UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIQUIDIA TECHNOLOGIES, INC.,

Petitioner

v.

UNITED THERAPEUTICS CORPORATION,

Patent Owner

U.S. Patent No. 9,604,901

Issue Date: March 28, 2017

Title: Process to Prepare Treprostinil, the Active Ingredient in Remodulin®

~~**DECLARATION OF JEFFREY D. WINKLER, PH.D.**~~

~~**IN SUPPORT OF**~~ **PETITION FOR *INTER PARTES* REVIEW**

OF U.S. PATENT NO. 9,604,901

~~VI.~~IV. SUMMARY ~~OVERVIEW~~ OF THE '901 PATENT

A. Brief Description of the '901 Patent

~~I understand that the~~The '901 patent is entitled "Process to Prepare Treprostinil, the Active Ingredient in Remodulin®." The claims of the '901 patent are product-by-process claims. These claims include one independent (claim 1) and eight dependent claims.

The '901 patent discloses an "improved process" to prepare prostacyclin derivatives such as treprostinil. (Ex. 1001, Abstract.) Claim 1 is drawn to a pharmaceutical batch comprising treprostinil or a salt thereof. (*Id.*~~,~~. at cols. 17-18, claim 1.)

The independent claim includes limitations that the claimed composition is made by a process comprising: (a) alkylating a benzindene triol; (b) hydrolyzing the resulting product to form a solution comprising treprostinil; (c) contacting that treprostinil solution with a base to form a salt of treprostinil; (d) isolating the salt of treprostinil and; (e) optionally reacting the salt of treprostinil with an acid to form treprostinil. The claimed composition contains at least 2.9 g of treprostinil or its salt.

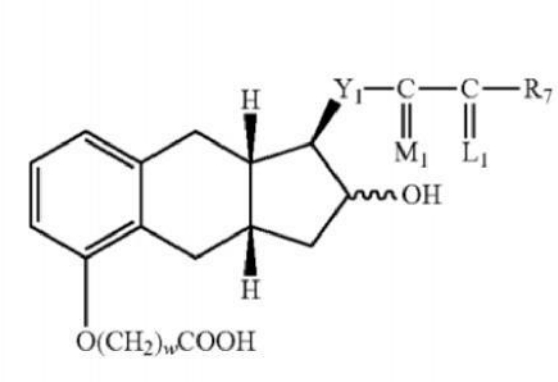
~~The claim limitations of the '901 patent are as follows:~~

	Claim Limitation
1[a]	A pharmaceutical batch consisting of treprostinil or a salt thereof and impurities resulting from:
1[b]	(a) alkylating a benzindene triol,
1[c]	(b) hydrolyzing the product of step (a) to form a solution comprising treprostinil,

1[d]	(c) contacting[1] the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil,
1[e]	(d) isolating the salt of treprostinil, and
1[f]	(e) optionally reacting the salt of treprostinil with an acid to form treprostinil, and
1[g]	wherein the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt.
2	The pharmaceutical batch of claim 1, which has been dried under vacuum.
3	A pharmaceutical product comprising a therapeutically effective amount of treprostinil from a pharmaceutical batch as claimed in claim 1.
4	A pharmaceutical product comprising a therapeutically effective amount of a salt treprostinil from a pharmaceutical batch as claimed in claim 1.
5	The product of claim 4, wherein the salt is the diethanolamine salt of treprostinil.
6	A method of preparing a pharmaceutical product from a pharmaceutical batch as claimed in claim 1, comprising storing a pharmaceutical batch of a salt of treprostinil as claimed in claim 1 at ambient temperature, and preparing a pharmaceutical product from the pharmaceutical batch after storage.
7	A method as claimed in claim 6, wherein the salt of treprostinil is a diethanolamine salt.
8[a]	A method of preparing a pharmaceutical batch as claimed in claim 1, comprising:
8[b]	(a) alkylating a benzindene triol,
8[c]	(b) hydrolyzing the product of step (a) to form a solution comprising treprostinil,
8[d]	(c) contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil,
8[e]	(d) isolating the salt of treprostinil, and
8[f]	(e) optionally reacting the salt of treprostinil with an acid to form treprostinil.
9	A method as claimed in claim 8, wherein the salt of treprostinil is a diethanolamine salt.

More specifically, the ~~The~~ '901 patent discloses a process for the preparation of a compound of Formula I (which includes treprostinil) shown below~~,~~:

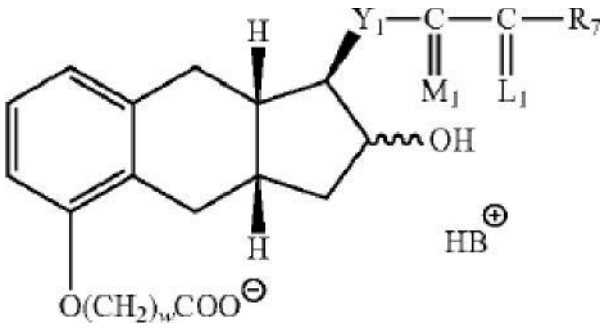
[1] Certificate of correction: "(c) containing the" should be –"(c) contacting the--." (Ex. 1006 ~~at~~, 2.)



(Ex. 1001 at col. 2:7-21.), where: w = 1, 2, or 3; Y_1 is trans-CH=CH-, cis-CH=CH-, $-CH_2(CH_2)_m-$, or —CC—, m is 1, 2, or 3; M1 is α-OH: β-R_5 or α-R_5: β-OH or α-OR_2: β-R_5 or α-R5: β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group; L_1 is α-R_3: β-R_4, α-R_4: β-R_3, or a mixture of α-R_3: β-R_4 and α-R_4: β-R_3, wherein R_3 and R4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro; and R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5 inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7, is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_3$—CH=$C(CH_3)_2$, wherein —$C(L_1)R_7$ taken together is: (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl, (2) 2-(2-furyl)ethyl; (3) 2-(3-thienyl)ethoxy; or (4) 3-thienyloxymethyl. *(Id. at* cols. 2:46-3:15.) Treprostinil is the specific Formula I compound where w = 1; Y_1 is—$CH_2(CH_2)$m- and m is 1; M_1 is α-OH: β-R_5 or α-R^5: β-OH, wherein R_5 is hydrogen; L_1 is α-R_3: β-R_4, α-R_4: βR_3, or a mixture of α-R_3: β-R_4 and α-R_4: β-R_3, wherein R_3 and R_4 are

hydrogen; and R_7 is —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5 inclusive (p=3). (*Id.* at cols. 2:46-3:20; Winkler Decl., ¶27.)

The '901 patent discloses alkylating benzindene triol (a.k.a. treprostinil triol) with an alkylating agent and then hydrolyzing with a base to form a solution comprising treprostinil. (*Id.* at cols. 10:12-12:18.) The '901 patent further discloses contacting the solution from the alkylation and hydrolysis steps with a base to form a salt (*e.g.* using the base diethanolamine to form treprostinil diethanolamine salt) of Formula IS shown below (where B is diethanolamine and where the other variables are the same as for the treprostinil-specific version of Formula I explained above):



(*Id.* ~~at.~~, *3*:30-40).

Formula I is a general formula, while Formula IV is specifically treprostinil. Formula IVs is the formula for a generic salt formed from treprostinil. When "B" in Formula IVs is diethanolamine, as taught at columns 9, 12, and 14 of the '901 patent, Formula IVs is treprostinil diethanolamine salt. The resulting salt is:

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