BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen
(D) [ ] No distribution

D E C I S I O N
of 2 October 2003

Case Number: T 0472/99 - 3.3.2

Application Number: 92924669.2

Publication Number: 0616525

IPC: A61K 9/00

Language of the proceedings: EN

Title of invention:
Pharmaceutical aerosol formulation

Patentee:
GLAXO GROUP LIMITED

Opponents:
LES LABORATOIRES SERVIER
SkyePharma AG
Novartis AG Patent and Trademark Dept.
Rhône-Poulenc Rorer Limited

Headword:
Aerosol/GLAXO

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main, first and second auxiliary requests - inventive step - no: obvious to try"

Decisions cited:
-

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0472/99 **-** 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 2 October 2003

Appellant: (Proprietor of the patent)
GLAXO GROUP LIMITED
Glaxo Wellcome House
Berkeley Avenue
Greenford,
Middlesex UB6 0NN (GB)

Representative:
Teuten, Andrew John
GlaxoSmithKline
Corporate Intellectual Property (CN9.25.1)
980 Great West Road
Brentford, Middlesex TW8 9GS (GB)

Respondent 1: (Opponent 1)
LES LABORATOIRES SERVIER
22 rue Garnier
F-92200 Neuilly-sur-Seine (FR)

Representative:
TER MEER STEINMEISTER & PARTNER GbR
Patentanwälte
Mauerkircherstrasse 45
D-81679 München (DE)

Respondent 2: (Opponent 2)
SkyePharma AG
Eptingerstrasse 51
CH-4132 Muttenz (CH)

Representative:
Zimmermann, Hans, Dr
c/o A. Braun Braun Héritier Eschmann AG
Patentanwälte VSP
Holbeinstrasse 36-38
Postfach 160
CH-4003 Basel (CH)

Respondent 4: (Opponent 4)
Rhône-Poulenc Rorer Limited
RPR House
52 St Leonards Road
Eastbourne, East Sussex BN21 3YG (GB)

Representative:
Jones, Stephen Anthony
AdamsonJones
BroadwayJones
Broadway Business Centre
32a Stoney Street
Nottingham NG1 1LL (GB)

Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 26 October 1999 revoking European patent No. 0616525 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: J. Riolo
J. H. P. Willems

Summary of Facts and Submissions

I. European patent No. 0 616 525 based on international application No. PCT/EP92/02810 was granted on the basis of 18 claims.

Independent claims 1, 2, 17 and 18 as granted read as follows:

"1. A pharmaceutical aerosol formulation which comprises particulate medicament, a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant and 0.01 to 5% w/w based upon propellant of polar cosolvent, which formulation is substantially free of surfactant.

2. A pharmaceutical aerosol formulation consisting essentially of one or more particulate medicament, one or more fluorocarbon or hydrogen-containing chlorofluorocarbon propellant and 0.01 to 5% w/w based upon propellant of a polar cosolvent.

17. A canister suitable for delivering a pharmaceutical aerosol formulation which comprises a container capable of withstanding the vapour pressure of the propellant used, which container is closed with a metering valve and contains a pharmaceutical aerosol formulation which comprises particulate medicament, a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant and 0.01 to 5%w/w based upon propellant of a polar cosolvent, which formulation is substantially free of surfactant.

18. A metered dose inhaler which comprises a canister as claimed in claim 17 fitted into a suitable channelling device."

II. Oppositions were filed against the granted patent by respondent 1 (opponent O1), respondent 2 (opponent O2), respondent 4 (opponent 4) and opponent 3. The patent was opposed under Article 100(a) EPC for lack of novelty and inventive step, under Article 100(b) EPC for insufficiency of disclosure and under Article 100(c) EPC because it contained subject-matter which had not originally been disclosed.

With its letter dated 8 October 1998, opponent 3 withdrew its opposition.

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

(1) EP-A-372777

(8) US-A-3219533

(3) Reprint from Pharmaceutical Technology, March 1990, pages 1 to 4, Dalby et al., CFC Propellant Substitution: P-134a as a Potential Replacement for P-12 in MDI's.

(22) The Pharmaceutical Journal, 245, September 1990, pages 428 to 429

(31) Journal of Aerosol Medicine, 4, No. 3, Fall 1991, pages 181 to 187, Kontny et al., Issues Surrounding MDI Formulation Development with Non-CFC Propellants. (Presented at the "Consensus Seminars on Issues of Aerosol Therapy" in Davos, Switzerland, April 1991.)

(45) Statement of C. Booles

III. By its decision pronounced on 22 September 1999, the Opposition Division revoked the patent under Article 102(1) EPC.

The Opposition Division held that neither the set of claims of the main request nor the set of claims of the auxiliary request filed during the oral proceedings met the requirements of the EPC.

It first noted that the objections pursuant to Article 100(b) EPC were not maintained by the opponents against these requests and it concluded that the requirements of this Article were fulfilled. However, regarding novelty, the Opposition Division was of the opinion that the subject-matter of the main request was anticipated by the prior art.

It moreover considered that the subject-matter of the first auxiliary request did not involve an inventive step vis-à-vis the teaching of document (8) in combination with document (1).

Starting from document (1), which described an aerosol suspension containing a pharmaceutical active substance, a propellant and ethanol, as closest state

of the art, the Opposition Division was of the opinion that the skilled person would be prompted to use HFA 134a (1,1,1,2-tetrafluoroethane) and HFA-227 (1,1,1,2,3,3,3-heptafluoro-n-propane) as a propellant combination in the light of the disclosure in document (1) as this document taught that these propellants were the leading ozone-friendly candidates to replace CFC (chlorofluorocarbon) propellants in aerosol compositions.

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

It filed a main request and two auxiliary requests during the appeal proceedings.

Claim 1 of the main request and of the first auxiliary request for all Contracting States except IE read respectively:

"1. A pharmaceutical aerosol formulation which comprises particulate medicament, 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane, or a mixture thereof as propellant, and 0.05 to 5% w/w based on propellant of polar cosolvent being a C_{2-6} aliphatic alcohol or polyol or a mixture thereof, which formulation contains less than 0.0001% surfactant by weight of the medicament."

"1. A pharmaceutical aerosol formulation which comprises particulate medicament, 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane, or a mixture thereof as propellant and 0.05 to 5% w/w based on propellant of polar cosolvent being a C_{2-6}

aliphatic alcohol or polyol or a mixture thereof, which formulation contains less than 0.0001% surfactant by weight of the medicament for use in inhalation therapy."

It also filed two sets of claims as main and first auxiliary request for the Contracting State IE. Claim 1 of these sets of claims corresponds to claim 1 of the sets of claims of the main and first auxiliary requests for the other Contracting States without the restriction to C_{2-6} aliphatic alcohol or polyol for the cosolvent. A third auxiliary request was held inadmissible by the Board because it had been filed conditionally.

The second auxiliary request consists of a single claim for all Contracting States which reads:

"A pharmaceutical aerosol formulation consisting essentially of: particulate medicament, 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane, or a mixture thereof as propellant and 0.05 to 3% w/w based on propellant of polar cosolvent being a C_{2-6} aliphatic alcohol or polyol or a mixture thereof, which formulation contains less than 0.0001% surfactant by weight of the medicament for use in inhalation therapy."

V. Oral proceedings were held before the Board on 2 October 2003.

VI. The line of argument which was developed by the appellant during the oral proceedings was that, contrary to the Opposition Division's opinion, the

skilled person would not have tried to replace CFC propellants by HFA-134a and/or HFA-227 in the prior art aerosol formulations. Indeed, it submitted that, having regard to the different chemical and physical properties of HFA-134a and HFA-227 compared to CFC propellants, as substantiated by documents (3), (22) and (31), the skilled person would have had no expectation of success.

During oral proceedings it did not maintain its proposition that there was in the art a prejudice against the omission of a surfactant and/or against the use of a (weakly) flocculating produce for inhalation therapy, for which proposition the Board had not seen any evidence.

It also requested the rejection of document (45) as late filed.

VII. The respondents contested the admissibility of the various requests because, in their opinion, they did not fulfil the requirements of Rule 57a EPC.

Moreover, in their view the expression "C_{2-6} aliphatic alcohol or polyol" was not clear and, in addition, there was no basis in the application as filed for the following three features in the claims:

– mixture of 1,1,1,2,3,3,3-heptafluoro-n-propane and 1,1,1,2-tetrafluoroethane

– 0.05 to 5% w/w based on propellant of polar cosolvent

– for use in inhalation therapy.

As regards inventive step, they argued that the skilled person was in fact prompted to use 1,1,1,2,3,3,3-heptafluoro-n-propane and 1,1,1,2-tetrafluoroethane as they were well known to be the most promising candidates as CFC alternatives at the priority date of the contested patent.

VIII. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request (faxed on 31 July 2003) or, alternatively, on the basis of first or second auxiliary request 2 (faxed on 31 July 2003).

The respondents requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Admissibility of document (45)*

The statement (45) was faxed on 29 August 2003 by respondent 4, ie one month before the oral proceedings and about 41 months after the filing of the grounds of appeal faxed on 3 March 2000.

In reply to the question of the Board during oral proceedings as to why this expert evidence was filed at that stage of the procedure, no reason was given.

Accordingly, in the absence of any reason for submitting it so late and having regard to the appellant's argument that it had no opportunity to prepare a counterstatement from one of its own advisers, document (45) is not admitted to the procedure.

The fact that, in the respondents' view, the document might be relevant does not constitute *per se* an excuse for its late filing.

3. *Main request, first and second auxiliary requests: admissibility.*

The Board notes that the subject-matter of these requests, which is, in any case, at least restricted to a narrower range of cosolvent and two specific propellants, constitutes a considerable limitation of the scope of the claims as granted, which, *a priori,* must be considered as occasioned by the novelty and inventive step objections of the grounds for opposition. The Board therefore does not agree with the respondents' view that these requests cannot be allowed under Rule 57a EPC merely because these limitations, in their opinion, do not provide for an inventive step vis-à-vis the prior art.

Accordingly, the Board judges that these requests fulfil the requirements of Rule 57a EPC and they are therefore admitted into the procedure.

4. *Main request, first and second auxiliary requests: Articles 84 and 123(2) and (3) EPC.*

As to the clarity objection relating to the fact that, in the expression "C_{2-6} aliphatic alcohol or polyol" used in the claims, the range "C_{2-6}" could refer either to alcohol or to aliphatic alcohol and polyol or only to aliphatic alcohol, the Board observes that the description as originally filed mentions ethanol, isopropanol, propylene glycol and mixtures thereof in that respect (page 5, lines 19 to 21).

Accordingly, the Board is convinced that the skilled person has no reason to believe that the range "C_{2-6}" could refer to aliphatic alcohol only, contrary to the respondents' view.

As to the features "mixture of 1,1,1,2,3,3,3-heptafluoro-n-propane and 1,1,1,2-tetrafluoroethane", "0.05 to 5% w/w based on propellant of polar cosolvent" and "for use in inhalation therapy", there is a basis in the application as originally filed.

In fact, dependent claim 8 of the application as originally filed discloses a formulation containing "1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane" as propellant, and claim 2, on which that claim depends, indicates that the formulations contain "one or more fluorocarbon" propellants so that a mixture of "1,1,1,2,3,3,3-heptafluoro-n-propane and 1,1,1,2-tetrafluoroethane" is implicitly but unambiguously disclosed.

As to the propellant range 0.05 to 5%, the Board notes that the application as originally filed describes a broader propellant range "up to 5%" and a narrower subrange "0.05 to 3%" (page 4, lines 9 to 13, page 5, lines 22 to 24).

Accordingly, there is a clear basis for the combined range 0.05 to 5%, which therefore does not constitute an unallowable selection.

Finally, the Board is also convinced that the wording "for the administration of medicaments by inhalation" on page 1, lines 4 and 5, provides an adequate basis for the expression "for use in inhalation therapy".

As these features restrict the scope of the claims as granted, the Board has no objections concerning Article 123(3) EPC.

5. *Main request*

Inventive step

5.1 The subject-matter of the contested patent relates to an aerosol formulation comprising an effective amount of a medicament, a chlorofluorocarbon (CFC-free propellant, (ie 1,1,1,2,3,3,3-heptafluoro-n-propane, 1,1,1,2-tetrafluoroethane or a mixture thereof), a polar cosolvent such as ethanol and less than 0.0001% surfactant by weight of medicament (page 2, lines 36 to 40, claim 1).

According to the description in the patent in suit the claimed formulation is stable and does not provoke the degradation of stratospheric ozone (page 2, lines 32 to 35 and page 3, lines 44 and 45).

The Board considers that document (8), which, as submitted by the appellant, also concerns a stable aerosol formulation for delivering various drugs by inhalation, represents the closest state of the art (column 1, lines 54 to 57, examples 1 to 10).

This document discloses in examples 1 to 10 aerosol formulations consisting of a medicament, a mixture of dichlorodifluoromethane (Freon 12, P-12) and 1,2-dichloro-1,1,2,2-tetrafluoroethane (Freon 114) as propellant (ie CFC's) and ethanol as polar cosolvent.

Document (8) teaches moreover that "ethanol can be utilized for the prevention of agglomeration or settling out of the medicated particles [which] permits the preparation of stable self-propelling medicated composition without the necessity of employing other agents such as surfactant for this purpose" (column 3, lines 20 to 31). The amount of ethanol present in the formulation is an amount of from 0.5 to 5% by weight of the formulation (column 4, lines 11 to 14).

Fluorinated lower saturated aliphatic hydrocarbons are mentioned among the propellants to be used in the aerosol formulations (column 2, line 58 to column 3, line 4).

There is moreover no evidence on file which demonstrates any effect achieved by the claimed

formulation over this closest prior art embodiment. In particular, there is no evidence showing that the claimed formulation is more stable than this prior art formulation or even equally stable.

5.2 Accordingly, the problem to be solved by the subject-matter of claim 1 of the main request of the patent in suit as against document (8) can only be seen in the provision of a further aerosol formulation for delivering a medicament which is sufficiently stable for its therapeutic purpose and which has no adverse effects on the earth's atmosphere, or at least fewer.

5.3 This problem is solved by the subject-matter of claim 1, ie by the use of 1,1,1,2,3,3,3-heptafluoro-n-propane, 1,1,1,2-tetrafluoroethane or a mixture thereof as propellant in the aerosol formulation containing a medicament. In the light of the working examples in the patent in suit, the Board is satisfied that the problem has been plausibly solved.

5.4 Thus the question to be answered is whether the proposed solution, ie providing an aerosol formulation containing 1,1,1,2,3,3,3-heptafluoro-n-propane, 1,1,1,2-tetrafluoroethane or a mixture thereof as propellant, would have been obvious to the skilled person in the light of the prior art.

In that respect, document (3) for instance teaches that 1,1,1,2-tetrafluoroethane (P-134a) is a particularly suitable propellant for replacing an ozone-layer-destroying chlorofluorocarbon propellant such as P-12 in aerosol formulations for delivering medicaments

(page 2, left column, first sentence of the last paragraph, title).

Accordingly, the Board is satisfied that the skilled person faced with the problem as defined above under 5.3 would be prompted to replace the propellant mixture disclosed in document (8) by the propellants in the patent in suit without an inventive step, just by following the teaching of document (3).

5.5 The Board does not agree with the main argument submitted by the appellant, that the claimed formulation is inventive because the skilled person would not expect the replacement of a CFC propellant by the P-134a propellant in the prior art formulation to be successful, so that it would not even try it.

It is indeed true, as pointed out by the appellant during the oral proceedings, that documents (3), (22) and (31) disclose that P-134a differs in its physico-chemical properties from CFCs ((3) page 3, heading "Difference between P-12 and P-134a; (22) page 428, middle column, third paragraph; (31) page 181, abstract).

Nevertheless, as acknowledged by the appellant itself during the oral proceedings and as shown by these very same documents, which sought precisely to replace P-12 in metered dose inhalers, P-134a remained one of the most interesting candidates as a substitute for P-12 at the priority date of the patent.

Accordingly, the Board concludes that, having regard to the degree of pressure put on industry by existing or

imminent legislation and by public interest in trying to replace P-12, it is of minor significance whether or not a particularly high degree of success was expected before starting experimental work with P-134a started.

Therefore the Board is convinced that the skilled person would have in any case tried to replace P-12 by P-134a in the prior art formulations, especially as there is nothing in the file which points out towards difficulties in carrying out the necessary experiments. This is also indirectly confirmed by the fact that the alleged invention was filed very soon (less than two years) after the publication of documents (3), (22) and (31), which were dealt with P-134a as a potential replacement for P-12.

As to the appellant's submission that document (1) would be a more suitable starting point for assessing inventive step, the Board observes that any claimed subject-matter must involve an inventive step vis-à-vis each prior art item in order to comply with Article 56 EPC, so that it is useless to determine whether the claimed subject-matter would be inventive when compared with another prior art document.

5.6 In the light of these facts, the Board can only conclude that the subject-matter of claim 1 of the main request does not involve an inventive step as required by Article 56 EPC.

Under these circumstances, there is also no need to consider the remaining claims of the main request.

These conclusions apply to the set of claims for IE and to the set of claims for the other Contracting States since the only difference between these sets of claims resides in the broader definition of the cosolvent.

6. *Auxiliary requests 1 and 2 for all Contracting States*

These requests differ from the main request in that the medicament is now restricted to its use in inhalation therapy and, in the case of the second auxiliary request, to a propellant range of 0.05 to 3%.

The appellant and respondents argued that the submissions presented with respect to inventive step remained valid for this set of claims as well.

As no further argument has been presented as to why these restrictions should involve an inventive step, the above conclusions hold good for these requests as well.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Townend U. Oswald