol formulations of formoterol fumarate in the propellant system HFA 134a/ethanol. These aerosol formulations represent the objective (realistic) starting point of the skilled person when looking for a solution to the stated problem. Since document (7) discloses both HFA 134a and HFA 227 as suitable alternatives for the propellant, the use of the system HFA 227/ethanol for formoterol fumarate appertains to the technical teaching of document (7).

Moreover, when the skilled person is looking for further pharmaceutical aerosol formulations he is aware

of document (1) which discloses stabilised medicinal aerosol formulations.

As becomes evident from the analysis of the content of document (1) made in point 2.2.1 above, said document discloses a generic teaching in relation to the addition of an organic or mineral acid to the propellant system of aerosol formulations when addressing chemical stability problems of the drug (related to the use of the propellant system), which were not necessarily recognised in other prior art documents (page 3, second paragraph).

Hence, the skilled person looking for further aerosol formulations of formoterol fumarate would seriously contemplate adding an acid to the propellant system.

Moreover, in the absence of any stability data showing the rate of degradation of formoterol fumarate in the aerosol system HFA 227/ethanol claimed in claim 1 of the main request, the choice of hydrochloric acid and the particular pH chosen merely reflect the practical consequences of following the general recommendation given in document (1) in relation to the selection of the acid and its concentration (see passage of document (1), page 10, last paragraph, quoted in point 2.2.1 above).

Therefore, claim 1 of the main request lacks inventive step (Article 56 EPC).

2.3.4 As regards the appellant's arguments, the following has to be considered:

The definition of the technical problem made by the appellant cannot be accepted as the subject-matter of claim 1 of the main request since, in the absence of evidence, it is not credible that the propellant system HFA 227/ethanol/HCl provides **improved** stable aerosol formulations of formoterol fumarate.

Whether the stability data displayed in connection with examples 5 and 6 of the application in suit for the specific case of the propellant system HFA 134a/ethanol/HCl can be extrapolated to the other propellant system encompassed by the claim is rather doubtful.

As becomes apparent from the reading of document (1), the selection of all the elements constituting the aerosol formulation is directly connected to the degradation behaviour observed by the drug. Hence, in the absence of any data, the skilled person would not be able to conclude whether or not an improved stability is achieved with HFA 227.

Furthermore, when facing a less ambitious problem, i.e. that of providing further aerosol formulations of formoterol fumarate, it is irrelevant whether or not the authors of document (7) recognised the chemical deterioration of formoterol. The skilled person knows the chemical structure of formoterol fumarate (and that it possesses chemical groups which are sensitive to chemical deterioration, *inter alia* a formamide residue and a secondary amino group) when addressing the technical problem starting from document (7). Furthermore, the proposed solution merely reflects the teaching of document (1).

As regards the argument that the applicant has developed a model for determining the appropriate pH (which depends anyhow on the pka and the concentration of the acid), it has to be said that it cannot be followed how the model of example 3 (which does not even use a perfluorinated hydrocarbon) can make it credible that the stability data for the HFA 227 propellant system is similar to that of the HFA 134a propellant system. Furthermore, even if the model may serve the purpose of optimising the apparent pH once the appropriate propellant system has been chosen, it has to be remembered that the claims do not relate to a method but to a formulation claimed as a product claim.

2.4 In conclusion, the main request has to be rejected for lack of inventive step of the subject-matter of claim 1 (Article 56 EPC).

3. *First and second auxiliary requests*

Since both claims 1 of the first and second auxiliary requests are identical to claim 1 of the main request, both auxiliary requests have to be rejected for lack of inventive step (Article 56 EPC).

4. *Third auxiliary request*

4.1 Claim 1 of the third auxiliary request differs from claim 1 of the main request (which has been found to meet the requirements of Article 123(2) EPC) in that the liquefied propellant has been restricted to HFA 134a. In other words, the claim relates to aerosol formoterol fumarate formulations in the propellant

system HFA 134a/ethanol. This particularised system is reflected as the preferred system by the examples. Additionally, all the examples use hydrochloric acid.

Claims 2 to 4 are identical to claims 2 to 4 of the main request.

Hence, the subject-matter claimed is directly and unambiguously derivable from the application as originally filed (Article 123(2) EPC).

4.2 The assessment of the novelty of the main request applies *mutatis mutandis* to the third auxiliary request.

4.3 As regards the assessment of inventive step, document (7) remains the closest prior art.

4.3.1 However, it is clearly visible that the definition of the problem to be solved is more ambitious in the case of the third auxiliary request than for the main request. Thus, the problem to be solved lies in the provision of solution aerosol formulations of formoterol fumarate **showing reduced chemical degradation** of formoterol fumarate.

The solution defined in claim 1 of the third auxiliary request relates to the addition of hydrochloric acid, wherein the solution (formulation) has an apparent pH between 3 and 3.5.

The board is satisfied that the problem has been plausibly solved in view of the examples, in particular examples 5 and 6, and in the light of the stability data under stressed storage conditions (obtained at

40°C and 50°C after 11 to 40 days) of the formoterol fumarate solutions according to claim 1 of the third auxiliary request.

4.3.2 It now has to be assessed whether the proposed solution is obvious in the light of the prior art.

As already mentioned in the present decision, document (7) states losses of the drug of about 15% by weight for the solutions of formoterol fumarate disclosed in examples 8 and 9. Furthermore, document (7) attributes these losses to the gasket materials and it does not report "signs of chemical deterioration" (page 10, first line).

However, document (7) focuses on the physical stability of the aerosol formulations and does not perform any in depth investigation, such as HPLC, in order to determine whether or not the "apparent" chemical stability proves lack of degradation of the formoterol fumarate.

Document (1) includes a general teaching for the skilled person looking for a solution to reduce chemical deterioration of active substances (drugs) in aerosol formulations. However, the specific teaching in document (1) concentrates on the substance ipratropium bromide (quaternary ammonium salt), which is chemically so different from formoterol fumarate that the skilled person would not be able to extract any valuable conclusions applicable to the case of the degradation behaviour of formoterol fumarate, without making use of inventive skills.

However, document (1) gives no guidelines for approaching the individual case.

On the contrary, document (1) states: "The selection of the acid in the aerosol formulations of this invention depends on the medicament used and the acid concentration needed to effect an acceptable rate of degradation of the medicament. **Ideally the preferred acid will have the same anion as that contained in the medicament, if any**" (page 10, last paragraph, *emphasis added*).

Therefore, there is no hint in document (1) leading the skilled person to the selection of hydrochloric acid, in an adequate concentration to achieve the apparent pH of between 3 to 3.5, as a solution to the above defined problem.

4.3.3 Since the further documents cited in the procedure do not come closer to the claimed subject-matter than documents (1) and (7), the subject-matter of claim 1 of the third auxiliary request involves an inventive step.

4.3.4 Having regard to the fact that claims 2 to 4 are dependent claims on claim 1, the set of claims of the third auxiliary request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside

2. The case is remitted to the first instance with the order to grant a patent on the basis of claims 1 to 4 of the third auxiliary request filed in the oral proceedings and a description to be adapted.

The Registrar: The Chairman:

A. Townend U. Oswald