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**DECISION**  
of 12 March 2003

**Case Number:** T 0287/99 - 3.3.2  
**Application Number:** 91919751.7  
**Publication Number:** 0556256  
**IPC:** A61K 9/12  
**Language of the proceedings:** EN

**Title of invention:**  
Aerosol medicaments

**Patentee:**  
GLAXO GROUP LIMITED

**Opponent:**  
SkyePharma AG  
Boehringer Ingelheim International GmbH  
Astra Zeneca AB

**Headword:**  
Aerosol medicaments/GLAXO

**Relevant legal provisions:**  
EPC Art. 52(1), 54, 56, 83, 84, 123

**Keyword:**  
"Main request: inventive step (no) - technical teaching of a prior art document which renders the claimed invention obvious is not confined to the detailed information given in the examples of how the invention is carried out but embraces any reproducible technical teaching described in that document"  
"Auxiliary requests: inventive step (no) - idem"

**Decisions cited:**  
T 0012/81, T 0032/82, T 0424/86, T 0250/87, T 0279/89,  
T 0522/90, T 0722/94, T 0839/95, T 0610/96, T 0743/96,  
T 0623/98, T 0799/98

**Catchword:**  
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Case Number: T 0287/99 - 3.3.2

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.2  
of 12 March 2003

**Appellant:**  
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**Decision under appeal:** Interlocutory decision of the Opposition  
Division of the European Patent Office posted  
21 January 1999 concerning maintenance of  
European patent No. 0556256 in amended form.

**Composition of the Board:**

**Chairman:** U. Oswald  
**Members:** G. F. E. Rampold  
C. Rennie-Smith

## Summary of Facts and Submissions

I. This appeal is from an interlocutory decision of the opposition division posted on 21 January 1999 to maintain in amended form European patent No. 0 556 256 ("the Patent") which is entitled "Aerosol medicaments" and is based on European patent application No. 91 919 751.7 (International application number PCT/GB91/01960). The two independent claims of the Patent read as follows:

- "1. An aerosol formulation comprising:
  - (A) a hydrogen-containing fluorocarbon or chlorofluorocarbon propellant;
  - (B) a co-solvent having higher polarity than said propellant, which co-solvent is present in an amount of up to 5% w/w based upon propellant; and
  - (C) a medicament in particulate form said medicament having a particle size of less than 100  $\mu\text{m}$  and having a surface coating of a surfactant, which surfactant has no affinity for said propellant.
  
11. A method for the preparation of an aerosol formulation as claimed in claim 1 comprising dispersing a surface-coated medicament in a hydrogen-containing fluorocarbon or chlorofluorocarbon propellant in an aerosol container and then adding the cosolvent."

Dependent claims 2 to 10 related to elaborations of the aerosol formulation according to claim 1 and dependent claim 12 to an elaboration of the method according to claim 11.

II. Oppositions to the patent were filed by three parties - opponent I (appellant I) and opponent II (party to the appeal proceedings as of right under Article 107 EPC, 2nd sentence) which both sought revocation on the grounds of lack of novelty and inventive step (Articles 54, 56 and 100(a)EPC), and opponent III (appellant III) which sought revocation on those grounds and also on the ground of insufficient disclosure (Articles 83 and 100(b) EPC).

III. Of the numerous documents cited in the course of the opposition and subsequent opposition appeal proceedings, the following are referred to in this decision:

- (1) EP-A-0 372 777
- (2) Reprint from R. Voigt, "Lehrbuch der Pharmazeutischen Technologie", 5th Edition, Verlag Chemie, 1984, Chapter 18, pages 359 to 370
- (3) Reprint from L. Lachman, H. A. Lieberman, J. L. Kanig, "The Theory and Practice of Industrial Pharmacy", Second Edition, Lea & Febiger, Philadelphia, 1976; Chapter 9, pages 276 to 280, J. J. Sciarra, "Pharmaceutical Aerosols"
- (4) J. Pharm. Pharmacol., 40, 7P, 1988
- (5) J. Pharm. Pharmacol., Suppl., 42, 9P, 1990
- (10) WO 90/07333
- (11) US-A-4 352 789

IV. By its interlocutory decision, the opposition division maintained the Patent in amended form on the basis of claims 1 to 11 submitted during the oral proceedings held on 24 November 1998 and corresponding to the proprietor's (respondent's) main request filed on 4 April 1997 with its letter of 26 March 1997. Claim 1 was based on claim 1 as granted (see I above), with the following amendments to components (B) and (C) of the claimed aerosol formulation indicated in bold italic letters below:

- "1. An aerosol formulation comprising:
- (A) a hydrogen-containing fluorocarbon or chlorofluorocarbon propellant;
  - (B) a cosolvent having higher polarity than said propellant, which cosolvent is present in an amount of *less than 1% w/w* based on propellant; and
  - (C) a medicament in particulate form said medicament having a particle size of less than 100  $\mu\text{m}$  and having a surface coating of a surfactant, which surfactant has no affinity for said propellant **and is present in an amount of from 0.05 to 5% w/w based on the medicament.**"

In the same request, claims 2 to 5 and 7 to 12 as granted were renumbered consecutively as claims 2 to 11 and the dependencies in claims 6 to 9 and 11 were amended to take account of the deletion of claim 6 as granted.

- V. The essence of the reasoning given in the opposition division's decision was as follows:

The opposition division found that the alleged insufficiency of disclosure did not prejudice the maintenance of the Patent as amended.

As regards novelty, the opposition division held that the proposed amendments to the Patent as granted (see IV above) conferred novelty on the claimed subject-matter in the patentee's main request over the state of the art according to (1). The opposition division noted in its decision that, as a consequence of the amendments, the opponents did not maintain their previous objections of lack of novelty as a ground for opposition.

As to inventive step, the opposition division determined the problem to be solved as that of avoiding the use of conventional CFC (chlorofluorocarbon) propellants in the preparation of stable aerosol formulations for the administration of finely powdered medicaments by inhalation. The solution to the problem suggested in the Patent was, in the opposition division's opinion, the provision of an aerosol formulation comprising the components (A), (B) and (C) as defined in claim 1 as amended.

The opposition division mentioned in its decision that there was general agreement that citation (1) constituted the closest state of the art available in the proceedings. This citation related to medicinal aerosol formulations comprising (A) a propellant selected from various types of conventionally used

propellants, including 1,1,1,2-tetrafluoroethane (hereinafter also referred to as propellant 134a), (B) a co-solvent of higher polarity than the propellant and (C) a medicament in particulate form in combination with a surface active agent.

In this context, the opposition division specifically referred (a) to the disclosure at lines 41 to 42 on page 4 of citation (1) where it is stated that "Propellant 134a and the component [co-solvent] of higher polarity are generally employed in the weight ratio of 50 : 50 to 99 : 1, preferably in the weight ratio 70 : 30 to 98 : 2 and more preferably in the weight ration of 85 : 15 to 95 : 5". It also referred (b) to the disclosure at lines 8 to 11 on page 5 of citation (1), where it is stated that "the surface active agents are generally present in amounts not exceeding 5 percent by weight of the total formulation" and that "they will usually be present in a weight ratio of 1:100 to 10:1 of surface active agent to drug". It finally referred (c) to the statements at lines 9 to 11 on page 5 of (1) that "the surface active agent may exceed this weight ratio [ie the upper end of the weight ratio of surface agent : drug of 10 : 1] in cases where the drug concentration in the formulation is very low".

From the latter statement in (1) the opposition division concluded a *contrario* that the lower end of the ratio relating to the amount of surfactant in (1) (ie a weight ratio of 1 : 100 of surface active agent : drug) was considered in (1) to be only useful in cases where a very high drug concentration was present in the aerosol formulation. It further concluded that in cases



where such a high drug concentration and, consequently, a low amount of surfactant was present in the aerosol formulation, those skilled in the art would not simultaneously select, in view of the high drug concentration, a concentration of co-solvent close to the lower end of the range relating to the amount of co-solvent in (1) (ie a weight ratio of 99 : 1 of propellant 134a : co-solvent). The opposition division accordingly considered that those skilled in the art would not have been led by the teaching of the cited document as a whole, including the examples, to choose a weight ratio of propellant 134a to the co-solvent in the range of 99:1 in combination with a weight ratio of surface agent to the drug in the range of 1 : 100, in order to obtain a stable aerosol formulation. The opposition division mentioned that the teaching of (1) was generally directed to the use of larger amounts of both the surfactant and the co-solvent and thus taught away from the claimed invention.

Further, the opposition division pointed out in its decision that citation (10) suggested the use of larger amounts of a co-solvent than those used in the patent in suit. Finally it mentioned that a number of other cited documents, for example (11), were essentially concerned with liquefied CFC's as propellants. Even if these documents taught the use of relatively low amounts of surfactants, the skilled person had no reason to combine the teaching of these documents with that of (1), since the technical/chemical characteristics of CFC propellants used in these documents were not comparable with those of the propellants used in the patent in suit.

VI. Appellants I and III lodged an appeal against the decision of the opposition division, paying the appropriate fees, and filing statements of grounds of appeal on 21 May 1999 and 31 May 1999 respectively.

With its letter of 12 October 1999, the respondent filed arguments supporting its main request for the appeal to be dismissed and submitted a first auxiliary request, in the event the board could not accept its main request.

VII. On 12 February 2003, in advance of the oral proceedings, fixed for 12 March 2003, the respondent withdrew the above-mentioned auxiliary request and presented, instead, a series of eight new auxiliary requests.

VIII. Claim 1 of auxiliary request 1 is based on claim 1 as maintained by the opposition division, with the further amendments indicated in bold italic letters below:

"1. An aerosol formulation comprising:

- (A) a **propellant selected from 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane;**
- (B) a cosolvent having higher polarity than said propellant, which cosolvent is present in an amount of less than 1% w/w based on propellant;  
and
- (C) a medicament in particulate form said medicament having a particle size of less than 100  $\mu\text{m}$  and having a surface coating of a surfactant, **which surfactant is selected from benzalkonium chloride, lecithin, oleic acid and sorbitan trioleate** and is

present in an amount of 0.05 to 5% w/w based on the medicament."

Claim 1 of auxiliary request 2a is based on claim 1 as maintained by the opposition division, with the further amendments indicated in bold italic letters below:

- "1. An aerosol formulation comprising:
- (A) *a propellant selected from 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane;*
  - (B) a cosolvent having higher polarity than said propellant, which cosolvent is present in an amount of less than 1% w/w based on propellant; and
  - (C) *a coated product comprising a medicament in particulate form, said medicament having a particle size of less than 100 µm and having a surface coating of a surfactant, which surfactant has no affinity for said propellant and is present in an amount of 0.05 to 5% w/w based on the medicament."*

Claim 1 of auxiliary request 2b is based on claim 1 as maintained by the opposition division, with the further amendments indicated in bold italic letters below:

- "1. An aerosol formulation comprising:
- (A) *a propellant selected from 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane;*
  - (B) a cosolvent having higher polarity than said propellant, which cosolvent is present in an

amount of less than 1% w/w based on propellant;  
and

- (C) **a coated product comprising a medicament in particulate form**, said medicament having a particle size of less than 100  $\mu\text{m}$  and having a surface coating of a surfactant, which surfactant is selected from benzalkonium chloride, lecithin, oleic acid and sorbitan trioleate and is present in an amount of 0.05 to 5% w/w based on the medicament."

Claim 1 of auxiliary request 3a is based on claim 1 as maintained by the opposition division, with the further amendments indicated in bold italic letters below:

"1. An aerosol formulation comprising:

- (A) **a propellant selected from 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane;**
- (B) a cosolvent having higher polarity than said propellant, which cosolvent is present in an amount of less than 1% w/w based on propellant;  
and
- (C) a medicament in particulate form said medicament having a particle size of less than 100  $\mu\text{m}$  and **having a surface coating which is a dry coating of a surfactant**, which surfactant has no affinity for said propellant and is present in an amount of 0.05 to 5% w/w based on the medicament."

Claim 1 of auxiliary request 3b is based on claim 1 as maintained by the opposition division, with the further amendments indicated in bold italic letters below:

- "1. An aerosol formulation comprising:
- (A) **a propellant selected from 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane;**
  - (B) a cosolvent having higher polarity than said propellant, which cosolvent is present in an amount of less than 1% w/w based on propellant; and
  - (C) a medicament in particulate form said medicament having a particle size of less than 100  $\mu\text{m}$  and having a **surface coating which is a dry coating of a surfactant,** which surfactant is **selected from benzalkonium chloride, lecithin, oleic acid and sorbitan trioleate** and is present in an amount of 0.05 to 5% w/w based on the medicament."

Claim 1 of auxiliary request 4a is based on claim 1 as maintained by the opposition division, with the further amendments indicated in bold italic letters below:

- "1. An aerosol formulation comprising:
- (A) **a propellant selected from 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane;**
  - (B) a cosolvent having higher polarity than said propellant, which cosolvent is present in an amount of less than 1% w/w based on propellant; and
  - (C) **a coated product comprising a medicament in particulate form,** said medicament having a particle size of less than 100  $\mu\text{m}$  and having a surface coating of a surfactant, which surfactant has no affinity for said propellant and is present

in an amount of 0.05 to 5% w/w based on the medicament,  
*wherein said coated product (C) is obtained by slurring particulate medicament with a solution of a surfactant in a substantially non-polar solvent and then removing the solvent."*

Claim 1 of auxiliary request 4b is based on claim 1 as maintained by the opposition division, with the further amendments indicated in bold italic letters below:

- "1. An aerosol formulation comprising:
- (A) *a propellant selected from 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane;*
  - (B) a cosolvent having higher polarity than said propellant, which cosolvent is present in an amount of less than 1% w/w based on propellant; and
  - (C) *a coated product comprising a medicament in particulate form, said medicament having a particle size of less than 100  $\mu$ m and having a surface coating of a surfactant, which surfactant is selected from benzalkonium chloride, lecithin, oleic acid and sorbitan trioleate and is present in an amount of 0.05 to 5% w/w based on the medicament,  
*wherein said coated product (C) is obtained by slurring particulate medicament with a solution of a surfactant in a substantially non-polar solvent and then removing the solvent."**

Claim 1 of auxiliary request 5 is based on claim 1 as maintained by the opposition division, with the further amendments indicated in bold italic letters below:

- "1. An aerosol formulation comprising:
- (A) **a propellant selected from 1,1,1,2-tetrafluoroethane;**
  - (B) a cosolvent having higher polarity than said propellant, which cosolvent is present in an amount of less than 1% w/w based on propellant; and
  - (C) **a coated product comprising a medicament in particulate form selected from salbutamol sulphate, salmeterol hydroxynaphtoate, beclomethasone dipropionate or fluticasone propionate, said medicament having a particle size of less than 100 µm and having a surface coating which is a dry coating of a surfactant, which surfactant is selected from benzalkonium chloride, lecithin, oleic acid and sorbitan trioleate and is present in an amount of 0.05 to 5% w/w based on the medicament;**  
**wherein the coated product (C) is present in an amount of 0.01-1% w/w based upon the total weight of the formulation."**

IX. Oral proceedings were held on 12 March 2003 in the absence of appellant I which had informed the board in advance that it would not attend.

X. The arguments of the appellants, presented in writing and orally at the hearing, as regards the current requests and related issues can be summarised as follows:

As regards clarity, the appellants submitted that a pre-coating step of the medicament with a suitable surfactant, using the particular preparative method described in the Patent for producing a pre-coated medicament (component C), was in their opinion a technical feature of the claimed invention which was apparently necessary to achieve the desired effect envisaged in the claimed invention. With reference to the principles set out in decision T 32/82 (OJ EPO 1984, 354) the appellants argued that claim 1 which did not include this essential technical feature contravened Article 84 EPC.

The appellants further argued as to clarity that the terminology used in claim 1 in the context of component (C), namely "medicament <.....> having a surface coating of a surfactant which surfactant has "no affinity" for the propellant", had no clear meaning and scope in the art. Nor did the description contain a clear definition of the term "affinity", nor was a clear explanation given as to how that term was to be understood in the Patent. This was in the appellants' opinion a further contravention of Article 84 EPC.

As to sufficiency, the appellants observed that product claim 1 and process claim 10 of the main request and also corresponding claims in certain auxiliary requests stipulated in general terms that the medicament (component C) be coated with a surfactant which has "no affinity" for the particular hydrofluorocarbon or hydrchlorofluorocarbon propellant used. Even if an attempt was made to interpret the obscure wording of the claim "surfactant which has no affinity for said



propellant" in the light of the description, the skilled reader was given no instructions as to how to select over the whole range claimed adequate surfactants fulfilling the requirement of having "no affinity" for the particular propellant used in each case. The statement in the Patent (see column 3, lines 33 to 35: - "The surfactants for use in the invention will have no affinity for the propellant (that is to say they will contain no groups which have affinity with the propellant.)" - was to be considered as a mere repetition of the vague and unclear terminology used in the claims relating to a surfactant having "no affinity" for the propellant, rather than as a serious attempt to explain its technical meaning and to provide usable instructions as to how to reduce the teaching of the claim to practice. From this the appellants concluded that the disclosure of the claimed invention in the Patent description was not an enabling one and, consequently, that the Patent did not comply with the requirements of Article 83 EPC.

Contrary to the finding of the opposition division in the decision under appeal, the claimed subject-matter in the Patent did not involve an inventive step in the light of the closest state of the art which was citation (1). The appellants did not agree with the opinion of the opposition division in the decision under appeal that the problem to be solved was the replacement of conventionally used CFC propellants in medicinal aerosol formulations with so-called "ozone-friendly" propellants. As this was the problem underlying citation (1) which already suggested solving this problem by the provision of aerosol formulations comprising a medicament, a surfactant, Propellant 134a

and at least one compound having higher polarity than the propellant, from an objective point of view the objective of the Patent could possibly be seen as the provision of stable aerosol formulations requiring smaller amounts of co-solvent than those disclosed in citation (1).

Citation (1) already disclosed medicinal aerosol formulations suitable for inhalation therapy comprising qualitatively and quantitatively the same components (A), (B) and (C) as the claimed inhalation aerosols in the Patent. The only feature in present claim 1 which was not expressly disclosed in (1) was the stipulation that the higher polarity co-solvent is present in an amount of less than 1% w/w based on propellant.

Citation (1) taught, however, that the propellant and the co-solvent were generally employed in the weight ratio of from 50 : 50 to 99 : 1 propellant : co-solvent. The addition of the wording "generally employed", on its proper construction in the context of the complete disclosure of citation (1), made it unmistakably clear to the skilled reader that the above-mentioned range relating to the amount of co-solvent in (1) should be considered as a preferred range only and that the lower end of this range was not an absolute limit of the amount of co-solvent required for the aerosol formulations disclosed in (1). To a person skilled in the art it was thus immediately clear that lower concentrations of co-solvent than those expressly referred to in (1) were equally useful in the preparation of the new type of inhalation aerosols disclosed in (1). This view was confirmed, in the appellants' opinion, by the disclosure at page 3,

lines 5 to 6, of citation (1) where it was stated that "the particular adjuvant(s) and the concentration of these adjuvant(s) is selected according to the particular medicament used and the desired physical properties of the formulation". From the disclosure at page 2, lines 39 to 50 it was clear to the skilled reader that the term adjuvant used in (1) included the co-solvent and the surfactant.

As agreed by the respondent during the proceedings before the opposition division, those skilled in the art would have been aware that it was desirable and advantageous to reduce the concentration of co-solvent in the claimed formulations to the lowest amount possible, in order to minimise the risk of dissolving the medicament in the co-solvent and to reduce the danger of spontaneous inflammability and to avoid toxicity problems.

The opposition division had erroneously interpreted the statement at page 3, lines 15 to 16, of citation (1) that "the presence of increased amounts of solubilised surfactant allows the preparation of stable, homogeneous suspensions of drug particles" as meaning that the state of the art according to (1) required the inclusion of large amounts of co-solvent in aerosol formulations in order to achieve solubilisation of sufficient surfactant. On the contrary, this statement had to be interpreted properly in the context of the preceding disclosure at page 3, lines 13 to 15, where it was stated that "the addition of a compound of higher polarity than Propellant 134a to Propellant 134a provides a mixture in which increased amounts of surfactant may be dissolved compared to their

solubility in Propellant 134a alone". In the context of this preceding disclosure, those skilled in the art would immediately understand the correct meaning of the cited statement, namely that the addition of co-solvent in any amount, even in a very small amount, was the essential criterion to enable conventional surfactants to be used in hydrofluorocarbon or hydrochlorofluorocarbon propellants and to achieve the formation of a stable dispersion of medicament in such propellants.

- XI. The arguments of the respondent, in writing and at the oral proceedings, as regards the issues which are relevant to the present decision, can be summarised as follows:

The patent contained a number of working examples and a list of surfactants which had been found to lack affinity for hydrogen-containing fluorocarbon or chlorofluorocarbon propellants. In view of this, there could be no objection to the use of the term "no affinity" on the grounds of insufficiency.

The claim specified that the medicament particles had a surface coating of a surfactant, but the preparative method used to achieve this was not an essential feature of the product. There was no justification for the respondent being required to limit the product *per se* claim in the Patent to include features of the disclosed method. From this it followed that the current version of the claim did not offend Article 84 EPC.

The respondent agreed with the appellants and the opposition division that citation (1) should be considered to represent the closest state of the art. The problem underlying the claimed invention was the replacement of CFC (chlorofluorocarbon) propellants with "ozone-friendly" propellants. This problem had involved a major reformulation problem for the pharmaceutical industry over at least the last ten years. Facing this problem, a skilled person would want to use known surfactants in the new formulations if possible, especially those surfactants which were present in CFC formulations which had already obtained regulatory approval, rather than develop new classes of solvents.

In attempting to prepare formulations in "ozone-friendly" propellants, a skilled person would have immediately come across the problem that many known surfactants had no effective affinity for hydrogen-containing propellants such as Propellant 134a. This was another problem underlying the claimed invention. It was also the problem underlying citation (1) which provided one solution for this problem. Thus, at page 2, lines 45 to 48, citation (1) stated that "the combination of one or more such adjuvants [cosolvents having a higher polarity than Propellant 134a] provides a propellant system which has comparable properties to those of propellant systems based on CFC's, allowing use of known surfactants and additives in the pharmaceutical formulations and conventional valve components".

Furthermore, it was stated in document (1), page 3, lines 13 to 17, that the addition of a compound of higher polarity than Propellant 134a to Propellant 134a provided a mixture in which increased amounts of surfactant may be dissolved compared to their solubility in Propellant 134a alone and that the presence of increased amounts of solubilised surfactant allowed the preparation of stable, homogeneous suspensions of drug particles. The use of a high polarity co-solvent was therefore essential in the formulations disclosed in (1) in order to dissolve the surfactant. Although the lower end of the range relating to the amount of co-solvent in (1) was close to the maximum amount claimed in the patent, the true teaching of citation (1) was that large amounts of co-solvents were necessary to solubilise the surfactant completely. Examples 1 to 18 of citation (1) illustrated the use of about 33% w/w of co-solvent based on the propellant and Examples 19 to 23 the use of about 11% w/w of co-solvent. Examples 24A and 24B of (1) showed an amount of 1.11% of co-solvent based on propellant. However, in the European patent granted pursuant to the European patent application (1), the value of 1.11% was amended to the correct value of 11.1%.

With regard to the surfactant, although there was some overlap between the range claimed in the Patent and that disclosed in citation (1), the true teaching of (1) was that large amounts of surfactants were required to obtain stable dispersions in Propellant 134a. The amounts of surfactant used in the examples of citation (1) were large and above the maximum claimed in the Patent. The overall teaching of (1) was that large

amounts of co-solvent were required in order to achieve the dissolution of large amounts of surfactant in Propellant 134a and hence the formation of stable homogeneous dispersions of medicament.

The problem underlying the Patent was to provide an alternative solution to that of (1) to the problem of replacing CFC propellants with "ozone-friendly" hydrogen-containing propellants. The solution proposed by citation (1) utilised large amounts of polar co-solvents, in particular ethanol. The use of large amounts of co-solvent was not advantageous for a number of reasons.

The solution to the problem provided by the Patent was the localisation of a small amount of surfactant on the surface of the medicament particles and the stabilisation of the resulting formulation by the addition of a small amount of co-solvent to overcome the lack of affinity of the surfactant for the propellant whilst leaving the coating on the surface of the medicament intact. This solution was, in the respondent's opinion, nowhere suggested in (1), and indeed citation (1), dealing as it did with solubilisation of the surfactant, taught away from such solution. None of the other prior art cited by the appellants led to the solution of the opposed patent either alone or in combination with (1).

The respondent could not accept the argument of the appellants that a skilled person seeking to use small amounts of surfactant in the formulations of (1) would automatically use small amounts of co-solvent, as small amounts of co-solvent would be sufficient to dissolve

small quantities of surfactant. This statement completely ignored the teaching of the Patent that dissolution of the surfactant was to be avoided. With the use of small amounts of co-solvent in accordance with the claimed invention, the surfactant was not solubilised but the co-solvent worked to provide affinity for the surfactant in the propellant/co-solvent continuous phase and thereby enabled the surfactant to function to provide a stable suspension formulation. This concept was not taught by citation (1) or any of the other cited art.

- XII. The appellants requested that the decision under appeal be set aside and that the Patent be revoked.

The respondent requested that the appeal be dismissed (main request) or alternatively that the patent be maintained on the basis of one of its auxiliary requests 1, 2a, 2b, 3a, 3b, 4a, 4b or 5 filed on 12 February 2003.

## **Reasons for the Decision**

1. The appeal is admissible.

### *Amendments*

2. There are no formal objections, under Article 123 EPC, to the claims in accordance with the main request or any of the auxiliary requests now on file, since the amendments made to the claims in all current requests are, in the board's judgment, adequately supported by the original disclosure and do not extend the scope of



protection conferred. In view of the later findings (see 17 below) a detailed consideration of this is not necessary.

*Clarity*

3. Clarity, a requirement of Article 84 EPC, is not *per se* a ground of opposition (see Article 100 EPC). However, when substantive amendments have been made to a patent, the opposition division and the board have the jurisdiction, and indeed the obligation, to deal with clarity issues arising from those amendments, even if they were not (and could not be) specifically raised by an opponent pursuant to Rule 55c EPC. (cf. Case Law of the Boards of Appeal, 4th edition 2001, VII.C.10.2, pages 488 to 489).
- 3.1 The appellants argued that claim 1 offended Article 84 EPC since the definition of component (C) in claim 1 as "a medicament <.....> **having a surface coating of a surfactant** was, in their opinion, inappropriate and insufficient to define clearly the object of the claimed invention, that is to say indicate all the essential features thereof which were necessary for solving the technical problem with which the Patent was concerned and achieving the desired effect (see for more details X above).
- 3.2 The appellants also objected to the clarity of the definition of the surfactant used for coating the medicament (component C) as surfactant which has "**no affinity**" for the propellant (for more details see X above).

- 3.3 Since the appeal fails for other reasons (see 17 below), the board only observes here that in the present case both objections of the appellants under Article 84 EPC do not arise out of the amendments made to claim 1 *post* grant and that the claims now on file were sufficiently clear that the issue of clarity was not crucial to the understanding of the other issues. No final decision on this issue is thus necessary in this case.

*Sufficiency of disclosure*

4. The appellants made in the course of the opposition and subsequent opposition appeal proceedings a detailed attack under Article 100(b) EPC on the sufficiency of the disclosure of the claimed aerosol formulation, in view of the broad definition of component (C) in claim 1 stipulating that the surfactant used for coating the medicament has "no affinity" for the propellant (for more details see X above).
- 4.1 An attack on the grounds of insufficiency under Article 100(b) EPC is of course based on Article 83 EPC which requires that the disclosure of the invention must be "sufficiently clear and complete for it to be carried out by a person skilled in the art". It is understood that this means that substantially any technically meaningful embodiment of the invention, as defined in the broadest claim, must be capable of being realised on the basis of the disclosure. While the board has some sympathy with the appellants' detailed arguments explaining why they consider that the requirements set forth above have not been met in the present case, it nevertheless concludes that the Patent satisfies the requirement of an enabling disclosure in

view of the specific examples of suitable surfactants having "no affinity" for the propellant which are disclosed in the Patent (see 5.5.2 below). It is, however, unnecessary to make a final decision on this issue since the appeal must fail on other grounds (see 17 below).

*The Patent's subject-matter in the light of the closest prior art*

5. It may be useful to recall that the Patent relates to an aerosol formulation comprising the following components:
- (A) a hydrogen-containing fluorocarbon or chlorofluorocarbon propellant;
  - (B) a co-solvent having a higher polarity than said propellant; and
  - (C) a medicament having a surface coating of a surfactant.

5.1 There was general agreement that citation (1) represents the closest and therefore the most relevant state of the art.

Citation (1) discloses at page 2, lines 33 to 38, and in claim 1 an aerosol formulation comprising the following components (reference signs (A) to (C) added by the board for convenience):

- (A) hydrogen-containing fluorocarbon or chlorofluorocarbon propellant, eg 1,1,1,2-tetrafluoroethane (Propellant 134a);
- (B) at least one compound having a higher polarity than 1,1,1,2-tetrafluoroethane (ie a co-solvent having a higher polarity than said propellant);
- (C) a medicament in combination with a surfactant.

5.2 As regards the nature and composition of components (A), (B) and (C), the following more detailed information can be derived from the Patent description on the one hand and disclosure of citation (1) on the other:

5.3 Ad component (A):

5.3.1 Citation (1) discloses that 1,1,1,2-tetrafluoroethane (Propellant 134a) has particularly suitable properties for use as a propellant for the medicinal aerosol formulations described therein (see for example page 2, lines 33 to 40). The Patent discloses in column 2, lines 31 to 32 and in Example 1 (see column 5, lines 3 to 22) and in claims 2 and 3 (main request) or claim 1 of all auxiliary requests that 1,1,1,2-tetrafluoroethane is also a particularly preferred propellant (component A) for the claimed invention. Other hydrochlorofluorocarbon or hydrofluorocarbon or propellants suitable for use in the claimed invention and already disclosed in (1) are, for example, Propellants 142b (1-chloro-1,1-difluoroethane) and 152a (1,1-difluoroethane) - see (1), page 2, lines 44 to 45.

5.4 Ad component (B):

5.4.1 Citation (1) discloses at page 2, lines 42 to 43, alcohols such as ethanol, isopropanol and propylene glycol as examples of suitable co-solvents, which all are similarly referred to in the Patent as being particularly preferred higher polarity co-solvents (component B) for the claimed invention (see column 2, lines 40 to 44).

5.4.2 Further, citation (1) discloses at page 4, lines 41 and 42, and in claim 7 that the propellant and the higher polarity compounds (co-solvents) are generally employed in the weight ratio 50 : 50 to 99 : 1; this lower limit of the preferred range of weight ratios specified in (1) corresponds to an amount of 1.01% w/w of high polarity co-solvent based on propellant; according to claim 1 of all requests on file the co-solvent (component B) is present in amount of less than 1% w/w based on the propellant.

5.5 Ad component (C):

5.5.1 Citation (1) discloses at page 5, lines 41 to 46 that the medicament is used in particulate form and has desirably a particle size of no greater than 100  $\mu\text{m}$ , preferably of less than 25  $\mu\text{m}$ ; the particle size of the powder for inhalation therapy should preferably be in the range of 2 to 10  $\mu\text{m}$ ; according to the disclosure in column 4, lines 10 to 16, of the Patent the particle size of the medicament (component C) should be such as to permit inhalation of substantially all of the medicament into the bronchial system upon administration of the aerosol

formulation and will thus be less than 100  $\mu\text{m}$ , desirably less than 20  $\mu\text{m}$ , and preferably in the range 2 to 10  $\mu\text{m}$ .

5.5.2 Further, citation (1) discloses, *inter alia*, sorbitan trioleate, (Span® 85 - see page 4, line 50), lecithins (see page 4, lines 55 to 56) and oleic acid (see page 5, line 5) as examples of particularly preferred surfactants, all of which are likewise referred to in the Patent as suitable surfactants having "no affinity" for Propellant 134a (see column 3, lines 32 to 40; claim 7; Example 1).

5.5.3 Still further, citation (1) discloses at page 5, lines 9 to 11, and in claim 11 that the surface active agents are generally present in amounts not exceeding 5 percent by weight of the total formulation and that the weight ratio of surfactant to medicament is from 1 : 100 to 10 : 1; this disclosure of the preferred range in (1) encompasses the claimed range in the Patent of from 0.05 to 5% w/w of surfactant based on medicament.

5.5.4 Claim 1 of the main request and auxiliary request 1 stipulates that component (C) is "a medicament in particulate form, said medicament having a particle size of less than 100  $\mu\text{m}$  and "having a surface coating of a surfactant.....".

Component (C) is somewhat differently defined

- in claim 1 of auxiliary requests 2a, 2b and 5 as "a coated product comprising a medicament in particulate form.....";

- in claim 1 of auxiliary request 3a and 3b as "a medicament in particulate form, said medicament having a particle size of less than 100  $\mu\text{m}$  and having a surface coating which is a dry coating of a surfactant....."; and
- in claim 1 of auxiliary requests 4a and 4b as "a coated product comprising a medicament in particulate form <.....>, wherein said coated product (C) is obtained by slurring particulate medicament with a solution of a surfactant in a substantially non-polar solvent and the removing the solvent".

5.5.5 Citation (3) is a standard textbook entitled "The Theory and Practice of Industrial Pharmacy" and therefore represents common general knowledge in the field. Chapter 9 of (3), which is specifically concerned with pharmaceutical aerosols, contains in the paragraph bridging pages 279 and 280 the following teaching: "Various surfactants and lubricants have been investigated in an attempt to control the rate of agglomeration..... . The addition of surfactants to aerosol suspensions has been most successful. These surfactants exert their activity by coating each of the particles in suspension and become oriented in solid-liquid interface. Agglomeration is reduced, thereby increasing stability by providing a physical barrier. According to investigations carried out by Young, Thiel and Laursen, nonionic surfactants were found to be most effective. Those surfactants having an HLB less than ten, such as sorbitan trioleate, could be utilized for aerosol dispersions. Other agents that were found to be

useful are sorbitan monolaurate, sorbitan monooleate, and sorbitan sesquioleate. These surfactants are effective in a concentration of 0.01% to 1% depending on the concentration of the suspensoid and the intended use of the product".

A similar teaching to the effect that the addition of surfactants to suspensions generally reduces the agglomeration of the solid particles in the suspension and increases the stability of the suspension by coating each of the particles with a fine film of the surface active agent can be found, *inter alia*, in the following prior art documents:

Citation (2) which is a standard textbook entitled "Lehrbuch der pharmazeutischen Technologie" and therefore likewise represents common general knowledge in the field - see especially Chapter 18.3.2 "Tenside und Peptisatoren als Dispergiermittel", page 362 to page 363, end of first full paragraph;

Citation (4) - see especially page 7P, lines 7 to 22; and

Citation (5) - see especially page 9P, lines 4 to 27.

- 5.5.6 The examples of aerosol formulations in citation (1) are prepared by **mixing the medicament and the surfactant**, then adding the high polarity co-solvent and finally the required amount of propellant, such as Propellant 134a, to provide the desired aerosol suspensions (see especially page 6, lines 10 to 14). The respondent's observation is correct that citation (1) does not explicitly refer to a surface coating of the drug particles suspended in the propellant. However, having regard to the common general knowledge in the



field as exemplified by the teaching of (3) and the other documents cited in 5.5.5 supra, the method of preparing the aerosol formulations disclosed in (1) does not, in the absence of any evidence to the contrary, give rise to doubts that in such aerosol formulations the surfactant is present as a coating on the particles of the medicament, as is the case in the Patent. Therefore, the feature "medicament <.....> having a surface coating of a surfactant" (main request, auxiliary request 1 - see 5.5.4 above) or "a coated product comprising a medicament in particulate form.....and having a surface coating of a surfactant <.....>" (auxiliary requests 2a, 2b and 5 - see 5.5.4 above) is clearly implicit in the disclosure of citation (1).

5.5.7 Moreover, the respondent itself has argued in its written submissions and orally at the hearing that claim 1 is a product claim *per se* and is thus not limited to a preparative method. The claim specifies that the medicament particles have a surface coating of a surfactant but the preparative method to achieve this is not an essential feature of the product. Further, the respondent pointed out that a pre-coating step was implicit in the method claim (claim 11 as granted corresponding to claim 10 as maintained by the opposition division - see I and IV supra), as this claim featured the step of "dispersing a surface-coated medicament in a <.....> propellant". It agreed that the pre-coating step is an essential feature of the method claim, but did not agree that it is an essential feature of the product claims, except in those requests where component (C) in claim 1 is explicitly limited to a pre-coated product (see paragraphs 2.3.1 to 2.3.3 of

the respondent's observations of 12 October 1999 to the grounds of appeal filed by appellants I and III).

- 5.6 In summary, from the foregoing it appears clear that the use of the higher polarity co-solvent (component B) in an amount of less than 1% w/w is the only technical feature of claim 1 which cannot be derived from the state of the art according to citation (1).

#### *Problem and Solution*

6. In the introductory portion of the Patent description (see especially column 1, lines 11 to 26) reference is made to the general knowledge at the priority date of the Patent that the most commonly used aerosol propellants for medicaments have been in the past a class of CFC propellants [eg Freon 11 ( $\text{CCl}_3\text{F}$ ), Freon 12 ( $\text{CCl}_2\text{F}_2$ ) and Freon 114 ( $\text{CF}_2\text{Cl}-\text{CF}_2\text{Cl}$ )] and that these propellants are now believed to provoke the degradation of stratospheric ozone. The description in column 1, lines 16 to 26, goes on to state that there was a need to provide aerosol formulations for medicaments which employ so-called "ozone-friendly" propellants and that hydrogen-containing chlorofluorocarbons and fluorocarbons belong to the class of "ozone-friendly" propellants which are believed to have minimal ozone-depleting effects. It is also noted that medicinal aerosol formulations using such "ozone-friendly" propellant systems are already disclosed in the state of the art, for example, in citation (1).
- 6.1 Turning now to the disclosure of citation (1), it is noted in the specification at page 3, lines 7 to 9, that the inventors of (1) had found that the use of so-

called "ozone-friendly" propellants, such as Propellant 134a, and a drug as (a) a binary mixture or (b) a ternary mixture in combination with surfactants which have conventionally been used as surface active agents for medicinal aerosol formulations comprising CFC propellants, such as sorbitan trioleate (Span® 85), did not provide aerosol formulations having suitable properties for use with pressurised inhalers.

- 6.2 In an effort to overcome these difficulties and to prepare suitable self-propelling medicinal aerosol formulations on the basis of "ozone-friendly" propellants, it has surprisingly been found in the state of the art according to citation (1) that Propellant 134a and other "ozone-friendly" hydrofluorocarbon or hydrochlorofluorocarbon propellants, such as, for example, Propellants 142b (1-chloro-1,1-difluoroethane) and 152a (1,1-difluoroethane), have particularly suitable properties for use as propellants for medical aerosol formulations when used in combination with a conventional surfactant and an adjuvant (co-solvent) having a higher polarity than the propellant. This finding was in the board's opinion, clearly a landmark in the development of inhalation aerosols which are free of CFC's.

The formulations provided in (1) accordingly comprise a medicament, a surfactant, Propellant 134a and at least one compound having higher polarity than the propellant (see (1), especially page 2, lines 33 to 45, and the explanations given in 3.1 to 3.6 *supra*).

Citation (1) goes on to say "That the combination of one or more of such adjuvants (higher polarity co-solvents) with Propellant 134a provides a propellant system which has comparable properties to those of propellant systems based on CFC's, allowing the use of known surfactants and additives in the pharmaceutical aerosol formulations and conventional valve components. This is particularly advantageous since the toxicity and use of such compounds in metered dose inhalers for drug delivery to the human lung is well established" (see page 2, lines 45 to 49).

- 6.3 In view of the foregoing, the board cannot agree with the opposition division's view in the decision under appeal (see end of page 7) that "The problem to be solved in the contested patent is by avoiding conventional chlorofluorocarbons to obtain stable dispersions of finely-powdered medicaments together with surfactant in hydrogen-containing fluorocarbon or chlorofluorocarbon propellants". On the contrary, given the closest state of the art according to (1), the problem to be solved by the claimed invention must be reduced to one of simply supplying an alternative to the known medicinal aerosol formulations disclosed in citation (1). This appears to correspond to the problem as seen by the respondent in its written submissions (see paragraph 3.1.6 of the respondent's observations of 12 October 1999 to the grounds of appeal filed by appellants I and III) and at the hearing before the board.
- 6.4 The solution to the problem offered by the claimed invention was the provision of medicinal aerosol formulations comprising the components (A), (B) and (C)

as defined more precisely in claim 1 of the main request (see IV and 3.1 to 3.6 *supra*) or in claim 1 of any of the auxiliary requests (see VIII *supra*).

In view of the disclosure of the invention and the example in the Patent, the Board is satisfied that the technical problem has been plausibly solved. This was anyway not contested by the appellants.

### Novelty

7. After examination of the cited documents, the board has come to the conclusion that none of them discloses the proposed solution for the above defined problem, ie an aerosol formulation comprising the combination of components (A), (B) and (C) in accordance with claim 1 as maintained by the opposition division (main request, see IV above); in particular, none of these documents discloses a formulation wherein the higher polarity co-solvent (component B) is present in an amount of less than 1% w/w based on propellant. The appended claims 2 to 9 are all dependent upon claim 1. Claims 10 and 11 relate to a method of preparing an aerosol formulation as claimed in claim 1. Therefore claims 2 to 11 are also novel.

7.1 The above conclusions apply *mutatis mutandis* to the claims of the auxiliary requests on file (see VIII above). Since in view of the amendments made to the claims as granted in all requests now on file the issue of novelty has not been raised by the appellants in the course of the appeal proceedings, it is not necessary to consider this matter in further detail.

*Inventive step*

8. It therefore remains to be considered whether the solution claimed involves an inventive step.

*Main request*

- 8.1 There cannot be any doubt that what is presented in the Patent as the *core idea* of the claimed invention, namely combining an "ozone-friendly" hydrofluorocarbon or hydrochlorofluorocarbon propellant with a small amount of a co-solvent having higher polarity than the propellant to obtain a propellant system which is free of CFC'S but has nevertheless particularly suitable properties as a propellant system for inhalation aerosols, has already been suggested in the state of the art according to (1).

It is clearly stated in citation (1) that this combination provides a propellant system which has comparable properties to those of propellant systems based on CFC's, allowing the use of known surfactants and additives in the pharmaceutical aerosol formulations and conventional valve components. It is also noted in (1) that this is particularly advantageous since the toxicity and use of such known surfactants and additives in metered dose inhalers for drug delivery to the human lung is well established.

- 8.1.1 Further, citation (1) does not relate to an abstractly conceived inventive idea, but gives the skilled person complete and precise instructions as to how he can reduce to practice the new and inventive concept for inhalation aerosols taught in the cited document. Thus,

facing the problem of providing alternative aerosol formulations, a skilled person would find in citation (1) useful guidance as to how to choose for this

- (a) suitable hydrogen-containing chlorofluorocarbon and fluorocarbon or propellants (component (A) - see 5.3.1 above),
- (b) suitable co-solvents having higher polarity than the propellant (component B - see 5.4.1 above),
- (c) suitable amounts of co-solvent based on propellant required to achieve the desired effect (see 5.4.2 above)
- (d) suitable particle sizes for the medicaments used making them useful for inhalation therapy (see 5.5.1 above);
- (e) suitable surfactants for use as a coating material for the medicament particles and which have no affinity for the propellant (component C - see 3.5.2 to 3.5.6 above), and
- (f) suitable amounts of surfactant based on medicament to achieve formation of stable homogeneous dispersions of medicament (see 5.5.3 above).

8.1.2 The board does not share the respondent's view expressed in its written submissions (see paragraphs 3.1.4 and 3.1.5 of the respondent's observations of 12 October 1999 to the grounds of appeal) and repeated orally at the hearing that the ranges relating to the preferred amounts of co-solvent (see 5.4.2 above) and

surfactant (see 5.5.3 above) in citation (1) have practically no meaning and that only the examples should be regarded as the "true teaching" of the cited document. This view completely ignores the established case law.

According to the consistent case law of the boards of appeal, when it comes to the evaluation of novelty or inventive step, the teaching of a cited document is not confined to the detailed information given in the examples of how the invention is carried out but **embraces any reproducible technical teaching described** in that document enabling a person skilled in the art to carry out the invention (see T 12/81, OJ EPO 1982, 296, see especially Reasons, point 7; confirmed, *inter alia*, by T 424/86 of 11 August 1988, see especially Reasons, point 4.1; T 250/87 of 11 October 1988, see especially Reasons, point 4; T 279/89 of 3 July 1991, see especially Reasons, point 4.4; T 522/90 of 8 September 1993, see especially Reasons, point 3.8; T 722/94 of 16 December 1997, see especially Reasons, point 2.2.2; T 839/95 of 23 June 1998, see especially Reasons, point 4.1; T 610/96 of 10 November 1998, see especially Reasons, point 4.3; T 743/96 of 4 April 2000; T 623/98 of 17 October 2001, see especially Reasons, point 4; T 799/98 of 29 August 2002, see especially Reasons, point 1.2.1; T 864/98 of 17 March 2003, see especially Reasons, point 2.3.2; T 941/98 of 30 March 1999, see especially Reasons, point 5.1; and T 664/00 of 28 November 2002, see especially Reasons, point 5.2.6).



- 8.1.3 In view of the foregoing and in absence of any evidence to the contrary, the board sees accordingly no reason why those skilled in the art, faced with the problem posed, should ignore the clear and unambiguous teaching of citation (1) that Propellant 134a and the co-solvent of higher polarity are generally employed in a weight ratio over the whole range of from 50 : 50 to 99 : 1 propellant : co-solvent (see page 5, lines 41 to 42). Contrary to the respondent's oral and written assertions (see for example paragraphs 3.1.4 and 3.1.6 of its observations of 12 October 1999), there is nothing in citation (1) which could lead the skilled reader to the conclusion that the desired effect of adding a co-solvent to the propellant is not achieved over the whole range relating to the amount of co-solvent used in (1), including the explicitly disclosed lower end of this range corresponding to an amount of 1.01% w/w co-solvent based on propellant.
- 8.1.4 With regard to the surfactant, the range claimed in the Patent (0.05 to 5% w/w based on the medicament) overlaps broadly with that disclosed in (1) (a weight ratio of 1 : 100 to 10 : 1, corresponding to 1 to 1000% w/w based on medicament). Thus citation (1) teaches clearly and unmistakably that, for example, the use of 1 to 5% w/w of a conventional surfactant based on the medicament in combination with a suitable amount of a co-solvent may be sufficient to achieve the formation of stable homogeneous dispersions of medicament in hydrochlorofluorocarbon or hydrofluorocarbon propellants.

8.2 In summary, seeking a solution to the problem of supplying alternative aerosol formulations for inhalation therapy, a skilled person would want to use in these new (alternative) formulations the known components, that is to say those propellants, co-solvents and surfactants which have already advantageously been used in the formulations disclosed in citation (1), before he would think, say, of changing these tried and tested components and developing completely new propellant systems or formulations. In the present case, those skilled in the art would not develop new components if a way could be found of solving the problem posed by using the known components which have been proved in citation (1) to be particularly advantageous for medicinal aerosol formulations free of CFC's.

8.2.1 Next, in seeking suitable amounts for the co-solvent and the surfactant, a skilled person would, simply on the basis of the technical teaching and explanations given in citation (1) and his general knowledge of the art, rule out combinations involving vastly different amounts of co-solvent and surfactant.

Citation (1) itself teaches that the particular adjuvant(s) and the concentration of these adjuvant(s) have to be selected according to the particular medicament and the desired physical properties of the formulation (see page 3, lines 5 to 6). Thus, although the concentration of both adjuvants, ie the co-solvent and the surfactant, may vary considerably in (1) according to the particular medicament and the desired physical properties of the formulation, it appears, *a priori*, clearly advantageous to employ, if possible,

both adjuvants in low amounts. For those skilled in the art the first obvious step would thus be to verify by tests whether or not the teaching of (1) is reproducible and the desired aerosol formulations can in fact be obtained using both adjuvants in an amount near to the lower end of the ranges which are explicitly recommended in (1) for the amounts of co-solvent (see 8.1.3 above) and surfactant (see 8.1.4 above). Such tests would be routine.

8.2.2 Since a person skilled in the art had absolutely no reason to doubt that the teaching of citation (1) as a whole is reproducible, this person, having carried out the above-mentioned tests, could not really have been surprised to find that even small amounts of co-solvent, say about 1% w/w based on propellant, in combination with small amounts of surfactant, say 1 to 5% w/w based on medicament, are sufficient to achieve the formation of stable homogeneous dispersions of a medicament in an "ozone-friendly" hydrofluorocarbon or hydrochlorofluorocarbon propellant and to obtain the desired inhalation aerosols.

8.2.3 In order to solve the technical problem posed (ie to provide alternative inhalation aerosols), it was then only necessary to carry out the smallest possible and, accordingly, most obvious modification of the closest state of the art, that is to say reducing the amount of co-solvent marginally below that of 1.01% as suggested (1) to any amount less than 1%, eg 0.999%, based on the propellant.

8.2.4 The respondent has failed to persuade the board with its argument that the teaching of (1) is that necessarily large amounts of co-solvent are required in order to achieve the dissolution of large amounts of surfactant in Propellant 134a and hence the formation of stable homogeneous dispersions of medicament.

On the contrary, already in citation (1) reference is made to the new and surprising finding (see page 2, lines 45 to 48) that the combination as such of one or more co-solvents of higher polarity (in any conceivable amount, including very small amounts) with Propellant 134a provides a propellant system which has comparable properties to those of propellant systems based on CFC's, allowing the use of conventional surfactants and additives.

Further the cited document teaches at page 3, lines 13 to 15 that the addition as such of a co-solvent of higher polarity than Propellant 134a (in any conceivable amount, including very small amounts) to Propellant 134a provides a mixture (propellant system) in which increased amounts of surfactant may be dissolved compared to their solubility in Propellant 134a alone. It is this increased amount of solubilised surfactant in the propellant system of (1) (note that the increase in the amount of solubilised surfactant may be very small compared to the amount of solubilised surfactant in Propellant 134 alone) which surprisingly enables conventional surfactants to be used in hydrofluorocarbon or hydrochlorofluorocarbon propellants. That, as citation (1) goes on to state at page 3, lines 15 to 16, the presence of increased amounts of solubilised surfactant [compared to their

solubility in Propellant 134a alone] allows the preparation of stable homogeneous suspensions of drug particles is no more than the inevitable result of this teaching. In view of the foregoing, the board cannot share the conclusion of the opposition division in the decision under appeal that the statement in (1) - "The presence of increased amounts of solubilised surfactant allows the preparation of stable, homogeneous suspension of drug particles" - should be interpreted as meaning that the use of large amounts of co-solvent and surfactants is necessary to obtain stable dispersions of the medicament in the propellant.

- 8.2.5 As has already been mentioned above, the real breakthrough was the new and surprising finding in citation (1) that the addition as such of a co-solvent having higher polarity than an "ozone-friendly" hydrofluorocarbon or hydrochlorofluorocarbon propellant, such as Propellant 134a, to aerosol formulations causes conventional surfactants to perform their required function (ie the function normally performed by such surfactants in CFC propellants) and provides stable dispersions of a medicament in the propellant. The claimed invention is based on this finding in the prior art of (1). Contrary to the respondent's oral and written assertions, there is no teaching or proposal whatsoever in citation (1) that the breakthrough achieved in (1) would depend on the use of large amounts of co-solvent and/or surfactant. On the contrary, the preferred ranges of the amounts of both adjuvants disclosed in (1) suggest the possibility of using both the co-solvent and the surfactant in amounts which are entirely comparable to those claimed in the Patent.

8.2.6 The board notes that the respondent has produced a new theory to explain the effect already found in the prior art of (1), namely that conventional surfactants perform their required function in hydrofluorocarbon or hydrochlorofluorocarbon propellants, if a small amount of a co-solvent having higher polarity than the propellant has been added to the propellant. However, a new theory explaining the known and desirable effect found in (1) cannot bestow inventive quality on the thoroughly obvious teaching of the Patent.

*Auxiliary request 1*

9. This request (a) limits in claim 1 "*propellant*" to "1,1,1,2-tetrafluoroethane" or "1,1,1,2,3,3,3-heptafluoropropane" and (b) replaces "*which surfactant has no affinity*" with a specific list of surfactants selected from benzalkonium chloride, lecithin, oleic acid and sorbitan trioleate (see VIII above).

9.1 Since "1,1,1,2-tetrafluoroethane" is already used as the most preferred propellant in citation (1) (see 5.3.1 *supra*) and the list of surfactants in (1) already includes lecithin, oleic acid and sorbitan trioleate (see 5.5.2 *supra*), none of the amendments made to claim 1 of auxiliary request 1 can therefore dispel, either alone or in combination, the conclusion of lack of inventive step on grounds of obviousness arising from the study of the main request in the light of the cited documents.

*Auxiliary request 2a*

10. This request (a) limits "propellant" to "1,1,1,2-tetrafluoroethane" or "1,1,1,2,3,3,3-heptafluoropropane" and (b) defines component (C) as "coated product" (see VIII above).

10.1 As regards (a), reference is made to the observations in 9.1 above.

10.2 As has already mentioned in 5.5.6 and 5.5.7 above, the board cannot recognise more than a mere difference in wording between the definition of component (C) in claim 1 of the **main request**:

- "a medicament in particulate form said medicament having a particle size of less than 100  $\mu\text{m}$  and having a surface coating of a surfactant";

and the definition of component (C) in claim 1 of **auxiliary request 2a**:

- "a coated product comprising a medicament in particulate form, said medicament having a particle size of less than 100  $\mu\text{m}$  and having a surface coating of a surfactant".

From the detailed technical explanations given in 5.5.4 to 5.5.7 above it is clear that no difference in substance is recognisable between component (C) of the medicinal aerosol formulations disclosed in citation (1) on the one hand, and component (C) as defined in the main request or auxiliary request 2a, on the other.

- 10.3 It follows that none of the above amendments made to claim 1 of auxiliary request 2a can, either alone or in combination, be regarded as contributing to the inventive merits of the proposed solution to the problem posed.

*Auxiliary request 2b*

11. This request (a) limits "propellant" to "1,1,1,2-tetrafluoroethane" or "1,1,1,2,3,3,3-heptafluoropropane" and (b) replaces "which surfactant has no affinity" with a specific list of surfactants selected from benzalkonium chloride, lecithin, oleic acid and sorbitan trioleate and (c) defines component (C) as "coated product" (see VIII above).
- 11.1 As regards both (a) and (b), reference is made to the observations in 9.1 above. As regards the amended definition (c) of component (C), the parties' attention is drawn to the observations in 10.2 above.
- 11.2 It follows that, as in the case of auxiliary request 2a, none of the above amendments made to claim 1 of auxiliary request 2b can, either alone or in combination, contribute to the acknowledgment of an inventive step.

*Auxiliary request 3a*

12. This request (a) limits "propellant" to "1,1,1,2-tetrafluoroethane" or "1,1,1,2,3,3,3-heptafluoropropane" and



(b) defines "surface coating" as "having a surface coating which is a dry coating of a surfactant" (see VIII above).

12.1 As regards (a), reference is made to the observations in 9.1 above.

12.2 As regards (b), citation (10) discloses medicinal fentanyl-containing aerosol formulations comprising the following components (reference signs (A) to (C) added by the board for convenience):

(A) an aerosol propellant, preferably 1,1,2-tetrafluoroethane (Propellant 134a) - see page 3, lines 15, 24, 27, Example 4;

(B) a co-solvent having a higher polarity than the propellant, eg ethanol, isopropanol or propylene glycol - see page 3, lines 26 to 28, Example 4;

(C) finely-divided solid fentanyl or a derivative thereof coated with a non-perfluorinated surfactant selected from eg sorbitan trioleate (Span® 85), oleic acids, lecithins - see page 2, lines 3 to 5 from the bottom, page 7, lines 10 to 12, or coated with a perfluorinated surface dispersing agent - see page 4, lines 18 to 19.

12.3 According to one specific embodiment of the invention disclosed in citation (10), "the fentanyl or derivative in the form of a finely divided solid is coated with a dry coating of a perfluorinated surface-active dispersing agent and thereafter mixed with an aerosol propellant" (see (10), page 4, lines 1 to 5). Such

coating systems are said in (10) - see page 4, lines 5 to 6 - to be disclosed generally in US-A-4 352 789 (ie citation (11) in the present proceedings). Citation (11) discloses self-propelling powder-dispensing aerosol compositions comprising a medicament in powder form coated with a dry coating of a surface-active dispersing agent and suspended in a halogenated propellant (see column 1 lines 62 to 66, column 2, lines 28 to 30).

- 12.4 From the foregoing it is clear that the reference in claim 1 to "a medicament in particulate form said medicament having a particle size of less than 100  $\mu\text{m}$  and *having a surface coating which is a dry coating of a surfactant*" results from a straightforwardly obvious combination of the teaching of citation (1) with that of (10) and/or (11).
- 12.5 It follows that the above amendments made to claim 1 of auxiliary request 3a cannot, either alone or in combination, make an obvious teaching inventive.

*Auxiliary request 3b*

13. This request (a) limits "propellant" to "1,1,1,2-tetrafluoroethane" or "1,1,1,2,3,3,3-heptafluoropropane", (b) replaces "no affinity" with a specific list of surfactants selected from benzalkonium chloride, lecithin, oleic acid and sorbitan trioleate and (c) defines "surface coating" as "having a surface coating which is a dry coating of a surfactant" (see VIII above).

13.1 As regards both (a) and (b), reference is made to the observations in 9.1 above. As regards (c), the parties' attention is drawn to the observations in 12.2 to 12.4 above.

13.2 It follows that the above amendments made to claim 1 of auxiliary request 3b cannot be used, either alone or in combination, to justify inventive step.

*Auxiliary request 4a*

14. This request (a) limits "propellant" to "1,1,1,2-tetrafluoroethane" or "1,1,1,2,3,3,3-heptafluoropropane", and (b) includes process limitation for component (C), ie "coated product, wherein said coated product (C) is obtained by slurring particulate medicament with a solution of a surfactant in a substantially non-polar solvent and then removing the solvent" (see VIII above).

14.1 As regards (a), reference is made to the observations in 9.1 above.

14.2 As regards (b), according to Example 1 of citation (11) a mixture of micronized epinephrine bitartrate (particulate medicament) and 0.5 g of a perfluorinated sulfonamide alcohol phosphate ester surfactant was dispersed mechanically in 50 g of isopropanol. After one to two minutes of mechanical agitation the mixture was allowed to settle for five minutes. The mixture was filtered and the solid-surfactant-coated drug was dried in a vacuum oven for thirty minutes. The basic synthetic methodology for preparing the "coated

product" in component (C) of claim 1 of auxiliary request 4a was thus already known from (11).

14.3 From the foregoing it is clear that the definition of Component (C) in claim 1 by the particular method for its preparation results from a straightforwardly obvious combination of the teaching of citations (1) with that of (11).

14.4 It follows that the above amendments made to claim 1 of auxiliary request 4a cannot, either alone or in combination, serve to provide an inventive step.

*Auxiliary request 4b*

15. This request (a) limits "propellant" to "1,1,1,2-tetrafluoroethane" or "1,1,1,2,3,3,3,3-heptafluoropropane" and (b) replaces "no affinity" with a specific list of surfactants and (c) includes process limitation for component (C), ie "coated product, wherein said coated product (C) is obtained by slurring particulate medicament with a solution of a surfactant in a substantially non-polar solvent and then removing the solvent" (see VIII above).

15.1 As regards both (a) and (b), reference is made to the observations in 9.1 above. As regards (c), the parties' attention is drawn to the observations in 14.2 and 14.3 above.

15.2 It follows that the above amendments made to claim 1 of auxiliary request 4b cannot, either alone or in combination, support the presence of inventive step.

*Auxiliary request 5*

16. This request (a) limits in claim 1 "propellant" to "1,1,1,2-tetrafluoroethane", (b) replaces "no affinity" with a specific list of surfactants, selected from "benzalkonium chloride, lecithin, oleic acid and sorbitan trioleate", (c) defines component (C) as "coated product", (d) defines "surface coating" as "having a dry coating of surfactant, and (e) specifies the w/w proportion of coated product in the formulation relative to the total weight of the formulation, ie 0.01-1% w/w (see VIII/8 above).
- 16.1 As regards both (a) and (b), reference is made to the observations in 9.1 above. As regards (c) and (d), the parties' attention is drawn to the observations in 10.2 (c), and 12.2 to 12.4 (d) above.
- 16.2 As regards (e), the w/w proportion of coated product in the formulation relative to the total weight of the formulation, ie 0.01-1% w/w, Examples 4 to 6 of citation (1) disclose aerosol formulations containing salbutamol (medicament) and either one of sorbitan trioleate (Span® 85), oleic acid or Lipoid S100 as the surfactant, ethanol (co-solvent) and Propellant 134a. Salbutamol and the surfactant are present in all these examples in an amount of about 0.41% based upon the total weight of the formulation.

Examples 10 to 12 of citation (1) disclose aerosol formulations containing beclamethasone dipropionate (medicament) and either one of sorbitan trioleate (Span® 85), oleic acid or Lipoid S100 as the surfactant, ethanol (co-solvent) and Propellant 134a.

Beclamethasone dipropionate and the surfactant are present in all these examples in an amount of about 0.20% based upon the total weight of the formulation.

Example 4 of citation (10) discloses a series of stable aerosol formulations containing fentanyl citrate (medicament), sorbitan trioleate, (Span® 85, surfactant), ethanol (co-solvent) and Propellant 134a. Fentanyl citrate (medicament) and sorbitan trioleate (surfactant) are present in an amount (based upon the total weight of the formulation) of about 0.37% w/w (see end of page 12); 0.57% w/w (first composition on page 13); 0.77% w/w (second composition on page 13); 0.28% (third composition on page 13); 0.29% w/w (end of page 13); 0.32% (top of page 14).

- 16.3 From the foregoing it is clear that the range of the numerous values of the w/w proportion of coated product in the formulation relative to the total weight of the formulation which is specified as an additional technical feature in claim 1 of auxiliary request 5 is obviously derivable from the state of the art according either of citations (1) or (10), alone or in combination.
- 16.4 With respect to auxiliary request 5 the board notes that the insertion of a series of straightforwardly obvious technical features into a claim which is in itself obvious cannot make an obvious teaching inventive.

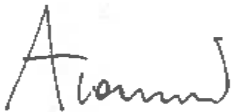
17. In conclusion, neither the respondent's main request nor any of its auxiliary requests relates to a patentable invention. Thus the appeal is clearly allowable.

**Order**

**For these reasons it is decided that:**

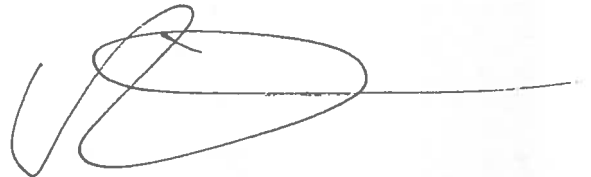
1. The decision under appeal is set aside.
2. The Patent is revoked.

The Registrar:



A. Townend

The Chairman:



U. Oswald

GR  
CRS

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