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Datasheet for the decision of 12 June 2013

Case Number: T 0295/09 - 3.3.02

Application Number: 01931894.8

Publication Number: 1284771

IPC: A61M 15/00

Language of the proceedings: EN

Title of invention:
Aerosol container for formulations of salmeterol xinafoate

Patent Proprietor:
GLAXO GROUP LIMITED

Opponent:
Jump, Timothy John Simon

Headword:
Aerosol container/GLAXO

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no): obvious to try"

Decisions cited:
-

Catchword:
-

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Case Number: T 0295/09 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 12 June 2013

Appellant: (Patent Proprietor)
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-

Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 10 December 2008 revoking European patent No. 1284771 pursuant to Article 101(2) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
R. Cramer

Summary of Facts and Submissions

I. European patent No. 1 284 771, based on application No. 01 931 894.8 from international application No. PCT/GB2001/002256 published as WO2001/089616 A1, was granted with 34 claims.

Independent claims 1, 17 and 34 as granted read as follows:

"1. A container comprising a canister sealed with a valve, which contains a pharmaceutical aerosol formulation comprising
(A) particulate salmeterol xinafoate in suspension in
(B) a liquefied propellant gas which is 1,1,1,2,3,3,3-heptafluoro-n-propane or 1,1,1,2-tetrafluoroethane and mixtures thereof;
said container **characterised in that** the valve contains one or more valve seals substantially constructed from polymer of ethylene propylene diene monomer (EPDM), the valve is sealed to the canister by means of a gasket seal which is substantially constructed from a polymer of EPDM, and the formulation is substantially anhydrous and remains so over a period of 12 months when stored at 25° C and at relative humidity of 60%.

17. A container comprising a canister sealed with a valve which contains a pharmaceutical aerosol formulation consisting essentially of:
(A) particulate salmeterol xinafoate optionally in combination with another particulate active ingredient as medicament suspended in

(B) a liquefied propellant gas comprising 1,1,1,2,3,3,3-heptafluoro-n-propane, 1,1,1,2-tetrafluoroethane and mixtures thereof;
wherein the formulation is substantially free of surfactant and components having polarity higher than the liquefied propellant gas; and said valve is **characterised in that** it contains one or more valve seals substantially constructed from a polymer of EPDM, and further **characterised in that** the valve is sealed to the canister by means of a gasket seal which is substantially constructed from a polymer of EPDM.

34. A method of reducing drug deposition and/or adsorption onto valve components, in a container sealed with a valve containing a pharmaceutical aerosol formulation consisting essentially of particulate salmeterol xinafoate and a liquid propellant which is HFA 134a, HFA 227 or mixtures thereof, which comprises use of a valve wherein at least the gasket seal is substantially constructed from a polymer of EPDM."

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

The documents cited during the proceedings before the opposition division and the board of appeal include the following:

(2) WO1995/002651 A1

(3) EP 0 990 437 A1

(6) WO2001/010742 A1

(7) WO2000/056632 A1

III. By its decision pronounced at oral proceedings on 19 November 2008 and posted on 10 December 2008, the opposition division revoked the patent under Article 101(2) EPC.

The opposition division held that the set of claims of the single request (claims as granted) was not deficient under Article 100(b) and (c) EPC.

Concerning Article 54(2) und (3) EPC, the opposition division was of the opinion that the invention was not anticipated by the teachings of any of the documents on file, especially documents (7), (6), (3) and (2).

However, regarding Article 56 EPC, inventive step, the opposition division took the view that document (3) as closest prior art, taken together with document (2), prejudiced the patentability of claims 17 and claim 1 in suit.

The problem to be solved with respect to claim 17 and claim 1 of the patent in suit was to be seen as the choice of a material having appropriate sealing properties especially for aerosol formulations of salts of salmeterol together with HFA 134a or HFA 227 propellants.

From document (2), the skilled person would learn that seals made of the polymer relating to ethylene propylene diene monomer (EPDM) were good seals in this

case and would thus arrive at the teaching of claim 17 without inventive activity.

The further differing feature in independent claim 1 of the patent in suit, namely that the formulation remained substantially anhydrous during storage, had not been plausibly shown to be the cause of a more stable fine particle mass (FPM) parameter during long periods of storage. Construction of at least one of the valve seals from EPDM already led to the effect of stable fine particle mass and the differing feature that the formulation remained anhydrous had no further effect. Thus, the subject-matter of claim 1 also lacked inventive step.

IV. The appellant lodged an appeal against that decision and filed grounds of appeal together with a request that the patent be maintained according to its main request (claims as granted) or one of auxiliary requests 1 to 3.

The main request corresponds to the sole request the opposition division decided on and concerns the patent as granted. Claim 1 of auxiliary request 1 is identical to claim 17 as granted, claim 1 of auxiliary request 2 is identical to claim 1 as granted, and claim 1 of auxiliary request 3 is identical to claim 34 as granted.

V. On 12 June 2013, oral proceedings took place before the board.

VI. During the oral proceedings, the appellant filed auxiliary requests 4 and 5, which were admitted into the proceedings. They relate to auxiliary requests 1

and 2 in that the method claim relating to claim 34 as granted has been deleted.

VII. The appellant's submissions may be summarised as follows:

The method claim contained in all requests filed with the grounds of appeal did not only concern drug deposition and/or adsorption onto but implicitly also **absorption into** valve components since the results set out in Table 1 clearly showed that active substance salmeterol xinafoate had been lost during storage under accelerated conditions. While any substance deposited and/or adsorbed onto valve components would have been found by the used method of determining total drug content (TDC), in nitrile sealed canisters there was less detection of total drug content than in EPDM sealed canisters. This was the result of salmeterol xinafoate deposited and adsorbed onto the surfaces subsequently also being absorbed into valve components, i.e. in the current case seals according to the state of the art.

Therefore, according to the patent in suit, the problem to be solved, under the overall aim of arriving at constant fine particle mass, was reduction of drug deposition onto and absorption into valve components.

In contrast, document (2) in its overall content concerned the sealing properties of EPDM with respect to propellant leakage when exposed to HFA 134a (1,1,1,2-tetrafluoroethane) or HFA 227 (1,1,1,2,3,3,3-heptafluoro-n-propane), and not the problem to be solved in the present case. Moreover, the skilled

person - in view of the experiments and tables in document (2) - could only see good leakage values in the absence of a polar co-solvent. Such co-solvents, however, were excluded in document (3) anyhow. For these reasons, it was not obvious to combine document (3) with document (2), and the claimed subject-matter was inventive.

Besides that, the tables in document (2) showed that leakage of propellant was not reduced by the use of EPDM seals together with ethanol-containing formulations. Therefore, in these cases there was no incentive to replace seals of the state of the art by EPDM seals.

VIII. The respondent contested the arguments of the appellant.

IX. The appellant (patentee) requests that the decision under appeal be set aside and that the patent be maintained on the basis of the claims as granted or on the basis of one of auxiliary requests 1 to 3 filed with its statement of grounds of appeal, or alternatively on the basis of one of the sets of claims filed as auxiliary request 4 or 5 during the oral proceedings.

X. The respondent (opponent) requests that the appeal be dismissed.

Reasons for the decision

1. The appeal is admissible.

2. The additional requests filed by the appellant as auxiliary requests 4 and 5 have to be regarded as a response to the arguments discussed during the oral proceedings with respect to auxiliary request 3.

Since they relate to auxiliary requests 1 and 2 in that method claim 34 as granted has been deleted, there is no need for new, complex considerations.

In these circumstances, the board uses its discretion and admits the additional auxiliary requests into the proceedings.

3. With regard to claim 34 of the main request (claims as granted) the board has no reason to disagree with the findings of the opposition division with respect to Articles 100(c) and 54 EPC.

It has its basis in the application as filed in original claim 37 together with page 5, lines 3-4 and page 5, lines 34-35 of the application as originally filed (citations referring to WO2001/089616 A1). The claim thus is not deficient under Article 100(c) EPC.

In addition, none of the documents cited during the opposition procedure and the procedure before the board disclosed in combination all the features of the subject-matter of claim 34 of the main request (Article 54 EPC).

4. *Claim 34 of the main request; Article 56 EPC (inventive step)*

4.1 The subject-matter of this claim 34 relates to a

(a) method applied
(b) to a container sealed with a valve
(c) containing a pharmaceutical aerosol formulation consisting essentially of
(d) particulate salmeterol xinafoate and a
(e) liquid propellant which is HFA 134a, HFA 227 or mixtures thereof,
(f) which comprises use of a valve wherein at least the gasket seal is substantially constructed from a polymer
(g) of ethylene propylene diene monomer (EPDM).

According to the wording of the claim, the method under point (a) exclusively concerns reduction of drug deposition and/or adsorption onto valve components of the container.

4.2 Document (3) represents the closest state of the art.

The disclosure of this document,

- with regard to the particular characteristics of the invention concerned, starting in line 30 on page 2 stating that "We have now surprisingly found …",
- read together with the characterisation of the container starting on page 4, line 33,

relates to a

(a) method applied
(b) to a container by means of sealing it with a valve incorporating a gasket (page 4, lines 36 to 38)
(c) containing a pharmaceutical aerosol formulation (page 4, lines 33 to 34) consisting essentially of
(d) particulate salmeterol xinafoate (as one of four medicaments indicated on page 2, lines 33 to 35, read in combination with page 3, lines 44 to 45 and all examples containing salmeterol which all relate to the xinafoate salt) and a
(e) liquid propellant which is HFA 134a (page 2, line 32) because of ozone-depleting effects of former propellants (page 2, lines 10 to 29 in particular page 2, lines 10 to 13)
(f) which comprises use of a valve wherein at least the gasket seal (within the meaning of the patent in suit according to point 4.2(b)) is substantially constructed from a polymer to be chosen from a **non-exclusive** list (page 4, lines 38 to 40) meaning to be chosen from the list or any appropriate material the skilled person would know.

Additionally, it seeks to address a concern of the state of the art that, as far as a surfactant was contained in the aerosol formulations, the valve needed it also as lubricant, thereby ensuring consistent reproducibility of valve actuation and accuracy of dose dispensed (see page 2, lines 24 to 26).

4.3 Starting from the teaching of document (3) as set out under point 4.2 above, the problem to be solved is the provision of a method for reduction of drug deposition and/or adsorption onto valve components in a container for administration of a pharmaceutical aerosol

formulation which includes the proper choice of the material used for constructing the gasket seal (see point 4.2 (f) above), in view of HFA 134a as the propellant to be used in the future, because former propellants have ozone-depleting effects (see point 4.2(e) above).

4.4 With regard to the experiments contained in the patent in suit (in particular showing advantages of the use of ethylene propylene diene rubber (EPDM) with respect to fine particle mass), the board can accept that the problem is plausibly solved by choosing EPDM as material for the gasket seal and optionally further valve seals.

4.5 The skilled person working in the field of containers for pharmaceutical aerosol formulations, including the use of HFA 134a as propellant, and knowing document (3) also knows contemporary document (2).

4.5.1 This document starts with the consideration that aerosol-delivering devices of the state of the art suffered impaired performance when used in connection with HFA 134a. Selection of suitable materials for use as diaphragms, representing seals in the devices, to contain aerosol formulations based on alternative propellants such as HFA 134a was complicated by interactions between the seal material and the formulation components, **including the propellant** (meaning *a priori* all the formulation components, not only the propellant). Moreover, the use of conventional sealing materials involved substantial leakage of HFA 134a over time, resulting in delivery of improper

doses in terms of fine particle mass (see document (2), page 1, line 37 to page 2, line 15).

Furthermore, with some formulations the valve stem tended to stick, pause or drag during the actuation cycle (see document (2), page 2, lines 16 to 17).

In view of such problems, devices according to document (2) wherein the diaphragm was in sealing engagement with the casing member and **comprising an ethylene propylene diene rubber (EPDM)** (see page 3, lines 16 to 30, in particular lines 24 to 27) found particular use in connection with aerosol formulations involving HFA 134a as a propellant (see page 4, lines 31 to 33 and page 11, lines 14 to 18). Leakage and smoothness of operation were improved in the devices compared to similar devices involving conventional diaphragm materials (see page 4, lines 33 to 36).

With respect to all the difficulties that are described as overcome by the choice of ethylene propylene diene rubber as sealing material, the skilled person recognises that problems concerning interactions between the seal material and the formulation components, e.g. the active drug (which is expressed by the added words "**including** the propellant"), and sticking, pausing or dragging of the valve stem during actuation were reduced by improved smoothness of operation (emphasis by the board). On this basis, he can only conclude that drug deposition (and adsorption) onto valve components as expressed in claim 34, which according to the common general knowledge of the skilled person, *inter alia* caused sticking and dragging

on the valve stem, are minimised by use of the sealing material ethylene propylene diene rubber (EPDM).

4.5.2 Consequently, for this reason and also because document (2) explicitly states that

- seals comprising an ethylene propylene diene rubber (EPDM) found particular use in connection with aerosol formulations involving HFA 134a as a propellant and
- generally any and all sealing members of aerosol delivery devices containing this composition could comprise this elastomer (see page 11, lines 9 to 13),

it was obvious to try this sealing material in any case requiring a choice of seals according to document (3).

4.5.3 Thus, the person skilled in the art, starting from document (3) and taking into account document (2), arrives at the teaching of claim 34 of the main request (patent in suit as granted) without inventive activity.

4.6 Consequently, the board concludes that the subject-matter of claim 34 of the main request does not involve an inventive step (Article 56 EPC).

5. Claim 18 of auxiliary request 1, claim 17 of auxiliary request 2 and claim 1 of auxiliary request 3 are identical to claim 34 as granted and, therefore, necessarily also in breach of Article 56 EPC. Thus, these requests are also not allowable.

6. *Claim 1 of auxiliary request 4; Article 56 EPC (inventive step)*

This request relates to a product claim containing features corresponding to the method claim already discussed and the additional feature "wherein the formulation is substantially free of surfactant and components having polarity higher than the liquefied propellant gas" which is also represented in document (3) (again in the paragraph starting with "We have now surprisingly found …"; see page 2, line 32) in a form reading "without recourse to the use of any surfactant or cosolvent in the composition").

In document (3) all problems associated with the pharmaceutical aerosol compositions of the state of the art and their containers are at least implicitly indicated to be solved by the invention claimed there. In addition, no particular embodiment of its teaching is disclosed in the form of a container comprising a composition, a valve and specified seals. Therefore, the only problem to be solved lies in putting the general teaching of document (3) into practice, particularly in the choice to be made with regard to the generic advice that the material used for constructing the gaskets should comprise "any suitable elastomeric material" (see page 4 of document (3), lines 38 to 40).

The problem is plausibly solved by the features of claim 1 of auxiliary request 4 in which the specific seal material is ethylene propylene diene monomer (EPDM) polymer.

For all the reasons set out under point 4.5 of this decision, and in particular because document (2) states that seals **comprising an ethylene propylene diene rubber (EPDM)** found particular use in connection with aerosol formulations involving HFA 134a as a propellant and generally any and all sealing members of aerosol delivery devices containing this composition could comprise this elastomer, it was obvious to try this sealing material in any case requiring a choice of seals according to document (3).

The result is the provision of a container according to the teaching of claim 1 of auxiliary request 4, which consequently does not involve an inventive step either (Article 56 EPC).

7. *Claim 1 of auxiliary request 5; Article 56 EPC (inventive step)*

The features of claim 1 of auxiliary request 5 correspond to those of claim 1 of auxiliary request 4 with the exceptions that the feature that no "surfactant and components having polarity higher than the liquefied propellant gas" were present has been deleted and that the feature "and the formulation is substantially anhydrous and remains so over a period of 12 months when stored at 25° C and at relative humidity of 60%" has been added.

In view of the results of the experiments set out in the patent in suit and in view of the teaching of its independent claims 17 and 34 that relate to the same result without the need for the added feature concerning the water content of the formulation, the

board concludes that the wording "and the formulation is substantially anhydrous and remains so over a period of 12 months when stored at 25° C and at relative humidity of 60%" merely describes the results achieved by the mere choice of polymer of ethylene propylene diene monomer (EPDM) as the material used for constructing at least the gasket seal.

Thus, under the same considerations and arguments already set out for claims 34 and 17 of the patent as granted (relating to auxiliary requests 3 and 4), the subject-matter of claim 1 of the auxiliary request 5 (claim 1 of the patent as granted) likewise does not involve an inventive step (Article 56 EPC).

8. Under these circumstances, the additional arguments of the appellant cannot hold.

The tables in document (2) showing about leakage do not affect the considerations and conclusions of this decision because - as has been shown above - the teaching of this document cannot be reduced to the phenomenon of leakage alone. In addition, it is clear that the tables do not allow any conclusion to be drawn about relative quality in terms of propellant leakage when using alcohol-free formulations and comparing EPDM and other seals, because they contain no comparative data in this respect. Data with respect to alcohol-containing formulations likewise have no bearing on this decision, because there is no request that is restricted to such formulations.

9. Consequently, the subject-matter of all claims 1 of all requests on file is in breach of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

K. Götz U. Oswald