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OUR REF: PB - M8996

YOUR REF: 90913839.8-2114/0493437

10th January 1997

The European Patent Office,
Erhardstrasse 27,
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Germany

by facsimile page 1 of 18
confirmation by mail

Dear Sirs, 90913839.8 - 2114 Opp.

Re: European Patent No. 0493437
of Riker Laboratories, Inc. and Opposition
Thereto by Jago Pharma AG

We file, herewith, our Observations in respect of the above matter.

Confirmation copy, together with a copy for the other party, will follow by mail.

Yours faithfully,

P.A. BOWMAN
LLOYD WISE, TREGEAR & CO.

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European Patent No. 0 493 437
of
Riker Laboratories, Inc.

and Opposition thereof by

Jago Pharma AG

Reply of Patentee

I. Request

Patentee requests that the Opposition be dismissed and the patent upheld in its granted form. In the event that the Opposition is not withdrawn or dismissed upon the basis of this reply, Patentee requests an Oral Hearing.

II. General Remarks

A. The grounds for opposition raised by the Opponent are those of Art. 100 a) EPC, in particular an alleged lack of novelty and inventive step (page 1 of the Opposition paper). Under Section 2 of the Opposition paper, the Opponent also criticizes the experimental investigations disclosed in the present patent, as they were carried out "only ... for the combination of the propellant 134a (1,1,1,2-tetrafluoroethane) with ... Epikuron 200, Span 85 and oleic acid."

The relevance of this criticism for the present opposition is unclear; it would appear to be an argument related to Art. 84 EPC, which is in any case unavailable in Opposition proceedings. Nevertheless it is to be noted that the experiments reported employ exemplary and relevant propellants (P134a and perfluoropropane) as well as exemplary and several relevant surfactants. A series of experiments were performed and disclosed in the patent, involving the comparison of a multitude of different aerosol compositions according to the invention, compositions prepared via the admixture of propellant, surfactant and medicament according to conventional procedures and compositions prepared with no surfactant. These experiments and their results are more than sufficient to demonstrate the effectiveness of the compositions according to the invention and to support the claimed subject matter.

B. The Opponent also claims under section 2 of the Opposition paper, that "claim 1 comprises aerosol compositions with coated medicament particles irrespective of how the coating comes about ..." and applies this line of argument throughout their opposition paper. The Opponent submits a number of prior art documents concerned with suspension aerosol formulations comprising of admixtures of CFC-propellants, propellant-soluble surfactants and medicament, in which in some documents it is disclosed that the soluble surfactants exert their activity by forming a film on the

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dispersed particles in the aerosol suspension. The Opponent tries to give the impression that such film formation is the same as the coating referred to in claim 1 of the present patent. This argument of the Opponent is however based on a misinterpretation of the wording of claim 1.

From the wording of the main claim and the description of the present patent, it is readily understandable that the solid medicament is coated with propellant-insoluble non-perfluorinated surfactant prior to dispersion in the aerosol propellant. This understanding is clearly supported by the patent specification, for example

> "It has been found that non-perfluorinated surfactants which are insoluble in a propellant may nevertheless be used with such a propellant to form stable dispersions of powdered medicament provided the powdered medicament is pre-coated with the non-perfluorinated surfactant prior to dispersing the powdered medicament in the propellant..." (page 3, lines 1-7, see also page 3, lines 17-25, emphasis added).

Further, the patent specification discloses that

> "This result is particularly surprising in view of the fact that the same stable dispersions cannot be achieved by simple admixture of the surfactant, propellant and medicament." (page 3, lines 25-28)

According to this observation, the coating in aerosol suspension (previously noted for propellant, propellant-soluble surfactant and drug systems) does not take place in those systems where the non-perfluorinated surfactant is substantially insoluble in propellant. Thus the argument presented by the Opponent that claim 1 refers to "...aerosol compositions with coated medicament particles irrespective of how the coating comes about ...", especially coating in aerosol suspension, is incorrect.

III. Subject Matter of the Claims

Claim 1 of the present patent claims

1) a self-propelling, powder dispensing aerosol composition comprising:
2) at least 0.001 wt % of finely-divided solid medicament
3) coated with a non-perfluorinated surface-active dispersing agent
4) which constitutes at least 0.001% wt of the coated solid material
5) and suspended in an aerosol propellant in which non-perfluorinated surfactant is substantially insoluble, requiring more than 10,000 parts of propellant to dissolve one part of the surfactant at room temperature.

Claims 2 to 10 relate to further embodiments of the aerosol compositions of claim 1, which are further defined with respect to the preferred amount of dispersing agent, average particle size of the medicament, amount of the medicament in the composition, preferred ratio of medicament:dispersing agent, preferred dispersing agents, medicaments, propellant and adjuvants and the preferred amount of propellant and adjuvant.

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Claim 11 discloses

1) a method for preparing a self-propelling, powder dispensing aerosol composition comprising:

2) a) coating a finely divided solid medicament with non-perfluorinated surface-active dispersing agent in a solvent in which the said medicament is substantially insoluble,

3) b) separating the coated solid material from the solvent by filtration,

4) c) drying the coated finely divided solid material

5) d) high energy dispersing said material in an aerosol propellant (in which surface-active dispersing agent is substantially insoluble, requiring more than 10,000 parts of propellant to dissolve one part of the surfactant at room temperature) such that the aerosol composition comprises at least 0.001 wt % of said medicament and at least 0.001 wt % of the said material is the non-perfluorinated surfactant.

Claim 12 is directed to a method of claim 11 for preparing a composition as defined in any one of claims 1 to 10.

IV. Novelty

Opponent argues under section 16 of the opposition paper that the claimed subject matter of the patent is anticipated by D17 and D18, which represent prior rights in respect of the present patent. The disclosures of D17 and D18 are discussed further in sections 13 and 14 of the opposition paper, respectively.

Section 13: The Opponent puts forth that D17 discloses suspension aerosol formulations comprising of a medicament (identical to patent at issue), with a concentration in the range 0.01 to 5 wt % of total formulation, a surfactant (substantially identical to patent at issue), weight ratio 1:100 to (>)10:1 surfactant: drug, P134a, 60-95 wt %, and an adjuvant, weight ratio 50:50 to 99:1 P134a : adjuvant.

In the aerosol formulations according to D17, the surfactant is dissolved and found (as a dissoluted species) in the liquified propellant system. D17 does not disclose aerosol compositions comprising surfactant-coated medicament particles (according to features 2) and 3) of claim 1, see Section III, *supra*) and propellant.

The invention according to the present patent teaches that non-perfluorinated surfactants which are insoluble in a propellant may be used to form a stable dispersion of powdered medicament provided the said medicament is coated with the said surfactant prior to dispersing the powdered medicament in the propellant (page 3, lines 1-7). Thus in the aerosol compositions of the present invention, the surfactant is concentrated as a coating on the suspended medicament particles.

D17 does not anticipate the teaching or the aerosol compositions of the present patent. The present patent is clearly new over D17.

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Section 14: The Opponent is of the opinion that the disclosure for fentanyl citrate formulations common to D18, WO-A-90/07333 filed 4.1.1990, and D19, the priority application GB 8900267.9 filed 6.1.1989, represents a prior art which is prejudicial as to novelty for the patent at issue.

In particular, the Opponent argues that D19 (and D18) teaches solution or suspension formulations comprising fentanyl citrate 0.1-1.0 wt %, surfactant, amounts to 01.-1.0 wt % for Span 85 or in the case of lecithin 1:1 to 1:16 ratio effective substance:lecithin, solvent 5-25 wt % and P134a as propellant, referring to D18 page 2, line 28 to page 3, line 4 and to D19 page 2, lines 8-11 and page 3, lines 7-11.

However, the priority application does not disclose the use of P134a alone as the propellant; this was only introduced in D18 at the International filing date. Rather, D19 discloses on page 4, 3rd paragraph "[o]ther preferred propellant systems ... comprise 1,1,1,2,-tetrafluoroethane, a surface active agent and at least one compound having a higher polarity than 1,1,1,2-tetrafluoroethane." Hence the "propellant" disclosed in D19 is in fact a ternary propellant system including P134a. In such ternary P134a-based propellant systems, the non-perfluorinated surfactant is soluble. Thus, the common disclosure for D18/D19 does not teach the application of substantially propellant-insoluble non-perfluorinated surfactants according to feature 5) of claim 1.

Furthermore the D18/D19 common disclosure for fentanyl citrate formulations does not disclose the application of surfactant-coated medicament particles according to features 2)-3) of claim 1 and features 2)-4) of claim 11 of the present patent for the preparation of aerosol formulations.

Thus, the present patent is novel over D19, and novel over the disclosure of D18 as far as it is prior art in respect of the present patent.

V. Inventive Step - Problem-Solution Approach

In the Opposition paper the Opponent offers a number of combinations to substantiate the alleged lack of inventive step of the independent claims 1 and 11. Basically the combinations can be ordered in two groups: D1 alone or with D3-D8 (and maybe D9) (see sections 4-5 and 9) and D11 with each D1, D3-D10 (see section 11). Apparently the Opponent was unable to decide between D1 or D11 as the closest prior art. Also, the Opponent obviously did not consider inventive step in view of the technical problem actually solved by the subject matter claimed. D1 and D11 as closest prior art will be discussed, individually, below.

A. D1 as Closest prior art

D1 filed on April 4, 1963 discloses compositions for inhalation therapy in which solid drugs, specifically epinephrine or isoproterenol, are dispersed in a non-toxic propellant employing a fatty alcohol as a dispersing agent, in particular oleyl alcohol or in

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