

UNITED STATES PATENT AND TRADEMARK OFFICE

---

BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

---

*Ex parte* SHERRY A. LEONARD  
and  
KEITH A. JOHNSON

---

Appeal 2007-4216  
Application 10/462,901<sup>1</sup>  
Technology Center 1600

---

Decided: 1 February 2008

---

Before TEDDY S. GRON, CAROL A. SPIEGEL, and  
DONALD E. ADAMS, *Administrative Patent Judges*.

SPIEGEL, *Administrative Patent Judge*.

DECISION ON APPEAL

---

<sup>1</sup> Application ("the '901 application") filed 17 June 2003 and said to claim priority benefit to provisional application 60/389,242, filed 17 June 2002, and to provisional application "Attorney Docket No. 02486.0077.PZUS00," filed 11 June 2003 (Specification 1:6-9). The real party-in-interest is said to be EPIGENESIS PHARMACEUTICALS LLC (**APPELLANTS' BRIEF PURSUANT TO 37 C.F.R. § 41.37**, filed 22 December 2006 ("App. Br.") at 1.

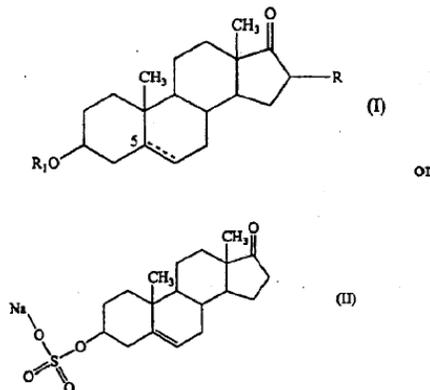
## INTRODUCTION

Sherry A. Leonard and Keith A. Johnson ("Appellants") appeal under 35 U.S.C. § 134 from an Examiner's final rejection of claims 1-22, all of the pending claims. We have jurisdiction under 35 U.S.C. § 6(b). We REVERSE.

## SUBJECT MATTER ON APPEAL

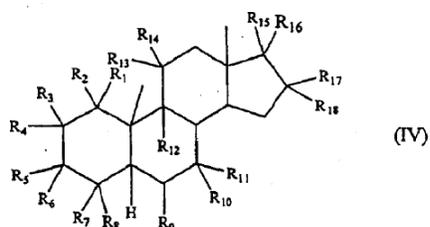
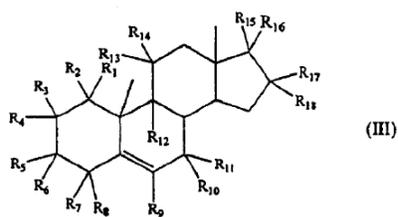
The subject matter on appeal is directed to (i) a pharmaceutical composition comprising anhydrous dehydroepiandrosterone ("DHEA," also known as prasterone, androstenolone, and dehydroandrosterone), or a salt or analog thereof, sealed in nebulizable form, as well as kits and uses thereof to treat asthma or chronic obstructive pulmonary disease or to reduce adenosine levels. Claim 1 is illustrative and reads as follows:

A pharmaceutical composition comprising an agent, wherein the agent comprises a compound as described by chemical formula (I), (II), (III), (IV) or (V), or a pharmaceutically or veterinarily acceptable salt thereof, in an anhydrous form thereof;



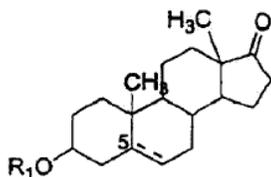
wherein the broken line represents a single or a double bond;

wherein R is hydrogen or a halogen; the H at position 5 is present in the alpha or beta configuration or the compound of formula (I) comprises either isomer or a racemic mixture of both configurations; and R<sub>1</sub> is hydrogen or a multivalent inorganic or organic dicarboxylate acid covalent[ly] bound to the compound of chemical formula (I);



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub> and R<sub>19</sub> are independently H, OH, halogen, C<sub>1-10</sub> alkyl or C<sub>1-10</sub> alkoxy; R<sub>5</sub> is H, OH, halogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy or OSO<sub>2</sub>R<sub>20</sub>; R<sub>15</sub> is (1) H, halogen, C<sub>1-10</sub> alkyl or C<sub>1-10</sub> alkoxy when R<sub>16</sub> is C(O)OR<sub>21</sub> or (2) H, halogen, OH or C<sub>1-10</sub> alkyl when R<sub>16</sub> is H, halogen, OH or C<sub>1-10</sub> alkyl or (3) H, halogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkenyl, C<sub>1-10</sub> alkynyl, formyl, C<sub>1-10</sub> alkanoyl or epoxy when R<sub>16</sub> is OH; or R<sub>15</sub> and R<sub>16</sub> taken together are =O; R<sub>17</sub> and R<sub>18</sub> are independently (1) H, OH, halogen, C<sub>1-10</sub> alkyl or C<sub>1-10</sub> alkoxy when R<sub>16</sub> is H, OH, halogen, C<sub>1-10</sub> alkyl or --C(O)OR<sub>21</sub> or (2) H, (C<sub>1-10</sub> alkyl)<sub>n</sub> amino, (C<sub>1-10</sub> alkyl)<sub>n</sub>, amino-C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, hydroxy-C<sub>1-10</sub> alkyl, alkoxy-C<sub>1-10</sub> alkyl, (halogen)<sub>m</sub>-C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, formyl, C<sub>1-10</sub> carbalkoxy or C<sub>1-10</sub> alkanoyloxy when

$R_{15}$  and  $R_{16}$  taken together are =O; or  $R_{17}$  and  $R_{18}$  taken together are =O or taken together with the carbon to which they are attached form a 3-6 member ring containing 0 or 1 oxygen atoms; or  $R_{15}$  and  $R_{17}$  taken together with the carbons to which they are attached form an epoxide ring; n is 0, 1 or 2; and m is 1, 2 or 3, with the proviso that (a)  $R_3$  is not H, OH or halogen when  $R_1, R_2, R_4, R_6, R_7, R_9, R_{10}, R_{12}, R_{13}, R_{14}, R_{17}$  and  $R_{19}$  are H and  $R_5$  is OH or  $C_{1-10}$  alkoxy and  $R_8$  is H, OH or halogen and  $R_{11}$  is H or OH and  $R_{18}$  is H, halogen or methyl and  $R_{15}$  is H and  $R_{16}$  is OH; (b)  $R_3$  is not H, OH or halogen when  $R_1, R_2, R_4, R_6, R_7, R_9, R_{10}, R_{12}, R_{13},$  and  $R_{14}$  are H and  $R_5$  is OH or  $C_{1-10}$  alkoxy and  $R_8$  is H, OH or halogen and  $R_{11}$  is H or OH and  $R_{18}$  is H, halogen or methyl and  $R_{15}$  and  $R_{16}$  taken together are =O; (c)  $R_5$  is not H, halogen,  $C_{1-10}$  alkoxy or  $OSO_2R_{20}$  when  $R_1, R_2, R_3, R_4, R_6, R_7, R_8, R_9, R_{10}, R_{12}, R_{13}, R_{14}$  and  $R_{17}$  are H and  $R_{11}$  is H, halogen, OH or  $C_{1-10}$  alkoxy and  $R_{18}$  is H or halogen and  $R_{15}$  and  $R_{16}$  taken together are =O; and (d)  $R_5$  is not H, halogen,  $C_{1-10}$  alkoxy or  $OSO_2R_{20}$  when  $R_1, R_2, R_3, R_4, R_6, R_7, R_8, R_9, R_{10}, R_{12}, R_{13}, R_{14}$  and  $R_{17}$  are H and  $R_{11}$  is H, halogen, OH or  $C_{1-10}$  alkoxy and  $R_{18}$  is H or halogen and  $R_{15}$  is H and  $R_{16}$  is H, OH or halogen;



wherein R is A-CH(OH)-C(O)- and A is hydrogen or a  $C_{1-22}$  alkyl or alkenyl group wherein the  $C_{1-22}$  alkyl or alkenyl group is not substituted or substituted with one or more  $C_1$ - $C_4$  alkyl groups, phenyls, halogens or hydroxyl groups, said phenyl is not substituted or substituted with one or more halogen [,] HO or  $CH_3O$ ;

wherein said dry powder pharmaceutical composition is [sic, in] particles of respirable or inhalable size.

[App. Br. at **VIII. CLAIMS APPENDIX**, emphasis and bracketed text added.]

### THE REJECTIONS AND ISSUES

The Examiner maintains that claims 1-13 and 15-22 are unpatentable under 35 U.S.C. § 102(e) as anticipated by Nyce<sup>2</sup> (Ans.<sup>3</sup> 3); that claim 14 is unpatentable under 35 U.S.C. § 103(a) as obvious over Nyce in view of Rossi<sup>4</sup> (Ans. 6); and, that claims 1-13 and 15-22 are provisionally unpatentable under the judicially created doctrine of obviousness-type double patenting in view of claims 1-20 of copending Application 10/462,927 ("the '927 Application") (Ans. 9).

The dispositive issues are whether Nyce discloses a pharmaceutical composition comprising an anhydrous DHEA-S compound; and, whether a pharmaceutical composition containing an anhydrous epiandrosterone compound as presently claimed would have been obvious in view of a prior art disclosure of a pharmaceutical composition containing a dihydrate epiandrosterone compound and its uses (App. Br. 3, 7 and 8).

---

<sup>2</sup> Nyce, Patent Application Publication US 2002/0032160 A1, entitled "Compositions & Formulations with an Epiandrosterone or a Ubiquinone & Kits & their Use for Treatment of Asthma Symptoms & for Reducing Adenosine/Adenosine Receptor Levels," published 14 March 2002.

<sup>3</sup> Examiner's Answer ("Ans."), mailed 12 March 2007.

<sup>4</sup> Rossi, US Patent 3,943,987, entitled "Reclosable Air-Tight Containers with Evacuation Means," issued 16 March 1976.

Appellants rely on Nakagawa<sup>5</sup> for teaching that dehydroepiandrosterone sulfate ("DHEA-S") is a dihydrate under normal temperature and humidity conditions, and that hydrated and anhydrous forms of DHEA-S have different properties (App. Br. 4).

#### FINDINGS OF FACT

The following findings of fact ("FF") are supported by a preponderance of the evidence of record.

##### A. Appellants' Application

[1] The disclosure of the '901 specification

relates to a sealed container containing a powder pharmaceutical composition comprising an agent and a pharmaceutically or veterinarily acceptable carrier or diluent, wherein the agent comprises a dehydroepiandrosterone (DHEA) compound, or analogue thereof, or hydrated form thereof, sealed in a nebulizable form wherein said dry powder pharmaceutical composition is particles of respirable or inhalable size. Preferably, the agent is dehydroepiandrosterone sulfate (DHEA-S), wherein the sulfate is covalently bound to DHEA. [901 Specification 8:28-33.]

[2] Preferably, the agent is DHEA-S in its dihydrate, rather than its anhydrous, form ('901 Specification 9:1 and 9-10; 14:14; 21:5-6; 37:16-18).

[3] Anhydrous DHEA-S is said to be very hygroscopic, with hydration occurring upon exposure to water, which causes interparticle bond

---

<sup>5</sup> Nakagawa et al. ("Nakagawa"), "The Properties of Water of Crystallization of Sodium Prasterone Sulfate," *Chem. Pharm. Bull.*, Vol. 29, No. 5, pp. 1466-69 (1981).

- formation resulting in larger agglomerates ('901 Specification 37:12-18; 39:10-11; 47:5-6).
- [4] "In contrast, the dihydrate form is already hydrated thus more stable, and thus . . . will not further form larger particles" ('901 Specification 37:16-18).
- [5] Thus, the "DHEA-S anhydrous form is stable as long as it picks up no water on storage" ('901 Specification 39:11-12).
- [6] Example 1 is said to describe jet milling anhydrous DHEA-S suspended in hexane and surfactant to produce particles of a size suitable for inhalation ('901 Specification 39:15-27).
- [7] Example 4 is said to describe the stability of anhydrous DHEA-S with and without lactose ('901 Specification 48:25-26).
- [8] According to the specification,

virtually anhydrous DHEA-S blended with lactose (50% w/w, nominally) stored at 50°C in sealed glass vials acquires a brown tinge that is darker for the lactose blend. . . .The higher rate of decomposition for the blend indicates a specific interaction between lactose and the virtually anhydrous DHEA-S. . . .The materials on accelerated storage became more cohesive with time as evidenced by clumping during sample weighing for chemical analysis. Based on these results, it is not possible to formulate virtually anhydrous DHEA-S with lactose. This is a considerable disadvantage since lactose is the most commonly used inhalation excipient for dry powder formulations. Continuing with the virtually anhydrous form would mean limiting formulations to neat powder or undertaking more comprehensive safety studies to use a novel

excipient. ['901 Specification 49:5-19, emphasis added.]

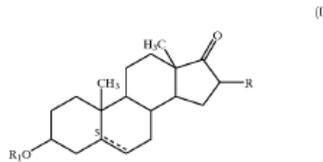
- [9] Anhydrous DHEA-S is also said to be more heat labile than hydrated DHEA-S ('901 Specification 9:10-11).

B. Nakagawa

- [10] According to Nakagawa, sodium DHEA-S exists in the dihydrate form (Nakagawa, 1467:1-2, 14-15; 1469:12-13).
- [11] Nakagawa reports that the anhydrous form of sodium DHEA-S is very hygroscopic, unstable to humidity, and readily transformed into the dihydrate form (Nakagawa, sentence bridging 1466-67; 1469:12-13).

C. Nyce

- [12] Nyce describes a pharmaceutical or veterinary composition comprising DHEA-S, i.e., the chemical of Formula (I)



wherein R is hydrogen, and R<sub>1</sub> is SO<sub>2</sub>OM, wherein M is Na, or analogs thereof, preferably administered as an aerosol or spray of respirable or inhalable particles (Nyce ¶¶ 18-23, 33 and 40).

- [13] Liquid pharmaceutical compositions may be prepared by combining the DHEA-S, e.g.,

with a stable vehicle, such as sterile pyrogen free water. Solid particulate compositions containing respirable dry particles of micronized active compound may be prepared by grinding dry active compound with a mortar and pestle, and then passing the micronized composition through a 400

mesh screen to break up or separate out large agglomerates. [Nyce ¶ 41.]

[14] Optionally, the pharmaceutical composition also comprises a dispersant, e.g., lactose, to facilitate formation of an aerosol (Nyce ¶ 41).

[15] Suitable compositions for use in a nebulizer typically comprises the active ingredient, e.g., DHEA-S, in water (Nyce ¶ 42).

D. Rossi

[16] Rossi describes a reclosable and resealable container having a primary vacuum tight seal which may be re-established after the container is opened and closed (Rossi 1:31-39).

[17] In one embodiment, the container is a drum which "may contain a variety of chemicals or pharmaceuticals or the like which require the absence of air to resist oxidation, loss of potency and the like" (Rossi 2:57-60).

E. The Examiner's position

[18] The Examiner found that Nyce disclosed the subject matter of appealed claims 1-13 and 15-22 (Ans. 3-6).

[19] In particular, the Examiner found that "the only disclosure of the compounds in question is as the anhydrous form" (Ans. 11).

[20] As to claim 14, the Examiner concluded that since Nyce disclosed a pharmaceutical composition, it would have been obvious to one of ordinary skill in the art to have placed Nyce's pharmaceutical composition in Rossi's vacuum-sealed container "to ensure the potency of said pharmaceutical, especially if the drug were susceptible to oxidation in the presence of air" (Ans. ¶ bridging 11-12).

F. Appellants' position

- [21] Appellants contend that "the Examiner's reference to a chemical formula showing no water does not establish that Nyce disclosed the anhydrous form" of DHEA-S (App. Br, 5).
- [22] In particular, Appellants point out that Nagakawa teaches that DHEA-S normally exists as the dihydrate since the anhydrous form of DHEA-S adsorbs water and is rapidly transformed into the dihydrate under normal conditions of temperature and humidity (App. Br. 4).
- [23] Appellants also point to the explicit teaching in their '901 specification at page 39, lines 10-13, that

. . .DHEA-S anhydrous form has low crystallinity and is very hygroscopic. The DHEA-S anhydrous form is stable as long as it picks up no water on storage. Keeping a partially crystalline material free of moisture requires specialized manufacturing and packing technology.

[App. Br. 4.]

- [24] Appellants argue that since Nyce fails to describe handling DHEA-S in a manner that would make or maintain its anhydrous form, Nyce does not anticipate any of claims 1-13 and 15-22 (App. Br. 5-6).
- [25] Appellants further argue that since Rossi does not make up for this deficiency in Nyce, all of the limitations of claim 14 are not taught by the combination of Nyce and Rossi, and the Examiner's obviousness rejection is in error (App. Br. 6-7).
- Other findings of fact follow below.

## DISCUSSION

### A. Nyce-based rejections

"For a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of a claimed invention must be identically shown in a single reference." *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990). Anticipation can be found when a claim limitation is inherent or otherwise implicit in the relevant reference. *Standard Havens Products, Inc. v. Gencor Industries, Inc.*, 953 F.2d 1360, 1369 (Fed. Cir. 1991). Thus, to affirm the Examiner's rejection of claims 1-13 and 15-22 in this case, each and every element of these claims must be identically shown in Nyce. The dispositive inquiry here is whether Nyce inherently or otherwise implicitly discloses a pharmaceutical composition comprising DHEA-S in its anhydrous form.

Nyce depicts DHEA-S in Formula (I), wherein R is hydrogen and R<sub>1</sub> is SO<sub>2</sub>ONa (FF 12). Evidently, the Examiner equates this chemical formula with the anhydrous form of DHEA-S (FF 19). However, chemical formulae "are mere symbols by which compounds can be identified, classified, and compared." *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963). Nyce does not expressly describe its disclosed compositions as comprising anhydrous DHEA-S or its analogs. Rather, Nyce describes compositions comprising DHEA-S in combination with water (FFs 13 and 15), optionally including lactose (FF 14). Nyce further describes using mesh screening to "break up or separate out large agglomerates" of dry DHEA-S when preparing pharmaceutical compositions (FF 13). Nyce fails to describe steps for making or maintaining DHEA-S in its anhydrous form. Thus, a fair reading of Nyce is that Nyce describes compositions implicitly comprising dihydrate DHEA-S as evidenced by Nagakawa (FFs 10-11). We note that such a

reading of Nyce is also consistent with the teachings in Appellants' specification (FFs 3-5 and 7-8).

Moreover, to the extent the chemical formulae in Nyce are generic to both forms of DHEA-S, this case is analogous to cases involving racemates. Courts considering issues related to racemates and their individual isomers have concluded that a prior art disclosure of a racemate does not anticipate the individual isomers of the racemate or render the individual isomers of the racemate obvious. *See In re May*, 574 F.2d 1082, 1090 (CCPA 1978) (holding that "the novelty of an optical isomer is not negated by the prior art disclosure of its racemate").

Based on the foregoing and in light of the evidence of record, we REVERSE the Examiner's rejection of claims 1-13 and 15-22 under § 102 as anticipated by Nyce. Additionally, in order to establish a prima facie case of obviousness, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). Since neither Nyce nor Rossi teaches or suggests a pharmaceutical composition comprising an anhydrous DHEA compound, we also REVERSE the Examiner's rejection of claim 14 under § 103(a) in view of Nyce and Rossi.

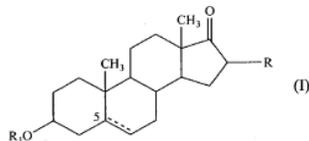
B. Provisional obviousness-type double patenting

Obviousness-type double patenting requires rejection of an application claim (1) when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned patent and (2) when the issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent. *See Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 967-68 (Fed. Cir. 2001). The courts have permitted "provisional" rejections to be made on the ground of double

patenting between the claims of two copending applications. *In re Mott*, 539 F.2d 1291, 1295-96 (CCPA 1976); *In re Wetterau*, 356 F.2d 556, 558 (CCPA 1966).

- [26] Appellants filed the '927 application, entitled "Dihydrate Dehydroepiandrosterone and Methods of Treating Asthma or Chronic Obstructive Pulmonary Disease Using Compositions Thereof," on 17 June 2003.
- [27] The '927 application is currently pending with no claims indicated as allowable.
- [28] The '927 application has one independent claim, claim 1, which reads as follows (emphasis added):

A powder pharmaceutical composition comprising an agent and a pharmaceutically or veterinarily acceptable excipient, wherein the agent comprises a compound as described by chemical formula (I), or a pharmaceutically or veterinarily acceptable salt thereof;



wherein R comprises H or halogen; the H at position 5 is present in the alpha or beta configuration or a racemic mixture of both configurations; and R<sub>1</sub> comprises a multivalent inorganic or organic dicarboxylic acid;

wherein said compound is a dihydrate crystal;  
wherein said dry powder pharmaceutical composition is particles of respirable or inhalable size.

[29] According to the Examiner, the anhydrous and dihydrate forms of the DHEA compounds in the claimed compositions of the instant application and the '927 application are not patentably distinct because both forms are known in the prior art and methods for interconverting the two forms are known (Ans. 12).

[30] Appellants argue that the two forms are patentably distinct because they differ in both structure and in physical and chemical properties as "illustrated throughout the specification including the examples" (App. Br. 8).

The involved subject matter is directed to pharmaceutical compositions containing DHEA, salts, and analogs thereof, in particles of respirable or inhalable size, wherein the DHEA, salts, and analogs thereof are either in anhydrous form, as instantly claimed, or in dihydrate form, as claimed in the '927 application. Whether both forms of DHEA compounds are known or can be interconverted is peripheral to the issue at hand, i.e., whether a person having ordinary skill in the art would have been replaced a pharmaceutical composition containing a dihydrate DHEA compound in inhalable or respirable particulate size form with an anhydrous DHEA compound with a reasonable expectation of success. Anhydrous DHEA compounds, e.g., DHEA-S, are very hygroscopic and unstable to humidity (FF 11). Appellants also point to the differences between anhydrous and dihydrate DHEA-S described in the instant specification and Examples (FF 30). For example, particles of anhydrous DHEA-S are said to form agglomerates whereas particles of dihydrate DHEA-S do not (FF 3); and, blends of lactose with "virtually" anhydrous DHEA-S are said to be impossible to formulate (FF 8).

The Examiner has not addressed the asserted or known differences in physical and chemical properties and all that would have been reasonably expected as a result e.g., the effect of agglomeration on pharmaceutical compositions requiring particles of respirable or inhalable size or the effect of the asserted inability to blend DHEA-S with lactose on compositions requiring a lactose excipient.

Therefore, based on the arguments and evidence before us, we must REVERSE the provisional rejection of claims 1-13 and 15-22 for obviousness-type double-patenting of claims 1-20 of the '927 Application.

#### MISCELLANEOUS REMARKS

Appellants and the Examiner should review the appealed claims for proper dependency and antecedent basis. For example, claim 4 limits the excipient recited in the pharmaceutical composition of claim 2 to a member of a specified Markush group. However, neither claim 2 nor claim 1 from which claim 2 depends, recites an excipient.

Appellants and the Examiner should also consider whether claims requiring a pharmaceutical composition containing a lactose excipient are enabled by a specification which states that "it is not possible to formulate virtually anhydrous DHEA-S with lactose" (FF 8).<sup>6</sup>

#### CONCLUSION

Upon consideration of the record and for the reasons given, it is ORDERED that the decision of the Examiner rejecting claims 1-13 and 15-22 under 35 U.S.C. § 102 as anticipated by Nyce is REVERSED;

---

<sup>6</sup> The definition of "virtually" anhydrous DHEA-S is not an issue before us.

Appeal 2007-4216  
Application 10/462,901

FURTHER ORDERED that the decision of the Examiner rejecting claim 14 under 35 U.S.C. § 103(a) as obvious in view of Nyce and Rossi is REVERSED;

FURTHER ORDERED that the decision of the Examiner provisionally rejecting claims 1-13 and 15-22 under the judicially created doctrine of obviousness-type double patenting is REVERSED; and

FURTHER ORDERED that the case be returned to the Examiner for action consistent herewith.

REVERSED

WILSON SONSINI GOODRICH & ROSATI  
650 PAGE MILL ROAD  
PALO ALTO, CA 94303-1050