

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 23

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte BARRY A. MURRER
and DAVID A. SCHWARTZ

Appeal No. 95-2603
Application 07/915,871¹

ON BRIEF

Before GARRIS, ***Administrative Patent Judge***, McKELVEY, ***Senior Administrative Patent Judge*** and WALTZ, ***Administrative Patent Judge***.

WALTZ, ***Administrative Patent Judge***.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 7, 8 and 23, which are

¹ Application for patent filed July 20, 1992. According to appellants, the application is a continuation of Application 07/677,411, filed March 29, 1991 (ABN), which is a division of Application 07/454,418, filed December 21, 1989, now Patent No. 5,021,409, granted June 4, 1991.

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all the claims remaining in this application.

According to appellants, the invention is concerned with pharmaceutical compositions comprising bicyclam or related polyazacyclohexa- or tetra-decanes, active against HIV-infected cells *in vitro*² (brief, page 1).

Claim 23 has been amended by an amendment filed with the reply brief dated Dec. 28, 1994 (Paper No. 19), and entered as noted by the examiner in the Supplemental Answer dated Mar. 13, 1995 (Paper No. 20). Claims 23, 7 and 8 are reproduced below:

23. A pharmaceutical composition which is active against HIV-infected cells in in vitro tests comprising, as active ingredient, a compound selected from the group consisting of bicyclam

3,3'-bis-1,5,9,13-tetraazacyclohexadecane

3,3'-bis-1,5,8,11,14-pentaazacyclohexadecane

5,5'-bis-1,4,8,11-tetraazacyclotetradecane

2,5'-bis-1,4,8,11-tetraazacyclotetradecane

² The grandparent of this application, Application No. 07/454,418, has become U.S. Patent No. 5,021,409, with claims directed to a method of treating infection by a retrovirus.

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2,6'-bis-1,4,8,11-tetraazacyclotetradecane
11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane
11,11'-(1,2-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane
11,11'-(1,2-butanediyl)bis-1,4,8,11-tetraazacyclotetradecane
11,11'-(1,2-pentanediy)bis-1,4,8,11-tetraazacyclotetradecane
11,11'-(1,2-hexanediy)bis-1,4,8,11-tetraazacyclotetradecane
and a pharmaceutically acceptable carrier therefor.

7. A composition as claimed in claim 23, wherein the active ingredient is 2,2'-bicyclam.

8. A composition as claimed in claim 23, wherein the active ingredient is 6,6'-bicyclam.

The references relied upon by the examiner as evidence of obviousness are:

Lehn 4,156,683 May 29,
1979

Zimenkovskii et al. (Zimenkovskii), Chemical Abstracts (CA),
Vol. 88, No. 15, No. 105292s (1978)

Williams et al. (Williams), CA, Vol. 96, No. 97239c (1981)

Kimura et al. (Kimura), CA, Vol. 99, No. 49518h (1983)

Rowatt et al. (Rowatt), CA, Vol. 107, No. 112499d (1987)

Ciampolini et al. (Ciampolini), CA, Vol. 107, No. 167695v

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(1987)³

References not previously of record which are relied upon
by

this merits panel are:

Barefield et al. (Barefield), "Characterization of 2,2'-Bi-(1,4,8,11-tetra-azacyclotetradecane): X-Ray Structure and Properties of the Dinuclear Complex", *J.C.S. Chem. Comm.*, 302-304 (1981)

Fabbrizzi et al. (Fabbrizzi), "Communications", 25 *Inorganic Chemistry*, No. 16, 2671-2672 (July 30, 1986).

Claims 7, 8 and 23 stand rejected under 35 U.S.C. § 103 as unpatentable over Lehn. Claims 7, 8 and 23 stand rejected under 35 U.S.C. § 103 as unpatentable over Lehn, Rowatt and Zimenkovskii in view of Williams. A new ground of rejection was made in the examiner's answer rejecting claims 7, 8 and 23 under 35 U.S.C. § 103 as unpatentable over Ciampolini and Lehn in view of Kimura. We reverse all stated rejections for reasons which follow. Pursuant to our authority under 37 CFR

³ Although only the Chemical Abstract is relied upon by the examiner in the answer, the full article is cited and supplied to appellants in the Supplemental Examiner's Answer dated Mar. 13, 1995 (Paper No. 20). Therefore, for purposes of this decision, we will refer to the full article.

§ 1.196(b), we enter the following new grounds of rejection:

(1) claim 23 is rejected under 35 U.S.C. § 102(b) as anticipated by Ciampolini;

(2) claims 8 and 23 are rejected under 35 U.S.C. § 102(b) as anticipated by Fabbrizzi;

(3) claims 7 and 23 are rejected under 35 U.S.C. § 102(b) as anticipated by Barefield; and

(4) claim 23 is rejected under 35 U.S.C. § 112, first paragraph, in view of Ciampolini, as being based upon a specification which fails to enable a person skilled in the art to make the invention as broadly as claimed, i.e., the enabling disclosure in appellants' specification is not commensurate in scope with the breadth of claim 23.

OPINION

A. The § 103 Rejection over Lehn

Claim 23 recites a pharmaceutical composition comprising an active ingredient selected from a group of eleven compounds⁴ and a pharmaceutically acceptable carrier.

⁴ Eleven "compounds" are recited in claim 23. The first, "bicyclam" is a recitation of a genus of compounds. The other ten "compounds" are specific compounds. The genus "bicyclam" encompasses the 2,2'-bicyclam and 6,6'-bicyclam isomers of claims 7

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The examiner states that "Lehn teaches the claim designated compounds as old and well known in combination with carriers..." (answer, page 4). The examiner contradicts this statement in the sentence bridging pages 8 and 9 of the answer by stating that "Lehn fails to teach the bis compounds recited in the instant claims". Appellants note this inconsistency and state that Lehn does not disclose the claimed active ingredients (reply brief, pages 1-2).

Lehn discloses bicyclic compounds containing nitrogen but fails to disclose or teach the bis compounds (which are two rings linked together) called for by the claims on appeal. The examiner has not pointed to any specific section of Lehn showing or teaching the compounds contained in the claims on appeal. Furthermore, Lehn teaches that the compounds of his invention must contain an oxygen or sulfur atom in the heterocyclic ring (column 3, lines 7-11) and no equivalency has been suggested by Lehn or shown by the examiner for these atoms and nitrogen.

and 8.

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For the foregoing reasons, the rejection of claims 7, 8 and 23 under 35 U.S.C. § 103 as unpatentable over Lehn is reversed.

B. The Rejection under § 103 over Lehn, Rowatt, and Zimenkovskii in view of Williams

Lehn has been discussed above. Rowatt and Zimenkovskii are similarly deficient in failing to disclose any compounds within the scope of the active ingredients in the appealed claims. Rowatt discloses "aliphatic polyamines" but does not disclose what structures are encompassed by this term. Zimenkovskii is even further removed in disclosing only heterocyclic compounds containing nitrogen and sulfur with no disclosure or teaching of any compounds similar to the bis compounds recited in the claims on appeal. The examiner has failed to point out what part of the references are being relied upon⁵ to show "the claimed designated compounds" (answer, page 5). Williams is relied upon by the examiner for the teaching as old and well known the treatment of Herpes virus with the claimed designated compounds (answer, page 6).

⁵ We consider only the references cited by the examiner, i.e., the abstracts, and not the underlying articles upon which these abstracts are based.

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Again the examiner has not specifically pointed out where this teaching occurs in Williams. Williams discloses tricyclic hetero compounds containing nitrogen and oxygen with amino acid substituents useful in the treatment of Herpes simplex virus. No disclosure can be found of the bicyclam compounds of the appealed claims.

For the foregoing reasons, this rejection under § 103 is reversed.

C. The Rejection under § 103 over Ciampolini and Lehn in view of Kimura

This new ground of rejection is actually two grounds of rejection. Ciampolini is applied alone with no secondary reference but Lehn is modified by Kimura (see the answer, pages 8-9). This rejection will be discussed accordingly.

Lehn has been discussed above. Kimura, which allegedly teaches the bridging of two macrocyclic polyamine complexes into the claimed bis compounds, is applied to provide guidance on how this chemical "configuration" would affect the biological systems of interest (answer, page 9). However, Kimura is not related to biological systems and the examiner

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fails to point out where the reference discloses the bis compounds of the claimed compositions. Kimura is directed to the study of macrocyclic complexes and their effects on superoxide dismutase activities. Thus there is no suggestion to combine this reference with Lehn and, even if properly combined, these references would not suggest the composition of the appealed claims. See *In re Bond*, 910 F.2d 831, 834, 15 USPQ2d 1566, 1568 (Fed. Cir. 1990).

Ciampolini, as characterized by the examiner, teaches the 11, 11'-positional isomer of one of the active ingredients in claim 23, along with its combination with various carriers (answer, page 8). The examiner concludes that "it is well settled patent law that positional isomers would have been obvious to the skilled artisan"⁶, citing *In re Wilder*.⁷ Appellants argue that the examiner has misidentified the disclosed bicyclic compound of Ciampolini but, regardless,

⁶ The examiner incorrectly includes the active ingredients of dependent claims 7 and 8 as positional isomers of the compounds disclosed by Ciampolini (answer, page 8). The compounds recited in dependent claims 7 and 8 are bicyclam isomers which contain no bridging group, i.e., no 1,2-ethanediyl group.

⁷ 563 F.2d 457, 195 USPQ 426 (CCPA 1977).

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there is no biological activity disclosed by the reference (reply brief, page 4).

Generalization is to be avoided insofar as specific structures are alleged to be *prima facie* obvious one from the other. *In re Grabiak*, 769 F.2d 729, 731, 226 USPQ 870, 872 (Fed. Cir. 1985). *See also In re Jones*, 958 F.2d 347, 349-50, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992). As stated by the court in *Grabiak*, 769 F.2d at 731, 226 USPQ at 872, "there must be adequate support in the prior art for the ester/thioester change in structure in order to complete the PTO's *prima facie* case and shift the burden of going forward to the applicant." Ciampolini is directed to a different utility than appellants' disclosed utility. We cannot find any suggestion or reasoning to modify any "positional isomers" of Ciampolini to investigate Ciampolini's described electrostatic effects on the redox behavior of pairs of metal ions. In fact, Ciampolini discloses at page 3528 that the specific compounds disclosed were "appropriately designed for the investigation of the redox activity in solution of pairs of 3d metal ions" and the most favorable framework for incorporation of 3d metal

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ions is this particular linking of two cyclam moieties. Therefore there is no motivation or suggestion to make the proposed molecular modifications needed to arrive at the claimed active ingredients. See *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) and compare *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990) (en banc), cert. denied, 500 U.S. 904 (1991). Thus the rejection of claims 7, 8 and 23 under § 103 in view of Ciampolini, as interpreted and applied by the examiner, cannot be sustained.

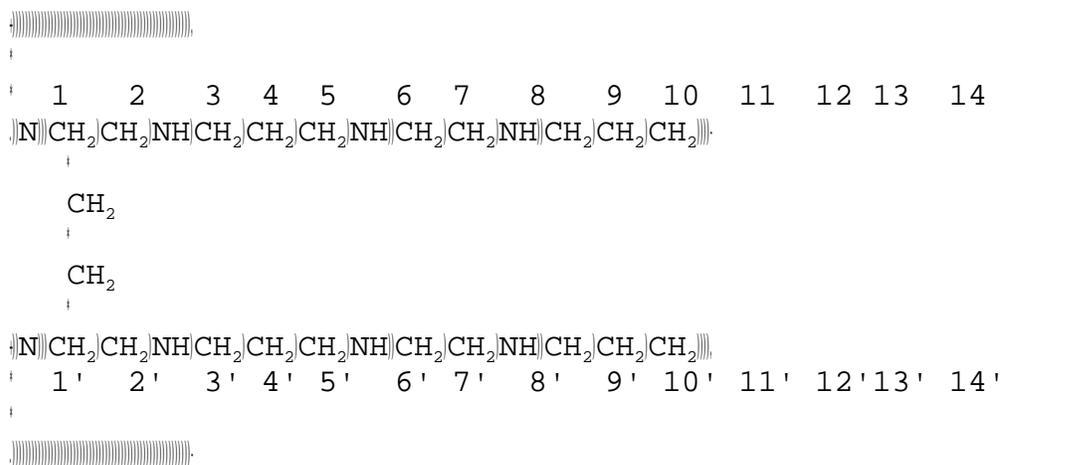
For the foregoing reasons, the examiner's new ground of rejection under § 103 is reversed.

D. The Rejections Under 37 CFR § 1.196(b)

The first new ground of rejection involves claim 23 under 35 U.S.C. § 102(b) as anticipated by Ciampolini. Compound 2 on page 3527 of Ciampolini is believed to be identical to the active ingredient 11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclo-tetradecane recited in claim 23. Initially, we find that appellants' use of the designation 11,11'- in identifying 11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane is somewhat odd. The compound named

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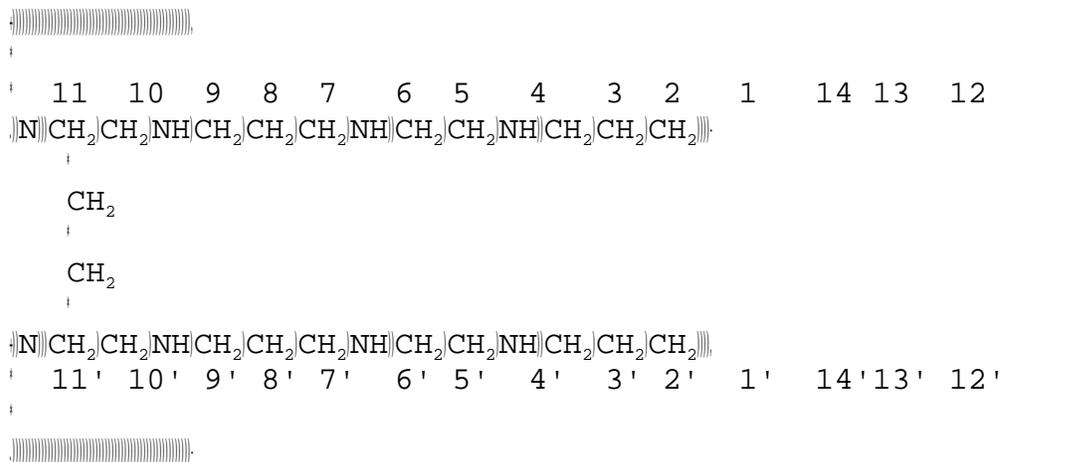
by appellants does not appear to have any substituent group at the 1- or 1'-positions of the tetraazacyclotetradecane groups. Hence, the compound 11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane could as easily have been, and normally would have been, identified as 1,1'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane, as is readily apparent by comparing the following chemical structures:



1,1'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 (when viewed from the top)

and

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11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 (when viewed from the bottom)

Ciampolini describes the compound which appellants identify as 11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane, because Ciampolini describes a process (page 3528, reaction scheme at the top of the page) for making Compound 2 (page 3527, col. 1) which has a structural formula identical to either formula set out above. Ciampolini also describes other bis-cyclams containing bridging groups. See Compounds 3, 4, 5 and 6.

Compounds 2, 3, 4, 5 and 6 were converted into nickel(II) and copper(II) complexes. Electrochemical parameters were

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measured for each nickel and copper complex (page 3529, col. 1, table 1). The complexes were made according to the following process (page 3529, col. 1, third full paragraph):

*** [C]omplexes were obtained *** by mixing ethanolic solutions of the ligand and of the metal perchlorate (1:2 molar ratio) and allowing to reflux for 30 min. The complexes, recrystallized from methanol, gave satisfactory C, H, N elemental analysis.

The "ligand" is any one of Compounds 2, 3, 4, 5 and 6. An ethanolic solution of the ligand is a solution of the ligand in ethanol. Ethanol is a known pharmaceutical carrier.⁸ The utility recited in the preamble of appellant's claim, i.e., activity "against HIV-infected cells in in vitro tests," means that purity for appellants' pharmaceutical composition is not as much a concern as it might be in a pharmaceutical administered to a human. Hence, Ciampolini's description of a mixture of the ligand which is Compound 2 and ethanol is a description of a species within the scope of

⁸ See, for example, Smiles et al., U.S. Patent No. 4,959,210, column 2, lines 44-46 (copy attached to this decision).

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appellants' pharmaceutical composition comprising 11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane and the pharmaceutically acceptable carrier.

We also note that appellants contemplate the use of their compounds in the form of a metal complex, including a nickel complex (specification, page 5, lines 1-2). To the extent claim 23 calls for a compound "comprising" 11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane, the claim also covers nickel complexes of 11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane. Ciampolini also describes a mixture of a nickel(II) complex of 11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane in ethanol prior to recrystallization with methanol.

We find and conclude that claim 23 lacks novelty over Ciampolini.

Claims 8 and 23 are rejected under § 102(b) as anticipated by Fabbrizzi. This reference, as disclosed on page 3 of the specification, is directed to 6,6'-bicyclam (see compound 2 on page 2671). Fabbrizzi discloses an aqueous

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solution of the biscyclam compound (page 2671, left column) ("1 equiv of $\text{Ni}(\text{NO}_3)_2$ was added to an aqueous solution of biscyclam at pH7" and "biscyclam" is Compound 2 (page 2671, column 2)). Since water is a known pharmaceutical carrier⁹, the claimed composition is anticipated by Fabbrizzi, even though the utility disclosed by Fabbrizzi is different than appellants' utility. See *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782, 227 USPQ 773, 779 (Fed. Cir. 1985); *In re Wilder*, 563 F.2d at 460-61, 195 USPQ at 429-30.

Claims 7 and 23 are rejected under § 102(b) as anticipated by Barefield. As characterized on page 3 of the specification, Barefield discloses the 2,2'-bicyclam derivative of claims 7 and 23 (compound 2 on page 303). Barefield teaches that this "octa-amine" (bicyclam) is very insoluble in water and most organic solvents (see the footnote on page 303). To recognize this insolubility, it is more likely true than not, that Barefield intermixed these materials, thus creating a composition of bicyclam and water which is one of the compositions embraced by appealed claim

⁹ *Ibid.*

23. Otherwise, we believe that it is unlikely Barefield would have made a positive scientific assertion that his Compound 2 "is very insoluble in water ***" (page 303, first footnote). In this regard, we point out that the language of appealed claim 23 merely calls for a "pharmaceutically acceptable carrier". Water is a known pharmaceutically acceptable carrier¹⁰ and thus the mixture of water and bicyclam of Barefield meets all the limitations of claims 7 and 23 (i.e., these claims on appeal do not require that the active ingredient is **soluble** in the carrier).

Claim 23 is rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement as to how to make the claimed active ingredients in view of Ciampolini. Claim 23 lists active ingredients with 2 to 6 carbon atom chains as linking groups between the cyclam rings. Appellants' only enablement regarding "how to make" is the disclosure that "[A] number of the active ingredients according to the invention are known, and the compounds may be prepared by identical methods or methods analogous thereto." (specification, page 4).

¹⁰ *Ibid.*

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However, all of Ciampolini's prior art bicyclam compounds with bridging groups are substituted at the ends of the bridging groups (i.e., 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, etc.). All of appellants' claimed active ingredients with corresponding bridging groups contain the cyclam rings in the 1,2-positions. Such a disposition is consistent with the prior art (Ciampolini) only with respect to the end bridged ethanediyl group of appealed claim 23. Clearly, the here claimed 1,2- disposition is inconsistent with the prior art with respect to the non-end bridged groups of appellants' claim 23. More particularly, it is not clear how this disposition can be accomplished with the steric hindrance expected from such large cyclic rings being substituted adjacent to each other at the 1,2 positions on the non-end bridging groups of propanediyl, butanediyl, pentanediyl and hexanediyl recited in claim 23. Therefore there is a lack of enabling disclosure as to how to make the claimed active ingredients with the bicyclam rings substituted in the 1,2-position for the above noted propanediyl, butanediyl, pentanediyl and hexanediyl bridging groups.

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This decision contains a new ground of rejection pursuant to 37 CFR § 1.196(b)(amended effective Dec. 1, 1997, by final rule notice, 62 Fed. Reg. 53,131, 53,197 (Oct. 10, 1997), 1203 Off. Gaz. Pat. & Trademark Office 63, 122 (Oct. 21, 1997)).

37 CFR

§ 1.196(b) provides that, "A new ground of rejection shall not be considered final for purposes of judicial review."

37 CFR § 1.196(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of proceedings (§ 1.197(c)) as to the rejected claims:

(1) Submit an appropriate amendment of the claims so rejected or a showing of facts relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the application will be remanded to the examiner. . . .

(2) Request that the application be reheard under § 1.197(b) by the Board of Patent Appeals and Interferences upon the same record. . . .

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No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED - 37 CFR § 1.196(b)

)	
BRADLEY R. GARRIS)	
Administrative Patent Judge)	
)	
)	
)	BOARD OF PATENT
FRED E. McKELVEY, Senior))
Administrative Patent Judge)	APPEALS AND
)	
)	INTERFERENCES
)	
THOMAS WALTZ)	
Administrative Patent Judge)	

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McKelvey, Senior Administrative Patent Judge, concurring.

I concur fully with, and have signed, the opinion of the merits panel. I write separately to place on the record a recurring problem faced by the Board of Patent Appeals and Interferences in resolving ex parte appeals which come before it. The recurring problem is the citation and reliance by examiners on abstracts, without citation and reliance on the underlying scientific article.

At the conclusion of Fiscal Year 1997, the board had an ex parte backlog of about 9200 ex parte appeals. It thus becomes imperative for the efficient administration of justice with respect to ex parte appeals before this board that the

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examiner, appellants (and in particular their counsel) and the board itself adopt practices which maximize the opportunity for prompt and full resolution of patentability issues in ex parte appeals.

In this appeal, the examiner relied upon several abstracts without citing (or apparently obtaining copies of) the underlying scientific article itself. Citation of an abstract without citation and reliance on the underlying scientific article itself is unacceptable. Abstracts sometimes are not written by the author of the underlying article and often are erroneous. Hence, the preferred practice would be for the examiner to cite and rely on the underlying article. Furthermore, when the examiner cites and relies only on an abstract, it would appear prudent for the applicant to obtain a copy of the underlying article and submit a copy to the examiner when responding to a rejection which has been entered by the examiner. In the past, when neither the examiner nor the appellant cites or relies on the underlying article, often the board itself has expended the resources necessary to obtain a copy of the underlying scientific article. In this case, it is not possible to

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know whether the examiner or the appellants had and reviewed the underlying articles abstracted in the abstracts upon which the examiner has relied. The board cannot examine, in the first instance, all applications which come before us in an ex parte appeal under 35 U.S.C. § 134. In this particular appeal, we have elected not expend board resources to obtain a copy of the abstracts relied upon by the examiner. Hence, the file wrapper of this particular patent application should clearly reflect the fact that we did not consider the underlying scientific article of the abstracts relied upon by the examiner in making the rejections which the merits panel now reverses.

In the future, it will be my general practice to vote to vacate and remand any rejection by an examiner which is based solely on abstracts without any reliance on the underlying article.

