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D E C I S I O N
of 13 January 1999

Case Number: T 0379/96 - 3.3.2

Application Number: 89312270.5

Publication Number: 372777

IPC: A61K 9/12

Language of the proceedings: EN

Title of invention:
Medicinal aerosol formulations

Patentee:
Riker Laboratories, Inc.

Opponent:
(01) Norton Healthcare Ltd
(02) Schering Corporation
(03) Boehringer Ingelheim GmbH
(04) Professor Sylvain RAULT
(05) SmithKline Beecham plc
(06) Fisons plc

Headword:
Aerosol formulations/RIKER

Relevant legal provisions:
EPC Art. 83, 56, 84, 123

Keyword:
"Inventive step - no - for all admitted requests - obvious substitution of a compound of a composition"
"Request on the basis of Article 125 EPC or Article 32 TRIPS to refer a question of law to the Enlarged Board of Appeal or to the

European Court of Justice - not admitted into the proceedings"

Decisions cited:
T 0560/89, T 0092/93

Catchword:
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Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0379/96 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 13 January 1999

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 10 April 1996 rejecting the opposition filed against European patent No. 0 372 777 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: U. Oswald
R. E. Teschemacher

Summary of Facts and Submissions

I. European patent No. 0 372 777 relating to medicinal aerosol formulations was granted on the basis of fourteen claims in response to the European patent application No. 89 312 270.5 filed on 27 November 1989 and claiming priority from the United Kingdom application GB 88 28 477 filed on 6 December 1988.

Claim 1 reads as follows:

"*A medicinal aerosol formulation suitable for administration to a patient by oral or nasal inhalation comprising a medicament, 1,1,1,2-tetrafluoroethane, a surface active agent and at least one compound having a higher polarity than 1,1,1,2-tetrafluoroethane, the formulation being in the form of a solution or a suspension of medicament particles having a median particle size of less than 10 µm and being substantially free of* $CHClF_2$, CH_2F_2 *and* CF_3CH_3."

II. Six oppositions were filed against the granted patent. According to the grounds of opposition, the patent was opposed under Article 100(a) EPC for lack of novelty and lack of inventive step and under Article 100(b) EPC for insufficiency of disclosure. Of the numerous documents cited during the opposition proceedings, the following remain relevant to the present decision:

(2) Dupont "UPDATE", Fluorocarbon/Ozone, March 1987;

(6) Rev. Int. Froid 1988, vol. 11, November, pages 389 to 392;

(8) US-A-4 174 295

(14) US-A-2 885 427

(19) "The Theory and Practice of Industrial Pharmacy", second edition (1976), Lea & Febiger Philadelphia, pages 270 and 276 to 280;

(50) EP-A-275 404.

III. By a decision posted on 10 April 1996, the Opposition Division rejected the oppositions under Article 102(2) EPC.

The Opposition Division took the view that the description of the patent in suit including the worked examples provided enough technical information for a clear definition of the compound required by claim 1 having a higher polarity than 1,1,1,2-tetrafluoroethane and accordingly concluded that there was no reason to follow the Opponent's objections under Article 100(b) EPC.

In the light of the disclosure in document (8) (equivalent to document (38b) DE-A-2 736 500) - the only documents cited under Article 54 EPC - the skilled person could arrive at the claimed subject matter only by a combination of selection steps. Therefore, the claimed subject matter was regarded as novel.

For the assessment of inventive step the Opposition Division considered that it was a matter of hindsight to start from document (50) comprising the same compounds as mentioned in claim 1 of the patent in suit

but using P12 instead of the propellant P 134a (1,1,1,2-tetrafluoroethane). Document (8) relating to both the generic teaching of the invention and the "background problem" underlying the invention, namely "the provocation of degradation of the stratospheric ozone by CFC's", in reality represented the closest prior art. Accordingly, in the light of the disclosure of document (8) the problem underlying the patent in suit was to "make available a MDI [metered dose inhaler] composition having a suitable propellant system, said propellant system being as little ozone damaging as possible".

Since both the solubility and toxicity aspect of P 134a in medicinal aerosol formulations was not clarified at the priority date of the patent in suit and since none of the documents cited in the course of the proceedings either taken alone or in combination comprised technical information on how to formulate medicinal aerosols comprising P 134a as the only propellant, the subject matter of the patent in suit involved an inventive step within the meaning of Article 56 EPC.

IV. The three Appellants (Opponents 01, 03 and 04) lodged appeals against the said decision. Reference was made to further prior art documents presented in the corresponding case before the High Court of Justice in the United Kingdom, inter alia to documents:

A(64) Financial Times, November 11, 1988, Article "The quest for ozone friendly 'gases", and

A(56) Chemistry and Industry, March 1988, page 132, Article "ICI caution on CFC 22".

During the written procedure the Respondent filed a - *main request* - on 30 December 1998 with an amended claim 1 which differed from claim 1 as granted by cancellation of the word substantially such that the medicinal aerosol formulation was "*free of chlorofluorocarbons and $CHClF_2$, CH_2F_2, and CF_3CH_3*".

On 8 January 1999, the Respondent filed five auxiliary requests with the following claims intended to replace claim 1 of the main request (in auxiliary requests 1 to 3 claim 1 is intended to be replaced by two claims):

Auxiliary Request 1

"*...the formulation being in the form of a suspension of medicament particles having a median particle size of less than 10 µm and being free of chlorofluorocarbons and $CHClF_2$, CH_2F_2, and CF_3CH_3.*"

"*...the formulation being in the form of a solution and being free of chlorofluorocarbons and $CHClF_2$, CH_2F_2, and CF_3CH_3, and in which the medicament is beclomethasone diproprionate.*"

Auxiliary Request 2

"*...the formulation being in the form of a suspension of medicament particles having a median particle size of less than 10 µm and being free of chlorofluorocarbons and $CHClF_2$, CH_2F_2, and CF_3CH_3, and in which the weight ratio of 1,1,1,2-tetrafluoroethane : compound of higher polarity is in the range 85:15 to 95:5.*"

"*...the formulation being in the form of a solution and being free of chlorofluorocarbons and $CHClF_2$, CH_2F_2, and CF_3CH_3, and in which the medicament is beclomethasone diproprionate.*"

Auxiliary Request 3

"*...the formulation being in the form of a suspension of medicament particles having a median particle size of less than 10 µm and being free of chlorofluorocarbons and $CHClF_2$, CH_2F_2, and CF_3CH_3, in which the weight ratio of 1,1,1,2-tetrafluoroethane : compound of higher polarity is in the range 85:15 to 95:5, and in which the medicament is sulbutamol sulphate.*"

"*... the formulation being in the form of a solution and being free of chlorofluorocarbons and $CHClF_2$, CH_2F_2, and CF_3CH_3.*"

Auxiliary Request 4

"*...the formulation being in the form of a solution or a suspension of medicament particles having a median particle size of less than 10 µm and being free of chlorofluorocarbons and $CHClF_2$, CH_2F_2, and CF_3CH_3, and in which the medicament is selected from antiallergics, analgesics, bronchodilators, antihistamines, antitussives, anginal preparations, antibiotics, antiinflammatory preparations, sulfonamides, alkaloids, steroids and synergistic combinations thereof*."

Auxiliary request 5

"*...the formulation being in the form of a solution or a suspension of medicament particles having a median particle size of less than 10 µm and being free of chlorofluorocarbons and $CHClF_2$, CH_2F_2, and CF_3CH_3, and in which the medicament is selected from isoproterenol [alpha-(isopropylaminomethyl) protocatechuyl alcohol], phenylephrine, phenylpropanolamine, glucagon, adrenochrome, trypsin, epinephrine, ephedrine, narcotine, codeine, atropine, heparin, morphine, dihydromorphinone, ergotamine, scopolamine, methapyrilene, cyanocobalamin, terbutaline, rimiterol, salbutamol, flunisolide, colchicine, pirbuterol, beclomethasone, orciprenaline, fentanyl, diamorphine, neomycin, streptomycin, penicillin, procaine penicillin, tetracycline, chlorotetracycline, hydroxytetracycline, cortisone, hydrocortisone acetate, prednisolone, insulin, cromolyn sodium, ipratropium bromid and isoprenaline*"

(Emphasis added)

V. Oral proceedings took place on 12 and 13 January 1999 during which the Respondent submitted two further auxiliary requests.

One of these requests was submitted at the beginning of the oral proceedings and contained a set of 10 claims. Claim 1 of this - *sixth auxiliary request* - related to a medicinal aerosol formulation comprising inter alia

"*at least one compound having a higher polarity than 1,1,1,2-tetrafluoroethane, selected so as (i) to be miscible with....(ii) to produce a mixture with a*

solubility parameter of from...and (iii) to provide a mixture in which increased amounts of..."

The request submitted last - *the seventh auxiliary request* - was submitted before the oral proceedings were adjourned for the deliberation by the Board. Referral of questions of law to the Enlarged Board of Appeal or to the European Court of Justice was requested based on the Repondent's view that revocation of a patent for the first time by a Board of Appeal was, in the absence of a further review, in contravention of Article 125 EPC as well as of Article 32 TRIPS.

VI. The arguments of the Appellants, both in the written procedure and at the oral proceedings, may be summarised as follows:

The last two auxiliary requests gave rise to complex technical and legal questions. Since the parties were prevented from studying these late documents and hence could not file counterarguments, these requests should be disregarded.

The patent in suit contained a reference to three methods of determining the polarity of an adjuvant but these methods gave different and contradicting results when testing one and the same adjuvant. There was no disclosure in the patent in suit to indicate that a person must try all three tests and since it was an unreasonable burden to find out whether or not an adjuvant fell within the scope of the patent, the ground of opposition under Article 100(b) EPC was maintained.

At the oral proceedings the Appellants did not continue to contest the novelty under Article 54 EPC of the subject matter of each of the requests then on file.

For the assessment of inventive step the Appellants submitted that the problem underlying the invention was actually caused by public pressure and government activities, in particular by the fact that the majority of the industrial states had forbidden or intended to forbid the use of propellants known to be harmful for the ozone layer around the earth and consequently that there was also a need for the manufacturer of a medicinal aerosol formulation to modify his product in such a way that it would be marketable in the future.

Under these circumstances it was clear that the closest prior art was a group of disclosures of inhalation pharmaceutical aerosol formulations comprising a drug, a propellant, a solvent and a surfactant, which prior art represented disclosures identical to the claimed invention except that the propellant CFC 12 was used instead of HFC 134a. Particular emphasis was put on document (50) as disclosing both suspension and solution formulations and the fact that propellant P 11 and/or ethanol in the same concentration might be used as co-solvent in such formulations.

As regards the relevant documents to be combined with the closest prior art, it was pointed out in particular that in the present case the problem to be solved was not solely addressed to a pharmacologist but more to a skilled person in the field of physical chemistry and more particularly one having knowledge of propellant systems in general. This knowledge was illustrated by

document (19) describing the relevant physicochemical parameters to be considered when developing aerosol formulations.

There was an overwhelming body of literature eg document (2) pointing towards HFC 134a as the most promising propellant for a direct replacement for CFC's. If there were any solubility problems with adjuvants, particularly with surfactants and HFC 134a, it was common practice to add a co-solvent, the most prominent one being ethanol as used in document (50). Therefore, the skilled person would arrive at the subject matter of the patent in suit without the exercise of an inventive step as required by Article 56 EPC.

Since the inclusion of different amounts of propellant, co-solvent and other adjuvants as well as of different types of drugs, in compositions known from document (50) did not cause experimental difficulties, the auxiliary requests also failed to meet the requirements of Article 56 EPC.

VII. The Respondent contested the validity of these arguments. In respect of the admissibility of the late filed requests, he argued that each of the auxiliary requests 1 to 6 contained a clear limitation in comparison with the subject-matter of the patent in suit as granted and clearly related to preferred embodiments of the invention. The last request filed related to important questions of law raised by the circumstances of the present case but also of general interest. Accordingly, each of these requests should be considered when deciding the present case.

The ground of opposition under Article 100(b) EPC should be rejected. The description of the patent in suit defined with equal preference three methods of testing the polarity of a compound. Furthermore, it was clear to a skilled person that if a compound did not give a satisfactory result according to one method, another method should be tried. Therefore, only if none of the three methods gave a satisfactory result was it clear that the compound was unsuitable as an adjuvant. In these circumstances, the claimed invention clearly met the requirements of sufficiency of disclosure.

The Respondent took the view that despite the fact that novelty over the disclosure of document (8) was no longer disputed, this document remained the starting point for the invention since it disclosed in reality a solution to the ozone depleting problem, the same problem as underlying the patent in suit, and provided the skilled person in an objective manner with background knowledge about what was technically meaningful when substituting one propellant by another.

In the Respondent's view, the Appellants way of discussing the possibilities of propellant substitution by a simple so-called drop-in argumentation saying that one propellant could be replaced by another by ignoring the propellant's influence on solubility parameters - the change which in turn made it necessary to change the proportionality by weight of the other aerosol components - was not founded by any written disclosure and was based on technically unrealistic allegations which the skilled person would never take into consideration.

Within the great volume of literature relating to medicinal inhalation formulations, document (50) in particular neither represented a conventional inhalation aerosol nor related to the problem of ozone depletion, and the choice of the formulations of document (50) by the Appellants as the most relevant prior art was only possible with knowledge of the invention of the patent in suit and thus was the result of hindsight. Moreover, document (50) indicated that the drug LHRH used in the formulation according to this prior art was practically insoluble in fluorocarbons and thus clearly established a prejudice to the use of a single fluorocarbon.

According to the case law of the Boards of Appeal, the most relevant state of the art had to solve the same problem as the invention. Therefore, in the light of document (8) as the closest prior art, the objective problem was "the provision of effective medicinal aerosol formulations suitable for administration to a patient by oral or nasal inhalation complying with the environmental constraints resulting from the use of CFC's as propellants".

Considering what at the priority date of the patent in suit a person skilled in the art actually knew with respect to alternative propellant compositions plus medicinal inhalation formulations as a whole and the technical effect and function of the individual formulation components from the cited documents, either taken alone or in combination, the invention as set out in the patent in suit was not obvious to a skilled person. Referring to several expert opinions and documents, the Respondent put particular emphasis on

the fact that at the priority date of the patent in suit no conclusive toxicity tests were available and only very little technical information about the physical and chemical properties of HFC 134a was available and that there was not the slightest hint in the literature as to whether HFC 134a was suitable for medicinal inhalation formulations and whether a stable product could be formulated. Since the density of HFC 134a was lower than that of P11/12, there was no reason to add ethanol having a density of only 0.8 into HFC 134a aerosols. Apart from serious flammability problems, the admixture of ethanol to suspension formulations also involved the risk of dissolving the drug accompanied by crystallisation. Moreover, since it was known eg from document (6) that in view of the bad solubility parameters of HFC 134a the use of this propellant as refrigerant would require the development of new lubricants and consequently when used in medicinal aerosols would require new surfactants in order to produce stable formulations, the search for alternative medicinal aerosol formulations went in different directions by using other alternative propellants such as P 22, P 123, P 124, P 141b, P 142b, P 152a as well as DME and hydrocarbons, with P 22 being the leading candidate. Accordingly, since the specific function of the surfactant and that of the co-solvent having higher polarity than HFC 134a - functions necessary to overcome the insolubility problem - were not predictable from any prior art, in the Respondent's view, the subject-matter of the patent in suit involved an inventive step.

The auxiliary requests also met the requirements of the EPC. The arguments presented with regard to the main

request applied in the same way to the subject-matter of these requests. The claims according to the auxiliary requests were restricted to unobvious aerosol solutions and suspensions covering a wide class of medicaments. In particular it was not possible before the priority date of the patent in suit to prepare stable aerosol formulations of the specific medicaments mentioned in the said claims as active agents.

VIII. The Appellants (Opponents 01, 03, 04) requested that the decision under appeal be set aside and that the patent be revoked.

The Respondent requested that the appeal be dismissed and that the patent be maintained on the basis of a set of claims with claim 1 as submitted on 30 December 1998 and claims 2 to 14 as granted - main request - or with the claims replacing claim 1 as submitted on 8 January 1999 and the remaining claims to be adapted thereto - auxiliary requests 1 to 5 or with claims 1 to 10 submitted during the oral proceedings - auxiliary request 6.

Furthermore, he requested to refer the question of law submitted during the oral proceedings to the Enlarged Board of Appeal or the European Court of Justice - auxiliary request 7.

IX. Opponents 02, 05 and 06 although duly summoned, did not attend the oral proceedings and did not file requests.

Reasons for the Decision

1. The appeal is admissible.

2. The late filing of the main request and the seven auxiliary requests raises the procedural problem of their admissibility. The same problem arises from the late filing of the documents presented by the Appellants and the Respondent including affidavits and documents taken from the corresponding case before the High Court of Justice in the United Kingdom.

2.1 Although filed at a late stage in the procedure - very close to the date of oral proceedings - the Board has decided to admit the new main request as well as auxiliary requests 1 to 5 into the proceedings. The sets of claims according to these requests contain amendments which can be easily derived from the independent claims and/or the description as originally filed and can be regarded as a fair response to the Appellants objections. In the Board's view there was no undue burden on the Appellants to comment on these requests since the relevant arguments were already on file.

2.2 As far as auxiliary request six is concerned, the Board notes that it is the purpose of oral proceedings to enable a final decision to be reached. Therefore, amendments requiring detailed further examination in general are not permissible at this stage in the proceedings (see eg T 92/93, cited in Case Law of the Boards of Appeal, 3rd ed 1998, VII-D, 14.2). The Respondents gave no reason for this late submission and no appropriate reason is apparent to the Board. In particular, the amendments cannot be said to have been filed in response to objections not raised before the

oral proceedings. Rather, the relevant objections had already been made in previous steps of the proceedings. In addition, the Respondent had clearly been given ample opportunity for amendments since the five auxiliary requests which were admitted had been filed less than one week before the oral proceedings. Taking into account this prerequisite and the complexity of the amendments of claim 1 of auxiliary request six: "*at least one compound ..., selected so as (i) to be miscible with....(ii) to produce a mixture with a solubility parameter of from...and (iii) to provide a mixture in which increased amounts of...*", which introduce a combination of features and functionalities never before under discussion and which, in order to prove the claimed advantage of "increased amounts of..", require for the first time a comparison with the prior art as to the said amounts, the admittance of this request would have prevented the Board from taking a final decision on the basis of the oral proceedings. Needless to say, any invitation to the Appellants to provide a substantiated statement on these complex amendments would have been an excessive demand. Moreover, the Board has doubts as to whether the introduction of the combination of functionalities "selected so as...to provide....increased amounts" finds basis in the original disclosure. Thus these claims do not appear to be clearly allowable under Articles 56 and 123(2) EPC.

2.3 Auxiliary request seven relates to complex legal matter and comprises a set of 32 pages including procedural questions and explanations relating to legal background. Any invitation to the Appellants to comment on this legal matter would also have been an excessive

demand in view of the fact that the other parties had neither an opportunity to study the submissions in detail nor to prepare their replies. The Appellants currently pointed out that the questions raised by this request involved problems of procedural and international law. Nothing in the previous proceedings had given reason to be prepared for such type of questions in the oral proceedings. In addition, this request is in contradiction to the Respondent's previous procedural conduct.

The last request was intended to come into effect only if the Board had refused each of the preceding requests relating to the substance of the patent in suit and would therefore have prevented the Board from revoking the patent for lack of substantive patent law requirements under the EPC. In other words the Respondent requested the Board to examine all sets according to the previous requests in substance. This implied inevitably that there was the possibility that the Board came to a negative result. The seventh auxiliary request means, however, that the Respondent is prepared to accept only a positive result as an outcome of the appeal proceedings. It is, however, inconsistent to accept the Board's competence for a positive result and to contest it for a negative result. If the Respondent had doubts about the competence of the Board he should have raised this question at the outset of the appeal proceedings. The failure to do so and to wait until the end of the proceedings amounts to an inadmissible exercise of a right under the well established prohibition of *venire contra factum proprium*.

2.4 The Board has decided not to admit auxiliary requests six and seven filed during the oral proceedings into the proceedings for the above reasons. Thus, they are refused.

2.5 As regards the late filed documents, the Board notes that in their written submissions and at the oral proceedings the parties took up these documents and apparently had no difficulties in commenting on their relevance. Accordingly, the Board sees no reason to exclude these documents from the proceedings in the present case.

3. The Appellants neither objected under Article 100(c) EPC with regard to the patent as granted, nor filed such objections with regard to the new main request and auxiliary requests 1 to 4 comprising only a combination and rearrangement of the claims as granted and originally filed with the inclusion of a list of medicaments from page 9 of the description as originally filed. The newly filed claims according to each of these requests are of narrower scope than the granted claims. Therefore, the Board considers that the requirements of Article 123(2) and (3) EPC are satisfied.

During the oral proceedings Appellant 01 noticed that according to claim 1 of auxiliary request 5 reference is made to ipratropium as a medicament instead of ipratropium bromide which was disclosed in claim 12 as originally filed. The Board notes that this lack of a part of the chemical name of one of the medicaments mentioned in a list of more than forty medicaments was accepted by each of the parties as an obvious typing

error. Therefore, in the circumstances of the present case, the Board has decided to continue substantive examination on the basis of auxiliary request 5 too.

4. As regards the Appellants objections under Article 83 EPC, the Board agrees that the three methods of determining the polarity of an adjuvant mentioned in the description of the patent in suit may give different results. However, having regard to the broad range of classes of medicaments covered by the disclosure of the invention as set out in the patent in suit, including different formulations for different types of medicaments, against the use of which there are *a priori* no reasons to object, in the Board's view, in the event of any uncertainty as to the results of these polarity tests the logical way to come to a final result is to accept the disclosure of the invention in its broadest sense and as a consequence to continue to carry out tests on the basis of each of the disclosed test methods. Since the Appellants did not contest the reproducibility of one of the three test methods, the Board can only conclude that the requirements of Article 83 EPC are satisfied.

5. Since the claims according to the main request as well as those according to auxiliary requests 1 to 5, comprise only a combination and rearrangement of the claims as granted and originally filed, with the inclusion of a list of medicaments from page 9 of the description as originally filed, and since there is no ambiguity when reading the claims in combination with the description, the Board is satisfied that the claims according to each of the said requests are clear and have adequate support in the description as required by

Article 84 EPC.

6. The novelty of the subject-matter of the claims according to the main request and according to auxiliary requests 1 to 5 was no longer disputed by the Appellants at the oral proceedings. Since the claims according to these requests are of narrower scope than those before the Opposition Division, and the Board sees no reason to deviate from the Opposition Division's conclusion under Article 54 EPC, there is no need to discuss this matter in detail.

7. For the assessment of inventive step the Board can accept the argument of the Respondent that document (8) already comprises a solution to the ozone depletion problem caused by aerosol propellant compositions. Since furthermore, according to the introductory part of the description, the patent in suit also seeks to solve the adverse effects of propellants on the ozone layer, the Board can also accept that the teaching of document (8) has to be analysed as to its relevance in the present case. However, there is neither an automatism nor a general rule that documents relating to an alternative solution of a problem as stated in the patent or application to be examined inevitably represent the closest prior art. The similarity of the components of the composition and the use of the composition in the specific technical field are also of great importance when choosing the suitable starting point for the discussion under Article 56 EPC of a claim relating to a composition.

The skilled person in the present case has special knowledge in the field of medicinal aerosol

formulations and is deemed to have access to the whole literature relating to that field. He must also have knowledge about the basic chemistry necessary to determine on the basis of physico-chemical properties of the components of a formulation their interactions and what follows from their use in a formulation. When difficulties resulting from the use of some components of a formulation also occur in an analogue manner in other fields, such fields can be considered as neighbouring technical fields. If it is the case, as here with environmental problems, the skilled person will of course be interested to know the solution proposed in such neighbouring fields (see also decision T 560/89, OJ 1992, 725).

The Board notes that the patent in suit specifically relates to a medicinal aerosol formulation suitable for administration to a patient but that document (8) in the form of a general teaching is focused on the optimisation of propellant systems as to their solvent power and does not describe concrete medicinal formulations. Fourteen worked examples in document (8) relate to hair lacquers and one example describes an insecticide formulation. This document furthermore exemplifies the said general teaching by five ternary phase diagrams of propellant systems.

8. In contrast to the more general teaching in document (8), several other prior art documents cited in the present case relate specifically to medicinal aerosol formulations, one of which is document (50) which was discussed extensively during the oral proceedings.

As regards the Respondent's criticism of how the selection of citations such as document (50) was made in the present case, it is unavoidable that the documents of the European search report and the literature presented in both the opposition and appeal proceedings are found with knowledge of the invention of the application or the patent in suit. As Article 54(2) EPC states expressly, the state of the art shall be held to comprise **everything** made available to the public before the relevant date. Therefore, any citation qualifies as state of the art and may be cited in the Search Report. However, it is to be noted that one of the prerequisites for the assessment of inventive step, is not purely the choice of documents on the basis of the written disclosure therein. Rather, before determining the relevance of prior art documents, the skilled person competent to solve the problem has to be defined and then as an essential prerequisite, in order to avoid subjective and individual points of view, account of the common general knowledge of this skilled person has to be taken before the question can be answered whether or not the skilled person would have taken a document in consideration. Needless to say the skilled person is at least aware of each of the prior art documents relating to the technical field under discussion, which means in the present case having knowledge of at least those documents relating to medicinal aerosol formulations in the form of a solution or suspension suitable for administration to a patient. He will consider more closely those documents from which he can expect a contribution to the solution of his problem.

Accordingly, the Respondent's arguments as to an *ex*

post facto selection of document (50) must fail.

9. In the Board's view, document (50) relating to solution and suspension aerosol formulations comprising LHRH (luteinising hormone releasing hormone) analogues indeed represents the closest prior art.

9.1 According to page 3, lines 24 to 31 of document (50), the suspension aerosol formulations comprise:

1. LHRH analogues (active ingredient)

2. surfactant (dispersing agent)

3. solvent (Freon 11 and or absolute alcohol)

4. propellant and optionally

5. surfactant (wetting agent and valve lubricant)

6. antioxidant

7. flavour fragrance.

The solution aerosol formulation comprises additionally a lipophilic counterion as solubilising agent, see page 2, line 55 and page 3, lines 1 to 8, particularly page 3, line 2.

It is indicated on page 2, lines 29/30 and lines 48 to 51, that the inclusion of said lipophilic counterions in solvent-based solution aerosol formulations eliminate solubility problems with LHRH analogues in fluorocarbons and that the technical and safety hazards

associated with preparing suspension aerosols can be overcome by liquid milling LHRH analogues and using a low boiling liquid propellant. According to the preferred embodiments on page 3, the formulations comprise dichlorodifluoromethane (P12) as propellant. Bioabsorption tests are carried out with beagle dogs (see page 6, last paragraph).

9.2 The aerosol formulations according to document (50) do not show *a priori* any medicinal disadvantages but it was undisputed by the parties that before the priority date of the patent in suit there was considerable pressure by various governments around the world to reduce substantially the use of chlorofluorocarbons (CFCs) as propellants because these propellants react with the ozone layer around the earth and contribute towards its depletion (see also description of the patent in suit page 2, lines 15 to 17).

9.3 Accordingly, starting from document (50) and taking into account legal requirements relating to and increasing public interest in environmental protection, the problem underlying the patent in suit may thus be seen in providing medicinal aerosol formulations having acceptable therapeutical effectiveness but being less destructive to ozone.

9.4 According to the Respondent the claimed solution to the said problem is a suspension or solution aerosol formulation comprising 1,1,1,2-tetrafluoroethane (abbreviation 134a) and at least one compound having a higher polarity than 1,1,1,2-tetrafluoroethane. Document (50) does not contain the teaching relating in general to a compound having said higher polarity.

However, since document (50) already discloses solution and suspension aerosol formulations containing alcohol (ethanol), and since according to the description and the worked examples of the patent in suit ethanol is shown as one of the preferred compounds having a higher polarity than 1,1,1,2-tetrafluoroethane, the Board can only see the contribution in the claimed solution to the above defined problem in proposing aerosol formulations comprising propellant 134a.

As regards the relevance of the remaining features in claim 1 of the main request for the solution of the said problem, the Board notes that during the opposition proceedings the Respondent accepted (see letter filed on 19 August 1994, page 19, first paragraph) that it is one of the requirements for suspension aerosols to be suitable for inhalation to contain drug particles having a median particle size of less than 10 µm.

Having regard to the worked examples of the patent in suit it appears credible that the problem has indeed been solved.

The three Appellants neither contested the results of the said worked examples nor the statement that propellant 134a has no adverse effect on the ozone layer.

10. It therefore remains for the Board to decide whether or not the said solution would, in view of the citations, have been obvious to a person skilled in the art faced with the problem defined above.

In this respect, it can be expected that the skilled person in the field of formulation of pharmaceutical aerosols is familiar with propellants and the effect the propellants will have upon the finished product (see for example document (19), pages 276/277 under the heading "Formulation of Pharmaceutical Aerosols").

10.1 There is indeed no hint in document (50) itself which might have given an incentive to the skilled person to investigate the propellant system of the LHRH formulations disclosed therein.

10.2 However, if confronted with the problem as stated above, the skilled person would inevitably turn to other prior art relating to propellant systems and, first of all, if available, to such systems having no ozone depleting potential and being suitable to replace the P12 CFC propellant used in the pharmaceutical aerosol formulation of document (50). In this respect, the skilled person will find a substantial body of literature for example

- document (2), second page, middle column, last paragraph:

  "*Fluorocarbon 134a is known to be a good candidate to replace CFC 12 because it contains no chlorine and, therefore has zero ozone depletion potential*". Subsequently reference is made inter alia to high costs and the need for further toxicity testing but then indicating "*However, FC-134a appears to be the best of any of the candidate alternatives to CFC-12,...*";

- document (6), page 389, left column, last paragraph:

  "*The leading candidate for CFC 12 substitution is HFC 134a, a material that contains no ozone depleting chlorine. Its thermodynamic properties are similar to those of CFC 12*";

- *d*ocument A(64), sixth column from left, last paragraph:

  "*The most promising future substitute for CFC 12 is a hydrofluorocarbon called HFC 134a, which contains no chlorine and therefore does not threaten the ozone layer.*"

10.3 As argued by the Respondent, the Board agrees that the cited prior art makes reference to further propellants such as HCFC 22, which may be used in aerosols. However, whereas HCFC 22, which at one time was widely seen as one of the most attractive substitutes for the CFCs 11 and 12, is less damaging to the environment it is not entirely harmless and because of possible teratogenicity appears to be not fully acceptable in medicinal aerosol formulations (see document A(64), third column from the left and A(56), first paragraph).

In the Board's view, it can be summarised in the light of the available prior art that just before the priority date of the patent in suit there was a clear trend towards P 134a as the leading candidate for CFC 12 substitution in aerosols.

10.5 Moreover, having regard to the degree of pressure put

on industry by existing or imminent legislation and by the public interest, to try to replace P12, in the Board's view, it is a minor matter whether or not there was a particularly high degree of expected success before starting experimental work with HFC 134a. The skilled person would in any case first of all start experimental work by testing a replacement with propellants having zero ozone depleting potential and allowing a long term solution to the problem before making a compromise with less environmentally beneficial candidates or with mixtures of CFCs and HFCs. In this respect it is to be noted that P 11 used in the suspension formulation of document (50) as an alternative solvent shows, as argued by the Respondent, indeed excellent solubility properties and could indeed be regarded alternatively or in addition to ethanol as a co-solvent, but in view of the extremely high ozone depleting potential of this component as proven by Table 1 of document (2), the skilled person would clearly try to avoid this component.

10.6 The Board does not misjudge the real situation in relation to toxicity and/or solubility problems caused when using HFC 134a as a replacement which are indeed postulated in the literature and which form the basis for the Respondent's arguments for the non-obviousness of the invention. However, the facts presented in the present case do not allow the conclusion that a skilled person - having the knowledge set out in document (19) (see point 10 above) and carrying out the experimental work necessary to reformulate the aerosols according to document (50) in order to overcome the problems caused by the P 12/11 components - was confronted with deterring difficulties. The Board notes furthermore

that thirty years before the priority date of the patent in suit, document (14) in column 2, lines 49 to 53, indicates that HFC 134a was a very stable compound. Its structure has been proved by mass spectroscopy and because of its low toxicity it has a high degree of utility as an aerosol propellant. Accordingly, there was, contrary to the Respondent's assertion, no prejudice to start the experimental work at a time at which toxicity studies of HFC 134a had not been completed. As regards the question of costs for further toxicity tests, it is clear that such costs were inevitably incurred when considering for the first time other possibilities of substituting CFC 12.

The Board notes furthermore that the aerosol formulations according to document (50) contain the surfactant(s), ethanol and the active agent in amounts which overlap with the preferred ranges of the said components in the patent in suit and that in the light of the disclosure in document (50) the skilled person had no reason to assume that he would be confronted with particular difficulties caused by a lack of solubility of any of the components. Once it was obvious to try P 134a, the Board can only conclude that the skilled person would first of all try to formulate the aerosol components in the amounts proposed in document (50).

10.7 In the absence of any counter evidence that the medicinal aerosol formulations according to document (50) containing up to 60% w/w ethanol (see page 3) cause flammability problems or do not properly work, there is no need to discuss the Respondent's argument in detail that the skilled person would avoid

the use of ethanol. In this respect the Board can accept the Appellants statement that MDIs contain ethanol in liquid form and not in the form of a highly flammable gas.

10.8 The Board can accept the Respondent's argument that the skilled person replacing P12 by HFC 134a is not in a so-called drop-in situation for the simple substitution of one component by another of a composition. However, in the Board's view, the mere fact that a modification of a product in order to maintain the product as marketable in the future involves complex research and is extremely time consuming does not automatically confer inventiveness on the product if the skilled person is provided with known and usual means for carrying out the research by routine work (see document (19) above defining the skilled person in the present case).

Accordingly, the Board can only conclude that the skilled person would arrive at the subject-matter of claim 1 of the main request without the exercise of inventive skill.

11. Since both alternative formulations - the suspension and the solution formulations - covered by claim 1 of the main request must be regarded as obvious in the light of the prior art, and since the first and second auxiliary requests comprise an independent claim relating exclusively to the said suspension formulation, and since the claim of the second auxiliary request relating to the suspension formulation is merely restricted to a weight ratio of 1,1,1,2-tetrafluoroethane : compound of higher

polarity, which ratio, as stated by the Appellants, is common practice and undisputedly covered by a broader weight ratio of the active ingredient LHRH to ethanol known from document (50), in the absence of any proof as to an advantage or specific effect related to the said restricted weight ratio for the assessment of inventive step, the above reasoning under point 10 also applies to these requests.

12. Since undisputedly even the public's attention had been drawn by press reports to the ozone depleting problem and the use of HFC 134a as a promising solution thereto, in the light of the facts on file, the Board can only conclude that the skilled person would also try, without the exercise of inventive skill, to include other active ingredients such as those mentioned in auxiliary requests 3 to 5 into the suspension and/or solution formulations, which are shown above as being obvious, in order to produce environmentally acceptable products marketable for the future.

The Board notes that the Respondent did not prove any particular advantage such as the alleged outstanding stability of the aerosol in comparison with the relevant prior art for one of the active ingredients mentioned in the large palette of alternatives according to auxiliary requests 3 to 5.

Accordingly, the reasoning set out above under points 10 and 11 also applies to the set of claims of the third to fifth auxiliary requests.

13. Within the reasoning set out above it was accepted that

document (8) represented prior art already providing a solution to the ozone depleting problem. Nevertheless, whatever might be the extent of the difference in substance between a known solution of a known problem and a claimed new solution of the said problem, this difference normally cannot render the new solution inventive if the solution is not inventive when starting from the properly assessed closest prior art. In the present case even when starting from document (8), the relevant information in document (50) could not have been neglected.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The requests for referrals of questions of law to the Enlarged Board of Appeal and the European Court of Justice are refused.

3. The patent is revoked.

The Registrar: The Chairman:

P. Martorana P. A. M. Lançon