

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

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Ex parte EDWARD N. HILL, THOMAS W. LEONARD,  
FREDERICK D. SANCILIO, KATHERIN M. SCHLIPP,  
DEAN SHIRAZI and ROBERT R. WHITTLE

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Appeal No. 2003-1019  
Application No. 09/524,132<sup>1</sup>

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HEARD: November 18, 2003

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Before WILLIAM F. SMITH, SCHEINER and GREEN, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the final rejection of claims 1-5, 8-22 and 25-48, the only claims remaining in the application.

Claims 1, 11, 15 and 30 are representative:

1. A composition of matter comprising:  
a mixture of estrogenic compounds, wherein said mixture comprises salts of conjugated estrone, conjugated equilin, conjugated  $\Delta^{8,9}$ -dehydroestrone, conjugated 17 $\alpha$ -estradiol, conjugated 17 $\alpha$ -dihydroequilin, conjugated 17 $\beta$ -dihydroequilin, conjugated 17 $\beta$ -estradiol, conjugated equilenin, conjugated 17 $\alpha$ -dihydroequilenin, and conjugated 17 $\beta$ -dihydroequilenin, and wherein said mixture comprises the same essential estrogenic compounds present in naturally derived equine conjugated estrogens;  
wherein said composition of matter is present in a chemically pure form.

11. A composition of matter comprising:  
a mixture of estrogenic compounds, wherein at least one of said estrogenic

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<sup>1</sup> Application for patent filed March 10, 2000.

compounds is a synthetic estrogenic compound, and wherein said mixture comprises the same essential estrogenic compounds present in naturally derived equine conjugated estrogens;

wherein said composition of matter is present in a chemically pure form.

15. A composition of matter comprising:

a mixture of estrogenic compounds, wherein said mixture comprises the same essential estrogenic compounds present in naturally derived equine conjugated estrogens;

wherein said composition of matter is present in a chemically pure form.

30. A method for analyzing conjugated estrogen constituents comprising the steps of :

preparing a solution containing conjugated estrogens, said solution comprising:  
a mixture comprising estrogenic compounds to be analyzed; and  
a mobile phase comprising:

an organic portion comprising between about 0.1% and about 30%  
(by volume organic portion) protic solvent and between about 70% and  
about 100% (by volume organic portion) polar aprotic solvent; and  
an aqueous portion;

and analyzing the conjugated estrogens solution utilizing a HPLC system.

The references relied on by the examiner are:

Townsend et al. (Townsend), "High-Performance Liquid Chromatographic Determination of Conjugated Estrogens in Tablets," Journal of Chromatography, Vol. 450, pp. 414-419 (1988)

Physicians' Desk Reference (the PDR), 46<sup>th</sup> Edition, pp. 2504-25-18 (1992)

Memorandum from Janet Woodcock, M.D. (The FDA Memorandum), Director for Drug Evaluation & Research, regarding Approvability of a Synthetic Generic Version of Premarin (May 5, 1997)

The claims stand rejected as follows:

I. Claims 1-5, 8-22 and 25-29 under 35 U.S.C. § 102 (b) as anticipated by the FDA Memorandum.

II. Claims 1-5, 8-22 and 25-29 under 35 U.S.C. § 102 (b) as anticipated by the PDR.

III. Claims 1-5, 8-22 and 25-29 under 35 U.S.C. § 102 (b) as anticipated by Townsend.

IV. Claims 1-5, 8-22 and 25-48 under 35 U.S.C. § 103 as unpatentable over

Townsend, the PDR and the FDA Memorandum.

We reverse each of these rejections.

### BACKGROUND

Premarin® (conjugated estrogens, USP)[, derived from the urine of pregnant mares,] has been known to contain a mixture of estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine . . . [and] is generally believed to contain a number of estrogenic compounds. However, despite numerous attempts to characterize Premarin® [ ] over the past several decades, the essential estrogenic compounds present in Premarin® [ ] have remained a mystery.

Specification, pages 1-2.

According to appellants, however, “the essential estrogenic compounds present in naturally derived equine conjugated estrogens have now been determined” (specification, page 4), using “[t]wo fundamental criteria” (specification, page 14). First, components of Premarin® “with a [lot-to-lot] variability of  $\pm 50\%$  were eliminated” from consideration as essential components (*id.*, page 15); second, “[a] structure-function approach to defining estrogenicity was taken” (*id.*) in order to avoid the conflicting results observed in various biological assays and estrogen receptor binding assays “due to differences in tissue-specific responses[,] metabolic activation or degradation of specific estrogens,” and “the existence of at least two receptor subtypes” (*id.*). Consequently, “essential estrogenic compounds” present in Premarin® and other conjugated estrogen preparations obtained from natural sources were “defined as estrogenic compounds that are consistent and controlled (i.e. less than +/- 50% variation between lots), are present in concentrations >0.1% by weight of the mixture of estrogenic compounds, and have a chemical structure that has the potential to have a meaningful estrogenic activity (i.e. has a phenolic A ring (at carbon 3) and a  $\beta$ -hydroxyl

or ketone group in position 17 of the D ring” (id., page 4).

Based on these criteria and an extensive chromatographic analysis, appellants found “the essential estrogenic compounds present in naturally derived equine conjugated estrogens . . . [to] consist of the following 10 compounds, the salts of their conjugates, or mixtures thereof: estrone; equilin;  $\Delta^{8,9}$ -dehydroestrone; 17 $\alpha$ -estradiol; 17 $\alpha$ -dihydroequilin; 17 $\beta$ -dihydroequilin; 17 $\beta$ -estradiol; equilenin; 17 $\alpha$ -dihydroequilenin; and 17 $\beta$ -dihydroequilenin” (specification, pages 4-5), which may “be present as conjugated estrogens . . . including, but not limited to, glucuronide and sulfate . . . [and] may also be present as salts of conjugated estrogens” (id., page 5). Moreover, appellants detected and identified a number of non-estrogenic impurities in Premarin® from the source material (mares’ urine), namely indican, sulfated benzyl alcohol, hippuric acid, benzoic acid, and creatinine (see, e.g., the results of the analyses of peaks 1, 4, 6, 7, and 8 isolated from Premarin®, specification pages 32, 34, 36, 37 and 40).

#### DISCUSSION

“The name of the game is the claim,” In re Hiniker Co., 150 F.3d 1362, 1369, 47 USPQ2d 1523, 1529 (Fed. Cir. 1998). As always, “[a]nalysis begins with a key legal question -- what is the invention claimed?” since “[c]laim interpretation . . . will normally control the remainder of the decisional process,” Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1567-68, 1 USPQ2d 1593, 1597 (Fed. Cir. 1987). In determining “the invention claimed,” we begin with the proposition that “the language employed [in a claim] must be analyzed - - not in a vacuum, but always in light of the of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art.” In re Moore, 439 F.2d 1232,

1235, 169 USPQ 236, 238 (CCPA 1971)(footnote omitted).

Each of claims 1-5 and 8-22 is directed to a composition of matter comprising a mixture of estrogenic compounds, “wherein said mixture comprises the same essential estrogenic compounds present in naturally derived equine conjugated estrogens,” and “wherein said composition of matter is present in chemically pure form” (see, e.g., claims 1, 11, 15 and 19). Claims 25-29 are directed to methods of treating mammals using the composition of claim 1. According to the specification, “[a]s used herein, ‘chemically pure form’ means substantially devoid of impurities present in naturally derived equine conjugated estrogens products” (specification, page 4). As discussed above, indican, sulfated benzyl alcohol, hippuric acid, benzoic acid, and creatinine were all identified as non-estrogenic impurities in Premarin®, a naturally derived equine conjugated estrogen product.

Interpreting these claims in “light of the of . . . the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art,” it is clear that the claimed compositions must minimally contain conjugates (or salts of conjugates, in the case of claims 1-10 and 19-22) of the ten “essential estrogenic compounds” (estrone; equilin;  $\Delta^{8,9}$ -dehydroestrone;  $17\alpha$ -estradiol;  $17\alpha$ -dihydroequilin;  $17\beta$ -dihydroequilin;  $17\beta$ -estradiol; equilenin;  $17\alpha$ -dihydroequilenin; and  $17\beta$ -dihydroequilenin), and the claimed compositions must be “substantially devoid of impurities present in naturally derived equine conjugated estrogens products,” i.e., they must be “in chemically pure form,” as that term is defined in the specification.

#### Anticipation

“[E]very limitation of a claim must identically appear in a single prior art reference for it to anticipate the claim.” Gechter v. Davidson, 116 F.3d 1454, 1457, 43 USPQ2d

1030, 1032 (Fed. Cir. 1997). According to the examiner, the subject matter of claims 1-5, 8-22 and 25-29 is anticipated by the FDA Memorandum, and by the PDR, each of which describes Premarin® and its usefulness in treating various consequences of menopause.

While we agree with the examiner that “the term ‘comprising’ is inclusive and does not exclude additional unrecited elements” (Answer, page 6), we cannot agree that the term is open to elements which eviscerate the express requirement that the claimed “composition of matter is present in chemically pure form,” i.e., the requirement that the composition must be “substantially devoid of impurities present in naturally derived equine conjugated estrogens products.” Inasmuch as Premarin® contains various impurities found in naturally derived equine conjugated estrogen products (e.g., indican, sulfated benzyl alcohol, hippuric acid, benzoic acid, and creatinine), neither the FDA Memorandum, nor the PDR can be said to describe the claimed compositions or methods.

Claims 1-5, 8-22 and 25-29 also stand rejected under 35 U.S.C. § 102 (b) as anticipated by Townsend, which describes high-performance liquid chromatographic (HPLC) analysis of “crushed conjugated estrogens tablets” (page 415). It is unclear whether the conjugated estrogen tablets contained only synthetic sodium estrone sulfate, sodium equilin sulfate, and sodium equilenin sulfate, or whether the tablets contained naturally derived equine conjugated estrogens (see page 414 and Tables I and II). In either case, however, it does not appear that Townsend describes a composition that meets all of the limitations of the claims, that is, a composition that contains the 10 essential estrogenic compounds present in naturally derived equine conjugated estrogens in chemically pure form.

Accordingly, we find that the subject matter of claims 1-5, 8-22 and 25-29 is not anticipated by the FDA Memorandum, the PDR, or by Townsend, and all three of the rejections of the claims under 35 U.S.C. § 102 are reversed.

### Obviousness

Claims 1-5, 8-22 and 25-48 stand rejected under as unpatentable over the combined teachings of Townsend, the PDR and the FDA Memorandum. Claims 1-5 and 8-22 are discussed above; claims 47 and 48 are directed to compositions of matter comprising salts of the same essential conjugated estrogenic compounds present in naturally derived equine conjugated estrogens, wherein the compositions are substantially devoid of one or all of the following impurities: indican, sulfated benzyl alcohol, hippuric acid, benzoic acid and creatinine. Finally, claims 30-46 are directed to methods of analyzing conjugated estrogen constituents by HPLC using a defined mobile phase.

According to the examiner, “the claimed composition[s] comprising various estrogenic compounds with or without additional compounds would be obvious to one having ordinary skill in the art,” “[b]ased on the combined teachings of the above cited prior art” (Answer, page 6).

“The PTO has the burden under section 103 to establish a prima facie case of obviousness. It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.” In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988) (citations omitted). An adequate showing of motivation to combine requires “evidence that ‘a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the

claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.” Ecolochem, Inc. v. Southern Calif. Edison Co., 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1075 (Fed. Cir. 2000).

In this case, we cannot agree that the cited references, viewed without the benefit of the instant specification, would have suggested the specific combinations of compounds required by the claimed compositions, especially in light of the position taken by the Center for Drug Evaluation and Research: “The Center’s conclusion is that because the reference listed drug Premarin is not adequately characterized at this time, the active ingredients of Premarin cannot now be definitively identified” (see the FDA Memorandum, page 1).

With respect to claims 30-46, the examiner concludes that “[t]he prior art [presumably Townsend] also makes obvious the use of a mobile phase consisting of acetonitrile, methanol and water and tetrabutylammonium hydroxide and adjusting the pH of the mobile phase to 3.0 in the HPLC analysis of conjugated estrogens” (Answer, page 6). Nevertheless, according to appellants, claim 30 requires “a mobile phase comprising an organic portion comprising between about 0.1% and about 30% (by volume organic portion) protic solvent [e.g., methanol] and between about 70% and about 100% (by volume organic portion) polar aprotic solvent [e.g., acetonitrile],” but Townsend uses only “a mobile phase having an organic portion including 46.6% methanol and 53.3% acetonitrile.” Appellants point out that Townsend states that “[b]aseline separation was obtained for all compounds,” and argue that the examiner “offers no particular evidence as to why one . . . would be motivated to modify a method that achieved baseline separation of all compounds” (Brief, page 24).

Appellants' point is well taken. We have no doubt that the prior art could be modified in a manner consistent with appellants' specification and claims. The fact that the prior art could be so modified, however, would not have made the modification obvious unless the prior art suggested the desirability of the modification. In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Here, we find no reason stemming from the prior art relied on by the examiner which would have led a person having ordinary skill in the art to modify Townsend's HPLC protocol to meet the specific limitations of the claims directed to analysis of conjugated estrogens.

In our view, the references cited by the examiner do not support a prima facie case of obviousness. Accordingly, the rejection of claims 1-5 , 8-22 and 25-48 under 35 U.S.C. § 103 is reversed.

SUMMARY

The references relied on by the examiner do not support a prima facie case of anticipation or obviousness. The rejections under 35 U.S.C. §§ 102 (b) and 103 are reversed.

REVERSED

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| William F. Smith            | ) |                 |
| Administrative Patent Judge | ) |                 |
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| Toni R. Scheiner            | ) | APPEALS AND     |
| Administrative Patent Judge | ) |                 |
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| Administrative Patent Judge | ) |                 |

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