

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 14

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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

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Ex parte GEORGE W. CUFF and  
ARVIND L. THAKKAR

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Appeal No. 2001-2157  
Application No. 08/918,741

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ON BRIEF

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Before WINTERS, WILLIAM F. SMITH, and SCHEINER, Administrative Patent Judges.  
WINTERS, Administrative Patent Judge.

DECISION ON APPEAL

This appeal was taken from the examiner's decision rejecting claims 1 and 3 through 10, which are all of the claims remaining in the application.

The Invention

Osteoporosis describes a group of diseases which arises from diverse etiologies, but which are characterized by the net loss of bone mass per unit volume. The consequence of this loss of bone mass and resulting bone fracture is the failure of the skeleton to provide adequate support for the body. One of the most common types of osteoporosis is associated with menopause. Most women lose from about 20% to

about 60% of the bone mass in the trabecular compartment of the bone within 3 to 6 years after the cessation of menses. This rapid loss is generally associated with an increase of bone resorption and formation. However, the resorptive cycle is more dominant and the result is a net loss of bone mass. Osteoporosis is a common and serious disease among postmenopausal women. (Specification, page 1).

At the time applicants' invention was made, raloxifene was a known therapeutic drug classified as a selective estrogen receptor modulator (SERM). As stated in the background section of applicants' specification, page 3, line 34 through page 4, line 3:

Raloxifene, a second generation SERM, displays potentially useful selectivity in uterine tissue with apparent advantages over triphenylethylene-based estrogen receptor ligands. As such, raloxifene appears to be well-suited at least for the treatment of postmenopausal complications, including osteoporosis and cardiovascular disease.

Applicants note, however, that:

The advancement of raloxifene, in particular, has been somewhat hampered by its physical characteristics, both as to bioavailability and manufacturing. For example, raloxifene is generally insoluble, which may affect bioavailability. Clearly, any improvement in the physical characteristics of raloxifene and in closely related compounds would potentially offer a more beneficial therapy and enhanced manufacturing capabilities.

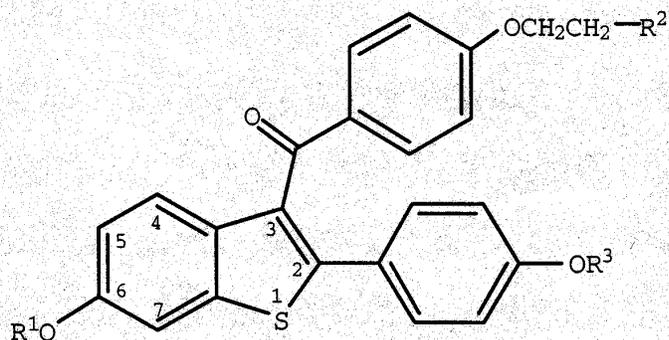
Thus, it would be a significant contribution to the art to provide amorphous forms of raloxifene and related compounds which have increased solubility, methods of preparation, pharmaceutical formulations, and methods of use. [Specification, page 4, lines 9-20].

Applicants' invention is drawn to raloxifene "in an amorphous form;" to a process for preparing same; to a pharmaceutical formulation comprising amorphous raloxifene in combination with a pharmaceutically acceptable carrier, diluent, or excipient; and to a method for inhibiting bone loss or bone resorption by administering to a patient in need thereof amorphous raloxifene.

Claims 1, 4, 7, and 8, which are illustrative of the subject matter on appeal, read as follows:

1. (Amended) A hydrochloride salt of a compound of formula

I



(I)

wherein:

$\text{R}^1$  and  $\text{R}^3$  are independently hydrogen;

$\text{R}^2$  is piperidinyl; or a pharmaceutically acceptable solvate thereof, in an amorphous form.

4. A process for preparing an amorphous form of a compound of Claim 1 which comprises preparing a solution of a crystalline form of a compound of formula I in a suitable solvent, and then spray drying said solution to recover an amorphous form of a compound of formula I.

7. A pharmaceutical formulation comprising a compound according to Claim 1 in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

8. A method for the inhibition of bone loss or bone resorption which comprises administering to a patient in need thereof a compound according to Claim 1.

#### The Prior Art References

In rejecting the appealed claims under 35 U.S.C. § 103(a), the examiner relies on the following prior art references:

Jones et al. (Jones)	4,358,593	Nov. 9, 1982
Ronsen et al. (Ronsen)	5,672,612	Sep. 30, 1997
Cameron (PCT Application)	WO 95/10513	Apr. 20, 1995

Evans, "An Introduction to Crystal Chemistry," 2<sup>nd</sup> edition, pp. 393-397 (Cambridge Press 1964)

Hannay, "Treatise on Solid State Chemistry," Vol. 3, pp. 89-90 (Plenum Press 1977)

Kai et al. (Kai), "Oral Absorption Improvement of Poorly Soluble Drug Using Solid Dispersion Technique," Chem. Pharm. Bull., Vol. 44, no. 3, pp. 568-571 (1996)

Matsuda et al. (Matsuda), "Amorphism and Physiochemical Stability of Spray-dried

Frusemide," J. Pharm. Pharmacol., Vol. 44, pp. 627-633 (1991)

Takeuchi et al. (Takeuchi), "Progress of Powder Technology. Particle Design and Manufacturing," Chem. Eng., Vol. 37, pp. 496-501 (1992)

Uekama et al. (Uekama), "Inhibitory Effect of 2-Hydroxypropyl- $\beta$ -cyclodextrin on Crystal- growth of Nifedipine During Storage: Superior Dissolutin and Oral Bioavailability Compared with Polyvinylpyrrolidone K-30," J. Pharm. Pharmacol., Vol. 44, pp. 73-78 (1991)

Yano et al. (Yano), "Crystal Forms, Improvements of Dissolution and Absorption of poorly Water Soluble (R)-1[2,3-Dihydro-1-(2'-Methylphenacyl)-2-Oxo-5-Phenyl-1H-1,4-Benzodiazepin-3-YL]-3-(3-Methylphenyl)Urea (YM022)," Yakugaku Zasshi, Vol. 116, no. 8, pp. 639-646 (1996)

Yasuhiko et al. (Yasuhiko), "Characterization of amorphous ursodeocycholic Acid Prepared by Spray-Drying Technique," JICST 03282368 (1992)

### The Rejections

In section (10) of the Examiner's Answer (Paper No. 13), the examiner does not set forth each prior art rejection of record. Rather, the examiner refers to multiple rejections in previous Office actions, Paper Nos. 4 and 8; characterizes those rejections as though they constituted a single "rejection;" and summarizes that "rejection" in two paragraphs. This is manifestly improper. See Manual of Patent Examining Procedure (MPEP) § 1208 (7<sup>th</sup> ed., July 1998) ("Only those statements of grounds of rejection appearing in a single prior action may be incorporated by reference. An examiner's answer should not refer, either directly or indirectly, to more than one prior Office action.").

As best we can judge, the appealed claims stand rejected as follows:

- (1) Claims 1 and 3 through 7 under 35 U.S.C. § 103(a) as unpatentable over the combined disclosures of Jones, Hannay, and Evans;
- (2) Claims 1 and 3 through 7 under 35 U.S.C. § 103(a) as unpatentable over the combined disclosures of Jones, Hannay, Evans, and Takeuchi;
- (3) Claims 1 and 3 through 7 under 35 U.S.C. § 103(a) as unpatentable over the combined disclosures of Jones, Hannay, Evans, Takeuchi, Kai, Yasuhiko, Matsuda, Uekama, Yano, and Ronsen; and
- (4) Claims 8 through 10 under 35 U.S.C. § 103(a) as unpatentable over the combined disclosures of Jones and Cameron.

#### Deliberations

Our deliberations in this matter have included evaluation and review of the following materials: (1) the instant specification, including all of the claims on appeal; (2) applicants' Appeal Brief (Paper No. 12); (3) the Examiner's Answer (Paper No. 13); and (4) the above-cited prior art references.

On consideration of the record, including the above-listed materials, we reverse each of the examiner's rejections under 35 U.S.C. § 103(a).

#### Discussion

A crystalline form of raloxifene was known in the art at the time applicants' invention was made. See the background section of the specification, page 3, line 21 through page 4, line 20; and see, Jones, column 20, Example 27. With respect to each ground of rejection, the dispositive question is whether it would have been obvious to prepare raloxifene "in an amorphous form" as recited in the appealed claims? We

answer that question in the negative.

The examiner argues that there is reason, suggestion, or motivation stemming from the prior art to prepare raloxifene in an amorphous form. According to the examiner, a person having ordinary skill would have recognized that an amorphous form of raloxifene would possess improved physical characteristics, e.g., increased solubility, compared with its known crystalline form. It follows, according to the examiner, that an amorphous form of raloxifene would possess improved bioavailability compared with its crystalline form; and that this would have been recognized by a person having ordinary skill in the art.

We shall not belabor the record on this point, because applicants concede that the prior art provides adequate reason, suggestion, or motivation to prepare raloxifene in an amorphous form. Applicants concede that

when the ordinarily skilled artisan is faced with a pharmaceutical that has poor oral-bioavailability properties [crystalline raloxifene], one technique for improving dissolution rates, and thus, hopefully, oral bioavailability, is to administer an amorphous form of that pharmaceutical. Once it is determined that an amorphous form is obtainable, Appellants have also conceded that it is well know [sic] in the art that preparing that amorphous form may be done by spray drying the material as taught, e.g., in Takeuchi. [Paper No. 12, page 4, 3<sup>rd</sup> full paragraph]

In other words, applicants do not controvert the examiner's position that the cited prior art suggests the desirability of preparing raloxifene in an amorphous form. Applicants

also acknowledge that spray drying is a conventional technique, known in the art for preparing amorphous products.

Applicants do not concede, however, that spray-drying was known for preparing

products structurally similar to raloxifene. At most, applicants contend, it would have been obvious to try preparing raloxifene in an amorphous form by spray-drying. But the result of that experiment, according to applicants, was not reasonably foreseeable. It was not reasonably foreseeable, e.g., that raloxifene has sufficient heat stability to withstand spray-drying as described in applicants' specification, page 8, lines 31 through 33. As stated more broadly in Paper No. 12, page 5, first complete paragraph:

Appellants respectfully assert that although it may have been considered obvious to perform the experiment (obvious to attempt to prepare the amorphous material), the result of that experiment (its success or failure) was not reasonably foreseeable. . . . The art as a whole teaches that preparing an amorphous form of a pharmaceutical compound is only a desired possibility. Appellants respectfully assert that the formulation sciences are an unpredictable art form and the ordinary artisan practicing in that art does not know and cannot predict, a priori, whether the amorphous form is obtainable.

Couched in terms of the case law, applicants' argument is predicated on a requirement that the prior art must lead a person having ordinary skill to the claimed invention with a reasonable expectation of success. As stated in In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991),

Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. [citations omitted]

Further, see In re Dow Chem. Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988)("The consistent criterion for determination of obviousness is whether the prior art

would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art . . . Both the suggestion and expectation of success must be founded in the prior art, not in the applicant's disclosure"). Applicants argue that when all of the prior art is considered together, persons having ordinary skill would not have a sufficient basis for the necessary predictability of success to sustain a rejection under 35 U.S.C. § 103(a). We agree.

Simply stated, the examiner has not adequately addressed applicants' argument based on the lack of a reasonable expectation of success founded in the prior art. The examiner argues that (1) the process (spray-drying) and its outcome (preparation of amorphous product) is a matter of "common sense" for a person having ordinary skill; and (2) the examiner should not be obliged to provide documentary proof that persons having ordinary skill would have arrived at the claimed subject matter with a reasonable expectation of success (Paper No. 13, page 5, second full paragraph). That argument, however, is contrary to prevailing case law. Again, "both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." In re Dow Chemical Co., 837 F.2d at 473, 5 USPQ2d at 1531. Nor may the examiner properly take official notice of facts to fill the particular gap in the record here challenged by applicants. To the extent the examiner would argue that those facts are capable of instant and unquestionable demonstration as being "well-known" in the art, without the citation of a reference, we disagree. See MPEP § 2144.03. To the extent that the examiner would rely on Eagleson's Concise Encyclopedia Chemistry, published by Walter de Gruyter, New York, page 67 (1994),

we point out that "[w]here a reference is relied on to support a rejection, whether or not in a 'minor capacity,' there would appear to be no excuse for not positively including the reference in the statement of rejection." In re Hoch, 428 F.2d 1341, 1342 n.3, 166 USPQ 406, 407 n.3 (CCPA 1970). The examiner has not included the Concise Encyclopedia Chemistry in a statement of any rejection under 35 U.S.C. § 103(a), and belated citation of that reference in Paper No. 13, page 5, is improper. Be that as it may, we have reviewed the Concise Encyclopedia Chemistry, page 67. In our judgment, this reference does not disclose that spray-drying was known for preparing products structurally similar to raloxifene. Nor does this reference refute applicants' contention that, at most, it would have been obvious to try preparing raloxifene in an amorphous form by spray-drying.

#### Conclusion

In conclusion, the examiner has not established that the prior art would have led a person having ordinary skill to the claimed invention with a reasonable expectation of success. Accordingly, the examiner has not established a prima facie case of obviousness of claims 1 and 3 through 10; and the examiner's decision rejecting those claims under 35 U.S.C. § 103(a) is reversed.

REVERSED

Sherman D. Winters )  
Administrative Patent Judge )

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) BOARD OF PATENT  
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William F. Smith ) APPEALS AND  
Administrative Patent Judge )  
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) INTERFERENCES  
)  
Toni R. Scheiner )  
Administrative Patent Judge )

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