IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Horst OLSCHEWSKI et al.
Title:	TREPROSTINIL ADMINISTRATION BY INHALATION
Appl. No.:	12/591,200
Filing Date:	11/12/2009
Examiner:	Sarah Elizabeth Townsley
Art Unit:	1629
Confirmation Number:	4093

PRE-APPEAL BRIEF CONFERENCE REQUEST FOR REVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants file this Pre-Appeal Brief Conference Request together with a Notice of Appeal.

REMARKS

The sole remaining rejection – a rejection of claims 18, 25, 27-30 and 32-40 under 35 U.S.C. § 103(a) over Chaudry (US 2004/0265238) in view of Cewers (USPN 6,357,671) – should be withdrawn. The Office has not established a reason to combine the references as relied upon in the rejection, and even if the references were combined as proposed, the combination does not teach or suggest several elements of the claims. In addition, objective indicia of non-obviousness, including unexpected results and commercial success, further undermine any hint of obviousness.

Chaudry generally relates to inhaled drugs for treating pulmonary hypertension and lists at least five categories of drugs encompassing a litany of specific compounds. (paragraphs 22-26). The rejection focuses on one element of this expansive disclosure: "[v]asodilators for use herein also include prostaglandins (Eicosanoids), including prostacyclin (Epoprostenol) and prostacyclin analogs, including Iloprost and Treprostinil" (paragraph 26). Importantly, Chaudry teaches that not only are these diverse categories of

4840-3273-2194.1

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

drugs interchangeable, but that "***any other compound*** capable of treating pulmonary hypertension" can be used (paragraph 27 (emphasis added)). Chaudry's disclosure regarding methods of administration is equally broad and, in fact, covers "***any*** [] conventionally known method of administering inhalable medicaments," but does disclose nebulization as a preferred approach (paragraph 52). Thus, Chaudry discloses administering "any" compound that can treat pulmonary hypertension using "any" known method of administering the drug by inhalation.

Despite this broad disclosure, Chaudry does not teach a "pulsed ultrasonic nebulizer," as required by the claims, and Cewers is cited to remedy this deficiency. Yet, the rejection offers no particular reason why one would combine Cewers with Chaudry as proposed, including a reason to select a pulsed ultrasonic nebulizer from among the many types of known nebulizers. This is reason enough to withdraw the rejection.

Even if Chaudry and Cewers were combined from among the many different permutations of drug-device combinations to arrive at a pulsed ultrasonic nebulizer and treprostinil combination, the combination would fail to teach at least two features of the claims: (1) the number of breaths per single event dose (all claims require 18 or less breaths per event); and (2) the amount of drug delivered to the patient per single event dose (all claims require 15 to 90 micrograms per event) (collectively, "Event Dose Features"). This is another independent reason to withdraw the rejection.

Any hint of obviousness is overshadowed by the surprising and unexpected advantages of the claimed invention. Chaudry teaches the interchangeability of the drugs and devices as discussed above. Thus, one of ordinary skill in the art would not have predicted the dramatic advantages that result from selecting treprostinil over iloprost, for example, for use in a pulsed ultrasonic nebulizer when adjusted to achieve delivery of the drug according to the Event Dose Features. For example, treprostinil, but not iloprost, can be administered with a pulsed ultrasonic nebulizer so that its therapeutically effective single event dose is inhaled in 18 or less breaths by a human. This could not be predicted based on Chaudry and Cewers. *See* Advisory Action at 2 ("One of ordinary skill in the pharmaceutical arts appreciates that clinical results for a given compound cannot be predicted in advance…."). And FDA has approved a product, Tyvaso®, for such an administration regimen. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) ("While FDA approval is

4840-3273-2194.1

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness."). These unexpected advantages are described in Rule 132 declarations from Dr. Rubin (filed May 23, 2012) and Dr. Gotzkowsky (filed Aug. 10, 2012). In addition, these advantages are directly connected to the Event Dose Features, which are absent in the combined disclosures of Chaudry and Cewers.

The Office asserts that one of ordinary skill in the art would somehow arrive at the therapeutically effective single event treprostinil dose "from 15 µg to 90 µg … inhaled in 18 or less breaths by the human" recited in the present claims from a treprostinil sodium concentration of 0.1-10 mg/ml in Chaudry's prophetic example 4. Advisory Action at p. 2. Yet, the Office does not explain how treprostinil sodium concentration in a solution *prior to* nebulization not associated with any particular type of nebulizer would permit one of ordinary skill in the art to achieve a therapeutically effective single event treprostinil dose that is (a) inhaled in 18 or less breaths by the human (b) such that 15 to 90 micrograms of treprostinil is delivered to the patient.

In fact, Voswinckel 2009 (submitted with the reply filed April 28, 2014) provides comparative experimental evidence that iloprost (disclosed in Chaudry's paragraph [0026] next to treprostinil) is *not* useful for treating pulmonary hypertension when administered by inhalation in less than 3 minutes (high dose, low breath regimen) because iloprost induces unacceptable side effects. This side-by-side experimental evidence represents an unexpected result based on selecting treprostinil for use with a pulsed ultrasonic nebulizer in a high dose, low breath regimen, which would not have been predicted or expected based upon Chaudry's teaching of interchangeability. *See e.g.*, Voswinckel (2009), p. 54, sentence bridging left and right columns: "A dose of more than 5 µg iloprost per inhalation or a reduction of inhalation time to less than 3 min induces in most patients caused considerable systemic prostanoid side effects like hypotension, dizziness, headache, jaw pain, nausea or [diarrhea]." Thus, one of ordinary skill in the art would not have expected to be able to reduce the number of breaths down to "**18 or less breaths** by the human" for any of the compounds disclosed in Chaudry's paragraphs 0022-0027, including treprostinil.

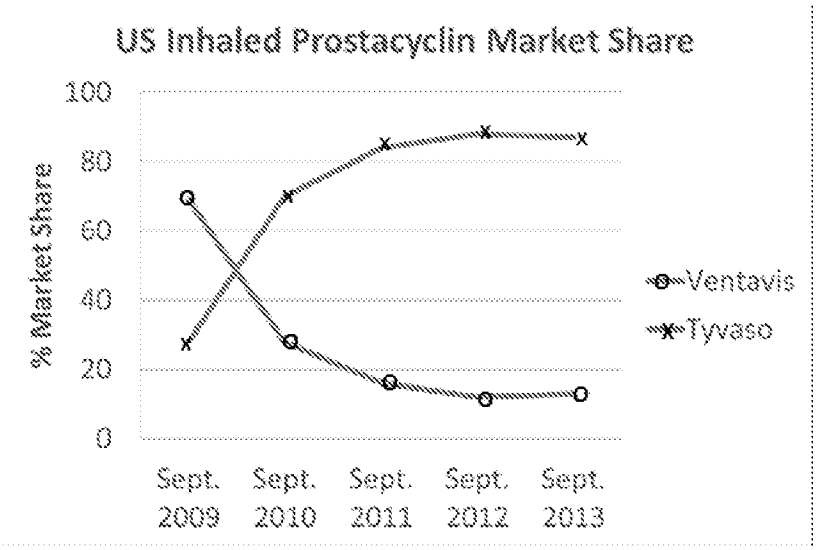
The PTO admits (Final Office Action, p. 16) that "treprostinil has certain advantages over iloprost, such as reduced or no side effects at higher doses." Despite this admission, the PTO did not find these advantages of treprostinil over iloprost to be surprising or unexpected.

4840-3273-2194.1

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

Yet, a person of ordinary skill in the art would not have had any way of knowing that this result would have been possible for treprostinil using a pulsed ultrasonic nebulizer, which had never before been tried in humans. Indeed, based on Chaudry, one of ordinary skill in the art would have expected (at best) that iloprost and treprostinil would be interchangeable and yield similar results. The PTO's disregard of treprostinil's documented advantages over iloprost because they are not unexpected in the PTO's view demonstrates that, contrary to *In re Piasecki*, 745 F.2d 1468 (Fed. Cir. 2012), the PTO is evaluating Applicants' rebuttal evidence against its obviousness conclusion, instead of evaluating the facts of the rebuttal evidence together with the facts upon which the initial obviousness conclusion was made, while restarting the evaluation of obviousness.

The rejection also overlooks other objective indicia of non-obviousness, such as commercial success of the presently claimed invention. Applicants submitted in the reply filed April 28, 2014 the following plot obtained from an independent tracking organization that compares the market share for two inhaled prostacyclin products: (1) Ventavis®, which is an inhalation solution containing iloprost formulated for inhalation via I-neb® AAD® (Adaptive Aerosol Delivery) System; and (2) Tyvaso®, which is a formulation of treprostinil intended for administration by oral inhalation using the Optineb-ir device. Both Ventavis® and Tyvaso® are prostacyclin analog products delivered by inhalation.



Tyvaso® was approved by FDA on or about July 30, 2009, whereas Ventavis® was approved in the U.S. on or about December 29, 2005. Despite the fact that Ventavis® was on

4840-3273-2194.1

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

the market around 3.5 years before Tyvaso®, Tyvaso® took away the majority of the U.S. market for inhaled prostacyclins from Ventavis® in a single year. During the time period from September 2009 to September 2010 when the majority of this rapid sales growth occurred for Tyvaso®, the assignee of the present application, which markets Tyvaso®, had an average 25.0% share of sales representative contacts in the pulmonary hypertension market compared to 30.7% share of sales representative contacts for the company marketing Ventavis® according to the data in the independent tracking service. Thus, Tyvaso® enjoyed tremendous commercial success during this period despite being supported by a substantially lower share of pulmonary hypertension sales representatives. This represents a strong case of commercial success that is attributable directly to the differences of the claimed invention over the prior art.

As previously explained by Dr. Rubin, one of the world's preeminent experts in treating pulmonary hypertension, patients who used both inhaled iloprost and the presently claimed invention reported statistically significant higher satisfaction based on the presently claimed invention's ease of use (Rubin Rule 132 Declaration at paragraphs 18-19). This ease of use results directly from the more convenient dosing reflected in the Tyvaso® label and recited in the instant claims. Thus, there is a clear nexus between the commercial success of Tyvaso and the present claims, confirmed by the above market share data and the patient satisfaction data reported by Dr. Rubin.

In view of the above remarks, the PTO should withdraw the sole remaining obviousness rejection.

Date March 9, 2015

Respectfully submitted,

By /Stephen B. Maebius/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicants
Registration No. 35,264

4840-3273-2194.1

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.