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**Datasheet for the decision
of 23 March 2006**

Case Number: T 0943/01 - 3.3.02

Application Number: 94903467.2

Publication Number: 0673240

IPC: A61K 9/00

Language of the proceedings: EN

Title of invention:

Stabilized medicinal aerosol solution formulations

Patentee:

Boehringer Ingelheim Pharmaceuticals Inc.

Opponent:

Chiesi Farmaceutici S.p.A.

Headword:

Aerosol formulations/BOEHRINGER

Relevant legal provisions:

EPC Art. 52(1), 54, 56, 99, 100(a), 106, 107, 108
EPC R. 55(c), 64

Keyword:

"Admissibility of requests filed late during oral proceedings
(no): no proper justification for the lateness"

"Inventive step (no): obvious alternative solution to a known
problem"

Decisions cited:

T 0009/91, T 0010/91, T 0892/94

Catchword:

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Case Number: T 0943/01 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 23 March 2006

Appellant: Boehringer Ingelheim Pharmaceuticals Inc.
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 21 June 2001
revoking European patent No. 0673240 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: G. Rampold
P. Mühlens

Summary of Facts and Submissions

I. The appellant is proprietor of European patent No. 0 673 240 ("the patent"), which was granted with effect from 24 March 1999 on the basis of European patent application No. 94 903 467.2 (International application No. PCT/US93/11801, published under the PCT as WO 94/13262) filed on 6 December 1993, claiming two US priorities of 9 December 1992 (Serial No. 987 852) and 22 November 1993 (Serial No. 153 549). The patent as granted contained two independent claims reading as follows:

- "1. An aerosol solution formulation comprising a medicament, selected from the group consisting of ipratropium bromide, oxitropium bromide, albuterol, tiotropium bromide and fenoterol, an HFC propellant, an organic cosolvent, and either an inorganic or an organic acid wherein the medicament chemically degrades or decomposes by interaction with the cosolvent or water or other mechanism, such chemical degradation having the capability of being reduced to acceptable levels by the addition of the inorganic or organic acid and wherein the acid is present in an amount sufficient to reduce the chemical degradation to an acceptable level.

9. An aerosol solution formulation comprising ipratropium bromide, an HFC propellant, ethyl alcohol and an inorganic acid or an organic acid wherein the ipratropium bromide chemical degradation by interaction with cosolvent or water is reduced to acceptable levels by the addition of

the inorganic or organic acid to the aerosol solution formulation."

Dependent claims 2 to 8 related to specific embodiments of the aerosol solution formulation according to claim 1 and dependent claims 10 to 16 to specific embodiments of the aerosol solution formulation according to claim 9.

II. The respondent originally filed notice of opposition requesting revocation in full of the European patent pursuant to Article 100(a) EPC on the ground of lack of inventive step (Article 56 EPC) and pursuant to Article 100(b) EPC on the ground of insufficiency of disclosure (Article 83 EPC).

III. Of the numerous documents cited during the first-instance opposition and subsequent appeal proceedings against the patentability of the claimed subject-matter in the patent in suit, the following remain relevant to the present decision:

(4) K.L. Rominger (C.H. Boehringer Sohn, Department of Biochemistry, Ingelheim) "Chemistry and Pharmacokinetics of Ipratropium bromide", Scand. J. Resp. Dis. Suppl. 103, 1979, pages 116 to 126;

(5) Advances in Pharmaceutical Sciences, edited by H.S. Bean et al, Volume 2, 1967, Academic Press London and New York, pages 2-83;

(10) EP-A-3 72 777;

- (11) ABPI Data Sheet Compendium, 1990-91, pages 215-216, Datapharm Publications Limited, 12 Whitehall, London SW 1A 2DY;
- (12) Compendium Suisse des Médicaments 1991, edited by J. Morant et al, Documed, pages 1158-1159;
- (13) Morrison/Boyd, Lehrbuch der Organischen Chemie, Dritte völlig neu bearbeitete Auflage, VCH, pages 939-942.

IV. During the oral proceedings before the opposition division, the proprietor presented as its new main request an amended set of claims which differed from those as granted only in that **albuterol** (i.e. a synonym for the medicament **salbutamol** mentioned in citation (10) - see page 5, lines 18-19; Example 5 and Example 24 with surfactant No. 6) - had been deleted from the list of the medicaments recited in claim 1 (see I above). In addition to its main request, the proprietor presented at the hearing before the opposition division two auxiliary requests, designated auxiliary requests 2 and 3. The only difference between the above main request and auxiliary request 2 was that the organic cosolvent had been specified in claim 1 as being ethyl alcohol.

Claim 1 of the auxiliary request 3 read as follows:

"1. An aerosol solution formulation comprising a medicament, selected from the group consisting of fenoterol, ipratropium bromide, oxitropium bromide and tiotropium bromide, an HFC propellant, ethyl alcohol,

and either an inorganic or an organic acid wherein the medicament chemically degrades or decomposes by interaction with ethyl alcohol or water, such chemical degradation having the capability of being reduced to acceptable levels by the addition of the inorganic or organic acid in a range of about 0.10 - 0.000 0001 normal for the inorganic acids corresponding to an aqueous pH range of about 1.0 to 7.0 and which must be calculated for the organic acids depending on their pKa values, and wherein the acid is present in an amount sufficient to reduce the chemical degradation to an acceptable level."

V. The essence of the reasoning in the opposition division's decision to revoke the patent was as follows:

(A) As regards the admissibility of lack of novelty as a ground for opposition, the opposition division noted that this ground was invoked by the opponent for the first time in its letter of 20 February 2001, i.e. more than one year after the time limit set in Article 99(1) EPC for giving notice of opposition had expired. With reference to decisions G 9/91 (OJ EPO 1993, 408) and G 10/91 (OJ EPO 1993, 420), the opposition division pointed out that consideration of grounds not properly covered by the statement pursuant to Rule 55(c) EPC should only take place before it in cases where, *prima facie*, there were clear reasons to believe that such grounds were relevant and would in whole or in part prejudice the maintenance of the European patent. The possibility of disregarding facts and evidence in support of fresh grounds not submitted in due time under Article 114(2) EPC should of course also be kept in mind. Since, in the opposition division's judgment,

the late-filed, allegedly novelty-destroying citation (10) was *prima facie* not prejudicial to the novelty of the claimed subject-matter in all three requests before it, it decided not to admit lack of novelty as a fresh ground of opposition into the proceedings.

(B) Although citation (10) was filed late together with the opponent's letter of 20 February 2001, and not relevant to the assessment of novelty, the opposition division found that this citation was of greater relevance to the assessment of inventive step than any of the prior-art documents already on file and decided to admit citation (10) into the proceedings.

(C) As regards inventive step, the decision under appeal stated that (10) taught aerosol formulations comprising an HCF propellant, a cosolvent, a medicament, preferably ipratropium bromide, and a surfactant (see (10), page 3, lines 16-17; page 5, lines 12-23). The opposition division did not share the opponent's submission, that (10) already taught the use of an acid for the stabilization of the aerosol formulation. It pointed out that the oleic acid mentioned in the cited document (see page 5, line 5; Example 24, page 9, No. 6; claim 10) was added in (10) as a surfactant and that (10) was silent about the possibility of using acids for stabilization of the aerosol formulation disclosed in (10).

(D), The opposition division referred, however, to citation (4), which disclosed that ipratropium bromide was in neutral and acid solutions rather stable, whereas the ester binding linking the two molecular parts of ipratropium bromide, namely the alcoholic N-

isopropyl-noratropine moiety and the tropic acid part, was hydrolysed rapidly in alkaline solution. The logical inference was, in the opposition division's view, that those skilled in the art, faced with the problem of reducing the degradation or decomposition of ipratropium bromide resulting from interaction of the active agent with the cosolvent or water in aerosol formulations and knowing the teaching of (4) would try to keep the concentration of hydroxyl ions as low as possible in such formulations by the addition of an acid to lower the pH value of the formulation.

(E) The opposition division also did not accept the proprietor's argument that the beneficial effect of using an acidic pH on the stability of the active agent was not foreseeable for non-aqueous systems because, as pointed out by the opposition division, neither the claimed aerosol solution formulations were limited in the claims to non-aqueous systems nor the total exclusion of water from the claimed aerosol formulations was possible, particularly if ethanol was used as the cosolvent.

(F) The opposition division found that the above-mentioned arguments against the presence of an inventive step equally applied to auxiliary requests 2 and 3 and decided to revoke the patent.

VI. The appellant lodged an appeal against this decision, paid the appeal fee and submitted a statement setting out the grounds of appeal within the time limit set in Article 108 EPC. In addition to its main request that the decision under appeal be set aside and that the patent be maintained on the basis of the main request

before the opposition division (see IV above), the appellant filed an auxiliary request, wherein in claim 1 the more general reference to "an organic cosolvent" was limited to "an alcohol cosolvent".

VII. In its reply, the respondent maintained its objections to the maintenance of the patent on the basis of the appellant's main request or auxiliary request on the grounds of lack of novelty and lack of inventive step and requested that the appeal be dismissed. At the appeal stage, the respondent did not maintain the ground for opposition under Article 100(b) EPC. Together with its reply, the respondent submitted the new citations (11) and (12).

VIII. In advance of the oral proceedings before the board, fixed for 23 March 2006, the appellant filed with its letter of 22 February 2006 further observations and submitted, in addition to its main request that the patent be maintained on the basis of the claims in the main request before the opposition division (see IV above), auxiliary requests 1 to 3.

Accordingly, claim 1 of the **main request** reads as follows:

"1. An aerosol solution formulation comprising a medicament, selected from the group consisting of ipratropium bromide, oxitropium bromide, tiotropium bromide and fenoterol, an HFC propellant, an organic cosolvent, and either an inorganic or an organic acid wherein (see I above, claim 1 as granted) acceptable level."

Claims 2 to 16 are identical to the corresponding claims in the patent as granted.

Claim 1 of the **first auxiliary request** reads as follows with the sole amendment to the main request (see VIII above) being indicated in bold italic letters:

"1. An aerosol solution formulation comprising a medicament, selected from the group consisting of ipratropium bromide, oxitropium bromide, tiotropium bromide and fenoterol, an HFC propellant, **an alcohol cosolvent**, and either an inorganic or an organic acid (see I above, claim 1 as granted) acceptable level."

As the **second auxiliary request** the appellant erroneously presented a set of claims which was identical to that in the first auxiliary request.

Claim 1 of the **third auxiliary request** reads as follows, the amendments to the main request (see VIII above) being indicated in bold italic letters:

"1. **The use of an inorganic or an organic acid for reducing the chemical degradation or decomposition of the medicament in an aerosol solution formulation comprising a medicament**, selected from the group consisting of ipratropium bromide, oxitropium bromide, tiotropium bromide and fenoterol, an HFC propellant, an alcohol cosolvent, wherein the medicament chemically degrades or decomposes by interaction with the

cosolvent or water or other mechanism, such chemical degradation having the capability of being reduced to acceptable levels by the addition of the inorganic or organic acid and wherein the acid is used in an amount sufficient to reduce the chemical degradation to an acceptable level."

IX. In reply to the appellant's new submissions and requests filed on 22 February 2006, the respondent filed with its letter of 16 March 2006 observations of its own and maintained its request that the appeal be dismissed.

X. Oral proceedings were held on 23 March 2006 in the presence of the appellant and the respondent. At the beginning of the proceedings, the appellant filed an amended second auxiliary request to replace the second auxiliary request filed on 22 February 2006 (see VIII above).

Claim 1 of the amended second auxiliary request reads as follows, the sole amendment to the main request (see VIII above) being indicated in bold italic letters:

"1. An aerosol solution formulation comprising a medicament, selected from the group consisting of ipratropium bromide, oxitropium bromide, tiotropium bromide and fenoterol, an HFC propellant, **ethyl alcohol**, and either an inorganic or an organic acid wherein (see I above, claim 1 as granted) acceptable level."

Claims 2 to 16 are identical to the corresponding claims in the patent as granted.

XI. Towards the end of the oral proceedings, the appellant announced its intention to file certain new requests and asked for a short break of the proceedings, which was allowed. After the break, it sought to introduce new auxiliary requests 4 to 7.

Claim 1 of the **fourth auxiliary request** reads as follows, the sole amendment to the main request (see VIII above) being indicated in bold italic letters:

"1. An aerosol solution formulation comprising a medicament, selected from the group consisting of ipratropium bromide, oxitropium bromide, tiotropium bromide and fenoterol, an HFC propellant, an organic cosolvent, **up to about 5% by weight of water** and either an inorganic or an organic acid wherein (see I above, claim 1 as granted) acceptable level."

Claim 1 of the **fifth auxiliary request** reads as follows, the amendments to claim 1 of the main request (see VIII above) being indicated in bold italic letters:

"1. An aerosol solution formulation comprising a medicament, selected from the group consisting of ipratropium bromide, oxitropium bromide, tiotropium bromide and fenoterol, an HFC propellant, an organic cosolvent, **up to about 5% by weight of water** and either an inorganic acid **selected from the group consisting of sulfuric**

acid, hydrochloric acid, nitric acid, and phosphoric acid, or an organic acid selected from the group consisting of ascorbic acid and citric acid, wherein (see I above, claim 1 as granted) acceptable level."

Claim 1 of the **sixth auxiliary request** reads as follows, the amendments to claim 9 as granted (see I above) and the identical claim 9 of the main request (VIII above) being indicated in bold italic letters:

"1. An aerosol solution formulation comprising ipratropium bromide, an HFC propellant, ethyl alcohol, **up to about 5% by weight of water** and an inorganic acid **selected from the group consisting of hydrochloric acid, sulfuric acid, nitric acid, and phosphoric acid, or an organic acid selected from the group consisting of ascorbic acid and citric acid**, wherein the ipratropium bromide chemical degradation by interaction with ethyl alcohol or water is reduced to acceptable levels by the addition of the inorganic or organic acid to the aerosol solution formulation."

Claim 1 of the **seventh auxiliary request** reads as follows the amendments to claim 9 as granted (see I above) and the identical claim 9 of the main request (see VIII above) being indicated in bold italic letters:

"1. An aerosol solution formulation comprising ipratropium bromide, an HFC propellant, ethyl alcohol, **up to about 5% by weight of water, and about 0.0039 to 27.7 mg/ml of citric acid**, wherein

the ipratropium bromide chemical degradation by interaction with ethyl alcohol or water is reduced to acceptable levels by the addition of citric acid to the aerosol solution formulation."

XII. After deliberation on this point, the board announced its decision not to admit the late-filed auxiliary requests 4 to 7 into the proceedings.

XIII. The arguments presented by the appellant in its written and oral submissions, in so far as they are relevant to the present decision, are summarised below:

[1] It was recalled by the appellant that, in the notice of opposition pursuant to Rule 55(c) EPC, only lack of inventive step (Articles 100(a) and 56 EPC) and insufficiency of disclosure (Articles 100(b) and 83 EPC), but not lack of novelty (Articles 100(a) and 54 EPC), were invoked as grounds for opposition. It was also recalled that only more than one year after expiry of the time limit set in Article 99(1) EPC, i.e. with its letter of 20 February 2001, did the respondent introduce lack of novelty as a new ground for opposition based on citation (10), which was submitted together with the respondent's above-mentioned letter and was accordingly also filed late. The appellant also noted that, in the decision under appeal, the opposition division considered that the new ground for opposition was not admissible because it found that the content of (10) was *prima facie* irrelevant to the novelty of the claimed subject matter. In the appellants opinion, the respondent was now, at the appeal stage, making a second attempt to introduce lack of novelty as a fresh ground for opposition. According

to the appellant, this attempt already had to fail for legal reasons in the light of decisions G 9/91 (*loc. cit.*) and G 10/91 (*loc. cit.*). Accordingly the respondent's request that this new ground for opposition be admitted had to be refused.

[2] Nevertheless, for illustration of the technical background, the appellant considered it useful and necessary to point out that, in referring to Examples 5 and 24 of (10) as the basis for attacking novelty, the respondent had apparently overlooked the fact that the claims in all current requests no longer covered salbutamol (i.e. a synonym for albuterol) as one of the medicaments comprised in the claimed aerosol solution formulations.

[3] In summary, on the basis of the observations in the foregoing points, it was, in the appellant's opinion, abundantly clear that novelty was neither on legal nor on technical grounds an issue to be treated in these appeal proceedings.

[4] As regards inventive step, the appellant stated that, as explained in section [0007] of the patent, the inventors of the claimed invention had found that the use of propellant systems containing an HFC propellant and an organic cosolvent in aerosol solution formulations presented a chemical stability problem that had neither been recognised previously nor resolved in the prior art. This chemical instability of certain medicaments, e.g. ipratropium bromide, in such HFC propellant/cosolvent systems resulted from a possible chemical interaction of the medicament with the cosolvent and/or traces of water present in the

system to produce decomposition or degradation products. Accordingly, the technical problem to be solved was to provide an aerosol solution formulation containing a medicament selected from a specific group of drugs, including ipratropium bromide, oxitropium bromide, tiotropium bromide and fenoterol, said aerosol solution formulation being stable against chemical degradation and decomposition of the medicament. In the context of the present invention, "stable" meant "long-term stability" as required for drugs to be stored in pharmacies, hospitals, etc., and not short-term stability as would be sufficient for pharmacokinetic studies and the like.

[5] Citation (4), which was cited by the opposition division against the presence of an inventive step, was an article on the "Chemistry and Pharmacokinetics of Ipratropium bromide". The passage of interest was at the end of page 118 and read as follows: "*Ipratropium bromide is a white, crystalline substance with a bitter taste. As a quaternary ammonium compound it is freely soluble in water and lower alcohols, but insoluble in lipophilic solvents, such as ether, chloroform and fluorohydrocarbons. In neutral and acid solutions the substance is rather stable; in alkaline solution the ester binding is hydrolysed rapidly.*" In this context the appellant observed that, as interpreted by the opposition division and the respondent, this passage motivated the expert to avoid alkaline media. Whilst the appellant admitted that this might possibly be true, it argued that the claimed invention was not about avoiding alkaline media. The present invention taught that, in order to stabilise certain medicaments

in HFC/cosolvent aerosol solutions, one should add an inorganic or organic acid.

[6] In the appellant's opinion, the skilled person was not at all motivated by the teaching of citation (4) to add an inorganic or organic acid to a solution of ipratropium bromide because it had been demonstrated in the appellant's experimental report, submitted with its letter date 22 February 2006, that 0.01-0.1% aqueous solutions of ipratropium bromide themselves exhibited a slightly acidic pH value of between 5.07 to 5.31. In view of the teaching of citation (4) that "*neutral and acid solutions of the substance are rather stable*", those skilled in the art had, in the appellant's opinion, absolutely no reason to expect any particular benefit from adding additional acid to an already slightly acidic ipratropium bromide solution in order to improve the medicament's chemical stability. The appellant concluded that (4) simply did not provide or even suggest such a teaching.

[7] Citation (10) disclosed a self-propelling aerosol formulation which comprised a medicament, HFC-134a as the propellant, a surface active agent and at least one compound having a higher polarity than HFC-134a as the cosolvent. In the appellant's view, citation (10) was primarily concerned with improving the physical dispersion stability of aerosol suspension formulations and did not disclose or suggest any solution to the problem of providing aerosol solution formulations stable against chemical degradation and decomposition of the medicament caused by interaction with the cosolvent or water. The "prophetic" sentence at page 3, lines 16-17, of (10) ("*The presence of large amounts of*

solubilised surfactant may also assist in obtaining stable solution formulations of certain drugs.") was, in the appellant's opinion, not helpful either as it lead away from the technical solution proposed in the patent in suit, i.e. to employ an inorganic or organic acid as a stabiliser to reduce chemical degradation and decomposition of the medicament. Even if oleic acid was mentioned as an example of a suitable surfactant, this acid was used in (10) as a surface active agent rather than as an acidifier. Even if those skilled in the art had consulted the teaching of (10), they would not have had any incentive to select the surfactant in (10) given its acidic functionality, let alone to substitute an acid for the surfactant used in (10).

[8] Documents (11) and (12) had been introduced by the respondent only at the appeal stage, together with its letter of 25 February 2002. Both these documents dealt with aqueous formulations of fenoterol hydrobromide and ipratropium bromide, respectively. Since neither of these documents related to HFC solution aerosol formulations, the appellant requested that these late-filed documents not be admitted into the proceedings as they were, in its opinion, irrelevant to the issues to be decided in the present case.

XIV. The respondent disagreed, relying in its written and oral submissions essentially on the following arguments:

[9] Aerosol solution formulations containing a broncho-dilator of the 2-phenylethylamine type as claimed (albuterol = salbutamol) as well as of the atropine type (ipratropium bromide), an HFC propellant, an organic cosolvent (ethanol) and an acid (oleic acid)

were known from citation (10) - see Example 5 and Example 24 with surfactant No. 6, and claim 12 in combination with claims 10, 6 and 1. Contrary to the opinion of the opposition division in section 3.2 of the decision under appeal, it was irrelevant whether the function of oleic acid in the formulations of (10) was that of a surfactant. In any case, oleic acid was an acid. The "discovery" that oleic acid was also a "surfactant" could not establish the novelty of the claimed subject-matter in the patent. The respondent submitted that its opinion was also consistent with the principles set out in decision T 892/94 (OJ EPO 2000, pages 1 to 18, in particular sections 3.4 to 3.7 of the Reasons and Headnote II).

[10] In the contested patent itself, it was admitted, in sections [0005] to [0006] on page 2, that broncholytic aerosol solution formulations for inhalation containing as the medicament an atropine derivative or a phenylethylamine derivative (epinephrine; isoproterenol HCl), a cosolvent, an HFC propellant and an acid were known in the state of the art. The respondent noted that in section [0007], on page 2, the patent alleged that the use of an HFC propellant and a cosolvent as the propellant system in aerosol solution formulations presented a chemical stability problem. In particular, the patent stated that in such HFC propellant/cosolvent systems, the medicament (the active compound) might interact with the cosolvent and/or water present in the system to produce decomposition or degradation products.

[11] It was pointed out by the respondent that the problem underlying the alleged invention as outlined in

section [0007] of the patent was to provide such aerosol solution formulations having "the requisite chemical stability" of the active compound. The solution of this technical problem was formulated in the patent as follows: *"the addition of an acid, either an inorganic acid or an organic acid, to the HFC propellant/cosolvent system provides the requisite chemical stability to the medicament"* (see section [0007], last sentence).

[12] The respondent referred to the decision under appeal (see especially page 6, lines 4-9) where it was stated as a ground for the revocation: *"When the patentee, starting from (10), is faced with the problem of increasing the stability of ipratropium bromide in solution aerosols, he would immediately try to provide for an acidic pH, i.e. to keep the concentration of OH ions as low as possible. Such a teaching is e.g. derivable from (4) (page 118, last complete paragraph), where the instability of ipratropium bromide in alkaline solution and its relative stability in neutral and acidic solution is clearly expressed."* It concluded that it would have been obvious, when starting from the closest state of the art according to (10), in view of the teaching of (4), to add an acid or to use the medicament in the form of an acidic salt (acid addition salt; see patent description page 4, line 19) to provide stable solution formulations of ipratropium bromide or fenoterol containing an HFC propellant and a cosolvent. Citation (4) advised persons skilled in the art that an alkaline medium is strictly to be avoided to prevent degradation or decomposition of ipratropium bromide, which, in turn, provided the clear teaching to those persons to adjust the pH of a solution of

ipratropium bromide to acidic conditions to be on the safe side. In this context, the respondent noted that the appellant's assertion that the claimed invention was not about avoiding alkaline media clearly contradicted the statement at page 5, lines 15 to 17, of the patent description that the pH of the claimed aerosol solution formulations should be adjusted to about 1.0-7.0 to effect an acceptable rate of decomposition of the medicaments.

[13] The respondent drew attention to citation (5), which gave a clear and complete explanation as to why, from a chemical point of view, ipratropium bromide was stable in acidic media, but unstable in alkaline media. Thus, citation (5) fully confirmed the teaching of (4) and taught that the concentration of hydroxyl ions should be kept as low as possible by adding an acid.

[14] The respondent submitted that, contrary to the appellant's opinion, the teaching of citations (11) and (12) was also relevant to the claimed subject-matter and the decision to be taken in the present case. Citation (11) described an aqueous solution of fenoterol hydrobromide for administration by inhalation wherein the solution has a pH of approximately 3.2 and (12) described an aqueous solution of ipratropium bromide containing hydrochloric acid. In this context, the respondent referred to page 4, lines 29 to 34, of the patent description where it is stated: "*In aqueous solution the rate of hydrolysis and esterification is typically pH dependent. In aqueous solution, the degradation of ipratropium bromide exhibits a pH-rate minimum at pH 3.5. This corresponds to a hydrogen ion concentration of 3.2×10^{-4} molar (M) at 25°C. Although*

the concept of pH is poorly defined in non aqueous systems, formulation evaluation studies were conducted using this concentration of hydrochloric acid in the HFC-134(a)/ethanol system containing ipratropium bromide. Samples stored at 50°C for five and one-half months exhibited less than 5.5% loss of ipratropium bromide. A summary of these results is illustrated in Figure 1".

The respondent concluded therefrom that, at the appellant's own admission, the proposed solution of the stated problem simply required *adding to the HFC-134(a)/ethanol system* the same concentration of HCl that was known (e.g., from (11) and (12)) to be necessary to minimise the degradation of ipratropium bromide or fenoterol in an aqueous solution.

- XV. The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of one of the main, first or third auxiliary request, filed with letter dated 22 February 2006 or of the second auxiliary request filed in the oral proceedings, or, as a further auxiliary request, that the case be remitted to the first instance for further prosecution.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 64 EPC and is, therefore, admissible.

2. *Admissibility of the late-filed requests (auxiliary requests 2 and 4 to 7)*

2.1 The amended second auxiliary request was presented by the appellant right at the beginning of the oral proceedings to replace its second auxiliary request filed on 22 February 2006, which erroneously contained a repetition of the set of claims in the first auxiliary request filed on the same date (see VIII and X above). The only difference between claim 1 of the second auxiliary request filed on 22 February 2006 and claim 1 of the presently effective second auxiliary request is that the organic (alcoholic) cosolvent has been specified as being ethyl alcohol (see X above). The meaning and scope of the proposed amendment was immediately clear to the respondent and the board. Coupled with the facts that the claims of the present second auxiliary request are identical with those in the second auxiliary request before the opposition division and that the respondent did not object to its admissibility, the board sees no objective reason not to admit the amended second auxiliary request into the proceedings.

2.2 As regards the auxiliary requests 4 to 7, the procedural situation was clearly different. In the course of the oral proceedings before the board, the appellant relied in support of the presence of an inventive step of the claimed aerosol solution formulation, *inter alia*, on the argument that, unlike the cited state of the art relating to aqueous systems, the claimed aerosol solution formulation in the patent relates to a non-aqueous system. Having been informed by the board that the appellant's above argument could

not support its case, in particular because none of the claims of the then existing requests was limited to such a non-aqueous aerosol formulation and none contained any limitation of the amount of water which may be present in the claimed aerosol formulation (see the wording of claim 1: "*An aerosol formulation comprising....* ."), the appellant presented at the latest possible moment in the proceedings, namely towards the end of the hearing, auxiliary requests 4 to 7 (see e.g. auxiliary request 4, claim 1: "*An aerosol solution formulation comprising a medicament, selected from the group consisting of ipratropium bromide, oxitropium bromide, tiotropium bromide and fenoterol, an HFC propellant, an organic cosolvent, **up to about 5% by weight of water** and either an inorganic or an organic acid* ."). The first question to be decided is, therefore, whether such late-filed alternative sets of claims should be admitted for consideration in this appeal. Admission of these requests into the proceedings is a matter to be decided at the board's discretion.

- 2.3 The appellant argued, as justification for the lateness of auxiliary requests 4 to 7, that these requests were filed in reaction to the respondent's and the board's above-mentioned objections and observations that the existing claims were not limited to a non-aqueous system.

However, precisely those objections and observations which were again brought up by the respondent at the hearing before the board were already known to the appellant from the proceedings before the first instance and are also clearly expressed in the decision

under appeal (see Reasons, end of point 3.2: "... . It was further argued by the Patentee that the beneficial effect of an acid on the stability of the active agent was not obvious for non-aqueous systems. Again the Opposition Division cannot agree. Firstly, it should be emphasized that claim 1 of the present main request is not limited to non-aqueous systems, secondly it is noted that particularly for compositions where an alcohol such as ethanol is used as cosolvent, the total exclusion of water is virtually impossible. As a consequence, stabilizing alkaline instable active agents in solution formulations disclosed in D10 by addition of an acid does not involve an inventive step. ..."; and Reasons, point 5.3: "... .secondly it is again emphasized that water can still be added to the composition and that it is virtually impossible to totally exclude water so that stabilizing solution aerosols comprising an alkaline unstable active compound as disclosed in D10 by adding an acid does not involve an inventive step. ...").

2.4 Claim 1 of all auxiliary requests 4 to 7 contains the newly added feature "up to about 5% by weight of water" and claim 1 of auxiliary requests 5 to 7 additionally specifies the nature and/or weight ranges (mg/ml) of the acids added to the claimed aerosol solution formulation. As in the case of auxiliary request 4, the appellant argued, as justification for the late filing of these requests, that they were likewise an attempt to overcome certain objections raised by the board and the respondent to an inventive step of the claimed subject-matter in the patent.

2.5 However, in the board's opinion, the late-filing of major amendments to auxiliary requests 4 to 7 prevented the respondent from having a proper opportunity to study carefully features which the appellant considered crucial to the decision in the present case, and, if necessary, to prepare arguments against them. Therefore, taking account of these additional amendments to claim 1 of auxiliary requests 4 to 7 at this very late stage during oral proceedings, after the parties had already made their main submissions, would have unduly and substantially delayed the proceedings.

2.6 For the foregoing reasons it appears clear that auxiliary requests 4 to 7, actually filed as late as shortly before the close of the hearing before the board, are requests which the appellant could have submitted earlier, not just because ample time had elapsed since the commencement of the appeal proceedings on the patent but also because they were clearly not submitted in reaction to objections which were raised for the first time at the hearing before the board but such as had already been raised in the proceedings before the first instance and were, among others, identified by the opposition division in the decision under appeal as grounds for the revocation of the patent. In the circumstances of the case, the appellant had to expect that those arguments in support of inventive step not accepted in the proceedings before the first instance would likewise not be accepted in appeal proceedings, unless it applied for an appropriate amendment (limitation) of the claims, in good time.

2.7 In summary, the board holds that the late-filed auxiliary requests 4 to 7 are not admissible because neither did the appellant give any cogent reasons nor were there were mitigating circumstances which could have justified the lateness of the filing.

3. *Admissibility of citations (11) and (12)*

3.1 Citations (11) and (12) were already filed by the respondent on 25 February 2002, together with its reply to the statement setting out the grounds of appeal. The appellant requested for the first time in its letter of 22 February 2006 that neither of these citations be admitted into the proceedings because they were late-filed and, in its opinion, irrelevant to the issues to be decided in the present case.

3.2 It is well established in the jurisprudence of the boards of appeal that, in principle, any new evidence filed on appeal is exceptional *per se* and its admissibility is a matter calling for the exercise of the board's discretion (see generally, "Case Law of the Boards of Appeal of the European Patent Office", 4th edition, 2001, pages 324 to 333).

3.3 Citation (11) discloses a Berotec® nebuliser solution formulation of fenoterol hydrobromide (0.5%; 5mg/ml) having a pH of approximately 3.2. This product was marketed by the appellant company before the earliest priority date of the patent. The solution of (11) is intrinsically acidic and therefore the medicament is stable.

Citation (12) discloses an Itrop[®] aqueous solution containing ipratropium bromide, sodium chloride and hydrochloric acid and was likewise marketed before the earliest priority date of the patent. This solution is also intrinsically acidic and therefore stable.

- 3.4 In the circumstance of the present case, the board considers that citations (11) and (12) should be admitted as evidence. These citations include information of clear relevance to the issues as developed during the first-instance opposition proceedings, including the reasons given for the decision under appeal. Moreover, the respondent's assertion that (11) and (12) were filed in response to the appellant's written arguments in the statement setting out the grounds appeal appears *prima facie* correct. Taking into account also that, in the circumstances of this case, the appellant had about four years in which to consider and prepare arguments in response to this evidence, the board exercises its discretion in favour of the respondent.

4. *Novelty*

- 4.1 On the basis of the principles set out in the decisions of the Enlarged Board of Appeal G 9/91 (*loc. cit.*) and G 10/91 (*loc. cit.*), the board considers that the opposition division exercised its discretion under Article 114(1) EPC correctly in not allowing the opponent (respondent) to introduce lack of novelty (Articles 100(a) and 54 EPC) as a fresh ground for opposition more than one year after expiry of the time limit set in Article 99(1) EPC.

4.2 With regard to fresh grounds for opposition, the Enlarged Board considered in the above-mentioned decisions (see especially Reasons, point 18) that, in principle, such grounds may not be introduced at the appeal stage. Consequently, the question of novelty does not arise in the present case. For the sake of completeness, it may nevertheless be noted that the board is not aware of any prior art, including citation (10), which would be prejudicial to the novelty of the claimed subject-matter in the patent following the amendment of claim 1 of all requests to exclude albuterol (i.e. a synonym for salbutamol) as one of the medicaments comprised in the claimed aerosol solution formulations (see XIII [2] above).

Main request

5. *Closest state of the art; the problem and its solution*

5.1 There was general agreement that citation (10) constitutes the closest state of the art. This citation discloses medicinal aerosol formulations in the form of either a suspension of medicament particles or a solution of certain drugs or [see e.g. claims 1 and 2, Examples 10 to 12 (beclomethasone dipropionate)]. Such aerosol solution formulations contain

- a medicament, for example, ipratropium bromide (see claims 1, 2 and 12); in point 2.1 of its statement setting out the grounds of appeal, the appellant stated that "*among the large variety of medicaments mentioned at page 5, lines 12-23 and in claim 12, only ipratropium bromide is of interest for the purposes of the present invention*".

- an HFC propellant, i.e. 1,1,1,2-tetrafluoroethane (P 134a), (see Examples 10 to 12; claim 1),
- an organic cosolvent (a compound of higher polarity than Propellant 134a), for example, ethanol (see Examples 10 to 12; claim 5), and
- a surface active agent selected from a broad variety of such agents (see page 4, line 45 to page 5, line 11), for example, oleic acid (see Examples 1, claim 10).

5.2 As regards the stability of the aerosol solution formulations disclosed in citation (10), the cited document teaches that *"the addition of a compound of higher polarity than Propellant 134a to Propellant 134a (i.e. the cosolvent) provides a mixture in which increased amounts of surfactant may be dissolved compared to their solubility in Propellant 134a alone. The presence of increased amounts of solubilised surfactant allows the preparation of stable, homogenous suspensions of drug particles. The presence of large amounts of solubilised surfactant may also assist **in obtaining stable solution formulations of certain drugs.**"* (see (10), page 3, lines 13-17, Examples 10-12).

In view of this clear reference in citation (10) to stable aerosol solution formulations, the board cannot accept the appellant's argument that whereas "stability" in the context of the present invention means long-term chemical stability against degradation of the medicament in solution, (10) was only concerned with the physical stability of suspension formulations against settling and deposition of solid components.

- 5.3 According to the statement in section [0007] on page 2 of the patent description, the problem underlying the patent as seen by the patentee/appellant is as follows:
"It has now been found that the use of propellant systems containing an HFC and a cosolvent in aerosol solution formulations presents a chemical stability problem that has not been previously recognized or resolved in the prior art. This is because in such HFC propellant/cosolvent systems, the medicament may interact with the cosolvent and/or water present in the system to produce decomposition or degradation products. It has now been found that the addition of an acid, either an inorganic acid or an organic acid, to the HFC propellant/cosolvent system provides the requisite chemical stability to the medicament."
- 5.4 Having regard to the disclosure in the prior art of (10) referred to in 5.2 above, it appears clear that the problem of the instability (decomposition or degradation) of certain medicaments or drugs in aerosol solution formulations containing an HFC propellant and a cosolvent was already known to those skilled in the art before the priority date of the patent and that this problem must be regarded as having already been solved in principle in (10) by different means.
- 5.5 Moreover, the appellant has not demonstrated, by comparison with the closest prior art of (10), any unexpected, e.g. superior, effect associated with the claimed solution to the known stability problem. Hence, from an objective point of view, the task of the disputed patent (the problem to be solved) can be seen only as to suggest an alternative solution to the known stability problem mentioned above. Having regard to the

results presented in the examples in the patent description, the problem underlying the disputed patent is, in the board's opinion, convincingly solved by the addition of either an inorganic or an organic acid to the claimed aerosol solution formulation in an amount sufficient to reduce the chemical degradation of the medicament to an acceptable level, an opinion which is not disputed by the respondent.

6. *Inventive step*

- 6.1 The question still remains whether or not an inventive step was necessary to arrive at the present invention when starting from the teaching of citation (10) as the closest state of the art and taking into consideration the teaching and information in the other documents and the arguments submitted by the parties in the present proceedings.

The appellant submitted that, for example in an aerosol formulation comprising ipratropium bromide, in addition to oxidation, three types of chemical reaction are responsible to differing extents for the degradation or decomposition of that medicament:

- (a) the principal degradation reaction in the presence of ethanol involves either the direct transesterification of ipratropium bromide with ethanol or first hydrolysis of the ester binding linking the quaternized atropine alcohol part and the tropic acid part of ipratropium bromide followed by esterification of tropic acid thereby formed with ethanol; in each of these cases tropic

- acid ethyl ester is the chief degradation product (see patent description, page 4, paragraph [0030];
- (b) a second degradation reaction consists of hydrolysis of the ester binding linking the quaternized atropine alcohol part and the tropic acid part of the molecule;
 - (c) a third minor degradation reaction consists of the dehydration of the α -hydroxymethyl group of the tropic acid part (α -(hydroxymethyl)benzeneacetic acid) of ipratropium bromide.

6.2 Citation (10) itself does not, in the board's judgment, contain any relevant teaching or suggestion pointing those skilled in the art in the direction of the proposed solution to the actual problem. In particular, the board does not share the respondent's opinion that the mention of the addition of oleic acid, which is used in (10) as one of the numerous surface active agents envisaged in the cited document, would generally suggest using an acid in order to improve the medicament's stability in aerosol solution formulations.

However, those skilled in the art seeking in the state of the art a solution to the problem posed would have come upon document (4), which they would certainly have considered with great interest because it is specifically concerned with all aspects of the chemistry of ipratropium bromide, including its stability in different media. Regarding certain relevant properties of ipratropium bromide, citation (4) provides in the last full paragraph on page 118 the following technical teaching: "*Ipratropium bromide is a white, crystalline substance with a bitter taste. As a quaternary ammonium compound it is freely*

soluble in water and lower alcohols, but insoluble in lipophilic solvents, such as ether, chloroform and fluorohydrocarbons. In neutral and acid solutions the substance is rather stable; in alkaline solution the ester binding is hydrolysed rapidly."

6.3 Consequently, from the teaching in (4) that ipratropium bromide is stable in neutral and acid solutions but instable in alkaline media, it must be concluded that the rate of decomposition or degradation (hydrolysis and esterification or transesterification, dehydration) is typically pH dependent and that the contact of ipratropium bromide with alkaline media is strictly to be avoided in order to improve stability. Accordingly, the skilled person would also be bound to infer from the teaching of citation (4) that the degradation or decomposition of ipratropium bromide exhibits a pH rate minimum in an acidic environment. This pH rate minimum is, in the board's opinion, readily detectable by routine laboratory experiments.

6.4 The appellant argued that, in its opinion, the skilled person would not be motivated by the above-mentioned teaching of (4) to add an acid to a solution of ipratropium bromide in order to improve its stability because 0.01-01% **aqueous** solutions of ipratropium bromide themselves exhibit a slightly acidic pH value of 5.07 to 5.31 (see XIII[6] above). This argument is not convincing. Apart from the fact that the skilled person faced with the problem stated above and knowing the prior art of (4) would routinely determine the pH-rate minimum for the degradation of ipratropium bromide in any kind of solution, this person would learn, for example, from citation (12) that **the addition of**

hydrochloric acid to an aqueous solution containing ipratropium bromide and sodium chloride leads to stable solution formulations which were marketed by the appellant company prior to the priority date of the patent. Citation (11) discloses that an aqueous hypotonic solution of fenoterol hydrobromide (i.e. a medicament recited in present claim 1) which was also marketed by the appellant company prior to the priority date of the patent is stable at a pH of approximately 3.2.

- 6.5 Nor is the appellant's argument convincing that a person skilled in the art would not apply the teaching of the cited prior art direct to the claimed aerosol solution formulations because such formulations represent, in contrast to those disclosed in the prior art, non-aqueous systems. This line of argumentation overlooks not only the fact that the claimed aerosol solution formulations are in no way limited to non-aqueous systems but also that, in accordance with the explicit disclosure of the claimed invention in the patent, *"up to about 5% by weight of water may be present in the propellant/cosolvent system"* (see page 3, lines 4-5) and that *"the decomposition and the degradation of the medicament may occur by various chemical mechanisms, the most significant being interaction of the medicament with the cosolvent or with **the water present in the system** to form hydrolysis, esterification, and/or ether products"* (see page 3, lines 37-39). The appellant itself admitted in the statement of the grounds of appeal (see the paragraph bridging pages 4 and 5) that the medicament may chemically interact with the cosolvent and/or **traces of**

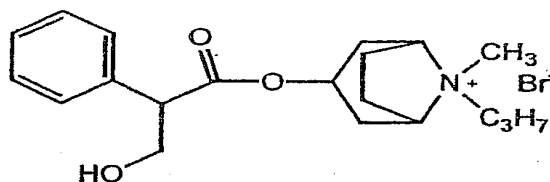
water present in an HFC propellant/cosolvent system to produce decomposition or degradation products.

6.6 Even less persuasive is the appellant's argument that the claimed invention is not about avoiding alkaline media but teaches that, to stabilise certain medicaments in HFC/cosolvent aerosol solutions, one should add an inorganic or organic acid. It would be immediately clear to those skilled in the art that, in a propellant system such as the present one where the presence of water is not excluded, the addition of an acid has the effect of lowering the hydroxyl ion concentration by shifting the pH from the basic toward the acidic area and thereby to minimise the possibility of an hydroxyl ion attack on the medicament.

6.7 With reference to the technical teaching of document (13) the appellant relied on the argument that those skilled in the art would have no incentive at all to solve the problem posed by adding an acid because, as the appellant submitted, all three types of degradation reactions mentioned in 6.1 above (transesterification, hydrolysis and esterification and dehydration) are normally catalysed by acids. While this teaching may generally be true for the cases which are treated and illustrated in (13), it **cannot be extended** to compounds having the specific structure of ipratropium bromide.

6.8 Citation (5) is concerned with kinetics and mechanisms in stability of drugs and specifically refers from page 38 onwards to alkaloids and other amine containing compounds. This citation gives an exhaustive explanation as to why ipratropium bromide, which belongs to the class of atropine/scopolamine

derivatives containing a quaternary amino group (see the formula below) is stable in acidic media, but unstable in alkaline media.



Citation (5) makes available to the skilled person the technical teaching that a series of compounds analogous to local anesthetics in their kinetics of solvolysis are the alkaloids. The specific hydroxyl ion catalysed solvolysis of scopolamine methyl bromide, atropine methyl bromide, acetylcholine chloride, scopolamine hydrobromide, atropine and several other exotic tertiary and quaternary amine-containing esters were studied by Moffett and Garrett (1955) in 48% ethanol-water at 25°, and their reactivities listed in descending order. The esters of quaternary amine alcohols are about 100 times more reactive than the corresponding esters of tertiary amino alcohols and are **highly resistant to acidic hydrolysis. The basic mechanisms appear to include a very slow hydrogen ion attack on the positively charged species** and hydroxyl ion attack on charged and uncharged species (see page 38, paragraphs 1 and 2).

Thus, the conclusion drawn in (5) is that the introduction of a pH-invariant positive charge into these alkaloids enhances the rates of hydroxyl ion attack over the non-quaternized esters of tropic acid and makes the compounds **almost totally resistant to hydrogen ion attack** (see the paragraph bridging

pages 38-39). The board notes that this conclusion in (5) equally applies to aqueous and non-aqueous systems.

6.9 A person skilled in the art who, starting from the aerosol solution formulations in (10), was seeking a solution to the problem posed would, relying on the information contained in (4) and (5) and also in (11) and (12), expect from the known properties of quaternized esters of tropic acid that an acidic environment responsible for the stability of such esters would produce this effect in the case of ipratropium bromide as well. In view of the almost total resistance of such compounds to hydrogen ion attack and their high susceptibility to hydroxyl ion attack, it would be immediately obvious to a person skilled in the art that he should try to solve the problem posed by protecting the compounds against hydroxyl ion attack. The most obvious way to achieve this goal would be to increase of the hydrogen ion concentration by adding an acid.

Once the possibility of stabilising ipratropium bromide in an acidic environment to avoid or at least to minimise the possibility of a hydroxyl ion attack on the medicament became obvious, determination of the pH value at which the degradation of ipratropium bromide (transesterification, hydrolysis and esterification and dehydration) exhibits a pH-rate minimum and of the concentration of a particular acid to be added to e.g. an HFC-134(a)/ethanol system known from (10) to achieve this minimum would purely a matter of routine experimentation.

First and second auxiliary requests

7. The first and the second auxiliary requests differ from the main request in one aspect only. In claim 1 of the first auxiliary request the organic cosolvent is specified as being an alcohol cosolvent and in claim 1 of the second auxiliary request as being ethyl alcohol. Alcohol cosolvents, such as isopropyl alcohol and ethyl alcohol, belong to the preferred cosolvents used in the aerosol solution formulations disclosed in (10) (see page 2, lines 42-43, Examples 10 to 12, claims 5 and 6).
- 7.1 The specification of the cosolvent as being an alcohol cosolvent or ethyl alcohol does not make any difference to the formulation of the technical problem or the assessment of inventive step so that the arguments developed by the board in 6.1 to 6.9 above apply equally to the subject-matter of the first and second auxiliary requests, in particular since the presence of water is not excluded from the propellant system used in both these requests.

Third auxiliary request

8. Citation (10) discloses the use of solubilised surfactants in a method for obtaining stable aerosol solution formulations comprising a medicament, e.g. ipratropium bromide, an HFC propellant (P134a) and an organic cosolvent (see Claims 1, 2, 12; page 3, lines 17-18).

Given this closest state of the art, the problem underlying the subject-matter of the third auxiliary request is that of supplying an alternative to the method described in document (10). The solution

proposed in claim 1 is the use of an inorganic or organic acid in that method. Having regard to what is said above in point 5.5 above as to the solution to the problem underlying the main request, the board considers that the above problem underlying the third auxiliary request is likewise plausibly solved.

8.1 On the basis of the explanations given in 6.2 to 6.9 above, those skilled in the art, starting from (10) and knowing the prior art of (4) and (5) and also (11) and (12), would readily expect the problem posed to be solvable by adding an acid.

9. In summary, the invention as claimed in the main request and auxiliary requests 1 to 3 does not meet the requirement of inventive step, precluding maintenance of the patent on the basis of the requested amendments.

Request for remittal to the first instance

10. None of the claim requests submitted by the appellant and introduced into the appeal proceedings have been considered to represent a valid basis for the maintenance of the patent allowing the decision under appeal could be set aside.

Since citations (11) and (12) were filed over four years before the date of the oral proceedings, the appellant had sufficient time and opportunity to study these documents and to present its arguments and comments on this prior art during the written appeal proceedings and the hearing before the board. Therefore, there is no reason whatsoever to remit the case to the opposition division for further

prosecution. Consequently, the request for remittal is refused.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

A. Townend

U. Oswald