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Datasheet for the decision of 10 August 2006

Case Number: T 0956/05 - 3.3.02

Application Number: 96200109.5

Publication Number: 0717987

IPC: A61K 9/00

Language of the proceedings: EN

Title of invention:
Suspension aerosol formulations

Patentee:
MINNESOTA MINING AND MANUFACTURING COMPANY

Opponent:
SkyePharma AG

Headword:
Suspension Aerosol Formulations/MINNESOTA MINING

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no) - no data supplied by the patentee to support improvement; further formulation obvious to obtain by replacing well known components"

Decisions cited:
-

Catchword:
-

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Case Number: T 0956/05 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 10 August 2006

Appellant: (Opponent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 31 May 2005 concerning maintenance of the European patent No. 0717987 in amended form.**

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
J. Willems

Summary of Facts and Submissions

I. European patent No. 717 987, filed as a divisional application of parent application No. 93 901 414.8, based on international patent application No. PCT/US92/10587, filed at the EPO as WO 93/11747 and claiming the priorities of 18 December 1991 and 4 May 1992, was granted with six claims.

Independent claims 1 and 6 as granted read as follows:

"1. A suspension aerosol formulation comprising a therapeutically effective amount of micronised albuterol sulfate and HFC 227 as the only propellant.

6. A metered dose aerosol canister containing a formulation as claimed in any preceding claim in an amount sufficient to provide a plurality of therapeutically effective doses of the drug."

II. Opposition was filed against the granted patent by the appellant. The patent was opposed under Article 100(a) EPC for lack of novelty and lack of inventive step.

The following documents were cited inter alia during the proceedings before the opposition division and the board of appeal:

(1) WO-A-92 22288, Article 54(3) EPC

(2) WO-A-93 05765, Article 54(3) EPC

(3) WO-A-93 11745, Article 54(3) EPC

(4) WO-A-93 11743, Article 54(3) EPC

(5) Keller, M.; "Alternativen zu FCKW-haltigen Dosieraerosolen", lecture held in the Maritim Hotel Köln, course 538, 11-12 March 1991

(6) EP-A-0 372 777

(7) WO-A-91 11496

(16) Kontny, M.J. et al., "Issues surrounding MDI formulation; development with non-CFC propellants", Journal of Aerosol Medicine, volume 4, number 3, Mary Ann Liebert, Inc., Publishers 1991, 181-187

(17) GB-A-2 001 334

III. The opposition division held that, account being taken of the amendments made by the proprietor, the set of claims of the main request met the requirements of the convention (Articles 106(3) and 102(2) EPC).

It first noted that the requirements of Article 123, paragraphs (2) and (3), EPC were fulfilled.

Concerning Article 54 EPC, the opposition division was of the opinion that the invention was neither anticipated by the teaching of document (1) nor by the teachings of document (2), (3) or (4). None of these documents disclosed the specific combination of features as defined in claim 1 (i.e. the combination of the features (i) suspension, (ii) micronised medicament, (iii) albuterol sulfate and (iv) HFC 227 as the only propellant).

Since the respirable fractions in examples 1 and 2 of the contested patent were very high, the opposition division came to the conclusion that the subject-matter of claim 1 of the main request involved an inventive step over a combination of document (6) and either document (5) or document (7). Taking document (17) as the closest prior did not lead to another conclusion.

IV. The appellant (opponent) filed an appeal against that decision and submitted grounds of appeal.

V. With a letter dated 5 April 2006, the respondent (patentee) introduced six sets of amended claims as the main request and the first to fifth auxiliary requests into the appeal proceedings.

The set of claims of the main request is the same that formed the basis for maintenance of the opposed patent before the opposition division. Its claim 1 contains a disclaimer with respect to document (1):

"A suspension aerosol formulation comprising a therapeutically effective amount of micronised albuterol sulfate and HFC 227 as the only propellant, but not a formulation consisting of 98.89 wt% HFC 227, 0.10 wt% albuterol sulfate, 0.01 wt% oleic acid and 1.00 wt% ethanol or 1.00 wt% transcutol."

In claim 1 of the first auxiliary request the subject-matter of claim 2 as granted was added to claim 1 (definition of the contents of ethanol); in claim 1 of the second auxiliary request the subject-matter of claim 4 as granted was added to claim 1 (definition of

the contents of albuterol sulfate); and in claim 1 of the third auxiliary request the subject-matter of both claim 1 and claim 4 as granted was added to claim 1 (definition of the contents of ethanol and albuterol sulfate). Consequently, the wording of claim 1 of the third auxiliary request is:

"A suspension aerosol formulation comprising from 0.2 to 0.5% by weight of micronised albuterol sulfate, HFC 227 as the only propellant and comprising from 5 to 15 percent by weight of ethanol."

Claim 1 of the fourth auxiliary request reads like claim 1 as granted, with the only difference that the word "comprising" was substituted by "consisting essentially of". Accordingly, its wording is:

"A suspension aerosol formulation consisting essentially of a therapeutically effective amount of micronised albuterol sulfate and HFC 227 as the only propellant."

In the fifth auxiliary request the word "comprising" was substituted by "consisting of".

VI. On 10 August 2006, oral proceedings took place before the board.

VII. The submissions of the appellant can be summarised as follows:

The values of the respirable fraction of the subject-matter of the patent in suit, in particular of examples 1 and 2, which the opposition division had

characterised as "very high", in fact were normal for such aerosol formulations. This was the common general knowledge of the person skilled in the art in the field of medicinal aerosol formulations. Additionally, this could be seen from documents published after the priority date of the patent in suit. Therefore, the problem was simply to provide another suspension aerosol formulation of albuterol sulfate exhibiting lower ozone-damaging properties and not an improved one.

In this respect, starting from different documents of the state of the art, it was obvious to use HFC 227, the closest prior art being document (6) for the main request and the first, second and third auxiliary requests.

The claims of document (7) represented the next closest state of the art with respect to the fourth and fifth auxiliary requests. Even the whole context of this international application supported the use of HFC 227 together with a drug in the absence of other ingredients, since the wording "in general additionally surfactants … (ferner im allgemeinen oberflächenaktive Stoffe)" implied the possibility of leaving them out. The drug salbutamol (a synonym of albuterol) could be selected from a list containing different drugs and the skilled person knew that the free base easily and regularly was substituted by the sulfate.

VIII. The respondent's arguments may be summarised as follows:

The burden of proof that the subject-matter of the opposed patent had no better respirable fraction than the aerosol compositions of the state of the art was on

the side of the appellant. Since the appellant had not filed any comparative examples, it had to be accepted that the problem of providing an improved suspension aerosol of albuterol sulfate was solved by the teaching of the opposed patent and that this was not obvious with regard to the state of the art.

Even if there were no better characteristics of the subject-matter of the opposed patent, its teaching was not obvious because, starting from different documents cited in the proceedings, there was no incentive to arrive at that teaching. Additionally, it was counter-intuitive to replace HFC 134a with HFC 227, because the vapour pressure of HFC 227 was too low. Furthermore, it was counter-intuitive to add ethanol to a formulation based on HFC 227, because the addition still lowered the vapour pressure. The skilled person would therefore never have thought that a mixture of drug, HFC 227 and ethanol would result in such a high respirable fraction as the patentee had surprisingly found.

IX. The appellant (opponent) requested that the decision under appeal be set aside and that the European patent No. 0 717 987 be revoked.

X. The respondent (patentee) requested that the appeal be dismissed and that the patent be maintained on the basis of the sets of claims of the main request or, alternatively, of the auxiliary requests 1 to 5, all requests being filed with letter dated 5 April 2006.

Reasons for the Decision

1. The appeal is admissible.

2. *Admissibility of the requests, formal requirements and novelty*

The board considers that, compared with the claims as granted, the amendments corresponding to the sets of claims of the requests are occasioned by the arguments of the appellant set out in writing.

Accordingly, the requests fulfil the requirements of Rule 57a EPC and they are admitted into the procedure.

Additionally, the clarity of the claims with respect to Article 84 EPC can be acknowledged.

Finally, the board is satisfied that the subject-matter of all requests complies with the requirements of Articles 123 and 54 EPC. This was not contested by the appellant in the appeal proceedings.

3. *Inventive step*

3.1 Main request and second auxiliary request

3.1.1 The subject-matter of these requests concerns a "suspension aerosol formulation comprising a therapeutically effective amount of micronised albuterol sulfate and HFC 227 as the only propellant".

In the second auxiliary request, the content of albuterol sulfate is defined in terms of the percentage

by weight of the whole formulation in the range of 0.2 to 0.5%.

3.1.2 Document (6) represents the closest state of the art.

According to the introduction in the description, page 1, paragraph 1, together with claim 1 of (6), the subject-matter of that prior art corresponds to medicinal aerosol formulations which are at least substantially free of chlorofluorocarbons and in particular to such formulations comprising a medicament and 1,1,1,2-tetrafluoroethane (HFC 134a).

On page 8 of the description, a formulation is disclosed as example 24A, consisting of 0.012g (0.23 wt%) of "salbutamol", 0.058g (1.10 wt%) of ethanol, 0.005g (0.09 wt%) of a surfactant and the rest (5.220g) of HFC 134a as the single propellant. Salbutamol is a synonym for albuterol and on page 5, line 57, in document (6) the term "salbutamol" in the table of contents is defined for example 24a as "salbutamol sulfate B.P., micronised". Based on this definition, in document (6) the term "salbutamol" represents micronised albuterol sulfate in the same way as BDP represents isopropyl alcohol solvate, micronised, or in the same way as DSCG stands for sodium cromoglycate B.P., micronised (see (6), page 6, lines 1 and 2).

In line 57 on page 8 of (6) the test samples are described as stable suspensions.

Therefore, in document (6) a suspension aerosol formulation is disclosed comprising from 0.2 to 0.5% by

weight of micronised albuterol sulfate and HFC 134a instead of HFC 227 as the only propellant.

3.1.3 In the absence of any comparative example referring to the closest state of the art, represented by example 24A of (6) (see point 3.1.2 above), the technical problem underlying the patent in suit can only be seen in the provision of a further suspension aerosol formulation.

The solution to this problem is the provision of a suspension aerosol formulation exhibiting the features of claim 1 of the main request or of the second auxiliary request.

3.1.4 Having regard to worked example 2 of the patent in suit and in the absence of any counter-evidence provided by the appellant, the board is convinced that the problem has been plausibly solved.

3.1.5 However, in order to supply merely a further suspension aerosol formulation with respect to the formulation disclosed in document (6), it is obvious to the skilled person to substitute HFC 134a by the other propellant that was well known at the time of the priority of the patent in suit as non-damaging to the ozone-layer of the atmosphere and as a good candidate for production of aerosol formulations in this context (it was for instance mentioned in document (16), in particular in the lines 7 to 10 of the abstract and in the headlines on pages 185 and 186).

3.1.6 Accordingly, the board can only conclude that the subject-matter of each of the claims 1 of the main

request or of the second auxiliary request does not involve an inventive step, as it merely amounts to taking the other of a pair of two well known propellants in the context of avoiding ozone-damaging propellants of the chlorinated hydrocarbon type.

3.2 First and third auxiliary requests

3.2.1 The subject-matter of the first and third auxiliary requests concerns suspension aerosol formulations that, with respect to the formulations of the main request and the second auxiliary request, contain additionally from 5 to 15 per cent by weight of ethanol.

In example 24A of document (6), the formulation contains 1.10 wt% of ethanol.

In the case of the teaching of the first and the third auxiliary requests, the closest prior art and the problem are the same with respect to the assessment of inventive step. The solution now has to be seen as substituting the propellant HFC 134a by HFC 227 and adjusting the contents of ethanol.

Having regard to worked example 2 of the patent in suit and in the absence of any counter-evidence provided by the appellant, the board is convinced that the problem has been plausibly solved.

Adjusting the ethanol content to obtain sufficient suspension aerosol formulations, however, is the usual task of the skilled person when substituting any of the components, for instance the propellant. Obviously, sufficient formulations are obtained when using 5 to 15

per cent by weight of ethanol (this at least is consistent with the teaching of the patent in suit).

Thus, with reference to the available state of the art, in particular document (16), it was obvious to substitute the propellant HFC 134a by HFC 227 and adjust the contents of ethanol to within the range of 5 to 15 per cent by weight in order to achieve a further suspension aerosol formulation of albuterol sulfate.

3.3 Fourth and fifth auxiliary requests

3.3.1 The subject-matter of these requests concerns a "suspension aerosol formulation consisting (essentially) of a therapeutically effective amount of micronised albuterol sulfate and HFC 227 as the only propellant".

In both these requests, the focus of the claimed invention now lies on two components representing the suspension aerosol formulation with (essentially) no other component being present. Ethanol is no longer necessary.

3.3.2 Since the focus of the claimed invention has changed, the document representing the closest state of the art changes too. In the present case, the closest prior art is now disclosed in document (7).

According to claim 5 of (7), together with claims 1, 6 and 11, one embodiment disclosed and even made a protected subject-matter by means of claims of this prior art, corresponds to aerosol formulations ("Arzneimittelzubreitungen zur Erzeugung von Pulveraerosolen" in claim 5) using HFC 227 as the

propellant ("TG 227" in claim 1) and containing salbutamol (one of the drugs listed in claim 6 and being the same as albuterol). The process of independent claim 11 describing that micronised drugs are suspended in the liquefied propellant refers to independent claim 5 (aerosol formulation).

Thus, in document (7) a suspension aerosol formulation is disclosed consisting of micronised albuterol instead of albuterol sulfate and HFC 227 as the only propellant.

3.3.3 In the absence of any comparative example referring to this state of the art, the technical problem underlying the patent in suit can only be seen in the provision of a further suspension aerosol formulation of this kind.

The solution to this problem is the provision of a suspension aerosol formulation exhibiting the features of claim 1 of either the fourth auxiliary request or the fifth auxiliary request.

3.3.4 Having regard to worked example 1 of the patent in suit, the board is convinced that the problem has been plausibly solved.

3.3.5 In the field of medicine it is well known and normal for the person skilled in the art to use any pharmaceutically acceptable salt of a drug instead of the free drug itself. Therefore, it is obvious to him to substitute albuterol by albuterol sulfate while providing a further suspension aerosol formulation with respect to the formulation disclosed in document (7).

3.3.6 Accordingly, the board can only conclude that the subject-matter of each of the claims 1 of the fourth or fifth auxiliary request does not involve an inventive step.

3.4 In these circumstances the arguments of the respondent cannot lead to success.

The respondent stated that there were no comparative examples in the proceedings that were reliably founded on the same parameters and conditions as the determination of the respirable fraction as disclosed in the patent in suit. Thus, there was no proof that any suspension aerosol formulation of the state of the art had the same or similarly good values as the formulations of the opposed patent. These values, however, were of a quality to be described as excellent by themselves, as every skilled person knew without having to rely on proof.

The appellant, in writing and during the oral proceedings, contested the self-evident excellence of these values for the respirable fraction of the examples in the opposed patent and submitted that, in his view, these values were in a normal and ordinary range as expected by any person skilled in the art for such formulations.

In the absence of any comparative data with respect to the closest state of the art, the excellence of the quality of the respirable fraction values relative to the subject-matter of the opposed patent is only based on a subjective statement of the proprietor. Since this statement is contested by the appellant, there is a

need for proof, and the party that relies on this statement, ie, in the present case the respondent, has the burden of providing supporting data.

Since, as the respondent correctly states, there are no such data in the proceedings, the characteristics of the subject-matter of the patent in suit are to be regarded as at best equal to the characteristics of the formulations of the state of the art.

In such a case, there need be no incentive in the state of the art to make the step defined as the difference between the closest state of the art and the subject-matter of the opposed patent. It is enough that this step is generally known to the skilled person.

Additionally, as is explicitly indicated in document (6), it was not counter-intuitive to use HFC 227 instead of HFC 134a. Because of its lower vapour pressure, HFC 227 even had to be preferred, since it was closer to the well known propellants used before those were banned because of their ozone-damaging properties (see (16), page 186, lines 4 to 6).

With respect to the addition of ethanol to a suspension aerosol formulation based on HFC 227, the skilled person obviously knew that its respirable fraction value would decrease because of a lowered vapour pressure, since even the respondent declared the lower values of example 2 in the opposed patent with respect to example 1 as still being very high in the given circumstances. The reason for the addition of ethanol is not the optimisation of respirable fraction values but the better physical stability of the formulation.

3.5 Thus, neither the subject-matter of the main request nor that of the first to fifth auxiliary requests meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The patent is revoked.

The Registrar: The Chairman:

A. Townend U. Oswald