

**BEFORE CONTROLLER OF PATENTS
THE PATENT OFFICE, DELHI**

THE PATENTS ACT 1970
(Section 15)

In the matter of divisional application
No.3513/DELNP/2005 dated 8th August, 2005
by Advanced Inhalation Research INC. US

Hearing held on 6th April, 2009

Present:

1. Shri Durga Das Bhatla ----- Agent representing the applicant
2. Dr.Rohit Rathore ----- Examiner of Patents & Designs

ORDER

M/s Advanced Inhalation Research INC. , a US Corporation filed the above mentioned application on 8th August, 2005 through M/s Remfry & Sagar, Gurgaon India, claiming the priority to PCT Application No.PCT/US2003/027618 dated 4th September, 2003 which in turn claimed the priority of US Patent Application No.10/392,333 dated 19th March, 2003.

2. On the receipt of the request for examination on 9th March, 2006 the said application was examined. The application as originally filed contained 28 claims. The claim 1 to 27 relates to method for treatment a disease characterised by airway (such as chronic obstructive pulmonary disease) comprising administering to a patient in need thereof via inhalation a pharmaceutical composition comprising trospium wherein such patient achieves an effective therapy for atleast 10 hours. Claim 28 relates to pharmaceuticals composition inhalation comprising trospium and formoterol. The First Examination Report was issued on 30th January, 2008 which interalia contained following objections.

1. Claims 1-27 fall within the scope of such clause (i) of section 3 and claim 28 falls within the scope of such clause (d) & (e) of section 3
 2. Claims 28 do not sufficiently define the invention as indicated therein.
3. The agents for applicant re-submitted the document on 19th June, 2008 along with their submissions in response to the above mentioned objections. In their submissions they stated that in the light of objections claims 1 to 27 have been deleted. They further stated that claim 28 has been revised to further define the

composition. On the scrutiny of the claims, it was observed that the applicants have submitted 11 claims related to a drive particular formulation. In response to the above mentioned objections relating to section 3 (d), the applicants submitted that the claimed invention is a novel composition and may accordingly not be objected to under section 3(d). Further, with respect to the objection under section 3(e), they submitted that the claimed composition is a dry powder wherein the particles that comprise the powder have specific physical characteristics. According to the applicants, it is the physical characteristics of the dry powder format of the particles in combination with the essential components that provides a novel and synergistic combination as opposed to a mere admixture resulting in simple aggregation of the properties.

4. The application with amended sets of claims was again re-examined and the examination report was sent to them on 30th January, 2009 with the following objections

(1) Subject matter of claims as amended lack inventive step in view of cited documents (i) US 5998430 (ii) WO03/079885 (iii) DE19921693 (iv) DE4425255 (v) US6461591 and (vi) WO01/13893. It was also pointed out that the claims before amendments related to method of treatment and a pharmaceutical composition. It may be further noted that amended claims relating to formulation comprises leucine and trospium. However in the description it has been mentioned that leucine in the composition is used as a preferred ingredient but not essential as a part of composition to bring out the synergism in the composition.

(2) Your observations vide letter dated 18.6.2008 regarding synergism of the formulation u/s 3(e) have been considered but still do not meet the requirement. In this connection it may be noted that revised claims 1-11 still fall within the scope of such clause (d) & (e) of section 3 of the Indian Patent Act. It may also be noted that use of leucine as a one of the ingredient of the composition has been described as a preferably used ingredient but not as a essential part of the composition in order to be responsible for synergism. Further the description also does not provide sufficient support for enhancement of the efficacy of the claimed formulation.

5. The applicants were offered an opportunity of being heard on 16th February, 2009. However, the said hearing was refixed on 6th April, 2009 as per the request made by the applicant's agent for the postponement of the said hearing date. Accordingly, applicants were given a notice to that effect vide this office letter dated 6th March, 2009 to attend the hearing on said date.

6. During the hearing as well as vide their letter dated 30th January, 2009 the applicants submitted the following observations.

(a) US Patent 5,998.430 is simply not relevant. The patent relates to a sterile aqueous solution of trospium chloride for intravesical administration (e.g., directly into the bladder by a catheter) for the treatment of bladder dysfunction. The claims are directed to a dry particulate formulation comprising trospium and at least 70% leucine with a defined fine particle fraction. There is no mention in the patent of an amino acid as an ingredient, much less in an amount of at least 70% by weight. The fact that the reference is missing that limitation alone should be sufficient to establish that the claims are novel. There is no teaching on this record that an intravesical formulation should be or even can be formulated with leucine. That is, why would you choose to introduce leucine to the bladder if trospium alone worked? Absent motivation to make the claimed invention, the claims should be considered inventive.

The claims require the product to have a fine particle fraction of at least 50%, thereby rendering it suitable for administration by inhalation. Because the patent relates to an intravesical formulation, there is obviously no teaching of fine particle fraction, as that is relevant only in the context of inhalation. That is the aerodynamic properties of the product are not relevant if one intends to dissolve or suspend the powder. Further, the claims are directed to a dry particulate form. The patent is related to an aqueous solution or suspension.

The claimed formulations are useful for treating obstructive respiratory ailments and are delivered directly to the airways. The patent is related to treating bladder ailments and administers directly to the bladder. The formulations differed because the ultimate use differs. Thus, although the reference teaches a formulation that contains trospium, the similarities between the claims and reference cease there.

With respect to showing a difference between the formulation of the prior art and the claims, the formulation in the patent is administered differently for a different purpose. While it is theoretically possible that one could administer trospium chloride in a sodium chloride solution to the pulmonary system and achieve a beneficial result, the reference does not teach that this is possible or desirable.

Therapeutic efficacy of the aqueous solution aside, please note that an aqueous solution cannot be administered by a dry powder inhaler. Dry powder inhalers have practical advantages over nebulizers used for administering aqueous solutions (many patents discussing dry powder inhalers discuss these practicalities). Therefore, while therapeutically beneficial, the aqueous solutions

also have practical disadvantages for pulmonary delivery.

Issues that arise in designing a formulation for dry powder delivery rests in making product that has good to excellent delivery (a high fine particle fraction) and stability little change in fine particle fraction when exposed to heat and humidity).

- (b) **U.S. Patent No.6, 461,591:** The document does not disclose any aerosol formulations that contain trospium or leucine. In fact, all of the formulations exemplified were based on ethanol as the solvent. The primary reference cited by the Examiner, the '430 patent was directed to aqueous compositions of trospium for the treatment of bladder and urinary dysfunctions. It is unlikely that such a composition can be used with the method described in the '430 patent.
- (c) **DE19921693:**The said document is directed to anticholinergically effective compounds and beta mimics. However the '693 fails to disclose a either trospium or leucine in combination with formoterol or salmetrol. The reference does not suggest or provide guidance to one skilled in the art to make a long acting aerosol formulation. The reference is simply not relevant to the claimed invention.
- (d) **DE4425255:** The document is directed to particulate formulations for administration by inhalation. The reference fails to teach either trospium or leucine in the aerosol formulation. The reference fails to disclose a long acting aerosol formulation. As such, the reference is simply not relevant.
- (e) **WO 03/13893:**The document discloses the use of leucine in formulations. However, the reference fails to disclose the use of trospium or formeterol.The reference does not provide any suggestions of combining leucine with trospium for a long acting aerosol formulation.
- (f) **WO 03/079885:**The '885 reference is not prior art against the instant application because the priority date of the instant application predates the publication date the '885 reference. It is respectfully submitted that the instant application is a continuation is part of U.S. Application NO.10/392,333 filed March 19, 1993 which claims the benefit of U.S. provisional application Nos.60/366,479, 60/366,449, 60/354, 60/366,487 and 60/366,440. The publication date of the '885 reference is 2 October, 2003.
- (g) None of the cited references teach the use of trospium in a long acting formulation or trospium in combination with leucine for aerosol formulation. The primary reference cited by the learned Examiner, U.S. Patent No.5,998,430, is directed to aqueous solutions of trospium which are not useful for the aerosol

formulation as claimed herein. Since the cited reference is not useable for the intended purpose here, the teaching itself cannot be combined to achieve the claimed invention. A mere admixture according to the prior art teachings, as suggested by the learned Examiner, will result in a combination that is non-useable for inhalation. Furthermore having an aqueous mixture will limit the use of the formulation for the delivery of a substantial number of drugs, peptides and proteins due to lack of long term stability and degradation. As such, the combination of trospium and leucine is novel and unobvious over the cited prior art.

(h) "In assessing the inventive step involved in a invention based on a combination of features, consideration must be given to whether or not the state of the art was such as to suggest to a skilled person precisely the combination of features claimed. The fact that an individual feature or a number of features were known does not conclusively show the obviousness of a combination." (Draft Manual 4.6.5). In the instant case there is no suggestion to a skilled person of the precise combination of elements claimed herein.

7. I have gone through the submissions made by the agents for the applicant as well description and claims of this application. As per the originally filed claims, only claim 28 was related to pharmaceutical composition for inhalation comprising trospium and formoterol and remaining were related to method of treatment. On the basis of this claim the applicants have amended the claims for a dry particulate formulation. In the amended claim 1 the applicants have claimed a particulate formulation comprising atleast 70% by weight of leucine and about 10 % or less by weight of trospium, wherein the composition is characterise by fine particle fraction of atleast 50% and also containing a phospholipid. On pursuing the description given on page 2 of the specification, the applicants have stated that the inventions relates to a pharmaceutical composition comprising trospium. However, a beta-2 agonist (formoterol) can be used as a second active agent in a preferred embodiment. Similarly, on page 4 of the specification it has been stated that use of leucine and phospolipid in the composition is a preferred one but not essential.

Therefore, from the above description it appears that invention of the applicant is in the use of trospium in the preparation of dry particulate formulation which is used to achieve and maintain relief of diseases such chronic pulmonary disorder. However, the applicants themselves have admitted on page 2 and 3 that the patient suffering from asthma, chronic obstructive pulmonary disease (COPD), restriction of bronchial airways, or bladder diseases, such as urinary incontinence can be treated by practicing the instant invention. The use of trospium chloride in

the aqueous solution form has been disclosed in the US Patent No.5,998,340 for the treatment of bladder dysfunction. Therefore use of tiroprium chloride for the treatment of diseases such as urinary incontinence or bladder dysfunction are already known. The other ingredients such leucine are used to prepare dry particulate formulation instead of aqueous solution. It can also be observed from the description given on page 15 (line 28 - 30) that while all formulations provide bronchial protection, the dry powder TrCl formulation provides even greater protection as compared to the aqueous TrCl formulation. It means that aqueous TrCl formulation also provide protection to bronchial diseases. In view of the above disclosure in the prior art and description of the instant application, it appears that instant invention is nothing but mere use of known substance without any enhancement in the efficacy of the composition which is not patentable under section 3(d) of the Patents Act, 1970.

I have also gone through the comparison of various formulations given in the specification on page 10, 11 and 12 as well as in the submissions but none of the formulations has been compared in the absence of leucine to prove that high leucine formulation with tiroprium result in excellent fine particle fractions as mentioned in their submissions. Further, the applicants have not given any comparative data with respect to aqueous TrCl formulation and dry powder TrCl formulation to prove enhancement in the efficacy of the instant invention. In the light of the above, I am of the opinion that instant invention is not patentable under section 3(d) of the Patents Act 1970.

Having considered all the facts, submission made by the agent for the applicant during the hearing and as well as all the documents on record and also in view of my above findings, I hereby refuse this application to proceed further for grant of patent as same is not patentable under the provisions of section 3(d) of the Patents Act 1970.

Dated, the 04th day of August, 2009.

(Dr. K.S. Kardam)
Deputy Controller of Patents & Designs

Copy to : M/S Remfry & Sagar,
Gurgaon, India