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Datasheet for the decision of 23 April 2008

Case Number: T 0868/05 - 3.3.02

Application Number: 99204248.1

Publication Number: 0990437

IPC: A61K 9/00

Language of the proceedings: EN

Title of invention:
Aerosol compositions

Patentee:
GLAXO GROUP LIMITED

Opponent:
Generics [UK] Limited

Headword:
Aerosol/GLAXO GROUP LIMITED

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Inventive step - yes: In a composition, the omission of a component, deemed to be required in the prior art, is not an obvious step"

Decisions cited:
-

Catchword:
-

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Case Number: T 0868/05 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 23 April 2008

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 10 May 2005 concerning maintenance of European patent No. 0990437 in amended form.**

Composition of the Board:

Chairman: U. Oswald
Members: J. Riolo
P. Mühlens

Summary of Facts and Submissions

I. European patent No. 0 990 437, based on European application No. 99 204 248.1 and claiming the priority of GB-9126378, GB-9126405 and GB-9202522, was granted on the basis of 22 claims.

Independents claims 1, 2, 8, 9, 15, 18 and 19 as granted read as follows:

1. A pharmaceutical aerosol formulation for use in the administration of medicaments by inhalation characterised in that it consists essentially of particulate fluticasone propionate as medicament, and 1,1,1,2-tetrafluoroethane as propellant, and that the formulation is free of surfactant, wherein said medicament is present in an amount of 0.01 to 1% w/w relative to the total weight of the formulation.

2. A pharmaceutical aerosol formulation for use in the administration of medicaments by inhalation characterised in that it consists of particulate fluticasone propionate and 1,1,1 ,2-tetrafluoroethane, wherein said fluticasone propionate is present in an amount of 0.01 to 1% w/w relative to the total weight of the formulation.

8. The use of a pharmaceutical aerosol formulation characterised in that it consists essentially of particulate fluticasone propionate as medicament, and 1,1,1,2-tetrafluoroethane as propellant, and that the formulation is free of surfactant, for the manufacture of a medicament for administration by inhalation, wherein said medicament is present in an amount of 0.01

to 1% w/w relative to the total weight of the formulation.

9. The use of a pharmaceutical aerosol formulation characterised in that it consists of particulate fluticasone propionate and 1,1,1,2-tetrafluoroethane, for the manufacture of a medicament for administration by inhalation, wherein said fluticasone propionate is present in an amount of 0.01 to 1% w/w relative to the total weight of the formulation.

15. A canister comprising a container closed with a metering valve which contains a pharmaceutical aerosol formulation according to any one of claims 1 to 7.

18. A process for preparing a pharmaceutical aerosol formulation for use in the administration of medicaments by inhalation characterised in that it consists essentially of particulate fluticasone propionate as medicament, and 1,1,1 ,2-tetrafluoroethane as propellant, and that the formulation is free of surfactant, wherein said medicament is present in an amount of 0.01-1% w/w relative to the total weight of the formulation, which process comprises dispersing the medicament in the propellant.

19. A process for preparing a pharmaceutical aerosol formulation for use in the administration of medicaments by inhalation characterised in that it consists of particulate fluticasone propionate and 1,1,1,2-tetrafluoroethane, wherein said fluticasone propionate is present in an amount of 0.01-1% w/w relative to the total weight of the formulation, which

process comprises dispersing the fluticasone propionate in the 1,1,1,2-tetrafluoroethane.

II. Opposition was filed against the patent under Article 100(a) EPC for lack of novelty and inventive step, Article 100(b) EPC for insufficiency of disclosure and under Article 100(c) EPC.

The following documents *inter alia* were cited during the proceedings before the Opposition Division and the Board of Appeal:

(GB1) GB 9126378 (12.12.1991)
(GB2) GB 9126405 (12.12.1991)
(1) (WO-A-9311745)
(2) (GB-A-2 088 877)
(A1) The Pharmaceutical Journal, September 29, 1990, pp 428-429

III. By its decision pronounced on 1 March 2005, the Opposition Division maintained the patent in amended form (set of claims of the main request as received on 16 June 2004) under Articles 102(3) and 106(3) EPC (1973).

The set of claims of the request before the Opposition Division corresponds to the set of claims as granted with the deletion of dependent claims 13, 14 and 17 and the addition of the wording "for the treatment of asthma" in the second medical use claims 8 and 9. The claims were moreover renumbered accordingly.

As to Article 123(2) EPC, the Examining Division was of the opinion that the subject-matter of the set of

claims of the main request was based on the application as originally filed.

In its view, claims 1, 3, 6 and 9 disclosed an aerosol formulation comprising specifically the particulate medicament fluticasone propionate and 1,1,1 ,2-tetrafluorethane (P1 34a) as the propellant as well as the feature that the formulation is substantially free of surfactant. Furthermore, on page 3, lines 11-13 of the description the claimed weight range of the medicament is indicted and there is definite disclosure of an aerosol formulation in examples 3, 4 and 5 comprising nothing other than the claimed propellant and the fluticasone propionate within the claimed weight range. Accordingly, the subject-matter of claim 1 was based on the application as originally filed.

It also had no doubt that the subject-matters of the further independent claims could *mutatis mutandis* be taken from the claims and or the description in the originally filed documents.

After a discussion on the requirements of sufficiency of disclosure, the opponent withdrew its request under Article 100(b) EPC during the oral proceedings (minutes of the oral proceedings, point 4, and the decision, section II, sentence bridging pages 1-2).

Novelty was also acknowledged by the Opposition Division as none of the citations discloses the subject- matter as now defined.

The opponent based the novelty objection on the disclosure in document (1) and argued that the present claims were not entitled to a priority date prior to the filing date and thus would represent prior art according to Article 54(3) EPC, in particular as document (l) disclosed aerosol formulations falling under the present claims.

Whether (l) represented prior art for the present case depended on whether the currently claimed priorities, in particular [GB1] and [GB2], could be acknowledged.

In that respect, the Opposition Divisions admitted that the present claim wordings could not be found explicitly in a priority document as the terms "consists essentially of" and "consists of" were not used therein.

However, it considered that the priority of the previous application could be acknowledged because the person skilled in the art could derive the subject-matter of the claims directly and unambiguously from the previous application as a whole, using common general knowledge.

In that respect, it observed that each of the priority documents [GB1] and [GB2] not only indicated explicitly several aerosol formulations containing only fluticasone propionate and 1,1,1 ,2-tetrafluoroethane (see Examples 3, 4 and 5 in each thereof), but also disclosed the teaching that the formulations should be free of surfactants (see e.g. [GB1] page 2, lines 9-14) and other excipients (see e.g. [GB1] the sentence bridging pages 1 and 2) and the quantity of the

medicament is 0,01 - 1% w/w (see eg [GB1] page 4, lines 29-31), both the latter requirements were meant to be applicable what ever the medicament or propellant was.

Accordingly, as the present claims were found to be entitled to the priorities of [GB1] and [GB2], the Opposition Division concluded that the disclosure of document (l) was of no relevance for novelty considerations in the present case.

With respect to inventive step, the Opposition Division considered document (2), which disclosed a fluticasone aerosol formulation with the ozone-depleting propellants fluorotrichloromethane (P11) and dichlorodifluoromethane (P12), as the closest state of the art.

Having regard to the available prior art documents, which taught that the ozone-friendly propellant 1,1,1,2-tetrafluoroethane (P134a) was a good alternative to P12 but that it was difficult to find a replacement for P11 because of its solvency properties, the Opposition Division concluded that the claimed subject-matter was inventive.

It was of the opinion that the replacement of both P11 and P12 by P134a without the addition of any surfactant, as recited in the claims, would not be envisaged in the light of the prior art.

IV. The appellant (opponent) lodged an appeal against the said decision.

V. In a letter dated 2 April 2008, the appellant informed the respondent and the Board that it would not attend, and not be represented at, the oral proceedings scheduled for 10 April 2008.

VI. In a letter dated 3 April 2008, the respondent recalled that its request for oral proceedings had been conditional, namely in case the Board did not intend to maintain the patent as upheld by the Opposition Division.

VII. In a communication from the Board dated 7 April 2008, the parties were informed that, having regard to the most recent letters from the parties, oral proceedings were not necessary.

VIII. In its written submissions, the appellant held essentially that claims 1, 2, 8, 9, 13, 15 and 16 introduced new matter into the application because no basis could be found for the precise combination of P134a with fluticasone propionate and for the wordings "consists" and "consists essentially" in these independent claims .

It did not maintain its objection regarding the entitlement to priority and the novelty of the subject-matter vis-à-vis document (1).

It introduced document (A1) into the proceedings and based its inventive step objection on the combination of document (2).

In its view, the disclosure in document (Al) was a good summary of the state of the art. It acknowledged the

fact that, at the time it was written (shortly before the priority date of EP 0 990 437), it was known that the use of CFCs (chlorofluorocarbons) in medicinal aerosol formulations would have to be phased out and that the preferred replacement for them was HFC (hydrofluorocarbon) 134a (first and second columns and the first paragraph in the third column).

At the top of column 2 of document (Al), CFC11 and CFC12 were identified as the main components of the propellants generally used in MDIs (metered-dose Inhalers). CFC11 was described as being useful in the MDI manufacturing process because of its comparatively low vapour pressure and CFC12 was described as the high-pressure propellant, added to allow efficient ejection of the product from the container.

In the fourth column of the article, in which the author discussed what the major MDI manufacturers were actually doing in order to replace CFCs, it was confirmed that a group of seven international pharmaceutical companies were backing HFC 134a for use in MDIs.

It was then stated that: "Glaxo said that it was working with major chemica1 companies, including ICI in the United Kingdom, to validate alternative propellants. Glaxo also had selected HFC 134a as the most promising substitute. It said that this propellant should be able to replace the high and the low pressure CFC combination that the company currently used."

Thus, in the appellant's opinion, document (Al) taught the skilled reader that one of the leading

manufacturers of medicinal aerosol formulations had decided to address this problem by replacing both the high- and the low-pressure CFC propellants that it used in its formulations (i.e. CFC11 and CFC12) with HFC 134a alone.

Accordingly, it concluded that the skilled person aware of the disclosure in document (Al), would have solved the problem of phasing out CFCs by replacing both the CFC11 and the CFC12 used in the formulation disclosed in document (2) with HFC 134a alone and, thus, would have produced a formulation lying within the scope of the independent claims maintained in this patent. The subject-matter of these claims, therefore, lacked an inventive step.

IX. As to Article 123(2) EPC, the respondent noted that the appellant did not say why the Opposition Division's decision was incorrect and that it merely restated the same arguments put forward in the opposition statement. It therefore also relied on its previous arguments and statements and agreed with the Opposition Division's favourable conclusions.

Concerning inventive step, the respondent essentially submitted that, even assuming that the skilled person would have referred to document (A1), a combination of this latter document with document (2) would also not lead the skilled reader to the surfactant-free formulations of the claimed invention.

Indeed, reading (A1) as a whole and following its teaching, the skilled person would have arrived at a

formulation containing HFC 134a and a surfactant, specifically oleic acid.

X. The appellant requested in writing that the decision of the Opposition Division be set aside and that the patent be revoked.

The respondent requested in writing that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Priorities*

The appellant did not maintain its objections raised during the opposition proceedings and the Board sees no reason to disagree with the favourable conclusions of the Opposition Division in that respect (see above under III, and the Opposition Division's decision, point 4.).

2.1 Article 100 b) EPC

The Opponent withdrew the request for revocation based on this ground at the oral proceedings held on 1 March 2005 (see the decision, section II, sentence bridging pages 1-2).

The Board has no doubt that the invention is sufficiently disclosed in the contested patent.

2.2 Article 84 EPC

The set of claims of the request correspond essentially to the set of claims as granted with the deletion of dependent claims 13, 14 and 17. Accordingly, Article 84 EPC is not at issue in the proceedings.

2.3 Article 100c) EPC

The Board agrees with the Opposition Division's favourable conclusions as to Article 100c) EPC.

Basis for the features of claim 1:

- "consists essentially of"
This language is found in the application as filed in claim 3.

- "particulate"
Support for this is provided in the application as filed on page 2, line 21, where it is stated that a "...particulate medicament..." is comprised in the formulations of the invention. There is thus clear basis in the application as filed for the particulate nature of the medicament.

- "fluticasone propionate as medicament"
The application as filed discloses a short list of medicaments for use in the invention on page 2, lines 23-24 and further on page 4 where it is stated: "a particularly preferred embodiment...provides..." followed by a list of four medicaments, including fluticasone propionate. Examples 3, 4, and 5 then disclose particular formulations of fluticasone

propionate and 1,1,1,2-tetrafluoroethane. There is thus a clear basis in the application as filed for the use of fluticasone propionate as the medicament.
Furthermore, the disclosure that two or more active ingredients "may be used if desired" is a clear teaching that formulations containing single medicaments are also intended to be a feature of the invention (see page 4, lines 22-24).

- "...1,1,1,2-tetrafluoroethane as propellant..."
It is disclosed in the application as filed that "in contradistinction to these (prior art] teachings, it is in fact possible to obtain satisfactory dispersions of certain medicaments in… propellants such as 1,1,1,2-tetrafluoroethane without recourse…", (statement of invention, page 2, lines 12-14).
And on page 3, lines 27-29:
"Particularly preferred as propellants are... 1,1,1, 2-tetrafluoroethane and 1,1, 1,2,3,3,3-heptafluoro-n-propane.. . There is thus clear support in the application as filed for using 1,1,1,2-tetrafluoroethane as the sole propellant.

- "free of surfactant"
It is disclosed in the statement of invention on page 2, lines 12-15 of the application as filed that: "in contradistinction to these (prior art] teachings, it is in fact possible to obtain satisfactorily dispersions.. .without recourse to the use of any surfactant" and on page 2, line 25. Thus, there is clear support in the application as filed for this feature.

- "said medicament is present in an amount of 0.01 to 1% w/w ."

This concentration of medicament is disclosed on page 3, line 13 in the application as filed as an especially desirable amount and is thus clearly supported thereby.

Furthermore it is to be noted that these elements are not isolated features but are clearly to be taken in combination.

It certainly would not be true to say that the patentee had to select from several lists to arrive at the claim. The Examples plainly individualise formulations of particulate fluticasone propionate as a medicament which contain 1,1,1,2-tetrafluoroethane as a propellant and are free of surfactant and other excipients. It cannot therefore be said that the combination of particulate fluticasone propionate and 1,1,1,2-tetrafluoroethane is a new combination of features not based on the application as filed. Furthermore, the quantity of medicament, that is 0.01 -1% w/w, is a general variable which applies whatever the medicament or propellant. This is clear from reading page 3, lines 12-14 in the application as filed and is further supported by the fact that the application as filed contains a number of formulations of particulate fluticasone propionate in 1,1,1,2- tetrafluoroethane covering a spread of concentrations. Therefore, limiting the claim by a ratio of ingredient amounts cannot be said to be adding a new feature not based on the application as filed either. Thus the subject matter of claim 1 does not contravene Article 123(2)(EPC).

Claim 2:
Claim 2 differs from claim 1 only in the use of the term "consists of" instead of "consists essentially of'. Support for the subject-matter of claim 2 is provided by examples 3, 4, and 5. In that respect, according to the case law, a specific example within a generic disclosure forming part of the description is part of the content of the application as filed for the purposes of Article 123(2) EPC if the skilled reader would seriously contemplate such a specific example as a practical embodiment of the invention described.

The skilled addressee, contemplating the disclosures of the application as filed, would be in no doubt that formulations of fluticasone propionate and 1,1,1,2-tetrafluoroethane are practical embodiments of the invention and would therefore "seriously contemplate" these examples as practical embodiments of the present invention. Examples 3, 4, and 5 form part of the content of the application as filed. Therefore, claims relating to formulations containing fluticasone propionate and 1,1,1,2-tetrafluoroethane do not constitute "an arbitrary selection" and hence do not contravene Article 123(2)(EPC).

Furthermore, as discussed in relation to claim 1, the relevant disclosure in the application as filed is clearly not limited to the Examples. The only respect in which the scope of claim 2 differs from that of the examples is that it recites the drug concentration in a range. However, this range is set out in the application as filed on page 3, lines 12-14. There are several examples, each of which describes a formulation

of fluticasone propionate in a different amount relative to the amount of 1,1,1,2-tetrafluoroethane.

The application as a whole clearly teaches that the examples are exemplary and that the remit of the invention extends to all formulations having a concentration of medicament of 0.01-1% w/w. Thus the subject matter of claim 2 does not contravene Article 123(2) (EPC).

Claims 8 and 9
The uses covered by claims 8 and 9 are disclosed in the application as filed on page 7, line 27 to page 8, line 28 and so the subject-matter of claims 8 and 9 does not contravene Article 123(2) (EPC).

Claim 13
The canister in claim 13 is disclosed in the application as filed on page 8, lines 10-28 and examples 3, 4, and 5. The subject-matter of claim 13 does not, therefore, contravene Article 123(2) (EPC).

Claims 15 and 16
The process of dispersal of the medicament in the propellant is disclosed on page 8, lines 14-17, support for the use of 1,1,1,2-tetrafluoroethane per se being provided on page 2, lines 12-14 of the application as filed. Accordingly, the subject-matter of claims 15 and 16 does not contravene Article 123(2) (EPC).

Thus the Board concludes that there is no grounds for appellant's submissions that claims 1, 2, 8, 9, 13, 15 and 16 introduced new matter into the application because no basis could be found for the precise

combination of P134a with fluticasone propionate and for the wordings "consists" and "consists essentially" in these claims, and that the subject-matter of the main request fulfils the requirements of Article 100 b) EPC(see also above under III, and the Opposition Division's decision, point 3).

2.4 Inventive step

2.4.1 The Board agrees with the analysis and the favourable conclusions of the Opposition Division in respect of inventive step(see above under III, and the Opposition Division's decision, point 5).

However, as the appellant introduced a new document(A1)with its ground of appeal, which it considered as particularly relevant with respect to the Opposition Division's conclusion in its decision that "nothing in the prior art indicates that P11 and P12 can both be replaced by P134a", inventive step needs to be assessed vis-à-vis this prior art document.

The contested patent relates to a pharmaceutical aerosol formulation for use in the administration of medicaments by inhalation, which consists (essentially) of particulate fluticasone propionate as a medicament, and 1,1, 1,2-tetrafluoroethane as the propellant. This formulation is free of surfactant (column 2, lines 12 to 19 and claims 1 and 2).

As agreed with both parties, the Board considers that document (2), which disclosed a fluticasone aerosol formulation with the ozone-depleting propellants fluorotrichloromethane (P11) and

dichlorodifluoromethane (P12) without any additives such as surfactants or cosolvents, represents the closest prior art (example C in combination with page 1, lines 43 and 44).

Vis-à-vis document (2), the objective technical problem may therefore be formulated as the provision of a pharmaceutical aerosol formulation of particulate fluticasone propionate as a medicament which does not deplete the ozone layer.

2.4.2 This problem is solved by the replacement of both fluorotrichloromethane and dichlorodifluoromethane with the ozone-friendly propellant 1,1,1,2-tetrafluoroethane without the use of any additives such as surfactants or cosolvents.

In the light of the description and examples in the patent in suit, and in the absence of any specific evidence to the contrary, the Board is satisfied that the problem has been solved.

2.4.3 Thus the question to be answered is whether the proposed solution would have been obvious to the skilled person in the light of the prior art.

In that respect, the Board note that (Al), on page 428, second column, teaches that P12 and P11 have separate and distinct functions: "CFC 11 was useful for filling and aerosol canister with drug. At room temperature, it was a liquid in which the drug could be dissolved or dispersed. The resulting slurry could then be transferred into a canister. CFC 11 did not have a very high vapour pressure, so a high pressure propellant,

usually CFC 12, was then added to allow efficient ejection of the product from the container."

The second column, third paragraph states that: "hydrofluorocarbon (HFC) 134a… was a possible substitute for the high pressure compound." and the third column, third and fourth paragraphs that: "nevertheless 134a was still thought to be a feasible substitute for the high pressure propellant. He said that replacements for low pressure propellants had proved more difficult to find.". The skilled reader would assume that a substitute for P11 would be required.

These statements are consistent with the conclusions of the Opposition Division.

Moreover, on page 428, third column, and third paragraph under the heading "Solubility Problems" indicates that
"… replacements for low pressure propellants (e.g. CFC 11) had proved more difficult to find."

There is therefore a clear teaching that those skilled in the art were searching not only for a replacement for P 12 but also for a replacement for P 11.

In the paragraph bridging pages 428 and 429, it is further
stated that "... the use of 134a with a CFC low pressure propellant such as CFC 11 had been suggested as an interim response to the problem but he was opposed to the idea and urged development of a comprehensive replacement system."

This disclosure thus makes it clear that a replacement for P 11 had not been found at that time and that at least some of those skilled in the art had suggested an interim solution which was to continue to use P 11 but with HFC 134a.

Moreover, document (A1) teaches that HFC 134a formulations require a surfactant if P11 is omitted.

Thus, in the column headed "Manufacturing Modifications", the first paragraph reads as follows: "He [Dr. Morén] said that specific concentrations of the surfactant oleic acid would allow HFC 134a to be used without the need for a low pressure propellant." Therefore, document (A1)teaches that HFA 134a alone would not be able to replace the high and low pressure CFC combination in example (C) of D2.

On the contrary, document (Al) discloses that, in order to be able to replace both high and low pressure propellants with HFC 134a, a surfactant must be used, and suggests a particular surfactant for this purpose, namely oleic acid.

Therefore, the Board is convinced that, by following the teaching of document (Al), when read as a whole and in context without knowledge of the invention, the skilled addressee would have arrived at a formulation containing HFA134a and a surfactant, specifically oleic acid.

Accordingly, whether the subject-matter of the set of claims cannot be one which specifically does not

require any surfactants or other additives cannot be decided from a combination of documents (2) and (A1) either, and thus the decision of the Opposition Division with respect to inventive step holds good.

The respondent has quoted the passage from document (A1) on page 429, sixth paragraph to argue that it would have been obvious to the skilled addressee at the priority date to replace both P11 and P12 with HFC134a: "Glaxo said that it was working with major chemical companies, including IC" in the United Kingdom, to validate alternative propellants. Glaxo also had selected HFC134a as the most promising substitute. It said that this propellant should be able to replace the high and low pressure CFC combination that the company currently used."

It is however clear from the above that this passage was read outside the context of the rest of the document and that the document in fact provides no indication as to how any substitution is to be made and what modifications to the formulation would be necessary in order to move from a CFC to an HFC 134a product, except the mention of a formulation containing HFA134a and a surfactant, specifically oleic acid.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

2. The case is remitted to the department of first instance for adaptation of the description.

The Registrar The Chairman

N. Maslin U.Oswald