In The United States Patent Office

In re Robert D. SOFIA, *Method For the Prevention and Control of* Epileptic Seizures, United States Letters Patent No. 4,978,680	Control No. 90/_____ Filed 28 March 2006 **REQUEST for *EX PARTE* REEXAMINATION UNDER 35 U.S.C. § 302 *et seq*.**

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I. INTRODUCTION

This is a request pursuant to 35 U.S.C. § 302 for *ex parte* reexamination of Robert Duane SOFIA, *Method for the Prevention and Control of Epileptic Seizures*, United States Letters Patent No. 4,978,680 ("the SOFIA patent").

The invention claimed by the SOFIA patent was not first invented by SOFIA. Rather, the invention claimed by SOFIA was disclosed in prior art as much as thirty years before the SOFIA patent was filed. The patentee had actual knowledge of this prior art, and was aware of its materiality, yet failed to disclose it to the Examiner. The Third-Party Requestor therefore respectfully believes that the SOFIA patent is invalid under 35 U.S.C. §§ 102 and 103.

The name and address of the person requesting reexamination is Pharmaceutical Patent Attorneys LLC, 55 Madison Ave., 4th floor, Morristown, NJ 07960.

To the best of the undersigned's knowledge, the patent at issue is not subject to any concurrent reissue, reexamination or interference proceeding, nor Federal Court litigation. The immediate patent is related to Robert D. SOFIA, *Method for the Prevention and Control of Epileptic Seizures…*, United States Patent No. 5,082,861, for which the requestor has also requested reexamination.

The Patentee is involved in concurrent litigation styled *MedPointe Pharma. Corp. d/b/a Wallace Pharmaceuticals v. Kozachuk*, CIV-04-2019 (United States District Court for the District of New Jersey, Trenton, NJ). Attached find copies of the AMENDED COMPLAINT and the ANSWER in that civil action. As indicated in these pleadings, the SOFIA patent is not subject to that proceeding.

The patent at issue is anticipated by Alan Joseph WILENSKY *et al*., *Pharmacokinetics of W-544 (ADD 03055) in Epileptic Patients*, 26 EPILEPSIA 602 (1985). The patent at issue is anticipated by Frank M. BERGER, *2-Phenyl-1,3 Propane Diol Dicarbamate*, United States Letters Patent No. 2,884,444 (1959). The patent at issue is obvious in light of Frank M. BERGER, *Dicarbamates of Substituted Propane Diols*, United States Letters Patent No. 2,724,720 (1955) combined with Frank M. BERGER, *2-Phenyl-1,3 Propane Diol Dicarbamate*, United States Letters Patent No. 2,884,444 (1959). The Patentee had actual knowledge of each of these references and understood their materiality. The Patentee did not, however, provide any of them to the Office.

We first present the SOFIA patent. We then compare the coverage of the SOFIA patent to each of the aforementioned references, and explain how the prior art teaches each and every element of the claim. We conclude by identifying other

prior art not yet of record which is, on information and belief, in the Patentee's possession, custody and control.

II. ROBERT DUANE SOFIA'S PATENT

The patent at issue ("the SOFIA patent") discloses and claims a method for treating seizures by using a compound called 2-phenyl,-1,3-propanediol dicarbamate. The SOFIA patent recites only one claim:

> What is claimed is:
> 1. A method for reducing the incidence and severity of epileptic seizures which comprises administering to a warm-blooded animal in need of such treatment a therapeutic amount of 2-phenyl,-1,3-propanediol dicarbamate.

SOFIA's claimed invention is thus quite straighforward: it entails administering a "therapeutic amount" of 2-phenyl,-1,3-propanediol dicarbamate to a warm-blooded animal. As part of his patent application, SOFIA included an oath swearing that he was the true first inventor of this invention. SOFIA's oath is incorrect, because this invention was apparently first invented not by SOFIA, but by SOFIA's colleague Frank M. BERGER.

III. THE '444 PATENT TEACHES EVERY CLAIM ELEMENT OF THE SOFIA PATENT

The SOFIA patent was filed on 26 September 1989. Thirty years before this, however, the same company patented the same drug for the same use.

Tthe Patent Office issued Frank M. BERGER, *2-Phenyl-1,3 Propane Diol Dicarbamate*, United States Letters Patent No. 2,884,444 (copy enclosed) on 28 April 1959, thirty years before SOFIA filed his patent. The '444 patent teaches the same chemical compound for the same use as is claimed by SOFIA.

For a prior art reference to anticipate, the reference must teach each and every element of the claimed invention. *E.g.*, *In re Bond*, 15 U.S.P.Q.2d 1566 (Fed. Cir., 1990). Where a reference teaches each claim element, the patent claim should be invalidated as anticipated. *See* 35 U.S.C. § 102.

In the instant case, the '444 patent teaches each and every element of the invention claimed by SOFIA:

The SOFIA patent, claim 1	The '444 patent
1. A method for reducing the incidence and severity of epileptic seizures	anti-convulsant activity, *see* 1:17; preventing the occurrence of seizures, *see e.g.*, 1:18, 2:26-30
which comprises administering to a warm-blooded animal in need of such treatment	Testing in warm-blooded animals such as mice, *see* 2:26-30
a therapeutic amount of	Doses that produce sleep, see 2:36; doses that protect from seizures, *see* 2:37
2-phenyl,-1,3-propanediol dicarbamate	2-phenyl,-1,3-propanediol dicarbamate. *See e.g.*, 1:19.

Because the '444 patent teaches each and every limitation of the invention which is claimed by SOFIA, SOFIA's patent claim is invalid as anticipated. *See* 35 U.S.C. § 102.

The Examiner did not know about the '444 patent during prosecution of the SOFIA patent. In prosecuting the patent in suit, the Examiner searched U.S. Classes 514/534 and 514/541 (certain pharmaceutical compounds). The '444 patent, however, is not classified in 514/534, nor in 514/541. To the contrary, it is not classified as a pharmaceutical at all; rather, it is classified in 560/164 – "miscellaneous organic compounds having a polyoxy alcohol moiety." The Examiner's search of prior art pharmaceutical patents did not encompass the '444 patent.

The Examiner did not know of the '444 patent. In contrast, the patentee did. This is because the SOFIA patent and the '444 patent were both assigned to the same company, Carter-Wallace. (The '444 patent was assigned at issue to Carter Products, the predecessor of Carter-Wallace.)

While the patentee had actual knowledge of the prior art '444 patent, the patentee failed to make it of record during prosecution of the SOFIA patent. The

'444 patent doe not appear among the references cited on the face of the SOFIA patent, nor among the references made of record during prosecution.

Rule 56 requires the Patentee to have disclosed to the Examiner "The closest information over which … any pending claim patentably defines." *See* 37 C.F.R. § 1.56(a)(2). The Patentee failed to do so. By failing to do so, the Patentee violated its Rule 56 duty of candor. The SOFIA patent should therefore be found invalid due to fraud on the Patent Office.

IV. WILENSKY *ET AL.*, (1985) TEACHES EACH ELEMENT OF THE SOFIA PATENT CLAIM

Alan Joseph WILENSKY *et al*., *Pharmacokinetics of W-544 (ADD 03055) in Epileptic Patients*, 26 EPILEPSIA 602 (1985) reports on the results of human testing of 2-phenyl,-1,3-propanediol dicarbamate (also known as "W-554") as an anti-epileptic medicine. In so doing, WILENSKY teaches the same chemical compound for the same use as is claimed by the SOFIA patent. WILENSKY teaches each and every element of the invention claimed by SOFIA:

The SOFIA patent, claim 1	WILENSKY *et al*.
1. A method for reducing the incidence and severity of epileptic seizures	"exhibits broad-spectrum antiepileptic activity," page 602, col. 1
which comprises administering to a warm-blooded animal in need of such treatment	"Eight male patients with chronic uncontrolled partial seizures," page 603, col. 1
a therapeutic amount of	"a moderate-to-marked reduction in seizure frequency," page 604, col. 2
2-phenyl,-1,3-propanediol dicarbamate	"W-544" is 2-phenyl-1,3-propanediol dicarbamate, *see* page 602, col. 1; *see also* Fig. 1

WILENSKY anticipates the SOFIA patent because WILENSKY teaches each and every element of SOFIA's claimed invention. *See* 35 U.S.C. § 102.

The Examiner did not know about WILENSKY during prosecution of the SOFIA patent. To the contrary, the Examiner appears to have, perhaps due to a lack of facilities, not searched the scientific literature at all.

While the Examiner did not know about WILENSKY, the patentee (Wallace Laboratories) apparently did. This is because in concluding their article, WILENSKY *et al*. expressly acknowledge the support of Wallace Laboratories for its "cooperation and the supply of W-554 used in this study." *Id*. at page 606, col. 1.

While the patentee knew of WILENSKY's study, the patentee failed to provide this information to the Patent Office. To the contrary, WILENSKY neither appears among the references cited on the face of the SOFIA patent, nor appears among the references which SOFIA voluntarily made of record during prosecution.

Rule 56 requires SOFIA to disclose to the Examiner "The closest information over which … any pending claim patentably defines." *See* 37 C.F.R. § 1.56(a)(2). The Patentee failed to do so. By failing to do so, the Patentee violated its Rule 56 duty of candor. The SOFIA patent should be found invalid due to fraud on the Patent Office.

V. THE '720 PATENT COMBINED WITH THE '444 PATENT TEACHES EVERY CLAIM ELEMENT OF THE SOFIA PATENT

On 22 November 1955, the Patent Office issued Frank M. BERGER, *Dicarbamates of Substituted Propane Diols,* United States Letters Patent No. 2,724,720 (copy enclosed). The '720 patent teaches a minor variant of the claimed chemical compound, for the same use, as is claimed by SOFIA. Thus, the invention claimed to be invented by SOFIA is in truth a mere obvious variant of the invention previously disclosed by BERGER in the '720 patent:

The SOFIA patent, claim 1	The '720 patent
1. A method for reducing the incidence and severity of epileptic seizures	Compounds possess "marked anti-convulsant" properties, *see e.g.*, 1:33, and prevent the occurrence of seizures, 1:44-55
which comprises administering to a warm-blooded animal in need of such treatment	Testing in warm-blooded animals such as mice, *see* 1:50-54, 2:33-35
a therapeutic amount of	Doses that are "distinctly effective in protecting animals from electroshock seizures even 150 minutes after administration," 2:37-40
2-phenyl,-1,3-propanediol dicarbamate	**2-ethyl**-2-phenyl,-1,3-propanediol dicarbamate. *See e.g.*, 1:35

The '720 patent therefore literally teaches every element of SOFIA's claimed invention, except one: while SOFIA literally claims an invention which uses 2-phenyl,-1,3-propanediol dicarbamate, the '720 patent teaches the 2-ethyl form of that same compound.

Where the prior art teaches two different compounds are useful for the same intendd purpose, however, it is as a matter of law *prima fac*ie obvious to substitute one compound for another. *See e.g., Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327 (1945); *In re Leshin*, 227 F.2d 197 (C.C.P.A., 1960); *Ryco, Inc. v. Ag-Bag Corp.*, 857 F.2d 1418 (Fed. Cir. 1988) .

In the instant case, the '444 patent teaches 2-phenyl,-1,3-propanediol dicarbamate, and the '720 patent teaches its 2-ethyl form. Both prior art patents teach the compounds' usefulness in preventing seizures. Because the two compounds were known in the prior art to be suitable for the same intended purpose, it would have been obvious to substitute 2-phenyl,-1,3-propanediol dicarbamate for the 2-ethyl form taught by the '720 patent. SOFIA therefore claims a mere obvious variant of the '720 patent.

The Examiner did not know about the '720 patent during prosecution of the SOFIA patent. To the contrary, in reviewing the patent in suit, the Examiner searched U.S. Classes 514/534 and 514/541 (certain pharmaceutical compounds). The '720 patent, however, is not classified as a pharmaceutical compound; rather, it is classified as a miscellaneous organic compound. Thus, the Examiner's search did not encompass the '720 patent.

While the Examiner did not know of the '720 patent, the patentee did. This is because the SOFIA patent and the '720 patent were both assigned to the same company. (The '720 patent was assigned at issue to Carter Products, the predecessor of Carter-Wallace, the assignee at issue of the patent in suit.)

While the patentee had actual knowledge of the ‘720 patent, SOFIA failed to make it of record during prosecution. The ‘’720 patent thus neither appears among the references cited on the face of the SOFIA patent, nor appears among the references which SOFIA made of record during prosecution.

Rule 56 requires SOFIA to disclose to the Examiner “The closest information over which … any pending claim patentably defines.” *See* 37 C.F.R. § 1.56(a)(2). SOFIA failed to do so. By failing to do so, the Patentee violated its Rule 56 duty of candor. The SOFIA patent should be found invalid due to fraud on the Patent Office.

VI. THE OFFICE SHOULD ISSUE A REQUIREMENT UNDER RULE 105 THAT THE PATENTEE MAKE OF RECORD EWARD A. SWINYARD *ET AL*. (1982)

WILENSKY at page 602, col. 1 notes that 2-phenyl,-1,3-propanediol dicarbamate (W-554) was shown to "exhibit[] broad-spectrum antiepileptic activity in pre-clinical animal models." As support, WILENSKY cites to another publication, Eward A. SWINYARD and H.J. KUPFERBERG, *The profile of anticonvulsant activity and acute toxicity of 03046, [2-phenyl,-1,3-propanediol dicarbamate] and some prototype antiepileptic drugs in mice and rats*, (National Institutes of Health, Epilepsy Branch, 1982). This article appears to be material because its title indicates that it discusses the same drug for the same use as the SOFIA patent claims.

On information and belief, one of the co-authors of the 1982 article (H.J. KUPFERBERG) is an employee of the patentee. Thus, it appears that the 1982 article is in the patentee's possession, custody or control.

The Office has "an obligation to not unjustly issue patents." *See* M.P.E.P. § 2001.04 (Aug. 2001). To aid the Office in that endeavor, the Office can require a Patentee to submit information necessary to properly examine a patent. *See* 37 C.F.R. § 1.105 and M.P.E.P. § 704 *et seq*. The Office thus has authority under

Rule 105 to require an applicant to submit all information necessary to evaluate an allegation of fraud on the Patent Office. *See* M.P.E.P. § 2005 (Aug. 2001).

The Office should therefore issue a Rule 105 Requirement for Information requiring the Patentee to make of record E.A. SWINYARD *et al*. (1982).

VII. SUMMARY

The SOFIA patent claims an invention which was not first invented by Robert Duane SOFIA. Rather, the SOFIA patent claims an invention which was previously taught by Frank BERGER (the '444 patent), by Dr. Alan J. WILENSKY *et al*., and by Frank BERGER (the '720 patent). The SOFIA patent thus is invalid under 35 U.S.C. 102 and 103.

In addition, the SOFIA patent appears invalid due to fraud on the Patent Office.

Enclosed find the fee to request reexamination, and copies of each of the references discussed together with a listing thereof on PTO Form 1449.

The Requestor respectfully requests the Director make a determination pursuant to 35 U.S.C. § 312(a) that a substantial new question of patentability exists, and issue an order pursuant to 35 U.S.C. § 313 ordering an *inter partes* reexamination of the SOFIA patent.

Respectfully submitted by
PHARMACEUTICAL PATENT ATTORNEYS, LLC
Attorneys for Reexamination Requestor

__/s/_____
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28 March 2006
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6 March 2006

Kevin B. CLARKE, Esq.
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Somerset, New Jersey 08873

BY PRIORITY MAIL
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No. 0304 0370 0001 6258 1743

Re: Request for *Ex Parte* Reexamination of Robert Duane SOFIA, United States Letters Patent No. 4,978,680 and Request for *Ex Parte* Reexamination of Robert Duane SOFIA, United States Letters Patent No. 5,082,861

Dear Mr. CLARKE:

Enclosed find Service copies of the two captioned Requests for *Ex Parte* Reexamination. I assume that you will forward copies of these to your outside counsel; if you would like me to do this, please advise.

Sincerely,

J. Mark POHL
Mbc:mp

Enclosures

United States Patent [19]

Sofia

[11] **Patent Number: 4,978,680**

[45] **Date of Patent: Dec. 18, 1990**

[54] **METHOD FOR THE PREVENTION AND CONTROL OF EPILEPTIC SEIZURE**

[75] Inventor: **Robert D. Sofia**, Willingboro, N.J.

[73] Assignee: **Carter-Wallace, Inc.**, New York, N.Y.

[21] Appl. No.: **412,964**

[22] Filed: **Sep. 26, 1989**

[51] **Int. Cl.**[5] **A61K 31/24**

[52] **U.S. Cl.** **514/534**; 514/541

[58] **Field of Search** 514/534, 541

[56] **References Cited**

PUBLICATIONS

Chem-Abst. 104-180056v (1986).

Primary Examiner—Stanley J. Friedman

Attorney, Agent, or Firm—Kevin B. Clarke

[57] **ABSTRACT**

A novel method for the prevention and control of epileptic seizures employing pharmaceutical compositions containing 2-phenyl-1,3-propanediol dicarbamate.

1 Claim, No Drawings

METHOD FOR THE PREVENTION AND CONTROL OF EPILEPTIC SEIZURE

The present invention relates to pharmaceutical compositions containing 2-phenyl-1,3-propanediol dicarbamate as an active component and to methods for the prevention and control of epileptic seizures by the use of such compositions

More particularly, the present invention further relates to methods for increasing epileptic seizure threshold and the prevention of epileptic seizure spread through the administration of therapeutic compositions which contain as an active ingredient 2-phenyl-1,3-propanediol dicarbamate commonly known as Felbamate.

Felbamate is a well known pharmaceutical compound having been described in U.S. Pat. Nos. 2,884,444 and 4,868,327.

Epilepsy, a disease which has been characterized as a paroxysmal, self-sustaining and self-limited cerebral dysrhythmia, genetic or acquired in origin and physiologic or organic in mechanism is generallY divided into four main types based on the type of seizure that occurs in those afflicted with the disease.

Based on clinical and electroencephalographic observations, the four general subdivisions of epilepsy are:

1. Grand mal
2. Petit mal
3. Psychomotor
4. Autonomic

Those afflicted with epilepsy may present with any one of or a mixture of the foregoing forms of the disease.

In theory, it is believed that anti-epileptic drugs act to prevent or control seizures by acting on the seizure focus which may be a collection of pathologically altered neurons or normal cells having restricted vascular supply or an injured area in which the neurons of a nerve net have been destroyed.

Up to the present time, all drugs used in the treatment of epilepsy function as prophylactics against the symptoms of epilepsy, i.e., the reduction and control of epileptic seizures as opposed to being curatives.

Although it is generally recognized that approximately 50% of epileptic patients can be controlled with presently available anti-epileptic medications, there is a continuing long felt need for more selective and less toxic anti-epileptic drugs. The desiratum of the art has been to provide a non-toxic, non-sedative, long-acting and highly effective anti-epileptic drugs.

Phenytoin and carbamazepine are presently the drugs of choice for control of both generalized tonic-clonic (grand mal) and complex partial (temporal lobe) epileptic seizures.

In addition to gingival hyperplasia and hirsutism peculiar to phenytoin, both drugs have been reported to induce cerebellar-vestibular effects, skin disorders, hepatic deficiencies and congenital abnormalities. The foregoing toxicity profile for both phenytoin and carbamazepine clearly demonstrates a need for less toxic substances for use as anti-epileptic medications.

One of the objects of the present invention is to provide compositions for the treatment of epilepsy comprising felbamate as the active ingredient.

Another object of the present invention is to provide relatively non-toxic compositions effective to control or prevent epileptic seizures which have a unique spectrum of anti-epileptic activity and which include felbamate as an active component.

A further object of the present invention is to provide compositions for the prevention and control of epileptic seizures which compositions are relatively non-toxic, have a high degree of effectiveness and continue to produce a therapeutic response over relatively long periods of time.

Moreover, it is an object of the present invention to provide methods for the prevention and control of epileptic seizures through the use of felbamate.

Accordingly, it has been found that felbamate chemically described as 2-phenyl-1,3-propanediol dicarbamate is a compound which has demonstrated superior properties when compared to prototype drugs, i.e., phenytoin with respect to increasing seizure threshold and prevention seizure spread.

The compositions for the treatment of epilepsy may take any of a variety of forms although theY are intended primarily for oral use and is suitable for forming into pills, capsules and tablets by well-known practices. When the active ingredient is in the form of a solid, a typical tablet composition comprises 500 milligrams of 2-phenyl-1,3-propanediol dicarbamate intermixed in a dry pulverulent state with suitable solid carriers and diluents.

In general, an effective daily dose of the active ingredient is in the range of from about 100 milligrams to about 5 grams.

Solid carriers and diluents suitable for use include sugars such as lactose and sucrose; cellulose derivatives such as carboxymethyl cellulose, ethyl cellulose, methyl cellulose, etc., gelatin including hard and soft gelatin capsules, talc, cornstarch, stearic acid and magnesium stearate.

The percentage of 2-phenyl-1,3-propanediol dicarbamate in the compositions may be varied over wide limits and the quantity of medicament furnished by each individual tablet or capsule is relatively unimportant since the indicated total daily dose can be reached by administering either one or a plurality of capsules or tablets. However, for convenience in manufacturing and ease of administration, it is preferable that each dosage form contains at least 25 milligrams and up to 500 milligrams of 2-phenyl-1,3-propanediol dicarbamate per unit dosage form.

EXAMPLE 1

2-phenyl-1,3-propanediol dicarbamate is constituted into 500 mg. dosage units by encapsulation without an adjuvant into hard gelatin capsules The yield from 1000 g. of 2-phenyl-1,3-propanediol dicarbamate is about 2000 capsules each containing 500 mg. of medicant.

EXAMPLE 2

A tableting formulation is prepared as follows:

83 g. 2-phenyl-1,3-propanediol dicarbamate
13 g. powdered sugar with 3% starch
76 g. corn syrup
q.s. water
13 g. talc U.S.P. powdered Italian
3 g. magnesium stearate
q.s alcohol
flavoring

The formulation is compressed into tablets, each containing 200 mg. of 2-phenyl-1,3-propanediol dicarbamate. The yield is about 1750 tablets.

Felbamate (2-phenyl-1,3-propanediol dicarbamate) has a very favorable preclinical profile characterized by a substantial margin of safety (protective index 16.9–19.1). The following example presents the results from a double-blind randomized clinical trial in patients with partial seizures. Criteria for patient entry into the study were 4 or more complex partial seizures per month in spite of treatment with both phenytoin and carbamazepine.

EXAMPLE 3

Fifty-six patients (mean age 31.4 years; male=32, female=24) completed the study. The mean seizure frequencies for the eight week periods analyzed were: baseline=39.8; felbamate=34.9; placebo=40.2. Felbamate was significantly superior to placebo by percent seizure reduction (P=0.018) and truncated percent seizure reduction (p=0.007).

The mean felbamate dose was 2300 mg/day. Plasma felbamate concentrations ranged from 18.4 to 51.9, mean=32.5 mg/ml.

Adverse effects were minor and consisted of nausea and CNS effects.

The superiority of felbamate over placebo in a population of persons with severely refractory epilepsy indicates this medication to be a major anti-epileptic agent.

It should be understood that the above examples are illustrative of the best mode only of the invention herein disclosed. Given the present disclosure, it is anticipated that numerous variations will occur to those skilled in the art. A latitude of modification, substitution and change is intended and in some instances, some features of the invention will be employed without a corresponding use of other features. Accordingly, it is intended that the spirit and scope of the invention disclosed herein should be limited only by the following claims.

What is claimed is:

1. A method for reducing the incidence and severity of epileptic seizures which comprises administering to a warm-blooded animal in need of such treatment a therapeutic amount of 2-phenyl-1,3-propanediol dicarbamate.

* * * * *

PTO/SB/08A (04-03)
Approved for use through 04/30/2003. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet | | of | |

Complete if Known	
Application Number	90/xxx,xxx
Filing Date	28 March 2006
First Named Inventor	Robert D. SOFIA
Art Unit	Central Reexam
Examiner Name	
Attorney Docket Number	Nexin

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US- 2,884,444	04-28-1959	Frank M. BERGER	1:15-20; 2:26-49
		US- 2,724,720	11-22-1955	Frank M. BERGER	1:32-35; 2:29-40
		US-			3:1-28; 1:44-60
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08B (04-03)
Approved for use through 04/30/2003. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of

Complete if Known	
Application Number	90/xxx,xxx
Filing Date	
First Named Inventor	
Art Unit	
Examiner Name	
Attorney Docket Number	

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		A.J. WILENSKY et al., Pharmacokinetics of W-544 (ADD 03055) In Epileptic Patients, 26 Epilepsia 602 (1985) (Raven Press, New York)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

United States Patent Office

2,884,444

Patented Apr. 28, 1959

2,884,444

2-PHENYL-1,3 PROPANE DIOL DICARBAMATE

Frank M. Berger, Princeton, and Bernard J. Ludwig, North Brunswick, N.J., assignors to Carter Products, Inc., New York, N.Y., a corporation of Maryland

No Drawing. Application January 13, 1956
Serial No. 558,848

1 Claim. (Cl. 260—482)

This invention relates to a novel organic compound and has for its object the provision of a new compound which possesses anti-convulsant activity of unusually high intensity in preventing the occurrence of electroshock seizures. This compound is 2-phenyl-1,3-propanediol dicarbamate.

The aforementioned compound of this invention is a white crystalline solid soluble in most organic solvents, but soluble to only a slight degree in water. It forms stable solutions in water and organic solvents. Upon heating or boiling with acid or alkali, this compound hydrolyzes to give the corresponding 2 substituted 1,3-propanediol, ammonia and carbon dioxide.

The novel compound may be prepared by reacting 2-phenyl-1,3-propanediol with phosgene to form the corresponding di-chlorocarbonate derivatives. This reaction is promoted by the addition to the reacting compounds of acid combining agents such as sodium hydroxide, antipyrine, dialkylaniline and the like. The di-chlorocarbonate derivative is then converted to the dicarbamate by ammoniation, using either anhydrous or aqueous ammonia.

The compound may also be prepared from the diol by ester exchange using a low molecular weight urethane. In this reaction the low molecular weight alcohol contained in 2 equivalents of urethane is replaced by 2-phenyl-1,3-propanediol to give the desired dicarbamate.

The 2-phenyl-1,3-propanediol used in making the novel compound may be prepared by any known method as, for example, by the reduction of the corresponding 2-substituted malonic ester.

To describe the invention more particularly, the following examples serve to illustrate the method of preparation of the novel compound of this invention. Example I serves to illustrate the preparation of the diol from which the novel dicarbamate is formed. Example II describes a method of preparing the novel dicarbamate from its corresponding diol.

Example I

The following example illustrates the preparation of 2-phenyl-1,3-propanediol:

50 g. of diethyl phenyl malonate were reduced in the usual manner with 12 g. of lithium aluminum hydride, the reduction being carried out in 500 ml. of anhydrous ether. The excess reducing agent was utilized using a small volume of ethyl acetate. The reaction mixture was worked up in the usual manner with water and dilute sulfuric acid, the organic components being extracted with

ether. 16 g. (approx. 50% of theoretical yield) of purified product melting at 49–52° C. was obtained. *Analysis.*—Calculated: C, 71.03; H, 7.95. Found: C, 71.04; H, 7.88.

Example II

The following example describes the preparation of 2-phenyl-1,3-propanediol dicarbamate using the urethane exchange method:

20 g. of 2-phenyl-1,3-propanediol and 25 g. of ethyl urethane were dissolved in 320 ml. anhydrous toluene. 3 g. of aluminum isopropylate were added and the mixture distilled to remove the ethanol formed in the condensation of ethyl urethane with the diol. The alcohol distills in the form of an azeotrope with toluene, boiling point approximately 77° C. Distillation is continued until essentially the theoretical quantity of ethanol has been removed. The toluene is distilled from the mixture under reduced pressure, and the resulting solid extracted with hot aqueous isopropanol solution. From this solution, on cooling, there is obtained 16.5 g. of purified product, representing a yield of approximately 52% of theoretical. The purified product has a melting point of 151–152° C., and is soluble to only a slight extent in water at ordinary room temperature. *Analysis.*—Calculated for $C_{11}H_{14}N_2O_4$: N, 11.8. Found: N, 11.7.

When the compound of this invention is tested in suitable experimental animals, such as mice, for its ability to prevent the occurrence of electroshock seizures, it is found to possess unique anti-convulsant activity. It has been found, however, to be relatively ineffective in protecting animals from convulsions produced by pentylenetetrazole. The novel compound does not possess effective sleep-inducing action and does not cause paralysis of voluntary muscles unless given in very large doses. Doses that will produce sleep or paralysis on mice are greater than 2,000 mg./kg., whereas doses protecting from electroshock seizures are of the order of 60–80 mg./kg. The compound is remarkable because of its very low toxicity. The mean lethal dose in mice after intraperitoneal administration is approximately 4,000 mg./kg. and the mean lethal dose in mice after oral administration is approximately 8,000 mg./kg.

The compound of this invention is primarily intended for oral use and formed into suitable pills, tablets or capsules by well-known practices. It may be dissolved in a suitable solvent such as a mixture of water and polyethylene glycol to give a solution suitable for injection or use as an enema.

We claim:

2-phenyl-1,3-propanediol dicarbamate.

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2,724,720 Berger et al. ---------- Nov. 22, 1955

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United States Patent Office

2,724,720

Patented Nov. 22, 1955

2,724,720

DICARBAMATES OF SUBSTITUTED PROPANE DIOLS

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No Drawing. Application August 3, 1953, Serial No. 372,144

4 Claims. (Cl. 260—482)

This invention relates to organic compounds and has for its object the provision of certain new compounds which have effective central depressant properties. The invention is based on our discovery that in the class of 2,2 - disubstituted - 1,3 - propanediol dicarbamates three compounds possess marked anti-convulsant and other properties. The three compounds are:

2-methyl-2-isopropyl-1,3-propanediol dicarbamate
2-ethyl-2-phenyl-1,3-propanediol dicarbamate
2-methyl-2-n-propyl-1,3-propanediol dicarbamate

These 2,2-disubstituted-1,3-propanediol dicarbamates are white crystalline solids soluble in most organic solvents but soluble to only a slight degree in water. They form stable solutions in water, and upon boiling with acid or alkali hydrolyze to give the corresponding 2,2-disubstituted-1,3-propanediol, ammonia and carbon dioxide.

These three compounds not only possess anti-convulsant properties of much greater intensity than other related compounds but they produce an action of much longer duration. For example, when these compounds have been injected into animals, they afford protection from electroshock seizures for several hours.

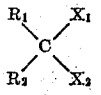
When the compounds of the invention are tested in suitable experimental animals, such as mice, for their ability to prevent the occurrence of electroshock seizures, it is found that they have a protective action of longer duration than the diols from which they are derived. In these test, first a strength of current was determined which, when administered through corneal electrodes, would produce a typical electro-convulsive seizure on all mice. It was found that a current strength of about 12 milliamperes applied for 0.2 second would effect this.

The tests themselves were carried out with a current strength of 50 milliamperes, that is, approximately 4 times the minimum effective dose. The apparatus used was arranged in such a way that the current administered was independent of external resistance. The various compounds were given to the mice at graded dose levels

by the oral route and the dose protecting 50% of the animals from electroshock seizures was determined by the customary methods of calculation.

Table I gives these mean protective doses of the compounds of the invention and the diols from which they are derived to prevent electroshock seizures in mice 30 minutes and 150 minutes after administration of the compounds. The mean protective doses are expressed in millimoles per kilo of animal weight and the standard error of the dose is also given.

Table I



Compound	Time, Mins.	R_1 methyl R_2 n-propyl	R_1 methyl R_2 iso-propyl	R_1 ethyl R_2 phenyl
Diol	30	2.0 ±0.1	3.2±0.28	1.2 ±0.04
X_1CH_2OH	150	Ineffective	Ineffective	Ineffective
X_2CH_2OH	30	0.76±0.04	1.5±0.09	1.5 ±0.15
Dicarbamate				
$X_1CH_2OCONH_2$	150	1.4 ±0.04	2.6±0.17	1.67±0.08
$X_2CH_2OCONH_2$				

These results show conclusively that these carbamates are distinctly superior to their parent compounds in possessing action of longer duration. This can be shown when animals given different doses of anti-convulsants are subjected to electroshock at different times after administration of the drug. In each case the diol compounds while fully effective in protecting animals 30 minutes after administration are completely ineffective 150 minutes after administration. The dicarbamate derivatives of these compounds, on the other hand, are distinctly effective in protecting animals from electroshock seizures even 150 minutes after administration.

The compound 2-methyl-2-n-propyl-1,3-propanediol dicarbamate not only has exceptional anti-convulsant properties but it also has when given in suitable dosage a marked paralyzing action on voluntary muscles. This paralyzing action manifests itself in animals in their complete inability to move. Animals paralyzed in this manner remain conscious and all their vital functions, such as respiration and heart action, continue in an unimpaired manner. An important characteristic of the compound is that the animals recover from the paralysis without any ill effects.

Pharmacological studies have shown that paralysis is produced by a depressant effect on the central nervous system. The nerves and nerve endings remain unaffected by the drug. The structure most sensitive to the effect of the drugs in the central nervous system are the interneurons. This may be of therapeutic value. The action of this compound is similar to that of mephenesin in numerous respects, but differs from it in possessing a very much longer duration of action, and in being somewhat more effective on oral administration. Mephenesin is a widely used drug of value in the treatment of muscle spasm, anxiety and many disorders of the nervous system. The very short duration of action of mephenesin is its greatest drawback. The duration of the action of mephenesin was compared with 2-methyl-2-n-propyl pro-

panediol dicarbamate in the series of tests recorded in Table II.

Table II

Dose, Mgm. per Kgm.	Mephenesin		2-Methyl-2-n-Propyl-1,3-Propanediol Dicarbamate	
	Percent Paralyzed	Duration of Paralysis in Minutes	Percent Paralyzed	Duration of Paralysis in Minutes
1,400	100	113.0±14.5	100	420
940	100	57.4±10.4	100	317.2±42.0
620	80	19.2± 2.0	100	182.1±24.8
420	50	11.0± 2.0	100	90.0±16.9
280	10	4.5	20	82.2

It will be noted that at the various dose levels at which the comparison was carried out the action of this compound of the invention was five to ten times as long as that of mephenesin. The action of the other two compounds, namely the 2-methyl-2-isopropyl-1,3-propanediol dicarbamate and 2-ethyl-2-phenyl-1,3-propanediol dicarbamate, is similar to the above mentioned compound but is not as intense. When the diols from which these dicarbamates are derived were investigated in a similar manner, it was found that they had only weak paralyzing action, the duration of which was even shorter than that of mephenesin.

The preparation of these new organic compounds involves the reaction of the selected 2,2-disubstituted-1,3-propanediol with phosgene to form the corresponding dichlorocarbonate derivative. This reaction is advantageously promoted by the addition to the reacting compounds of any suitable acid-combining compound such as sodium hydroxide, antipyrine, dialkylaniline, and the like. This step in the method is followed by ammoniation of the dichlorocarbonate derivative to form the desired dicarbamate, using anhydrous ammonia or aqueous ammonium hydroxide as suitable sources of ammonia for this purpose. The following examples serve to illustrate the method of preparation of the 2,2-disubstituted-1,3-propanediol dicarbamates of our invention.

Example 1

To a solution of 100 parts by weight of phosgene in 900 parts of anhydrous toluene there is added gradually with stirring 66 parts of 2-methyl-2-isopropyl-1,3-propanediol. The reaction mixture is stirred until a clear solution is obtained. While cooling the reaction vessel so that the temperature is maintained at about room temperature 380 parts of antipyrine dissolved in a minimum volume of chloroform are added gradually to promote the reaction between phosgene and the diol. Formation and separation of the hydrochloride of antipyrine takes place rapidly and the reaction mixture is stirred until the reaction is complete.

The solid antipyrine hydrochloride is removed by filtration and the filtrate saturated with anhydrous ammonia, while stirring and cooling the reaction vessel. The solid formed during this ammoniation is removed by filtration, dried and extracted with cold water, leaving a residue of crude reaction product. It is purified by recrystallization from hot water. The purified 2-methyl-2-isopropyl-1,3-propanediol dicarbamate is obtained in 60% yield as a white crystalline solid, M. P. 99–100°, soluble in water to the extent of about 0.15% at 27° C.

Analysis of this compound gave: N, 12.6%. Calculated for $C_9H_{18}N_2O_4$:N, 12.8%.

Example 2

100 parts phosgene dissolved in 500 parts benzene, 90 parts 2-ethyl-2-phenyl-1,3-propanediol and 190 parts antipyrine dissolved in a minimum volume of chloroform are reacted together as described in Example 1. The solid antipyrine hydrochloride is removed by filtration and the filtrate is poured gradually into a well stirred cooled solution of an excess of ammonium hydroxide. The reaction product separates in the form of a semi-solid and is removed by filtration. The crude dicarbamate is dried and purified by recrystallization from hot benzol. 2-ethyl-2-phenyl-1,3-propanediol dicarbamate is obtained in 70% yield as a white crystalline solid, M. P. 119–120°; slightly soluble in water at ordinary room temperature. Analysis of this compound gave: N, 10.3%. Calculated for $C_{13}H_{18}N_2O_4$:N, 10.5%.

Example 3

A solution containing 52.8 parts of 2-methyl-2-n-propyl-1,3-propanediol and 128 parts of acetone is added with stirring to 112 parts of liquid phosgene at such a rate that the temperature of the reaction is maintained at −5° to 0° C. The reaction is stirred one hour at about 0° then cooled to −15°. A cooled 30% solution of 32 parts of sodium hydroxide is added with stirring to the reaction at such a rate that the temperature is maintained at −15 to −5°. The mixture is stirred for an additional ½ hour at about 0° then cooled to −20°. 180 parts of cooled ammonium hydroxide solution (28.6% NH_3) are added while cooling and with stirring at such a rate that the temperature rises slowly to 20° and stirring is continued for an additional ½ hour. The mixture is poured with agitation into 1700 parts of ice water. The solid which separates is removed by filtration and dried. Recrystallization from water gives 55 parts (63% of theoretical yield) of 2-methyl-2-n-propyl-1,3-propanediol dicarbamate, M. P. 104–105°; approximately 0.2% soluble in water at ordinary room temperature. Analysis of this compound gave: N, 12.5%. Calculated for $C_9H_{18}N_2O_4$:N, 12.8%.

All temperatures herein are in ° C.

This application is a continuation-in-part of our copending application Serial Number 176,764, filed July 29, 1950, and now abandoned.

We claim:

1. The 2,2-disubstituted 1,3-propanediol dicarbamates of the group consisting of 2-methyl-2-isopropyl-1,3-propanediol dicarbamate, 2-ethyl-2-phenyl-1,3-propanediol dicarbamate, and 2-methyl-2-n-propyl-1,3-propanediol dicarbamate.

2. 2-methyl-2-isopropyl-1,3-propanediol dicarbamate.

3. 2-ethyl-2-phenyl-1,3-propanediol dicarbamate.

4. 2-methyl-2-n-propyl-1,3-propanediol dicarbamate.

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Epilepsia, 26(6):602–606, 1985
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Pharmacokinetics of W-554 (ADD 03055) in Epileptic Patients

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Summary: W-554 (ADD 03055, 2-phenyl-1,3-propanediol dicarbamate) has broad-spectrum antiepileptic activity in animal models of epilepsy. We evaluated its pharmacokinetics and toxicity as an adjunctive medication in eight adult male patients with uncontrolled seizures, treated with phenytoin (n = 4) or carbamazepine (n = 4). After a single 200-mg dose, peak W-554 serum levels of 2.65–4.10 mg/L were achieved in 1–4 h. Half-lives were 11.2–16.1 h and clearance varied from 34.2–64.6 ml/h × kg. The apparent volume of distribution was 0.726–1.046 L/kg. Chronic dosing at 400, 800, 1,200, and 1,600 mg/day resulted in median steady-state trough levels of 5.1, 10.2, 14.6, and 20.3 mg/L. A second kinetic study at the end of chronic dosing indicated no change in volume of distribution, decreased clearance, and increased half-life, compared with single dose data. Urinary excretion of unchanged drug was 13.8–28.6% of the dose. Only one subject had toxicity (mild blurred vision and tremor) possibly attributable to W-554. Seizure control was improved in six of eight subjects, and seizures were less severe in three, while on W-554. Addition of W-554 resulted in increases in serum phenytoin levels, and small decreases in serum carbamazepine levels. **Key Words:** W-554 (ADD 03055)—Antiepileptic drugs—Pharmacokinetics—Epilepsy.

W-554 (ADD 03055, 2-phenyl-1,3-propanediol dicarbamate) is an experimental antiepileptic drug under development by Wallace Laboratories (Fig. 1). Its chemical structure is similar to that of the antianxiety agent meprobamate. However, in contrast to meprobamate, W-554 exhibits broad-spectrum antiepileptic activity in preclinical animal models (Swinyard and Kupferberg, 1982). This study was a Late Phase 1 evaluation of W-554 with the following objectives: (a) to assess the pharmacokinetics and toxicity of W-554 in epileptic patients at doses up to 1,600 mg/day; (b) to determine the effect of W-554 on seizure frequency when given as an add-on medication; and (c) to determine the effects of addition of W-554 on the serum concentrations of phenytoin (PHT) and carbamazepine (CBZ).

METHODS

Chronology (Table 1)

Subjects were maintained on stable doses of their standard anticonvulsant medication, either PHT or CBZ, for 7 weeks prior to the initiation of W-554 administration. All medications were given twice a day. One week before W-554 was begun, subjects were admitted to the University of Washington Epilepsy Center's Inpatient Unit for evaluation of their baseline antiepileptic therapy. Blood samples were collected immediately before and at 2, 4, 6, 8, 10, and 12 h after the subjects' usual morning dose, and PHT or CBZ serum levels determined. The subjects were discharged the following morning, and returned to hospital 6 days later for a 17-day stay (study days 8–24). On study day 8, a single 200-mg dose of W-554 was given to the subjects along with their regular PHT or CBZ dose, at 8 a.m. after an overnight fast. Blood samples were collected immediately before, and at 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, and 24 h postdose, and the serum analyzed for W-554 and PHT or CBZ. On day 9 upward titration of the W-554 dose began (Table 1). Daily fasting morning blood samples were collected from day 9 to 25, and thereafter on day 26, 28, 30, 32, and 34 (subjects were outpatients on days 25–35). On day 36 the subjects were again hospitalized for 24 h and another pharmacokinetic study was performed, with the same blood collection schedule and assays as on day 8. The final 800-mg dose of W-554 was administered at 8 a.m. on day 36. Twenty-four–hour urine samples were collected on days 1, 8, 16, 24, 29, and 36. Subjects returned to the Epilepsy Center outpatient clinic on day 43 for follow-up. Physical and neurological exams, and

Received June 10, 1985.
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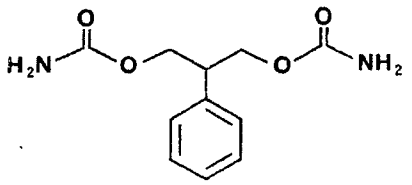

FIG. 1. Chemical structure of W-554.

blood chemistry and hematology panels were performed at intervals throughout the study. Subjects were instructed to keep seizure calendars and to return any unused medication throughout the course of the study.

Subjects (Table 2)

Eight male patients with chronic uncontrolled partial seizures, with or without secondary generalization, who did not have renal or hepatic disease, participated in the study after giving written informed consent, obtained according to University of Washington regulations. Subjects 1–4 were on stable PHT regimens, and subjects 5–8 were on stable CBZ regimens.

Analytical methods

PHT concentrations were analyzed by gas-liquid chromatography (CV 3%) (Midha et al., 1976). CBZ was determined by high-performance liquid chromatography (CV 5%) (Sawchuk and Cartier, 1982). W-554 also was analyzed by high-performance liquid chromatography (CV 4%) (Kelton, 1982). W-554 assays on subjects 1–4 were carried out using a 39% methanol/water mobile phase and a C18 column. W-554 assays on subjects 5–8 were carried out using a 20% acetonitrile/water mobile phase and a C18 column, because of interferences caused by CBZ metabolites when the methanol/water mobile phase was employed.

TABLE 1. *Study chronology*

Study phase	Study day	Standard anticonvulsant	W-544 dose
Baseline/ Stabilization	−42–7	x	—
Single dose[a]	8	x	200 mg
Titration	9–12	x	200 mg b.i.d.
	13–16	x	400 mg b.i.d.
	17–20	x	600 mg b.i.d.
	21–24	x	800 mg b.i.d.
Maximum dose	25–35	x	800 mg b.i.d.
Final dose[a]	36	x	800 mg
Follow-up	37–43	x	—

[a]Pharmacokinetic study of W-554.

Calculations

Area under the concentration-time curve (AUC) after the single 200-mg dose of W-554 was calculated as:

$$\text{AUC} = \text{AUC}\,(0\text{–}24\text{ h}) + \frac{\text{concentration}\,(24\text{ h}) \times t_{1/2}}{0.693}$$

AUC (0–24 h) was calculated using the trapezoidal rule. AUC after the last 800-mg dose of W-554 was calculated using the trapezoidal rule on serum concentrations from 0–12 h postadministration (Levy, 1982). Serum half-life ($t_{1/2}$) was estimated by linear regression on log serum concentrations during the postabsorptive phase. Clearance (divided by the fraction absorbed, F) was calculated from the expression:

$$\text{Clearance/F} = \frac{\text{dose}}{\text{AUC} \times \text{body weight}}$$

The apparent volume of distribution V(B) was estimated from the expression:

$$\text{V(B)/F} = \frac{\text{dose} \times t_{1/2}}{0.693 \times \text{AUC}}$$

The median was chosen as the best descriptive measure of central tendency for the pharmacokinetic data because of the small sample size and because distributions of some parameters appeared to be skewed.

TABLE 2. *Patient data*

Patient	Age (yr)	Weight (kg)	Standard anticonvulsant, dose (mg/day), level (mg/L)			Monthly seizure frequency	
			Drug	Baseline/Stabilization	Final day W-554	Baseline/Stabilization	On W-554
1	27	58	PHT	400, 12	400, 24	2.7	1
2	36	84	PHT	400, 20	400, 21	4.5	4
3	27	72	PHT	400, 14	350, 19	14	16
4	24	54	PHT	600, 9	400, 11	4	1
5	34	94	CBZ	1,400, 10	1,400, 8	6	2
6	32	107	CBZ	1,000, 10	1,000, 8	4.6	1
7	35	70	CBZ	800, 10	800, 9	0.5	1
8	21	91	CBZ	1,200, 7	1,200, 7	28	22

PHT, phenytoin; CBZ, carbamazepine.

RESULTS

Compliance

Estimates of compliance with the protocol were based on serum drug concentrations, pill counts, nursing observations, and specific interviews with each subject. Aside from subject 4, who took his medications erratically except when hospitalized, medication compliance was good to excellent for each subject. Subjects 1 and 3 had some difficulty recognizing all their seizures, but were otherwise reliable. Some urine collections were unsatisfactory on subjects 6, 7, and 8.

W-554 kinetics

The 200-mg single dose data are shown in Table 3. Peak W-554 serum concentrations of 2.65 to 4.10 mg/L were observed 1–4 h after dosing, indicating an adequate absorption rate. Half-lives were 11.2–16.1 h. Clearance varied by approximately twofold (34.2–64.6 ml/h × kg). The apparent volume of distribution (0.726–1.046 L/kg) indicates distribution into extravascular tissues.

Based on the range of half-lives in the single dose study, W-554 dose increases were scheduled at 4-day intervals in order to allow levels to reach "steady-state" plateaus at each dose (Table 1). Table 4 gives the trough W-554 concentrations corresponding to the 4th day of each dose step (i.e., on the morning immediately before the next dose change). The dose-level relationship was linear, with doses of 400–1,600 mg/day producing levels of ~5–20 mg/L in our subjects. However, there was a tendency for levels to increase slightly from days 25 to 36, while patients remained on W-554 1,600 mg/day.

W-554 kinetics after chronic administration of 800 mg b.i.d. are shown in Table 5. Clearance values were lower after chronic administration, compared with the single dose study, in six of eight subjects ($p < 0.05$, Wilcoxon sign rank test). There were no consistent changes in apparent volume of distribution. The decreased clearance after chronic administration is reflected in an increase in half-life in six of eight subjects. The changes were generally not dramatic, although W-554 clearance in subjects 5–7 did drop by 30–40% after chronic administration. Urinary excretion of unchanged W-554 after chronic administration (measured on day 29, or day 36 if urine collection was unsatisfactory on day 29) varied from 13.8–28.6% of the dose.

Toxicity

Most of the toxicity recorded during the study was associated with increased levels of PHT or CBZ. Subjects 1, 3, and 4 experienced PHT toxicity when their serum PHT levels rose from baseline levels of 9–14 mg/L into the 20–30 mg/L range, during W-554 administration. PHT dosage was reduced in subjects 3 and 4, and toxicity cleared. Subject 6 had transient side effects associated with a brief increase in CBZ serum levels to 11–12 mg/L at the start of W-554 administration. CBZ levels returned to baseline levels of 8–10 mg/L, and toxicity cleared, without a change in CBZ dose. Subject 8 had mild blurred vision and tremor during W-554 dose titration which may have been related to that drug, since CBZ levels were not elevated at the time. There were no clinically significant changes in vital signs, blood chemistry, or hematology values during the study.

Seizure control (Table 2)

There was a moderate-to-marked reduction in seizure frequency in six of eight subjects during W-554 administration. In terms of patient report, subject 1 felt that his seizure control was definitely improved on W-554, but this may have been the result of his increased PHT level. Subjects 3, 4, and 6 had less severe seizures on W-554. While each of these subjects experienced at least two episodes of secondary generalization of his partial seizures during the baseline/stabilization period, no generalized tonic-clonic attacks occurred during W-554 administration. Subject 5 felt that his seizure control was markedly improved while on W-554. Changes in seizure frequency for subjects 2, 7, and 8 were of doubtful clinical significance.

TABLE 3. *W-554 pharmacokinetics after a single 200-mg dose*

Patient	t_{max} (h)	C_{max} (mg/L)	AUC (mg × h/L)	$t_{1/2}$ (h)	Clearance/F (ml/h × kg)	V(B)/F (L/kg)
1	1	4.08	64.6	12.0	53.6	0.926
2	3	2.85	69.0	15.7	34.4	0.779
3	3	3.18	74.3	14.4	37.4	0.779
4	2	4.10	73.8	12.2	50.1	0.885
5	4	2.65	32.9	11.2	64.6	1.046
6	3	2.84	46.7	14.7	39.8	0.848
7	3	3.54	67.8	11.9	42.2	0.726
8	1	2.74	64.2	16.1	34.2	0.796
Median	3	3.02	64.4	13.3	41.0	0.822

t_{max}, time to peak level; C_{max}, peak level.

TABLE 4. *"Steady-state" trough W-554 concentrations (mg/L)*

Patient	Day 13 (400 mg/day)	Day 17 (800 mg/day)	Day 21 (1,200 mg/day)	Day 25 (1,600 mg/day)	Day 36 (1,600 mg/day)
1	5.2	9.8	14.5	18.7	24.1
2	5.8	9.8	13.2	18.1	23.8
3	5.1	11.4	19.5	22.4	20.1
4	5.2	11.3	14.6	20.7	23.2
5	3.4	7.2	9.5	14.0	15.1
6	5.0	10.2	15.8	20.8	22.4
7	4.5	10.6	17.8	22.5	26.9
8	4.7	10.1	14.2	19.8	14.4
Median	5.1	10.2	14.6	20.3	23.5

Drug interactions

W-554 kinetics in this group of patients with epilepsy are similar to those observed in normal, drug-free individuals, suggesting that PHT and CBZ do not alter W-554 disposition (I. Weliky, personal communication). PHT levels rose dramatically in three of four subjects when W-554 was added; in two of these, the PHT dose had to be reduced because of intolerable toxicity (Table 2). As noted previously, medication intake in subject 4 was erratic, so that the increase in his PHT level might be attributable to improved medication compliance during hospitalization for W-554 titration. The increases in PHT level in subjects 1 and 3 cannot be explained by changes in compliance; rather, they appear to reflect a true drug interaction. Subject 2, who also was treated with PHT, experienced a very slight increase in PHT level, from 20 to 21 mg/L, during W-554 administration.

CBZ levels declined slightly in three subjects and remained the same in one during W-554 administration (Table 2).

DISCUSSION

Peak serum concentrations at 1–3 h and half-lives of 11–20 h were measured after chronic administration of W-554. Thus, twice daily dosing should be satisfactory and did in fact result in a less than twofold fluctuation in serum levels during each dosing interval (Table 5). Waiting at least 4 days after a dose change should result in serum levels reaching a new steady-state plateau. The trend toward increased $t_{1/2}$ values and reduced clearance at maximum dose compared with single dose (Tables 3 and 5), and the trend for trough levels to drift upward over time at the maximum dose (Table 4), suggest that a nonlinear dose-level relationship may be encountered at doses of 1,600 mg/day (20 mg/kg) and above.

Only one of eight subjects in our study experienced toxicity that may have been attributable to W-554 (mild blurred vision and tremor), indicating that the maximum tolerated dose is greater than 1,600 mg/day. Even at this dosage, improved seizure control was observed in six of eight subjects, and a reduction in secondary generalization of partial seizures was observed in three subjects. The reductions in seizure frequency and severity are not definitive because of (a) increased PHT levels in some subjects during W-554 administration; (b) the open, unblinded nature of the study; (c) hospitalization of patients, which can result in improved seizure control, during W-544 therapy; and (d) the short duration of the trial. Nevertheless, the results with respect to efficacy are promising, and further controlled studies are indicated.

PHT levels increased in each subject during W-554 administration. In one case the increase was slight, and in another it may have been due to improved medication compliance, but in the other two subjects there is little

TABLE 5. *W-554 pharmacokinetics after chronic administration of 800 mg b.i.d. (day 36)*

Patient	t_{max} (h)	C_{min} (mg/L)	C_{max} (mg/L)	AUC (mg × h/L)	$t_{1/2}$ (h)	Clearance/F (ml/hr × kg)	V(B)/F (L/kg)	Urinary W-554 (% of dose)
1	3	24.1	33.9	332.1	11.4	42.6	0.699	21.0
2	1	23.8	31.7	318.8	19.6	30.0	0.848	19.2
3	1.5	20.1	27.3	295.3	16.3	37.6	0.888	28.6
4	1	23.2	41.0	353.7	11.9	41.8	0.716	13.8
5	3	15.1	23.4	208.1	12.4	41.2	0.737	14.3
6	3	22.4	30.1	289.5	15.1	24.7	0.539	20.0
7	2	26.9	39.4	372.2	14.1	30.7	0.627	16.3
8	2	14.4	25.9	236.8	16.7	37.1	0.892	18.0
Median	2	23.5	30.9	307.1	14.6	37.4	0.727	18.6

C_{min}, trough level. Other abbreviations as in Table 3.

doubt that a drug interaction occurred. Our findings suggest that this interaction may occur to varying degrees with different patients, but that it can result in dramatic (>100%) increases in serum PHT levels in some individuals. Paradoxically, there was a trend toward slight (20% or less) decreases in serum CBZ levels during W-554 therapy.

Studies of W-554 at higher doses in a larger group of patients are required to answer the following questions: (a) Does the trend toward reduced clearance at 1,600 mg/day indicate that the dose-level relationship will be nonlinear at higher doses? (b) What is the maximum tolerated dose? (c) Can the improved seizure control found in this study be confirmed under blinded conditions? and (d) Can the drug interactions seen in this group of patients, resulting in unpredictable but sometimes dramatic increases in serum PHT, and small decreases in serum CBZ, be extrapolated to the epilepsy patient population at large?

Acknowledgment: We are grateful to Dr. Irving Weliky and Wallace Laboratories for their cooperation and the supply of W-554 used in this study. Mr. Frank Nice and Dr. William Pitlick provided guidance and assistance throughout the study. Karen McCormick (nurse clinician), Dana Miller (clinical chemist), and Jane Shofer (biostatistician) provided excellent technical assistance. This study was supported by NIH Contract NO1-NS-1-2368-TO#3.

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Swinyard EA, Kupferberg HJ. The profile of anticonvulsant activity and acute toxicity of 03046, 03055 and some prototype antiepileptic drugs in mice and rats. Bethesda, Maryland: Epilepsy Branch, NINCDS, NIH, April, 1982.

RÉSUMÉ

Le W-554 (ADD 03055, 2-phényl-1,3-propanediol dicarbamate) a un spectre étendu d'action antiepileptique dans les modèles animaux. Nous avons étudié sa pharmacocinétique et sa toxicité en tant que médicament surajouté chez 8 adultes mâles présentant des crises non contrôlées, traités soit par la phénytoïne (4 cas) soit par la Carbamazépine (4 cas). Après une dose unique de 200 mg, un pic de taux sérique de 2,65 à 4,10 mg/l est atteint en 1 à 4 heures. Les demi-vies étaient de 11,2 à 16,1 heures et la clearance variait de 34,2 à 64,6 mg/heure x kg. Le volume apparent de distribution était de 0,726 à 1046 L/kg. L'administration chronique aux doses de 400, 800, 1200 et 1600 mg/j entraînait un état d'équilibre médian pour des taux de 5.1, 10.2, 14.6, et 20.3 mg/L. Une seconde étude cinétique à la fin de l'administration chronique montrait, par comparaison avec les données obtenues à partir d'une dose unique, une absence de modification du volume de distribution, une clearance diminuée et une demi-vie augmentée. L'excrétion urinaire du produit inchangé est de 13,8 à 28,6% de la dose. Un seul sujet a présenté des signes de toxicité (vision trouble et tremblement) pouvant être possiblement attribués au W-554. Le contrôle des crises a été amelioré chez 6 des 8 sujets, et les crises étaient moins intenses chez 3. L'addition de W-554 entraîne une augmentation du taux sérique de la phénytoïne, et une faible élimination de celui de la carbamazepine.

(J. Roger, *Marseille*)

RESUMEN

El W-554 (ADD 03055, 2-fenil-1,3-propanediol dicarbamato) tiene un amplio espectro de actividad antiepiléptica en modelos animales de epilepsia. Hemos evaluado las propiedades farmacocinéticas y la toxicidad de este producto como medicación complementaria en 8 varores adultos que padecían ataques incontrolados tratados con Fenitoína (n = 4) o Carbamacepina (n = 4). Después de una dosis única de 200 mg, los picos de niveles séricos del W-554 fueron de 2.65–4.10 mg/L entre una y cuatro horas. Las vidas medias fueron de 11.2–16.1 h y el aclaramiento varió de 34.2–64.6 ml/h x kg. El volumen aparente de distribución fue de 0.726–1.046 L/kg. Dosis crónicas de 400, 800, 1.200 y 1.600 mg/día produjeron medias de estado constante de 5.1, 10.2, 14.6 y 20.3 mg/L. Un segundo estudio cinético al final de la dosificación crónica no reveló ningún cambio en el volumen de distribución, y reveló un decremento del aclaramiento y un incremento de la vida media comparando estos resultados con los obtenidos con una dosis única. La excreción urinaria de la droga no modificada fue de 13.8–28.6% de la dosis. Solamenta un sujeto mostró toxicidad (visión borrosa ligera y temblor) atribuible posiblemente al W-554. El control de los ataques fue mejorado en 6 de los 8 individuos y estos ataques fueron mucho menos severos en 3 mientras estaban tomando W-554. La incorporación al tratamiento del W-554 produce un incremento en los niveles séricos de la Fenitoína y una reducción muy pequeña en los niveles de la Carbamacepina.

(A. Portera Sanchez, *Madrid*)

ZUSAMMENFASSUNG

W-554 (ADD 03055, 2 Phenyl-1,3-Propanediol-Dicarbamat) hat ein breites antiepileptisches Spektrum im epileptischen Tiermodell. Wir untersuchten seine Pharmakokinetik und Toxicität als Zusatzmedikation bei acht Männern mit unkontrollierten Anfällen, die mit Phenytoin (n = 4) oder Carbamazepin (n = 4) behandelt wurden. Nach einer Einzeldosis von 200 mg traten im Serum maximale Spiegel von W-554 in einer Höhe von 2,65 bis 4,10 mg/l nach 1 bis 4 Stunden auf. Die Halbwertszeiten betrugen 11,2 bis 16,1 Stunden und die Clearance variierte zwischen 34,2 und 64,6 ml/ Stunde mal kg. Das offenbare Verteilungsvolumen betrug 0,726 bis 1,046 l/kg. Chronische Dosierung mit 400, 800, 1200 und 1600 mg täglich zeigte mediane steady state Minimalwerte von 5,1 10,2, 14,6 und 20,3 mg/l. Eine zweite kinetische Studie am Ende einer chronischen Verabfolgung zeigte keine Änderung im Verteilungsvolumen, eine verminderte Clearance und eine erhöhte Halbwertszeit, verglichen mit den Daten einer Einmaldosis. Die Urinausscheidung des unveränderten Medikaments betrug 13,8 bis 28,6 % der Dosis. Nur ein Patient zeigte toxische Veränderungen (milde Sehstörung und Tremor), die wahrscheinlich dem W-554 zuzurechnen sind. Die Anfallskontrolle wurde bei sechs von acht Patienten verbessert, und die Anfälle verliefen bei drei Patienten während W-554-Verabfolgung weniger schwer. Die Zulage von W-554 führte zu einer Erhöhung der Serumpspiegel von Phenytoin and einer geringen Abnahme des Carbamazepinspiegels.

(D. Scheffner, *Heidelberg*)

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

MEDPOINTE PHARMACEUTICALS CORPORATION, Plaintiff, v. WALTER E. KOZACHUK, M.D. Defendant.	Civil Action No. 04-2019 (MLC) (Document Electronically Filed)

AMENDED COMPLAINT

Plaintiff, MEDPOINTE PHARMACEUTICALS CORPORATION, through its attorney, Pitney Hardin LLP, for its Amended Complaint against this defendant alleges as follows:

JURISDICTION

1. This Court has original jurisdiction over this civil action pursuant to 28 U.S.C. §1338(a) because the action arises under an Act of Congress relating to Patents. This Court also has original jurisdiction over this civil action pursuant to 35 U.S.C. §256 because the action arises under Title 35, United States Code, Chapter 26. This Court has original jurisdiction over

this civil action pursuant to 28 U.S.C. §1331 because this civil action arises under the laws of the United States. This Court has jurisdiction pursuant to 28 U.S.C. §1332 in that this is an action between citizens of different states where the matter in controversy exceeds $75,000, exclusion of interest and costs. This Court has supplemental jurisdiction pursuant to 28 U.S.C. §1367 over all state law or common law claims in this civil action because the state law or common law claims are so related to claims over which this court has original jurisdiction that the state law or common law claims form part of the same case or controversy under Article III of the United States Constitution.

PERSONAL JURISDICTION AND VENUE

2. Personal jurisdiction and venue are proper in this district pursuant to 28 U.S.C. §1391(b) because for purposes of personal jurisdiction and venue a substantial part of the events or omissions giving rise to the claims occurred in this judicial district.

THE PARTIES

3. Plaintiff, MedPointe Pharmaceuticals Corporation, d/b/a WALLACE PHARMACEUTICALS ("Wallace Pharmaceuticals"), is a corporation organized under the laws of the state of Delaware, with its principal place of business at 265 Davidson Avenue, Somerset, New Jersey 08873.

4. Defendant, Walter E. Kozachuk, M.D. ("Defendant"), is a citizen and resident of the State of Maryland at 11430 Cam Court, Kensington, Maryland 20895.

FACTUAL ALLEGATIONS APPLICABLE TO ALL CLAIMS FOR RELIEF

5. Plaintiff, Wallace Pharmaceuticals, is the successor in interest to Carter-Wallace, Inc., whose primary business is the research, development, manufacture and marketing of pharmaceuticals.

6. Defendant is the record owner of all rights, title and interest in the following three United States Letters Patent relating to the medical use of Felbamate: U.S. Patent No. 5,728,728, U.S. Patent No. 5,942,540, and U.S. Patent No. 6,515,019, in which all claim the benefit of an April 10, 1996 filing date. True copies of these Letters Patent are attached to this Complaint as Exhibits A-C, respectively.

7. Defendant was an employee of Carter-Wallace, Inc., between February 1, 1993 and October 4, 1994, whose responsibilities included the supervision of clinical studies regarding potential uses of Felbamate.

8. Defendant as a requirement, term and condition of and for his employment at Carter-Wallace, Inc., agreed, *inter alia,* that all inventions discovered, conceived or acquired by him during his course of employment would belong to Carter-Wallace, Inc., and its successors and assigns. A true copy of the signed agreement is attached to this Complaint as Exhibit D.

9. The subject matter claimed in U.S. Patent Nos. 5,728,728, 5,942,540 and 6,515,019, was developed at Carter-Wallace, Inc., prior to or at least during the Defendant's employment at Carter-Wallace, Inc.

10. Defendant is not the true inventor or, at least, not the sole inventor of the subject matter claimed in U.S. Patent Nos. 5,728,728, 5,942,540 and 6,515,019 (collectively referred to herein as "the Patents-in-Suit").

I. FIRST CLAIM FOR RELIEF
CORRECTION OF INVENTORSHIP UNDER 35 U.S.C. §256

11. Plaintiff Wallace Pharmaceuticals repeats and makes a part hereof the allegations set forth in paragraphs 1 through 10 inclusive.

12. This is a claim arising under 35 U.S.C. §256, as amended, to correct the

inventorship of the Patents-in-Suit, due to non-joinder and mis-joinder of inventors.

13. Robert D. Sofia, while an employee of Carter-Wallace, Inc., conceived the subject matter claimed in the Patents-in-Suit and thus is the true inventor of the claimed subject matter.

14. In the alternative, Robert D. Sofia significantly contributed to the conception and/or reduction to practice of the subject matter claimed in the Patents-in-Suit and thus is the joint inventor of the claimed subject matter of the Patents-in-Suit.

15. The error in not listing Robert D. Sofia as the inventor of the subject matter in the Patents-in-Suit arose without any deceptive intent on his part.

16. Under Robert D. Sofia's arrangements with Carter-Wallace and/or by operation of law, all right, title and interest in the foregoing inventions were assigned to Carter-Wallace.

II. SECOND CLAIM FOR RELIEF
BREACH OF CONTRACT UNDER NEW JERSEY STATE LAW

17. Plaintiff repeats and makes a part hereof the allegations set forth in paragraphs 1 through 16 inclusive.

18. Defendant's employment agreement, as a condition precedent for employment, is under a continuing duty to assign to Carter-Wallace, Inc., its successors and assigns, all inventions discovered, conceived or acquired by him during his course of employment.

19. Plaintiff, as the legal successor in interest of Carter-Wallace, Inc. is entitled to have Defendant assign the Patents-in-Suit to Plaintiff.

20. On information and belief, Defendant during his course of employment acquired, discovered, or conceived the subject matter claimed in the Patents-in-Suit.

21. Defendant has willfully refused to assign ownership of the Patents-in-Suit to the Plaintiff (the successor of Carter-Wallace, Inc.).

22. Defendant's refusal to assign ownership of said Letters Patent constitutes a material breach of his employee agreement.

III. THIRD CLAIM FOR RELIEF
BREACH OF DUTY OF LOYALTY UNDER NEW JERSEY STATE LAW

23. Plaintiff repeats and makes a part hereof the allegations set forth in paragraphs 1 through 22 inclusive. This is a claim arising under the common law of the state of New Jersey for breach of duty of loyalty.

24. Defendant having signed the employee agreement as alleged in paragraph 8, as a condition precedent for employment, has a common law duty of loyalty to Carter-Wallace, Inc., its successors and assigns, not to misappropriate any inventions discovered, conceived or acquired by him during his course of employment.

25. Plaintiff, as the true legal successor in interest of Carter-Wallace, Inc., is entitled to the benefit of Defendant's obligations to Carter-Wallace, Inc.

26. On information and belief, Defendant during his course of employment acquired, discovered, or conceived the subject matter claimed in the Patents-in-Suit.

27. Defendant's act of filing and obtaining said Letters Patent in his own name constitutes a breach of the duty of loyalty that Defendant owed to the Plaintiff (the successor of Carter-Wallace, Inc.).

WHEREFORE, Plaintiff respectfully prays for an Order of this Court holding that:

A. The Defendant, by obtaining said Letters Patent on subject matter that he is not the true inventor or at least not the sole inventor thereof, has resulted in U.S. Patent Nos. 5,728,728, 5,942,540 and 6,515,019 being granted with incorrect inventorship due to the non-joinder and/or mis-joinder of others who are the true inventors or at least joint inventors of the

patented subject matter.

B. The Defendant, by his refusal to assign ownership of U.S. Patent Nos. 5,728,728, 5,942,540 and 6,515,019 to the Plaintiff, has breached his continuing, contractual duty to the Plaintiff as set forth in his employee agreement to *inter alia* assign all inventions discovered, conceived or acquired by him during his course of employment.

C. The Defendant, by obtaining said Letters Patent on subject matter that he discovered, conceived or acquired during his course of employment, breached his common law duty of loyalty to the Plaintiff.

D. For such other and further relief as this Court shall deem just and equitable.

PITNEY HARDIN LLP
Attorneys for Plaintiff
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d/b/a Wallace Pharmaceuticals

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Dated: February 24, 2005

CERTIFICATION OF FILING

I hereby certify that on this date that the within Amended Complaint was electronically filed with the United States District Court for the District of New Jersey, Clarkson S. Fisher Federal Building and U.S. Courthouse, 402 East State Street, Trenton, New Jersey 08608.

RICHARD H. BROWN

DATED: February 24, 2005

CERTIFICATE OF SERVICE

I hereby certify that J. Mark Pohl, Esq. is listed as an electronic filer with the District of New Jersey. I further certify that on this date a true copy of the within Amended Complaint was served on the following via facsimile and regular mail from Morristown, New Jersey:

John E. Harris, Sr., Esq.
757 Frederick Road, Suite 102
Catonsville, MD 21228

RICHARD H. BROWN

Dated: February 24, 2005

J. Mark Pohl, Esq. (JP-4457)
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Attorneys for Defendant

MEDPOINTE PHARMACEUTICALS CORPORATION Plaintiff, vs. WALTER E. KOZACHUK, M.D. Defendant.	UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY Civil Action No. 04-2019 (MLC) Hon. Mary L. COOPER **ANSWER AND** **DEMAND FOR TRIAL BY JURY**

Defendant Walter E. Kozachuk, M.D. for its Answer to the AMENDED COMPLAINT of Plaintiff, states as follows:

JURISDICTION AND VENUE

1. Defendant admits the allegations in Paragraph 1.

2. Defendant admits the allegations in Paragraph 2.

3. Defendant is without sufficient knowledge or information to admit or deny the allegations in Paragraph 3.

4. Defendant admits the allegations in Paragraph 4.

FACTUAL BACKGROUND

5. Defendant is without sufficient knowledge or information to admit or deny the allegations in Paragraph 5.

6. Defendant admits the allegations of the first sentence of Paragraph 6. Copies of the Letters Patent are not attached to the Amended Complaint.

7. Defendant admits the allegations of Paragraph 7.

8. Defendant admits the allegations of Paragraph 8.

9. Defendant denies the allegations of Paragraph 9.

10. Defendant denies the allegations of Paragraph 10.

FIRST COUNT
Correction of Inventorship under 35 U.S.C. § 256

11. Defendant repeats its responses to Paragraphs 1-10 as if set forth herein at length.

12. Defendant admits that the Amended Complaint alleges a claim arising under 35 U.S.C. § 256.

13. Defendant denies the allegations of Paragraph 13. Defendant notes that Robert D. Sofia is named as inventor of record on at least six Carter-Wallace patents (United States Patent Nos. 4,978,680; 5,055,489; 5,256,690; 5,290,808; 5,292,772; 5,492,930). The United States Patent Office knew of Dr. Sofia's work; this is clearly evidenced by the first page of each of Dr. Kozachuk's patents, copies of which are appended here. The United States Patent Office compared Dr. Kozachuk's work to that of Dr. Sofia. *Id.* The Patent Office concluded that Dr. Kozachuk's work is *different from* Dr. Sofia's - so different that Dr. Kozachuk deserved his own patents.

14. Defendant denies the allegations of Paragraph 14. Defendant repeats the specific denial recited in Paragraph 13.

15. Defendant denies the allegations of Paragraph 15.

16. Defendant is without sufficient knowledge or information to admit or deny the allegations of Paragraph 16.

SECOND COUNT
(Breach of Contract Under New Jersey State Law)

17. Defendant repeats its responses to Paragraphs 1-16 as if set forth herein at length.

18. Defendant admits the allegations of Paragraph 18.

19. Defendant denies the allegation of Paragraph 19.

20. Defendant denies the allegations of Paragraph 20. Defendant specifically denies that this allegation is "on information." To the contrary, Plaintiff has already said that it makes this allegation not on *information*, but on *speculation*. Plaintiff says, "the fact that all three patents claim the benefit of the April 10, 1996 filing date leaves no doubt that the patented inventions were developed with the knowledge [Defendant] acquired at Carter-Wallace." *See* A. Marchetta, Letter (July 24, 2003) at page 2 (copy appended). Plaintiff therefore alleges (correctly) that Dr. Kozachuk did not apply for a patent for least eighteen months after he left Carter-Wallace. Plaintiff then alleges that this "leaves no doubt" that Dr. Kozachuk discovered the patents-in-suit precisely 18 to 30 months before he in fact began to apply for the patents. This allegation is pure speculation.

21. Defendant refuses to assign ownership of the patents-in-suit to the Plaintiff because Defendant has no duty to do so. Defendant therefore denies that this refusal is "willful."

22. Defendant denies the allegations of Paragraph 22.

THIRD COUNT
(Breach of "Duty of Loyalty")

23. Defendant repeats its responses to the allegations of Paragraph 1-22 as if set forth at length herein.

24. Defendant admits the allegations of Paragraph 24.

25. Defendant is without sufficient knowledge or information to admit or deny the allegations of Paragraph 25.

26. Defendant denies the allegations of Paragraph 26. Defendant repeats the specific denial of Paragraph 20.

27. Defendant denies the allegations of Paragraph 27.

Defendant Walter E. Kozachuk, M.D., states as follows:

FIRST AFFIRMATIVE DEFENSE

All counts recited in the AMENDED COMPLAINT are barred by the doctrines of waiver and estoppel.

SECOND AFFIRMATIVE DEFENSE

All counts recited in the AMENDED COMPLAINT are barred by the doctrine of *res judicata*.

WHEREFORE, Defendant Walter E. Kozachuk, M.D. prays that the Court:

1. Find that the Plaintiff has not carried its "heavy burden" of proving error in the inventorship or ownership of the patents-in-suit by clear and convincing evidence.

2. Award to Defendant its legal fees and costs of suit, pursuant to 35 U.S.C. § 285.

3. Permanently enjoin Plaintiff from infringing the patents-in-suit pursuant to 35 U.S.C. § 283.

4. Award to Defendant such further relief as the Court deems just and proper.

JURY DEMAND

Defendant demands a trial by jury as to all issues so triable.

PHARMACEUTICAL PATENT ATTORNEYS, LLC
Attorneys for Defendant

By: _____/s/_____
J. Mark Pohl (JP-4457)

THE LAW OFFICES OF JOHN HARRIS, SR.
Attorneys for Defendant

By _____/s/_____
John E. Harris, Esq.

Dated: Monday, March 07, 2005

In The United States Patent Office

In re Robert D. SOFIA, *Method For the Prevention and Control of Epileptic Seizure…*, United States Letters Patent No. 4,978,680	Control No. 90/007,991 Filed 31 March 2006 **SUPPLEMENTAL REQUEST for *EX PARTE* REEXAMINATION**

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STATUTES

REGULATIONS

I. INTRODUCTION

The patent at issue is Robert Duane SOFIA, *Method for the Prevention and Control of Epileptic Seizure*, United States Letters Patent No. 4,978,680 ("the SOFIA patent").

On 31 March 2006, the Requestor filed a REQUEST FOR *EX PARTE* REEXAMINATION of the SOFIA patent because SOFIA claims credit for making an invention which he did not in fact make. To the contrary, SOFIA copied his claimed invention from other inventors' prior published work. The SOFIA patent is therefore invalid under 35 U.S.C. § 102 as anticipated by another scientist's prior publication.

The REQUEST also explains how SOFIA had actual knowledge of this prior work, yet intentionally concealed it from the Examiner; thus, the SOFIA patent should be found invalid due to fraud on the Patent Office.

Since filing the REQUEST, the Requestor has identified two more relevant prior art references. Each of these shows that the SOFIA patent is invalid. Further, SOFIA knew of these two references, because he is *a named co-author* on both of them. Nonetheless, SOFIA failed to provide these to the Examiner. These

two references show that the SOFIA patent is invalid under 35 U.S.C. §§ 102, and should also be invalidated due to intentional fraud on the Patent Office.

This supplemental request is believed timely filed because the Office has not yet acted on the REQUEST FOR REEXAMINATION.

II. EWART A. SWINYARD *ET AL*. (1986) TEACHES EVERY CLAIM ELEMENT OF THE SOFIA PATENT

Ewart A. SWINYARD *et al., Comparative Anticonvulsant Activity and Neurotoxicity of Felbamate*…, 27 EPILEPSIA 27 (1986) teaches each and every element of the invention claimed by SOFIA.

The SOFIA patent recites only one claim. SOFIA claims an invention which is not his own; to the contrary, this invention was previously published by SWINYARD *et al.* (1986):

The SOFIA patent, claim 1	SWINYARD (1986)
1. A method for reducing the incidence and severity of epileptic seizures	"antiepileptic agent with a unique spectrum of anticonvulsant activity." *See* page 27, col. 1
Which comprises administering to a warm-blooded mammal	Male albino mice and male albino rats (Sprague-Dawley strain), e.g., page 27, col. 2, are both warm-blooded mammals
in need of such treatment	Potentially-fatal seizures were induced by administering pentylenetetrazol, page 27, col. 2, maximal electroshock, page 28, col. 1, bicuculline, *id*., et cetera
A therapeutic amount of	Therapeutically effective dosages of, *inter alia*, 132 to 549 milligrams per kilogram of rat body weight are taught to reduce or prevent seizures. *See* Table 3, column 9.
2-phenyl,-1,3-propanediol dicarbamate.	Another name for 2-phenyl,-1,3-propanediol dicarbamate is "felbamate." *See* page 27, col. 2

SOFIA therefore claims an invention which was in fact previously published by SWINYARD (1986). The SOFIA patent is therefore invalid under 35 U.S.C. § 102.

III. EWART A. SWINYARD *ET AL.*, (1987) TEACHES EVERY CLAIM ELEMENT OF THE SOFIA PATENT CLAIM

Ewart A. SWINYARD *et al.*, *The Effect of Chronic Felbamate Administration on Anticonvulsant Activity…*, 28 EPILEPSIA 295 (1987) teaches each element of the invention claimed by SOFIA:

The SOFIA patent, claim 1	SWINYARD (1987)
1. A method for reducing the incidence and severity of epileptic seizures	"a candidate antiepileptic drug … with a unique profile of anticonvulsant activity." *See* page 295, col. 1
Which comprises administering to a warm-blooded mammal	Male albino mice and male albino rats (Sprague-Dawley strain), *e.g.*, page 295, col. 2, are both warm-blooded mammals
in need of such treatment	Potentially-fatal seizures were induced by administering pentylenetetrazol, maximal electroshock, et cetera. *See* page 296, col. 1
A therapeutic amount of	Therapeutically effective dosages are taught to reduce or prevent seizures. *See e.g.*, Table 1.
2-phenyl,-1,3-propanediol dicarbamate.	Another name for 2-phenyl,-1,3-propanediol dicarbamate is "felbamate." *See* page 295, col. 1

SOFIA claims credit for the exact same invention which SWINYARD *et al.* made published in 1987, years before SOFIA filed his patent application. SOFIA's patent is therefore invalid under 35 U.S.C. § 102.

IV. SOFIA COMMITED FRAUD ON THE PATENT OFFICE

SOFIA is listed as a co-author of for both SWINYARD (1986) and SWINYARD (1987). Thus, SOFIA had actual knowledge of this prior work. While SOFIA knew of this work, he failed to disclose to the Patent Office his colleagues' contributions. To the contrary, SOFIA concealed this prior work from The Patent Office completely.

Rule 56 requires SOFIA to have disclosed to the Examiner all information which is material to patentability. *See* 37 C.F.R. § 1.56(a)(2). SOFIA failed to do so. By failing to do so, SOFIA violated his Rule 56 duty of candor. The SOFIA patent should therefore be found invalid due to fraud on the Patent Office.

V. SUMMARY

The SOFIA patent claims an invention which was not first invented by Robert Duane SOFIA. Rather, SOFIA claims an invention is a mere obvious variant of an invention previously described by Eward A. SWINYARD *et al.* several years before SOFIA filed his patent application. The SOFIA patent thus is invalid under 35 U.S.C. §102 as anticipated by another scientist's prior publication.

In addition, the SOFIA patent appears invalid due to fraud on the Patent Office.

Respectfully submitted by
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Epilepsia, 27(1):27–34, 1986
Raven Press, New York

Comparative Anticonvulsant Activity and Neurotoxicity of Felbamate and Four Prototype Antiepileptic Drugs in Mice and Rats

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Summary: Felbamate (2-phenyl-1,3-propanediol dicarbamate), phenytoin, phenobarbital, ethosuximide, and valproate were evaluated in mice and rats with a battery of well-standardized anticonvulsant test procedures. The results obtained indicate that felbamate exhibits a wider range of experimental anticonvulsant activity than either phenytoin or ethosuximide and a somewhat more restricted range than either phenobarbital or valproate. Felbamate is effective in nontoxic intraperitoneal doses in mice by the maximal electroshock seizure (MES), pentylenetetrazol (s.c. PTZ), and picrotoxin (s.c. Pic) tests but ineffective against bicuculline- and strychnine-induced seizures; it is effective after nontoxic oral doses in both mice and rats by the MES and s.c. PTZ tests. When compared on the basis of protective indices (PI = TD_{50}/ED_{50}) calculated from the intraperitoneal data in mice, the PIs for felbamate were from 1.05 to 2.37 times higher than those of the prototype antiepileptics. Overall, except for the s.c. PTZ test in mice and rats after oral administration, the PIs were equal to or higher than those of the prototype agents. The PIs for the s.c. PTZ test in mice and rats after oral administration were within the range of the prototype agents. These data indicate that felbamate is a relatively nontoxic agent with a unique profile of anticonvulsant action. **Key Words:** Neurotoxicity—Anticonvulsant activity—Antiepileptics—Experimental seizures.

Although it is generally recognized that 50% of epileptic patients can be controlled with presently available antiepileptic medication (Coatsworth, 1971), there is still a need for more selective and less toxic antiepileptic drugs. The lack of clinical selectivity is indicated by the fact that phenytoin and carbamazepine are the drugs of choice for both generalized tonic-clonic (grand mal) and complex partial (temporal lobe) seizures (*The Medical Letter*, 1983). The need for less toxic substances is illustrated by the toxicity profile of these substances; in addition to gingival hyperplasia and hirsutism peculiar to phenytoin, both drugs have been reported to induce cerebellar-vestibular effects, skin disorders, hepatic deficiencies, and congenital abnormalities (Dam, 1982; Masland, 1982; Pisciotta, 1982).

It is the objective of this presentation to describe the anticonvulsant properties of felbamate, a relatively nontoxic candidate antiepileptic agent with a unique spectrum of anticonvulsant activity.

Received July 30, 1985; revision accepted October 17, 1985.
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MATERIALS AND METHODS

Male albino mice (CF no. 1 strain, 18–25 g; Charles Rivers, Wilmington, MA, U.S.A.) and male albino rats (Sprague–Dawley strain; 100–150 g; Simonsen, Gilroy, CA, U.S.A.) were used as experimental animals. All animals were allowed free access to both food (S/L Custom Lab Diet-7) and water, except when they were removed from their cages for the experimental procedure.

Felbamate (2-phenyl-1,3-propanediol dicarbamate) was administered in the requisite volume of a 30% aqueous solution of polyethylene glycol 400, whereas phenytoin, phenobarbital, ethosuximide, and valproate were administered in 0.9% sodium chloride solution. The vehicle used for the candidate substance, as shown in Table 1, has no significant effect on the threshold for minimal seizures induced in mice by the timed intravenous infusion of pentylenetetrazol (PTZ) (Swinyard and Woodhead, unpublished observations, 1985).

The drugs were administered either orally or intraperitoneally in a volume of 0.01 ml/g body weight in mice and 0.04 ml/10 g body weight in rats. All tests were conducted at the previously determined time of

TABLE 1. *Effects of vehicles on threshold for minimal seizures induced by the timed intravenous infusion of PTZ*

Vehicle (i.p.)[a]	Time(s) to: First twitch	Clonus
0.9% saline	28.8 ± 0.8	35.9 ± 1.6
30% PEG 400	29.4 ± 0.8	34.1 ± 1.1

[a]Tested 2 h after administration. PEG, polyethylene glycol 400.

peak drug effect (TPE). To determine either anticonvulsant activity or toxicity, groups of at least eight mice or rats were tested with various doses of the drug until at least four points were established between the limits of 100% protection or toxicity and 0% protection or toxicity. The dose of drug required to produce the desired end point in 50% of animals (ED_{50}) in each test, the dose eliciting evidence of minimal neurological toxicity in 50% of animals (TD_{50}), 95% confidence interval, slope of the regression line, and the SE of the slope were then calculated by means of a computer program based on the method described in *Probit Analysis* (Finney, 1971). All values were rounded off to three significant figures.

Anticonvulsant tests

The details of the anticonvulsant and toxicity tests employed have been published previously (Swinyard, 1972; Krall et al., 1978; Swinyard and Woodhead, 1982). The profile of anticonvulsant activity for each substance was established by five tests—one electrical and four chemical. The electrical test employed was the maximal electroshock seizure (MES) pattern test (mice: 50 mA, 60 Hz, 0.2 s; rats: 150 mA, 60 Hz, 0.2 s). Abolition of the hindlimb tonic extensor component was used as the end point in this test. The four chemical tests included the subcutaneous pentylenetetrazol seizure threshold test (s.c. PTZ test; convulsant dose for 97% of animals (CD97): 85 mg/kg in mice, 70 mg/kg in rats), bicuculline seizure threshold test (s.c. Bic test; CD97: 2.70 mg/kg), picrotoxin seizure threshold test (s.c. Pic test; CD97: 3.15 mg/kg), and the strychnine seizure pattern test (s.c. Strych test; CD97: 1.20 mg/kg). Except for the s.c. Strych test, abolition of even a minimal threshold seizure (3 s of clonus) was used as the end point. For the s.c. Strych test, abolition of all tonic components of the seizure was used as the end point.

PTZ, Pic, and Strych were dissolved in sufficient 0.9% sodium chloride solution to make a concentration of 0.85, 0.032, and 0.012%, respectively. Bic was dissolved in 1 ml warmed 0.1 N HCl with the aid of a micromixer, and sufficient 0.9% sodium chloride was added to make a 0.027% solution; the solution was used immediately. PTZ (3.5%) was administered to rats in a solution of 0.9% sodium chloride. The convulsant drugs were administered subcutaneously at the previously determined TPE for the test substance into a loose fold of skin on the back of the neck in a volume of 0.01 ml/g body weight in mice; PTZ was injected in a volume of 0.02 ml/10 g body weight in rats. The mice or rats (8 animals/group) given PTZ, Bic, or Strych were then observed for at least 30 min for the presence or absence of a seizure. Those given Pic were observed for periods of 45–60 min, since previous experience had shown the onset of action for this convulsant is somewhat longer.

In vitro receptor binding studies

Benzodiazepine receptor binding studies

The crude synaptic membranes (mouse whole brain) were prepared according to the method of Enna and Snyder (1977). [^{3}H]Flunitrazepam binding studies were performed by a slightly modified method of Braestrup and Squires (1977).

γ-Aminobutyric acid receptor binding studies

The crude synaptic membranes (mouse whole brain) were prepared according to the method of Ticku and Burch (1980). γ-Aminobutyric acid (GABA) binding studies were done by the method of Zukin et al. (1974) and Enna and Snyder (1975) by a centrifugation assay.

Neurotoxicity tests

The median minimal neurotoxic dose (TD_{50}) for each test drug was established in mice by the rotorod (Dunham and Miya, 1957) procedure at the time of peak effect (TPE) of the test substance. Inability of the mouse to maintain its equilibrium for 1 min in each of three trials on this rotating rod (1-in diameter) was used as an indication of minimal neurotoxicity. Minimal neurotoxicity in rats was determined by overt evidence of ataxia, abnormal gait and stance, and loss of placing response and muscle tone. The dose at which 50% of animals lost their righting reflex (HD_{50}) and the dose that caused death in 50% of the animals within 24 h (LD_{50}) were also determined.

RESULTS

The minimal neurotoxicity and anticonvulsant potency of felbamate and the four prototype antiepileptic drugs after intraperitoneal administration are shown in Table 2. It may be seen from the table that phenytoin and phenobarbital were most toxic (TD_{50}s: 65.5 and 69.0 mg/kg, respectively) and felbamate the least toxic (TD_{50}: 816 mg/kg). Ethosuximide and valproate were intermediate in toxicity with TD_{50}s of 441 and 426 mg/kg, respectively. With respect to anticonvulsant activity as measured by the MES test, phenytoin was the most potent (ED_{50}: 9.50 mg/kg) and ethosuximide the least

TABLE 2. *Minimal neurotoxicity and anticonvulsant potency of intraperitoneally administered felbamate and some prototype antiepileptic drugs in mice*

Substance	Time of test[a] (h)	Rotorod TD_{50} (mg/kg)	ED_{50} (mg/kg) and PI				
			MES	s.c. PTZ	s.c. Bic	s.c. Pic	s.c. Strych
Felbamate	2,2	816 (590–1,024) [5.64]	16.3 50.1 (35.6–61.7) [5.15]	5.51 148 (121–171) [6.64]	— >300 (cont. running seizures & death)	5.23 156 (122–202) [4.93]	— >700 (all mice had tonic exten. & died)
Phenytoin	2,2	65.5 (52.5–72.1) [15.2]	6.89 9.50 (8.13–10.4) [13.7]	<0.22 No protection up to 300	<0.65 No protection up to 100	<0.65 No protection up to 100	<0.65 Maximum 50% protection at 55–100
Phenobarbital	½,1	69.0 (62.8–72.9) [24.7]	3.17 21.8 (15.0–25.5) [15.0]	5.24 13.2 (5.87–15.9) [5.93]	1.83 37.7 (26.5–47.4) [4.07]	2.51 27.5 (20.9–34.8) [4.79]	0.72 95.3 (91.3–99.5) [18.5]
Ethosuximide	½,½	441 (383–485) [18.4]	<0.44 No protection up to 1,000	3.38 130 (111–150) [10.1]	0.96 459 (350–633) [3.21]	1.82 243 (228–255) [26.4]	— Maximum 62.5% protection at 250–1,000
Valproate	¼,¼	426 (369–450) [20.8]	1.57 272 (247–338) [12.8]	2.87 149 (123–177) [11.8]	1.18 360 (294–439) [7.51]	1.10 387 (341–444) [8.35]	1.45 293 (261–323) [11.8]

TD_{50}, dose eliciting evidence of minimal neurological toxicity in 50% of animals; ED_{50}, dose required to produce the desired end point in 50% of animals; MES, maximal electroshock seizure; s.c. PTZ, subcutaneous pentylenetetrazol; s.c. Bic, subcutaneous bicuculline; s.c. Pic, subcutaneous picrotoxin; s.c. Strych, subcutaneous strychnine. The 95% confidence interval in parentheses; slope of regression line in brackets. Protective index (PI = TD_{50}/ED_{50}) in upper right-hand boxes.

Protective Index (PI) = TD_{50}/ED_{50}

[a]First number, TD_{50}; second number, ED_{50}.

TABLE 3. *Minimal neurotoxicity and anticonvulsant potency of orally administered felbamate and some prototype antiepileptic drugs in mice and rats*

Substance	Time of test[a] (h)		TD_{50} (mg/kg)		MES ED_{50} (mg/kg)		s.c. PTZ ED_{50} (mg/kg)	
	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats
Felbamate	2,2,2	—,4,4	1,545 (1,299–1,987) [4.40]	>3,000	19.1 81.1 (72.0–92.8) [7.62]	>62.8 47.8 (41.0–57.3) [7.62]	2.82 548 (434–751) [5.00]	>12.6 238 (132–549) [1.24]
Phenytoin	2,2,2	½,4,4	86.7 (80.4–96.1) [13.0]	No ataxia up to 3,000	9.59 9.04 (7.39–10.6) [6.28]	>100 29.8 (21.9–38.9) [2.82]	<0.29 No protection up to 300	NA No protection up to 800
Phenobarbital	2,2,2	½,5,5	96.8 (79.9–115) [8.51]	61.1 (43.7–95.9) [3.00]	4.82 20.1 (14.8–31.6) [5.20]	6.68 9.14 (7.58–11.9) [4.12]	7.69 12.6 (7.99–19.1) [3.84]	5.29 11.6 (7.74–15.0) [4.08]
Ethosuximide	1,½,½	2,2,2	879 (840–934) [30.5]	1,012 (902–1,109) [15.3]	<0.44 No protection up to 2,000	<0.84 No protection up to 1,200	4.56 193 (159–218) [7.39]	18.8 54.0 (45.6–60.9) [9.05]
Valproate	2,1,1	1,½,½	1,264 (800–2,250) [4.80]	280 (191–353) [4.63]	1.90 665 (605–718) [18.2]	0.57 490 (351–728) [2.90]	3.26 388 (349–439) [8.12]	1.56 180 (147–210) [8.62]

Abbreviations as in Table 1. The 95% confidence interval in parentheses; slope of regression line in brackets. Protective index (PI = TD_{50}/ED_{50}) in upper right-hand boxes. NA, not applicable.

[a]Toxicity, MES, and s.c. PTZ, respectively.

potent (no protection up to 1,000 mg/kg). Phenobarbital, felbamate, and valproate were effective in nontoxic doses (ED_{50}s: 21.8, 50.1, and 272 mg/kg, respectively). Felbamate was also effective by the s.c. PTZ and s.c. Pic tests (ED_{50}s: 148 and 156 mg/kg, respectively) and ineffective against Bic- and Strych-induced seizures. Phenytoin exhibited a maximum of 50% protection by the s.c. Strych test at doses of 55–100 mg/kg but was ineffective by the s.c. PTZ, s.c. Bic, and s.c. Pic tests. Phenobarbital and valproate were effective by all four anticonvulsant tests; however, phenobarbital had to be given in toxic doses in order to protect against Strych-induced seizures (TD_{50} of 69.0 mg/kg vs. s.c. Strych ED_{50} of 95.3 mg/kg). Ethosuximide, on the other hand, was effective by the s.c. PTZ, s.c. Bic, and s.c. Pic tests (ED_{50}s: 130, 459, and 243 mg/kg, respectively); however, the ED_{50} by the s.c. Bic test was in the minimal neurotoxic dose range. Moreover, nontoxic doses of ethosuximide provided only partial protection (maximum of 62.5%) against Strych-induced seizures. When evaluated on the basis of protective indices (PI), felbamate had the highest PI by the MES (16.3), s.c. PTZ (5.51), and s.c. Pic (5.23) tests of any of the drugs included in this study. Phenobarbital exhibited the highest PI by the s.c. Bic test (1.83), and valproate by the s.c. Strych test (1.45).

The minimal neurotoxicity and anticonvulsant potency of the five drugs determined after oral administration to mice and rats are shown in Table 3. This table shows that felbamate and valproate were the least toxic in mice (TD_{50}s: 1,545 and 1,264 mg/kg, respectively), whereas felbamate and phenytoin were the least toxic in rats (>3,000 mg/kg). Phenytoin and phenobarbital were the most toxic in mice (TD_{50}s: 86.7 and 96.8 mg/kg, respectively), and phenobarbital was the most toxic in rats (TD_{50}: 61.1 mg/kg). Ethosuximide was intermediate in toxicity in mice (TD_{50}: 879 mg/kg), and ethosuximide and valproate were intermediate in toxicity in rats (TD_{50}s: 1,012 and 280 mg/kg, respectively). With respect to anticonvulsant potencies of the five drugs, Table 2 also shows that by the MES test phenytoin and phenobarbital were the most potent in both mice (ED_{50}s: 9.04 and 20.1 mg/kg, respectively) and rats (ED_{50}s: 29.8 and 9.14 mg/kg, respectively). Ethosuximide and valproate were the least potent in both mice (ED_{50}s: >2,000 and 665 mg/kg, respectively) and rats (ED_{50}s: >1,200 and 490 mg/kg, respectively). Felbamate, although somewhat less potent than phenobarbital, was effective in both mice and rats (ED_{50}s: 81.1 and 47.8 mg/kg, respectively). When evaluated by the s.c. PTZ test, phenobarbital was the most potent in both mice and rats (ED_{50}s: 12.6 and 11.6 mg/kg, respectively), whereas felbamate was the least potent of the effective compounds in both species (ED_{50}s: 548 and 238 mg/kg, respectively). Ethosuximide and valproate were intermediate in potency in mice (ED_{50}s: 193 and 388 mg/kg, respectively) and in rats (ED_{50}s: 54.0 and 180 mg/kg, respectively). Phenytoin was ineffective by the s.c. PTZ test in both species.

TABLE 4. *Quantitative toxicity profile of intraperitoneally administered felbamate and some prototype antiepileptic drugs in mice*

Substance	Time of test[a] (h)	Dose 50 (mg/kg) Lethality (LD_{50})	Righting reflex (HD_{50})	Rotorod (TD_{50})
Felbamate	24,4,2	>3,000	>2.10 1,428 (1,029–1,789) [4.44]	>3.68 816 (590–1,024) [5.64]
Phenytoin	24,12,2	230 (216–259) [15.9]	1.29 178 (153–195) [14.0]	3.51 65.5 (52.5–72.1) [15.2]
Phenobarbital	24,1,½	265 (242–286) [16.0]	1.95 135 (115–177) [8.41]	3.84 69.0 (62.8–72.9) [24.7]
Ethosuximide	24,½,½	1,752 (1,607–1,867) [14.8]	2.06 851 (751–918) [16.4]	3.98 441 (383–485) [18.4]
Valproate	24,¼,¼	1,105 (1,022–1,254) [11.4]	1.25 886 (821–947) [12.5]	2.59 426 (369–450) [20.8]

LD_{50}, dose that caused death in 50% of animals; HD_{50}, dose at which 50% of animals lost righting reflex; other abbreviations as in Table 1. The 95% confidence interval in parentheses; slope of regression line in brackets. Ratio LD_{50}/HD_{50} or LD_{50}/TD_{50} in upper right-hand boxes.
[a]Lethality, righting reflex, and rotorod, respectively.

With respect to PIs, felbamate had the highest PI in mice by the MES test (19.1), whereas felbamate and phenytoin had the highest PI in rats (>62.8 and >100 mg/kg, respectively). Phenobarbital had the highest PI by the s.c. PTZ test in mice (7.69), whereas ethosuximide had the highest PI in rats (18.8). Felbamate had a PI by the s.c. PTZ test of 2.82 in mice and >12.6 in rats.

The quantitative toxicity profiles after intraperitoneally administered felbamate and the four prototype agents in mice are summarized in Table 4. This table shows that the times of peak toxicity for felbamate by the rotorod and righting reflex tests were 2 and 4 h, respectively; the TPEs for phenytoin were 12 and 2 h, respectively. Phenytoin and phenobarbital were the most toxic by all three tests, while felbamate was the least toxic by all three tests. Ethosuximide and valproate were intermediate in toxicity by all three tests. The LD_{50}/HD_{50} ratio was highest for felbamate (>2.10), whereas the LD_{50}/TD_{50} ratio was higher for ethosuximide (3.98). The LD_{50}/TD_{50} ratio for felbamate was >3.68.

Studies on the displacing potency of felbamate and the four prototype antiepileptics on [^{3}H]flunitrazepam (BDZ; benzodiazepine) and [^{3}H]GABA receptor binding indicate that phenytoin in a concentration of 800 μM inhibited BDZ receptor binding 20.4%. In contrast, felbamate, ethosuximide, phenobarbital, and valproate, in concentrations of 400, 500, 800, and 10,000 μM, respectively, had no effect on BDZ receptor binding. Felbamate in a concentration of 400 μM inhibited GABA receptor binding 18.3%; whereas ethosuximide, phenytoin, phenobarbital, and valproate, in concentrations of 100, 800, 800, and 10,000 μM, respectively, had no measurable inhibitory effect on GABA receptor binding.

DISCUSSION

The data presented in Tables 1 and 2 indicate that felbamate is an effective anticonvulsant substance. It has a unique profile of anticonvulsant action characterized by activity by the MES, s.c. PTZ, and s.c. Pic tests. Thus, it differs from phenytoin which is effective by the MES test and ineffective by all the chemoshock tests, and from ethosuximide which is ineffective by the MES test and exhibits activity by all four chemoshock tests. It differs from phenobarbital and valproate in that these two agents are effective by all five tests, whereas felbamate is inactive by the s.c. Bic and s.c. Strych tests. Similarly, felbamate is a less potent anticonvulsant agent than either phenytoin or phenobarbital but more potent than either ethosuximide or valproate. Overall, felbamate compares very favorably with the four prototype agents.

Since all PIs are based on the assumption that the slopes of the regression lines for minimal neurotoxicity and anticonvulsant activity are parallel, it is important to note the effect of slope on the safety ratio (SR = TD_3/ED_{97}) of the five agents. It may be seen from Table 5 that felbamate given in nontoxic doses (either p.o. in rats or i.p. and p.o. in mice) will protect 97% of mice or rats in the MES test; phenytoin is the only prototype agent that will provide a similar level of safety. On the other hand, the SR of felbamate by the s.c. PTZ test is 1.3 after intraperitoneal administration in mice and 0.4 after oral administration in either mice or rats. Thus, the SR for felbamate by the s.c. PTZ test resembles that for valproate but differs from ethosuximide, the only agent that has a SR by the s.c. PTZ test >1 in both mice (i.p. and p.o.) and rats (p.o.). These observations also suggest that felbamate compares favorably with clinically useful antiepileptic drugs such as phenytoin, phenobarbital, and valproate.

The above data show that the profile of anticonvulsant action for felbamate differs markedly from that for phenytoin, but is more closely related to that for phenobarbital and valproate. Thus, felbamate increases seizure threshold and prevents seizure spread. With respect to threshold, it should be noted that felbamate is ineffective against Bic-induced seizures. This is in agreement with the fact that extremely high concentrations of felbamate (400 μM) interact only modestly (18.3%) with GABA receptors. However, felbamate is very effective against PTZ- and Pic-induced seizures. Since PTZ and Pic induce seizures through their interaction with Pic receptors (Ramanjaneyulu and Ticku, 1984; Squires et al., 1984), it is tempting to speculate that the threshold effects of felbamate are mediated by its interaction with the barbiturate-Pic receptors. With respect to preventing seizure spread, it is important to note that valproate has been shown to interact with Pic receptors (Ticku and Davis, 1981). Therefore, felbamate may also prevent seizure spread by interacting with barbiturate-Pic receptors. This notion should be explored more carefully.

An overall comparative evaluation of felbamate and the four prototype agents reveals that felbamate is su-

TABLE 5. *Safety ratios[a] (TD_3/ED_{97}) for felbamate, phenytoin, phenobarbital, valproate, and ethosuximide*

Parameter	Species and route admin.	Substance and test							
		Felbamate		Phenytoin[b]	Phenobarbital		Valproate		Ethosuximide[c]
		MES	s.c. PTZ	MES	MES	s.c. PTZ	MES	s.c. PTZ	s.c. PTZ
TD_3	Mouse, i.p.	370	370	49	57	57	345	345	345
ED_{97}		118	280	13.5	29	27	380	218	200
Ratio		3.1	1.3	3.6	2.0	2.1	0.9	1.6	1.7
TD_3	Mouse, p.o.	580	580	62	58	58	500	500	795
ED_{97}		142	1,300	18.5	46	38	840	680	350
Ratio		4.1	0.4	3.4	1.3	1.5	0.6	0.7	2.3
TD_3	Rat, p.o.	>3,000	>3,000	NA	14	14	105	105	770
ED_{97}		84	7,300	95	26	34	2,200	300	86
Ratio		>35.7	>0.4	—	0.5	0.4	0.05	0.4	8.9

TD_3, dose eliciting evidence of minimal neurological toxicity in 3% of animals; ED_{97}, dose required to produce the desired end point in 97% of animals; NA, not applicable. Other abbreviations as in Table 1.

[a]Ratios <1 indicate that 97% protection is obtained only with some minimal neurotoxicity.

[b]Ineffective by s.c. PTZ test (MES test only).

[c]Ineffective by MES test (s.c. PTZ test only).

perior to the prototype agents in terms of the PIs by the MES and s.c. Pic tests, toxicity ratio (HD_{50}/TD_{50}), absorption ratio (TD_{50} p.o./TD_{50} i.p.), and SR (TD_3/ED_{97}, MES). It is inferior to the prototype agents in terms of its absorption ratio by the s.c. PTZ test (ED_{50} p.o./ED_{50} i.p.). Felbamate compares favorably with the prototype agents in terms of slopes of the regression lines (MES, s.c. PTZ, s.c. Pic) and absorption ratio by the MES test (ED_{50} p.o./ED_{50} i.p.). Overall, the profile of experimental anticonvulsant activity displayed by felbamate compares favorably with that for phenytoin and phenobarbital and somewhat better than that for ethosuximide and valproate. Consequently, it should have a somewhat broader profile of clinical activity than phenytoin and perhaps a somewhat more restricted profile of clinical activity than valproate.

Acknowledgment: This research was supported by NIH Contract No. NO1-NS-4-2361 awarded by the Epilepsy Branch, National Institute of Neurological and Communicative Disorders and Stroke, PHS/DHEW.

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RESUME

Le Felbamate (2-phenyl-1,3 propanediol dicarbamate), la phenytoine, le phénobarbital, l'ethosuximide et le valproate ont été étudiés chez la souris et le rat avec une batterie de tests anticonvulsivants bien standardisés. Les résultats obtenus montrent que le felbamate a une action anticonvulsivante plus étendue que celle de la phenytoine ou de l'ethosuximide et quelque peu plus restreinte que celle du phénobarbital ou du valproate. Le Felbamate administré à doses intrapéritonéales non toxiques chez la souris est efficace dans les tests à l'électrochoc maximal (MES) au pentylentetrazol (sc PTZ) et à la picrotoxine (scPIC) mais inefficace sur les crises induites par la bicuculline et la strychnine. Comparés sur les indices de protection (PI = TD50/ED50) calculés à partir des données intrapéritonéales chez la souris, les PI du felbamate sont de 1.05 à 2.37 fois plus élevés que ceux des antiépileptiques prototypes. Dans l'ensemble, excepté pour le test scPTZ chez la souris et le rat après administration orale, les PI sont égaux ou supérieurs à ceux des agents prototypes. Les PIs pour le test scPTZ chez la souris et le rat après administration orale sont comparables à ceux des agents prototypes. Ces résultats montrent que le felbamate est une substance relativement non toxique ayant un profil unique d'activité anticonvulsivante.

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RESUMEN

En ratones y ratas, mediante una batería de test anticonvulsivos bien estandarizados, se han valorado los efectos del felbamato (dicarbamato de 2-fenil-1,3-propanodiol), la fenitoína, el fenobarbital, la etosuximida y el valproato. Los resultados indican que el felbamato muestra un rango más amplio de actividad anticonvulsiva experimental que la fenitoína o la etosuximida y un rango, en cierto modo más restringido, que el fenobarbital o el valproato. El felbamato es efectivo a dosis no tóxicas intraperitoneales en ratones sobre los ataques de electroshock máximo (MES), el pentilentetrazol (sc PTZ), y la picrotoxina (sc Pic), pero no mostró eficacia contra los ataques inducidos por la bicuculina y la estricnina; resultó eficaz tras dosis orales no tóxicas en ratones y ratas contra los MES y los sc PTZ. Cuando se compararon, teniendo en cuenta los índices de protección (PI = TD50/ ED50) calculados según datos intraperitoneales en los ratones, los PI's para el felbamato variaron desde 1.05 a 2.37 veces más altos que los de los antiepilépticos prototipo. Se observó que, de modo general, con la excepción de los test sc PTZ en ratones y ratas después de la administración oral, los PI's son iguales o más elevados que los de los agentes prototipo. Los PI's para los test sc PTZ en ratones y ratas después de la administración oral se encuentran dentro del rango de los agentes prototipo. Esta información indica que el felbamato es un agente relativamente no tóxico con un perfil único de acción anticonvulsiva.

(A. Portera Sanchez, *Madrid*)

ZUSAMMENFASSUNG

Felbamat (2-Phenyl-1, 3-Propanediol Dicarbamat), Phenytoin, Phenobarbital, Ethosuximid und Valproat wurden bei Mäusen und Ratten mit einer Batterie gut standardisierter antikonvulsiver Testverfahren geprüft. Die Ergebnisse zeigen, daß Felbamat ein größeres Spektrum experimenteller antikonvulsiver Aktivität besitzt als Phenytoin oder Ethosuximid und ein etwas begrenzteres Spektrum als Phenobarbital und Valproat. Felbamat ist bei Mäusen in nicht-toxischen intraperitonealen Dosen unter maximalen Elektroschockkrämpfen (MES) bei

Pentylentrazolanwendung (sc PTZ) und bei Picrotoxin (sc Pic) wirkungsvoll aber unwirksam gegen Bicucullin- und Strychnin-induzierten Krämpfen. Es ist sowohl bei Mäusen und Ratten bei nicht toxischen oralen Dosen wirkungsvoll im MES und sc-PTZ-Test. Wendet man protektive Indices an (PI = TD 50/ED 50) die man von intraperitonealen Daten bei Mäusen berechnet, lagen die PI's für Felbamat zwischen 1,05 und 2,37 mal höher als diejenigen der üblichen Antiepileptika. Insgesamt—mit Ausnahme des sc PTZ-Tests bei Mäusen und Ratten nach oraler Verabfolgung—entsprechen die PI's denen der üblichen Antikonvulsiva oder sind höher. Die PI's für den sc-PTZ-Test bei Mäusen und Ratten nach oraler Verabfolgung liegen im Bereich der von üblichen Antiepileptika. Diese Ergebnisse zeigen, daß Felbamat ein relativ nicht-toxisches Mittel mit einzigartigen antikonvulsivem Profil ist.

(D. Scheffner, *Heidelberg*)

Epilepsia, 28(3):295–300, 1987
Raven Press, New York
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The Effect of Chronic Felbamate Administration on Anticonvulsant Activity and Hepatic Drug-Metabolizing Enzymes in Mice and Rats

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Summary: The possibility of tolerance development from chronic administration of felbamate (FBM) was investigated in mice and rats. Chronic administration (15 days) of FBM (150 mg/kg i.p.) in mice had no significant effect on either intravenous pentylenetetrazol (PTZ) seizure threshold or hexobarbital sleep time; however, hexobarbital sleep time was significantly increased after a single dose. Chronic administration (5–7 days) of FBM (48 or 95 mg/kg orally) in rats also had no significant effect on either maximal electroshock seizure activity or hexobarbital sleep time. Chronic administration of FBM at 238 mg/kg slightly decreased anti-subcutaneous PTZ activity in chronically treated rats (one of eight protected) as compared with those receiving only a single dose (three of eight protected), but there was no significant change in hexobarbital sleep time. Chronic treatment of rats for 7 days with 48 mg/kg had no significant effect on any hepatic parameters. However, 95 or 238 mg/kg of FBM significantly increased *p*-nitroanisole *O*-demethylase activity. It is concluded that the increased hexobarbital sleep time induced by an acute dose of FBM reflects the CNS-depressant effect of the substance. The increased *p*-nitroanisole *O*-demethylase activity observed after chronic administration may be indicative of some liver microsomal induction. Overall, FBM in doses ranging from 48 to 238 mg/kg appears to have minimal potential for tolerance development. **Key Words:** Anticonvulsants—Pharmacology—Drug therapy—Anticonvulsant potency—Tolerance—Hepatic drug metabolism—Felbamate.

A previous report from this laboratory indicates that felbamate (FBM) (2-phenyl-1,3-propanediol dicarbamate), a candidate antiepileptic drug currently under clinical study, is a relatively nontoxic agent with a unique profile of anticonvulsant action (Swinyard et al., 1986). It is effective in nontoxic intraperitoneal doses in mice by the maximal electroshock seizure (MES), subcutaneous pentylenetetrazol (s.c. PTZ), and subcutaneous picrotoxin tests and ineffective against bicuculline- and strychnine-induced seizures; it is effective after nontoxic oral doses in both mice and rats by the MES and s.c. PTZ tests. Its protective indexes (PI = TD_{50}/ED_{50}) are from 1.05 to 2.37 times higher than those for phenytoin, carbamazepine, phenobarbital, and valproate. Since antiepileptic drugs must be given chronically over long periods of time, it was thought important to study the effect of chronic administration on the anticonvulsant activity of FBM. The results obtained provide the basis for this report.

Received November 1986; revision accepted March 1987.
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EXPERIMENTAL METHODS AND PROCEDURES

Male albino mice (CF no. 1 strain; 18–25 g) obtained from Charles Rivers, (Wilmington, MA, U.S.A.) and male albino rats (Sprague-Dawley; 100–150 g) from Simonsen (Gilroy, CA, U.S.A.) were used as experimental animals. All animals were allowed free access to both food (S/L Custom Lab Diet-7) and water, except when they were removed from their cages for the experimental procedure.

FBM was administered intraperitoneally in mice and orally in rats in the requisite volume of a 30% aqueous solution of polyethylene glycol 400 (PEG). The doses and time of test were selected from previously published data (Swinyard et al., 1986) summarized in Table 1.

Four tests and an evaluation of liver microsomal activity were used to estimate the presence or absence of tolerance: (a) Timed intravenous infusion of PTZ (timed i.v. PTZ). PTZ (0.5% in heparinized saline, 10 U/ml) was infused into the tail vein of a mouse at a constant rate (0.37 ± 0.002 ml/min by means of a Sage syringe pump, model 341, 10 ml/B-D plastic syringe, 27-gauge stainless-steel needle, and no. 20 p.c. tubing) and the time in seconds to the first twitch was recorded (Orloff et al., 1949) and converted to milligrams per kilogram. This is a very sensitive measure of individual animal seizure threshold. (b) s.c. PTZ test. PTZ (70 mg/kg) was injected subcutaneously into rats and the animals observed for the next 30 min for the presence or absence of a minimal seizure; 3 s of sustained clonus was indicative of a minimal threshold seizure (Swinyard and Woodhead, 1982). (c) Maximal electroshock seizure (MES) test. MES (corneal electrodes, 150 mA stimulus intensity, 60 Hz, delivered for 0.2 s) seizures were induced in rats and the seizure pattern timed to the nearest 0.1 s. The number of rats protected (abolition of hindleg tonic extensor component) in each group and the mean pattern ± SEM were recorded (Swinyard and Woodhead, 1982). (d) Hexobarbital sleep time test. Each mouse (or rat) subjected to the test was injected with 100 mg/kg of hexobarbital (intravenously for mice; intraperitoneally for rats); sleep time was considered the time in minutes from the end of the hexobarbital injection to the time each animal regained its righting reflex. Righting reflex was considered present when a mouse or rat gently placed on its back was able to right itself within 5 s in three consecutive trials. (e) Liver microsomal studies. The rats were killed and the livers perfused with 0.9% soldium chloride solution. The liv were removed, blotted dry, weighed, and homog nized in 0.25 *M* sucrose. Preparation of the micr somes and the subsequent tests (microsomal pr tein yield, cytochrome P-450 concentration, *p*-n troanisole *O*-demethylase activity, and NADP cytochrome *c* reductase activity) were performe by the methods documented in Franklin and Finkl (1985).

The above tests were integrated into two experi mental protocols: one 15-day chronic study in mice and two 5-day chronic studies in rats. The 15-day chronic study was conducted as follows: Sixty mice were randomly divided into three groups of 20 mice each (untreated control group, treated control group, and treated group). The untreated control group was given the requisite volume (0.1 ml/g body weight) of 30% PEG for 15 days; the treated control group was given 30% PEG for 14 days and on the fifteenth day 150 mg/kg i.p. of FBM; the treated group was given 150 mg/kg i.p. of FBM for 15 days. On day 15, at the previously determined time of peak effect (2 h), eight to nine mice in each group were subjected to the timed i.v. PTZ test and six to eight mice in each group were subjected to the hexobarbital sleep time test. The mean i.v. PTZ threshold (mg/kg ± SEM) and mean hexobarbital sleep time (min ± SEM) for each group were then calculated.

The 5-day chronic studies were conducted as follows: Twenty-four male rats were randomly divided into three groups of eight rats each (untreated control group, treated control group, and treated group). The untreated control group was given the requisite volume of PEG orally for 5 days; the treated control group was given the requisite volume of solvent for 4 days and on day 5 the requisite dose of FBM (s.c. PTZ, 238 mg/kg; MES, either 48 or 95 mg/kg); the treated group was given the appropriate dose of FBM for 5 days. At the previously determined time of peak effect of FBM (4 h), all three groups were subjected to the appro-

TABLE 1. *Minimal neurotoxicity and anticonvulsant activity of felbamate in mice and rats*

Species	Route	Time of test (h)	TD_{50} (mg/kg)	ED_{50} (mg/kg) MES	PI	s.c. PTZ	PI
Mouse	i.p.	2,2,2	816 (590–1,024)	50.1 (25.6–61.7)	16.3	148 (121–171)	5.5
Rat	p.o.	—,4,4	>3,000	47.8[a] (41.0–57.3)	>62.8	238 (132–549)	>12.6

Values in parentheses are 95% confidence intervals. See text for abbreviations.
[a] ED_{99}, 95 mg/kg.

priate test; the s.c. PTZ groups were observed for the next 30 min for the presence or absence of a minimal seizure (3 s of sustained clonus) and the MES group was subjected to a maximal electroshock and the seizure components timed as described above. The number of rats protected and the number tested in each group were recorded. All rats subjected to the 5-day tolerance studies were continued on their respective original treatment regimen for 1 more day (day 6), and on day 7 all three groups were given the same dose of FBM as given on day 5. Twenty-four hours later (day 8), all three groups were subjected to the hexobarbital sleep time test. All three groups subjected to the hexobarbital sleep time test were then continued on their respective original treatment regimen for 1 more day (day 9); 24 hours later the rats were killed, the livers were perfused, and microsomal enzyme activities were determined. The results obtained were subjected to statistical analysis (mean ± SEM) and the significance of the difference determined.

RESULTS

The effect of 15 days of treatment with 150 mg/kg of FBM on i.v. PTZ seizure threshold and hexobarbital sleep time in mice is shown in Table 2. As may be seen from the table, there was no significant difference in the i.v. PTZ threshold in the three groups of mice; the i.v. PTZ threshold was 32.7 ± 1.8, 37.1 ± 1.5, and 34.8 ± 1.6 mg/kg in the solvent control, treated control, and treated groups, respectively. Likewise, there was no significant difference in the hexobarbital sleep times for the solvent control and chronically treated groups of mice (29.7 ± 0.8 and 27.5 ± 2.3 min, respectively). In contrast, the sleep time of the acute control group (single dose of FBM) was significantly increased (44.9 ± 2.6 and 29.7 ± 0.8 min for acute control and solvent control, respectively).

The effect of chronic FBM treatment on the anticonvulsant activity (MES and s.c. PTZ) and hexobarbital sleep time in rats is shown in Table 3. This table indicates that when rats were treated with 48 mg/kg of FBM and subjected to the MES test, two of eight of the chronically treated group were protected; whereas after 4 days of the solvent and a single 48-mg/kg dose of FBM on day 5, one of eight was protected. The MES extensor/flexor (E/F) ratios of the solvent control, acute control, and treated groups were 6.3 ± 0.6, 2.7 ± 0.4, and 3.9 ± 0.3, respectively. Similarly, when rats were given 95 mg/kg of FBM, seven of eight in the treated group were protected; whereas after 4 days of the solvent and a single 95-mg/kg dose of FBM, six of eight were protected. The MES E/F ratios of the solvent control, acute control, and treated groups were 6.2 ± 0.7, 1.7 ± 0.9, and 1.8, respectively. Table 3 also indicates that after five daily doses of 238 mg/kg of FBM, one of eight rats was protected by the s.c. PTZ test; whereas after four daily doses of solvent and a single dose of FBM (238 mg/kg) on the fifth day, three of eight rats were protected. It should also be noted that none of the eight rats given five daily doses of the solvent were protected from either the MES or the s.c. PTZ test. The hexobarbital sleep time studies indicate that neither acute nor chronic administration of FBM had any significant effect on hexobarbital sleep time. Thus, animals given 30% PEG for 4 days and a single dose of 48 or 238 mg/kg of FBM slept 22.8 ± 2.5 and 27.2 ± 2.0 min, respectively, whereas those given these doses chronically for 5 days slept 23.7 ± 1.9 and 21.3 ± 2.0 min, respectively. These were not significantly different from those observed in solvent control animals (26.7 ± 2.5 and 20.9 ± 2.0 min, respectively). Likewise, there was no significant difference in the hexobarbital sleep time of rats given 95 mg/kg (solvent control, 37.0 ± 4.3 min; acute control, 37.5 ± 3.1 min; chronic, 41.0 ± 2.6 min).

The influence of chronic FBM treatment on the liver microsomal system in rats is shown in Table 4. It is readily apparent that 7 days of treatment with

TABLE 2. *Effect of chronic (15-day) felbamate treatment on anticonvulsant activity (i.v. PTZ) and hexobarbital sleep time in mice*

Test group	Dose (mg/kg)	No. days administered		No. Animals	Time of test (h)	Test	
		Solvent	Drug			i.v. PTZ (mg/kg)	Hexobarbital (min)
Control (solvent)	—	15	0	8,7	1	32.7 ± 1.8	29.7 ± 0.8
Control (acute)	150	14	1	9,8	1	37.1 ± 1.5	44.9 ± 2.6[a]
Treated	150	0	15	8,6	1	34.8 ± 1.6	27.5 ± 2.3

Values are means ± SE. Felbamate, 150 mg/kg, 30% PEG, i.p.; i.v. PTZ, 0.5% in heparinized saline, 0.34 ml/min; hexobarbital, 100 mg/kg i.v. See text for abbreviations.

[a] Significantly longer, $p \leq 0.05$, than solvent or chronically treated groups.

TABLE 3. *Effect of chronic felbamate treatment on anticonvulsant activity (MES and s.c. PTZ) and hexobarbital sleep time in rats*

Test group	Dose (mg/kg)	No. days administered		s.c. PTZ	MES		Hexobarbital sleep time (min)
		Solvent	Drug	(Protected/tested)	Protected/tested	E/F ratio	
Control (solvent)		5–7	0		0/8	6.3 ± 0.6	26.7 ± 2.5
Control (acute)	48	4–5	1–2		1/8	2.7 ± 0.4	22.8 ± 2.5
Treated		0	5–7		2/8	3.9 ± 0.3	23.7 ± 1.9
Control (solvent)		5–7	0		0/8	6.2 ± 0.7	37.0 ± 4.3
Control (acute)	95	4–5	1–2		6/8	1.7 ± 0.9	37.5 ± 3.1
Treated		0	5–7		7/8	1.8	41.0 ± 2.6
Control (solvent)		5–7	0	0/8			20.9 ± 2.0
Control (acute)	238	4–5	1–2	3/8			27.2 ± 2.0
Treated		0	5–7	1/8			21.3 ± 2.0

Values are means ± SE. Hexobarbital, 100 mg/kg i.p. See text for abbreviations.

48 mg/kg of FBM had no significant effect on any liver parameters. Likewise, 7 days of treatment with 95 mg/kg of FBM produced no significant change in liver weight, microsomal protein yield, cytochrome P-450 concentration, or NADPH cytochrome *c* reductase, but at this dose *p*-nitroanisole *O*-demethylase activity was significantly increased (0.38 ± 0.07 vs. 0.58 ± 0.06 nmol/mg/min). Animals treated with 238 mg/kg for the same period of time exhibited no significant change in liver weight, cytochrome P-450 concentration, or NADPH cytochrome c reductase activity; however, these animals exhibited a significant increase in microsomal protein yield (59.0 ± 4.2 vs. 91.0 ± 20.5 mg) as well as *p*-nitroanisole *O*-demethylase activity (0.44 ± 0.01 vs. 1.52 ± 0.18 nmol/mg/min).

DISCUSSION

The results presented indicate there is no significant difference in the i.v. PTZ threshold in solvent control, acute control, and treated mice. It is interesting to note, however, that rats given 238 mg/kg of FBM and subjected to the s.c. PTZ test exhibit more protection after a single dose (acute control) than after five daily doses (three versus one out of eight, respectively). In contrast, rats given a single dose of 48 or 95 mg/kg of FBM and subjected to the MES test exhibit slightly less protection (one and six of eight, respectively) than those given the same dose for 5–7 days (two and seven of eight, respectively). These observations are in agreement with the fact that both the treated control and the chronically treated groups subjected to the MES test display less severe seizures than the solvent control animals. Thus, the E/F ratios for solvent control, acute control, and treated groups after 48 mg/kg of FBM are 6.3 ± 0.6 vs. 2.7 ± 0.4 and 3.9 ± 0.3, respectively, and after 95 mg/kg 6.2 ± 0.7 vs. 1.7 ± 0.9 and 1.8, respectively. Except for mice given 14 daily doses of solvent and a single dose of 150 mg/kg i.p. of FBM, the test substance does not sig-

TABLE 4. *Effect of chronic felbamate treatment on the liver microsomal system in rats*

Treatment	Dose i.p. (mg/kg)	Body weight (g)	Liver weight (g)	Protein yield (mg)	Cytochrome - P-450 (nmol/mg)	*p*-Nitroanisole *O*-demethylase (nmol/mg/min)	Cytochrome *c* reductase (nmol/mg/min)
Experiment 1							
Control	0	188 ± 3	9.3 ± 0.8	59.0 ± 4.2	1.11 ± 0.05	0.44 ± 0.01	171 ± 31
FBM	48	177 ± 5	8.9 ± 0.6	47.5 ± 1.9	1.02 ± 0.03	0.61 ± 0.09	143 ± 12
FBM	238	181 ± 4	9.8 ± 1.3	91.0 ± 20.5[a]	1.20 ± 0.09	1.52 ± 0.18[a]	177 ± 12
Experiment 2							
Control	0	147 ± 7	7.5 ± 0.5	48.8 ± 2.7	0.61 ± 0.08	0.38 ± 0.07	140 ± 46
FBM	95	150 ± 3	7.8 ± 0.4	49.9 ± 6.4	0.78 ± 0.08	0.58 ± 0.06[a]	129 ± 13

Values are means ± SE, n = 3.
[a] Significantly different from control.

TABLE 5. *Summary: indications of possible tolerance*

Dose (mg/kg)	48	95	150	238
Duration of treatment (days)	5–7	5–7	15	5–7
Species	Rat	Rat	Mouse	Rat
i.v. PTZ			–	
s.c. PTZ				±
MES	–	–		
MES E/F ratio	–	–		
Hexobarbital sleep time	–	–	–	±
Microsomal protein yield	–	–		+
Cytochrome P-450	–	–		–
p-Nitroanisole *O*-demethylase	–	+		+
NADPH cytochrome *c* reductase	–	–		–

+, significant tolerance; ±, suggestive of tolerance, not significant; –, not suggestive of tolerance. See text for abbreviations.

nificantly alter hexobarbital sleep time. FBM in a single dose of 150 mg/kg increases hexobarbital sleep time over that of either the solvent control or the chronically treated groups (44.9 ± 2.6 vs. 29.7 ± 0.8 and 27.5 ± 2.3 min, respectively). This suggests that large single doses of FBM may have some CNS-depressant properties.

It is generally agreed that some tolerance has been induced when chronic treatment, if compared with acute (single-dose) treatment, results in one or more of the following: decreased anticonvulsant activity (less protection, s.c. PTZ or MES test), lower minimal seizure threshold (smaller i.v. PTZ convulsant dose), more severe seizures (higher MES E/F ratio), or increased drug metabolism (shorter hexobarbital sleep time and/or higher liver microsomal enzyme values). The overall tolerance potential of FBM, as revealed by an evaluation of the data in terms of this basic hypothesis, is summarized in Table 5. This summary suggests that some metabolic tolerance is induced by high doses (95 and 238 mg/kg) of FBM in rats. In contrast, no evidence of tolerance is present after the chronic administration of either 48 mg/kg of FBM in rats or 150 mg/kg in mice.

Acknowledgment: This research was supported by NIH contract no. NO1-NS-4-2361 awarded by the Epilepsy Branch, National Institute of Neurological and Communicative Disorders and Stroke, PHS/DHEW.

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Swinyard EA, Sofia RD, Kupferberg HJ. Comparative anticonvulsant activity and neurotoxicity of felbamate and four prototype antiepileptic drugs in mice and rats. *Epilepsia* 1986; 17:27–34.

Swinyard EA, Woodhead JH. Experimental detection, quantification and evaluation of anticonvulsants. In: Woodbury DM, Penry JK, Pippenger CE, eds. *Antiepileptic drugs*. New York: Raven Press, 1982:111–26.

RÉSUMÉ

Nous avons étudié chez la souris et le rat la possibilité de survenue d'une tolérance après administration chronique de felbamate (FBM). L'administration chronique (15 j) de FBM (150 mg/kg i.p.) n'a pas eu chez la souris d'effet significatif sur le seuil convulsif au pentylènetétrazol (PTZ) ni sur le temps de sommeil aprés hexobarbital; cependant, le temps de sommeil après hexobarbital a été significativement *augmenté* après administration unique. L'administration chronique (5 à 7 j) de FBM (48 ou 95 mg/kg per os) chez le rat n'a pas non plus eu d'effet significatif sur l'activité convulsive maximale à l'électrochoc ou le temps de sommeil après hexobarbital. L'administration chronique de FBM à la dose de 238 mg/kg a légèrement diminué l'activité du PTZ chez les rats traités de façon chronique (1/8 protégé) par comparaison aux animaux traités par dose unique (3/8 protégés) sans qu'il y ait de modification significative du temps de sommeil après hexobarbital. Chez le rat, le traitement chronique pendant 7 jours n'a en aucun effet significatif sur les paramètres hépatiques. Cependant, les doses de 95 ou 238 mg/kg ont entraîné une augmentation significative de l'activité p-nitroanisole-O-déméthylase. Nous concluons que l'augmentation du temps de sommeil induite par l'administration en aigu de FBM reflète l'effet dépresseur du CNS de la molécule. L'augmentation d'activité p-nitroanisole-O-déméthylase observée après administration chronique témoigne sans doute d'une certaine activité inductrice microsomiale hépatique. Globalement, le FBM, à des doses de 48 à 238 mg/kg, ne semble pas devoir provoquer de phénomène de tolérance.

(P. Genton, *Marseille*)

RESUMEN

Se ha investigado la posibilidad del desarrollo de una tolerancia a la administración crónica de felbamato (FBM) en ratones y ratas. La administración crónica (15 días) de FMB (150 mg/kg, i.p.) en ratones no produjo ningún efecto significativo sobre el umbral para ataques de la administración i.v. de pentilentetrazol (PTZ) o sobre el tiempo de sueño producido por el hexobarbital; sin embargo el tiempo de sueño del hexobarbital se incrementó significativamente después de una dósis única. La administración crónica (5 a 7 días) de FPM (48 ó 95 mg/kg, por vía oral) a ratas tampoco produjo un efecto significativo sobre la actividad epiléptica que sigue al electroshock máximo (MES) y sobre el tiempo de sueño del hexobarbital. La administración crónica del FBM a razón de 238 mg/kg redujo ligeramente la actividad PTZ en las ratas tratadas crónicamente (1/8 de protección) comparándolas con las que recibian solamente una dósis única (3/8 de protección) pero no se produjo ningún cambio significativo en el tiempo de sueño del hexobarbital. El tratamiento crónico de ratas durante 7 días con 48 mg/kg no produjo ningun efecto significativo en los parámetros hepático. Sin embargo 95 ó 238 mg/kg de FBM incrementarón significativamente la actividad de la p-nitroanisol-O-demetilasa. Se concluye que el incremento del tiempo de sueño del hexobarbital inducido por una dósis aguda de FBM refleja los efectos depresores sobre el sistema nervioso central de esta sustancia. La reducción de la actividad de la p-nitroanisol-O-demetilasa conservada tras la administración crónica puede indicar la inducción de algunos microsomas hepáticos. En general las dósis de FBM que oscilan entre 48 y 238 mg/kg parecen tener una mínima capacidad de desarrollo de tolerancia.

(A. Portera-Sánchez, *Madrid*)

maw

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/007,991	03/30/2006	4978680	NEXIN	9538

27162 7590 04/26/2006

CARELLA, BYRNE, BAIN, GILFILLAN, CECCHI,
STEWART & OLSTEIN
5 BECKER FARM ROAD
ROSELAND, NJ 07068

EXAMINER	
Bennett Celsa	
ART UNIT	**PAPER NUMBER**
3991	IFW

DATE MAILED: 04/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Order Granting / Denying Request For Ex Parte Reexamination	Control No.	Patent Under Reexamination	
	90/007,991	4978680	
	Examiner	Art Unit	
	Bennett Celsa	3991	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

The request for *ex parte* reexamination filed *30 March 2006* has been considered and a determination has been made. An identification of the claims, the references relied upon, and the rationale supporting the determination are attached.

Attachments: a)☐ PTO-892, b)☒ PTO-1449, c)☐ Other: _____

1. ☒ The request for *ex parte* reexamination is GRANTED.

RESPONSE TIMES ARE SET AS FOLLOWS:

For Patent Owner's Statement (Optional): TWO MONTHS from the mailing date of this communication (37 CFR 1.530 (b)). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**

For Requester's Reply (optional): TWO MONTHS from the **date of service** of any timely filed Patent Owner's Statement (37 CFR 1.535). **NO EXTENSION OF THIS TIME PERIOD IS PERMITTED.** If Patent Owner does not file a timely statement under 37 CFR 1.530(b), then no reply by requester is permitted.

2. ☐ The request for *ex parte* reexamination is DENIED.

This decision is not appealable (35 U.S.C. 303(c)). Requester may seek review by petition to the Commissioner under 37 CFR 1.181 within ONE MONTH from the mailing date of this communication (37 CFR 1.515(c)). **EXTENSION OF TIME TO FILE SUCH A PETITION UNDER 37 CFR 1.181 ARE AVAILABLE ONLY BY PETITION TO SUSPEND OR WAIVE THE REGULATIONS UNDER 37 CFR 1.183.**

In due course, a refund under 37 CFR 1.26 (c) will be made to requester:

a) ☐ by Treasury check or,

b) ☐ by credit to Deposit Account No. _____, or

c) ☐ by credit to a credit card account, unless otherwise notified (35 U.S.C. 303(c)).

Bennett Celsa
Primary Examiner
Art Unit: 3991

cc:Requester (if third party requester)

DETAILED ACTION: ***Reexamination: Granting of Request***

Procedural Posture:

The 3rd party Request (dated March 30, 2006:control no. 90/007,991) for *ex parte* reexamination of claim 1 of United States Patent Number 4,978,680 (Sofia) is acknowledged.

Decision Granting the Order

A substantial new question of patentability of claim 1 of United States Patent Number 4,978,680 (Sofia) is raised by the request for reexamination.

Ongoing Duty To Disclose:

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 4,978,680 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Substantial New Question of Patentability Raised By The Request

For "a substantial new question of patentability" to be present, it is only necessary that:

A. The prior art patents and/or printed publications raise a substantial question of patentability regarding at least one claim i.e. the prior art teaching is such that there is a substantial likelihood that a reasonable examiner would consider the teaching to be

important in deciding whether or not the claim is patentable; and it is not necessary that the prior art establish a prima facie case of unpatentability and;

B. The same question of patentability as to the claim has not been decided by the Office in a previous examination or pending reexamination of the patent or in a final holding of invalidity by the Federal Courts in a decision on the merits involving the claim. See MPEP 2242.

For a reexamination that was ordered on or after November 2, 2002 (the date of enactment of Public Law 107-273; see Section 13105, of the Patent and Trademark Office Authorization Act of 2002), reliance *solely* on old art (as the basis for a rejection) does not necessarily preclude the existence of a substantial new question of patentability (SNQ) that is based exclusively on that old art. Determinations on whether a SNQ exists in such an instance shall be based upon a fact-specific inquiry done on a case-by-case basis. For example, an SNQ may be based solely on old art where the old art is being presented/viewed in a new light, or in a different way, as compared with its use in the earlier concluded examination(s), in view of a material new argument or interpretation presented in the request. MPEP 2258.01.

If a substantial new question of patentability is found as to one claim, all claims will be reexamined during the ex parte reexamination process. See MPEP 2216.

The Claimed Invention

The claimed invention follows:

1. A method for reducing the incidence and severity of epileptic seizures which comprises administering to a warm-blooded animal in need of such treatment a therapeutic amount of 2-phenyl-1,3-propanediol dicarbamate.

Newly Cited Documents

1. Berger et al., U.S. Pat. No. 2,884,444 (issued April 28, 1959);

2. Wilensky et al., Epilepsia : 26(6) : 602-606 (1985);

3. Berger et al., U.S. Pat. No. 2,724,720 (issued November 25, 1955).

The Raising of a Substantial New Question of Patentability

1. Berger et al., U.S. Pat. No. 2,884,444 (Berger '444 patent)

The request (e.g. pages 6-9) alleges that the Berger '444 patent raises a substantial new question of patentability regarding anticipation.

The Berger '444 patent (e.g. at col. 1, lines 15-20; col. 2, lines 26-49) reference teaches the action of 2-phenyl-1,3-propanediol dicarbamate as an anti-convulsant compound to prevent electroshock seizures in animals (e.g. mice).

The Berger '444 patent raises an SNQ since there is a substantial likelihood that a reasonable examiner would consider the teaching of the Berger '444 patent important in deciding the patentability of claim 1 of the Sofia patent.

2. Wilensky et al., Epilepsia : 26(6) : 602-606 (1985)

The request (e.g. pages 9-11) alleges that the Wilensky article raises a substantial new question of patentability regarding anticipation.

The Wilensky article (e.g. see abstract) teaches that 2-phenyl-1,3-propanediol dicarbonate (called W-554) has antiepileptic activity in animals and further reports on results in human epileptic patients with respect to the control of seizures.

The Wilensky reference raises an SNQ since there is a substantial likelihood that a reasonable examiner would consider the teaching of the Wilensky reference important in deciding the patentability of claim 1 of the Sofia patent.

3. Berger et al., U.S. Pat. No. 2,724,720 (Berger '720 patent)

The request (e.g. pages 11-14) alleges that the Berger '720 patent raises a substantial new question of patentability regarding obviousness when combined with the Berger '444 patent reference.

The Berger '720 patent (e.g. at col. 1, lines 32-65; col. 2, lines 29-40; col. 3, lines 1-28) reference teaches the ability of alkyl (e.g. 2-ethyl form) derivatives of 2-phenyl-1,3-propanediol dicarbamate to act as an anti-convulsant compound to prevent electroshock seizures in animals (e.g. mice).

The Berger '720 patent reference raises an SNQ since there is a substantial likelihood that a reasonable examiner would consider the teaching of the Berger '720 patent reference important in deciding the patentability of claim 1 of the Sofia patent.

Conclusion

In view of the above, the request for reexamination is GRANTED. Clairn 1 of United States Patent Number 4,978,680 (Sofia) will be reexamined.

Extensions of Time

Extensions of time under 37 CFR 1.136 (a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to an applicant and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that *ex parte* reexamination proceedings "will be concluded with special dispatch" (37 CFR 1.555(a)). Extensions of time in ex parte reexamination proceedings are provided for in 37 CFR 1.550(c).

Patent Owner Amendment

Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c).

Future Correspondences

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on M-F from 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones can be reached at 571-272-1535.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this ex parte reexamination proceeding should be directed:

By Mail to:	Mail Stop ex parte Reexam Central Reexamination Unit Office of Patent Legal Administration United States Patent & Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450
By FAX to:	(571) 273-9900 Central Reexamination Unit
By hand:	Customer Service Window Randolph Building 401 Dulany St. Alexandria, VA 22314

Bennett Celsa
Primary Examiner
Art Unit 3991

Conferees:

PTO/SB/08A (04-03)
Approved for use through 04/30/2003. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	90/xxx,xxx
Filing Date	28 March 2006
First Named Inventor	Robert D. SOFIA
Art Unit	3991 Central Reexam
Examiner Name	
Attorney Docket Number	Nexin

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US- 2,884,444	04-28-1959	Frank M. BERGER	1:15-20; 2:26-49
		US- 2,724,720	11-22-1955	Frank M. BERGER	1:32-35; 2:29-40
		US-			3:1-28; 1:44-60
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	4/19/06

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, Washington, DC 20231.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PTO/SB/08B (04-03)
Approved for use through 04/30/2003. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	90/xxx,xxx
Filing Date	
First Named Inventor	
Art Unit	
Examiner Name	
Attorney Docket Number	

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		A.J. WILENSKY et al., Pharmacokinetics of W-544 (ADD 03055) In Epileptic Patients, 26 Epilepsia 602 (1985) (Raven Press, New York)	

Examiner Signature		Date Considered	4/19/06

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/007,991	03/30/2006	4978680	NEXIN	9538

26111 7590 11/21/2006

STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 11/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action in Ex Parte Reexamination	Control No. 90/007,991	Patent Under Reexamination 4978680	
	Examiner Bennett Celsa	Art Unit 3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

a☒ Responsive to the communication(s) filed on *31 October 2006*. b☒ This action is made FINAL.
c☐ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire 2 month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Information Disclosure Statement, PTO/SB/08.
3. ☐ Interview Summary, PTO-474.
4. ☐ _____.

Part II SUMMARY OF ACTION

1a. ☒ Claims *1-3* are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled in the present reexamination proceeding.
3. ☐ Claims _____ are patentable and/or confirmed.
4. ☒ Claims *1-3* are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a)☐ approved (7b)☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a)☐ All b)☐ Some* c)☐ None of the certified copies have
   1☐ been received.
   2☐ not been received.
   3☐ been filed in Application No. _____.
   4☐ been filed in reexamination Control No. _____.
   5☐ been received by the International Bureau in PCT application No. _____.
   * See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: _____

cc: Requester (if third party requester)

DETAILED ACTION: *Reexamination: Final Rej ction*

Procedural Posture:

The 3rd party Request (dated March 30, 2006:control no. 90/007,991) for *ex parte* reexamination of claim 1 of United States Patent Number 4,978,680 (Sofia) was granted on April 26, 2006. No Patent Owner's Statement was received.

The present amendment dated 10/31/06 in response to the first office action dated August 31, 2006 is acknowledged.

Ongoing Duty To Disclose:

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 4,978,680 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

The Instant Claimed Invention (as amended on 10/31/06)

1. (amended) A method for reducing the incidence and severity of epileptic seizures which [comprises] consists essentially of administering to a [warm-blooded animal] human in need of such treatment a therapeutic amount of 2-phenyl-l,3-propanediol dicarbamate.

2. A method for reducing the incidence and severity of epileptic seizures which consists essentially of administering to a human in need of such treatment 2-phenyl-l,3-propanediol dicarbamate in a daily dosage of from about 100 milligrams to about 5 grams.

3. The method of claim 2, wherein the daily dosage of 2-phenyl-l,3-propanediol dicarbamate is 2300 mg.

Withdrawn Obj ction(s) and/or R jection(s)

In response to the amended claims, the rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by *Wilensky* et al., Epilepsia : 26(6) : 602-606 (1985) is withdrawn *in lieu* of the modified anticipation rejection appearing *infra.*

The amendment to claim 1 necessitated withdrawal of the rejection of original claim 1 under 35 U.S.C. 102(b) as being anticipated by *Swinyard*, Epilepsia 27(1): 27-34 (1986) as evidenced by the instant Sofia US 4,978,680 patent to demonstrate inherency. See MPEP 213.01.

New Objection (s) and/or Rejection (s)

1. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by *Wilensky* et al., Epilepsia : 26(6) : 602-606 (1985).

The *Wilensky* article teaches that 2-phenyl-1,3-propanediol dicarbamate (called W-554) has broad-spectrum antiepileptic activity in animals (citing Swineyard and Kupferberg, 1982) and further reports on results in human epileptic patients with respect to the control and severity of seizures. See page 602, left column and Abstract.

In the Wilensky human clinical study, four epileptic patients receiving phenytoin (PHT) and four epileptic patients receiving carbamazepine (CBZ), upon being separately administered (e.g. in pill form: page 604, line 2) W-554 in dosages of 200, 400, 800, 1200 and 1600 mg/day ("a therapeutic amount" as in instant claim 1; and "about 100 milligrams to about 5 grams" as in instant claim 2) experienced a reduction in seizure frequency and severity. See Wilensky Abstract; page 603, left column; page 604, right column; and "Discussion" on pages 605-606.

The Wilensky method for reducing the incidence and severity of epileptic seizures by administering up to 1600 mg/day of 2-phenyl-1,3-propanediol dicarbamate (aka W-554 or felbamate) as an adjunct to phenytoin or carbamazepine is within the scope of the instant claimed method that "consists essentially of" administering 2-phenyl-1,3 propanediol dicarbamate since the instant patent specification (columns 1-2 and example) and the instantly claimed method acknowledges that the same basic and novel anti-epileptic properties is possessed by phenytoin and carbamazepines in treating epileptic seizures. Accordingly, co-administration of phenytoin or carbamzepines with 2-phenyl-1,3 propanediol dicarbamate is within the scope of "consisting essentially of", as amended. Additionally, there is no evidence of record that the presence of phenytoin and carbamazepines would materially affect the basic and novel anti-epileptic characteristics of 2-phenyl-1,3 propanediol dicarbamate as used in the instantly claimed method. This is especially true in light of the Wilensky clinical data demonstrating that coadministration of W-554 with phenytoin or carbamazepine resulted in an improvement in the control of seizures in patients already receiving PHT or CBZ. E.g. see Wilensky Abstract.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Wilensky* et al., Epilepsia : 26(6) : 602-606 (1985).

The *Wilensky* article teaches that 2-phenyl-1,3-propanediol dicarbamate (called W-554) has broad-spectrum antiepileptic activity in animals (citing Swineyard and Kupferberg, 1982) and further reports on results in human epileptic patients with respect to the control and severity of seizures. See page 602, left column and Abstract.

In the Wilensky human clinical study, four epileptic patients receiving phenytoin (PHT) and four epileptic patients receiving or carbamazepine (CBZ), when also separately administered (e.g. in pill form: page 604, line 2) W-554 in dosages of 200, 400, 800, 1200 and 1600 mg/day ("a therapeutic amount" as in instant claim 1; and "about 100 milligrams to about 5 grams" as in instant claim 2) experienced a reduction in seizure frequency and severity ("reducing the incidence and severity"): "Seizure control was improved in six of eight subjects and seizures were less severe in three, while on W-554". See Wilensky Abstract; page 603, left column; page 604, right column; and "Discussion" on pages 605-606.

The Wilensky method for reducing the incidence and severity of epileptic seizure by administering 2-phenyl-1,3-propanediol dicarbamate as an adjunct to phenytoin or carbamazepine therapy is within the scope of the instant claimed method that "consists essentially of" administering 2-phenyl-1,3 propanediol dicarbamate (AKA: W-554 or felbamate) since the instant patent specification (columns 1-2 and example) acknowledges the same basic and novel anti-epileptic properties of phenytoin and carbamazepines in treating seizures. Accordingly, co-administration of phenytoin or carbamzepines with 2-phenyl-1,3 propanediol dicarbamate is within the scope of

"consisting essentially of". Additionally, there is no evidence of record that the presence of phenytoin and carbamazepines would materially affect the basic and novel anti-epileptic characteristic of 2-phenyl-1,3 propanediol dicarbamate as used in the instantly claimed method since in accordance with the Wilensky method W-554 W-554 control of seizures was improved in patients already receiving PHT or CBZ. E.g. see Wilensky Abstract.

Although disclosing administration of 2-phenyl-1,3 propanediol dicarbamate in amounts up to 1600 mg/day, the Wilensky method differs from the instant claim 3 invention which is drawn to administering 2300 mg/day.

However, the Wilensky reference further provides explicit motivation to administer dosages greater than 1600 mg/day to address questions relating to dose-level relationships, maximum tolerated dose, confirm improved seizure control at higher doses under blinded conditions and to determine drug interactions (see page 606, left column). Absent evidence of criticality, it is well within the skill of the art to optimize concentration amounts to arrive at the presently claimed amount ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also MPEP 2144.05 Accordingly, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to increase the administered dose of 2-phenyl-1,3 propanediol dicarbamate to greater than 1600 mg/day and arrive at the instantly claimed amount in light of the Wilensky teaching of higher tolerated dosages and motivation to optimize dose-level

relationships to achieve greater efficacy in reducing the incidence and/or severity of epileptic seizures.

3. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Wilensky* et al., Epilepsia : 26(6) : 602-606 (1985) alone, or further in view of *Swinyard*, Epilepsia 27(1): 27-34 (1986).

The *Wilensky* article teaches that 2-phenyl-1,3-propanediol dicarbamate (called W-554) has broad-spectrum antiepileptic activity in animals (citing Swinyard and Kupferberg, 1982) and further reports on results in human epileptic patients with respect to the control and severity of seizures. See page 602, left column and Abstract.

In the Wilensky human clinical study, four epileptic patients receiving phenytoin (PHT) and four epileptic patients receiving or carbamazepine (CBZ), when also separately administered (e.g. in pill form: page 604, line 2) W-554 in dosages of 200, 400, 800, 1200 and 1600 mg/day ("a therapeutic amount" as in instant claim 1; and "about 100 milligrams to about 5 grams" as in instant claim 2) experienced a reduction in seizure frequency and severity ("reducing the incidence and severity"): "Seizure control was improved in six of eight subjects and seizures were less severe in three, while on W-554". See Wilensky Abstract; page 603, left column; page 604, right column; and "Discussion" on pages 605-606.

The instantly claimed invention differs from the Wilensky method :

a. For instant claims 1-2: to the extent that the instant method encompasses the administration of the 2-phenyl-1,3-propanediol dicarbamate **alone** ("consisting essentially of" equals "consisting of") and not as an adjunct to phenytoin or carbamazepine anti-seizure therapy.

b. Further for instant claim 3: by disclosing administration of 2-phenyl-1,3 propanediol dicarbamate in amounts up to 1600 mg/day, the Wilensky method fails to exemplify the administration of 2300 mg/day.

With respect to items a and b. above, the following Wilensky clinical study results are noted:

a. "Most of the toxicity recorded during the study was associated with increased levels of PHT or CBZ" (Wilensky p. 604, right column under "Toxicity") while little side-effects were attributable to W-554 even at the highest W-554 1600 mg/day dosage (Wilensky p. 605, right column);
b. The study indicated maximum tolerated W-554 dosages greater than 1600 mg/day; with promising efficacy of W-554 in reducing the incidence and severity of seizures at concentrations up to 1600 mg/day (Wilensky p.605, right column: "... results with respect to efficacy are promising"; and Abstract: "Seizure control was improved in six of eight subjects, and seizures were less severe in three, while on W-554."); and
c. Wilensky provides explicit motivation to study human administration of dosages greater than 1600 mg/day to address questions relating to dose-level relationships, maximum tolerated dose, confirm improved seizure control at higher doses under blinded conditions and determine drug interactions (see p.606, left column).

Accordingly, the Wilensky reference provides motivation to one of ordinary skill in the art to solely administer 2-phenyl-1,3-propanediol dicarbamate in order to reduce PHT or CBZ associated side-effects (as described in item a. above) and/or in light of the study evidence of efficacy attributed to 2-phenyl-1,3-propanediol dicarbamate in controlling epileptic seizures (as described in item b. above).

Additionally, the Wilensky reference further provides explicit motivation (as described in items b. and c. above) to increase 2-phenyl-1,3-propanediol dicarbamate dosage to greater than 1600 mg/day since such a dosages is tolerated and would be

expected to achieve anti-epileptic efficacy analogous to that achieved at the 1600 mg/day dose. Additionally, higher 2-phenyl-1,3-propanediol dicarbamate doses would be necessary in order to compensate for the loss of anti-epileptic effects attributable to the PHT or CBZ medications. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also MPEP 2144.05.

Accordingly, in light of the Wilensky reference teaching taken alone, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to solely administer 2-phenyl-1,3 propanediol dicarbamate in dosages up to 1600 mg/day, or greater than 1600 mg/day, and arrive at the instantly claimed therapeutic amounts in light of the Wilensky teaching of higher tolerated dosages; motivation to optimize dose-level relationships in order to achieve greater efficacy in controlling seizures absent the anti-epileptic effects of PHT or CBZ.

The Swinyard reference provides additional motivation to modify the Wilensky reference method to utilize 2-phenyl-1,3 propanediol dicarbamate alone in controlling epileptic seizures, since Swinyard teaches that felbamate (2-phenyl-1,3-propanediol dicarbamate) possesses *a wider range of anti-convulsant activity* than other prototype antiepileptic drugs, including phenytoin in mice and rat models (page 27, abstract). Administering (orally or intraperitoneally) felbamate to mice or rats ("warm-blooded animals") in "therapeutically effective" amounts (434-751 mg/kg for mice; and 132-549 mg/kg for rats: see Table 3: columns 8-9; and page 27, right column mice: 18-25 g and

rats: 100-150 g) increases seizure threshold and prevents seizure spread (page 32, column 2) which inherently results in "*reducing the incidence and severity of epileptic seizures*" as instantly claimed (emphasis provided).

Thus, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify the Wilensky method to administer 2-phenyl-1,3-propanediol dicarbamate alone, and not as an adjunct phenytoin or carbamazepine therapy as in the Wilensky clinical study, further in view of the Swinyard teaching that 2-phenyl-1,3-propanediol dicarbamate possesses a wider range of anti-convulsant activity than other prototype antiepileptic drugs (including phenytoin) and thus arrive at the instant method.

Discussion

Patentee's arguments, as applicable to the above newly-raised rejections, were considered but deemed nonpersuasive for the following reasons.

Patentee Arguments:

Argument 1: Regarding anticipation by the Wilensky article, patentee argues that amending the claims to utilize a method "consisting essentially of" human administration of 2-phenyl-1,3-propanediol dicarbamate is outside the scope of the Wilesky administration of 2-phenyl-1,3-propanediol dicarbamate as an adjunct therapy with phenytoin or carbamazepine to reduce the incidence and severity of seizures since these two standard anti-convulsants "clearly have 'material effects' ". It is noted that Wilensky teaches (at page 605, left column, first paragraph) drug interactions (i.e. increase serum phenytoin levels and decrease serum carbamazepine levels) between W-554 and carbamazepine or phenytoin.

Examiner Response: This argument is not persuasive for the following reasons.

The term "consisting essentially of" does not limit the claims so as to exclude other things when the specification or claims clearly indicates other constituents may be present. *Ex parte Boukidis* 154 USPQ 444 (POBA 1966). The instant patent specification at columns 1-3 and examples clearly indicate the known anti-epileptic use

of phenytoin and carbamazepines in treating seizures; thus possessing the same basic and novel characteristics of the instantly invention. Thus, "consisting essentially of" language found in the instantly amended claims would encompass the additional step of administering phenytoin or carbamazepines as taught by the Wilensky reference.

Additionally, the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). The burden is on the patent applicant to define the scope of the phrase "consisting essentially of" by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention. See, e.g. *PPG Industries v. Guardian Industries*, 156 F.3d 1351, 1355, 48 USPQ2d 1351, 1355 (Fed. Cir.1998). If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. *In re De Lajarte*, 337 F.2d 870, 143 USPQ 256 (CCPA 1964). See also *Ex parte Hoffman*, 12 USPQ2d 1061, 1063-64 (Bd. Pat. App. & Inter.1989). See MPEP 2105.

In the present instance the claimed invention is drawn to reducing the incidence and severity of epileptic seizures; and the known anti-epileptic use of phenytoin and carbamazepines in treating seizures indicates that these medicines possess the same basic and novel characteristics of the claimed invention. Additionally, there is no evidence of record that the presence of phenytoin (PHT) and carbamazepines (CBZ) would materially affect the basic and novel characteristic of 2-phenyl-1,3 propanediol dicarbamate. In this respect, the Wilensky reference study concluded that control of seizures **was improved** in patients administered 2-phenyl-1,3 propanediol dicarbamate in addition to PHT or CBZ. E.g. see Wilensky Abstract.

The drug interaction referred to by the patentee is not believed to be germane to the instantly claimed basic and novel characteristic of reducing the incidence and severity of epileptic seizures. Any drug regimen will have side-effects. In fact, as

discussed in the obviousness rejection above, the Wilensky teaching of drug interactions resulting from increased serum phenytoin levels provides a *teaching toward* administration of 2-phenyl-1,3 propanediol dicarbamate alone as encompassed by the instantly claimed invention *if* "consisting essentially of" is interpreted to be equivalent to "consisting of".

Argument 2: Regarding anticipation by the Wilensky article, patentee argues that since Wilensky fails to disclose the use of W-554 alone it also fails to disclose the proper therapeutic dose or dosage range of this compound for independent use in humans; including the range and daily dosage amounts of new claims 2 and 3. Similarly, it is pointed out that Swinyard's administration of felbamate to animals (e.g. mice and rats) "cannot teach or suggest the appropriate therapeutic amount of felbamate for humans that would be efficacious for reducing the incidence and severity of epileptic seizures, as required by the present claims".

Examiner Response: These arguments are not persuasive for the following reasons.

To the extent that the instant claims use of "consisting essentially of" includes the additional step of administering phenytoin and carbamazepines, the Wilensky reference method anticipates the instantly claimed invention. See anticipation rejection, *supra*.

To the extent that the claims encompass only administering 2-phenyl-1,3-propanediol dicarbamate or are additionally drawn to a specific daily dosage amount (2300 mg/day in claim 3) not explicitly taught by either the Wilensky or Swinyard reference, the patentee is directed to the above newly-raised obviousness rejections. In this regard, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also MPEP 2144.05. In this respect, the Wilensky article provides guidance for determining optimal 2-phenyl-1,3-propanediol dicarbamate human dosages. Additionally, correlating animal dosages (as disclosed in Swinyard) to obtain human dosages is well within the skill of the art; especially in light of the additional guidance provided in the Wilensky article regarding human dosages.

Conclusion:

4. Patent owner's amendment filed 10/31/06 necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

A shortened statutory period for response to this action is set to expire **two months** from the mailing date of this action.

Extensions of time under 37 CFR 1.136(a) do not apply in reexamination proceedings. The provisions of 37 CFR 1.136 apply only to "an applicant" and not to parties in a reexamination proceeding. Further, in 35 U.S.C. 305 and in 37 CFR 1.550(a), it is required that reexamination proceedings "will be conducted with special dispatch within the Office."

Extensions of time in reexamination proceedings are provided for in 37 CFR 1.550(c). A request for extension of time must be filed on or before the day on which a response to this action is due, and it must be accompanied by the petition fee set forth in 37 CFR 1.17(g). The mere filing of a request will not effect any extension of time. An extension of time will be granted only for sufficient cause, and for a reasonable time specified.

The filing of a timely first response to this final rejection will be construed as including a request to extend the shortened statutory period for an additional month, which will be granted even if previous extensions have been granted. In no event, however, will the statutory period for response expire later than SIX MONTHS from the mailing date of the final action. See MPEP § 2265.

Future Correspondences

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on M-F from 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones can be reached at 571-272-1535.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this ex parte reexamination proceeding should be directed:

By Mail to: Mail Stop ex parte Reexam
Central Reexamination Unit
Office of Patent Legal Administration
United States Patent & Trademark Office
P.O. Box 1450 Alexandria, VA 22313-1450

By FAX to: (571) 273-9900
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/007,991	03/30/2006	4978680	2286.019REX0	9538

26111 7590 01/17/2007

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EXAMINER	
Bennett Celsa	
ART UNIT	**PAPER NUMBER**
3991	IFW

DATE MAILED: 01/17/2007

Please find below and/or attached an Office communication concerning this application or proceeding.

Ex Parte Reexamination Interview Summary	Control No.	Patent Under Reexamination	
	90/007,991	4978680	
	Examiner	Art Unit	
	Bennett Celsa	3991	

All participants (USPTO personnel, patent owner, patent owner's representative):

(1) *Bennett Celsa*

(2) *Evelyn Huang*

(3) *Karen R. Markowicz*

(4) *Brian J. Del Buono*

Date of Interview: ~~12 November 2007~~ 01 January

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal (copy given to: 1)☐ patent owner 2)☐ patent owner's representative)

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.
Any other agreement(s) are set forth below under "Description of the general nature of what was agreed to..."

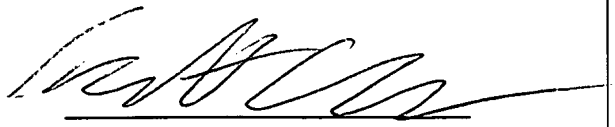
Claim(s) discussed: *1-3*.

Identification of prior art discussed: *Wilensky, Swinyard*.

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
Patentee will consider amending the method claims to recite "consisting of" and sole administration of the instant compound to address prior art (particularly Wilensky). Patentee will further consider providing arguments and/or 132 Declaration evidence addressing the patentability of the claims.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims patentable, if available, must be attached. Also, where no copy of the amendments that would render the claims patentable is available, a summary thereof must be attached.)

A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION MUST INCLUDE PATENT OWNER'S STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. (See MPEP § 2281). IF A RESPONSE TO THE LAST OFFICE ACTION HAS ALREADY BEEN FILED, THEN PATENT OWNER IS GIVEN **ONE MONTH** FROM THIS INTERVIEW DATE TO PROVIDE THE MANDATORY STATEMENT OF THE SUBSTANCE OF THE INTERVIEW (37 CFR 1.560(b)). THE REQUIREMENT FOR PATENT OWNER'S STATEMENT CAN NOT BE WAIVED. **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**



cc: Requester (if third party requester)

Examiner's signature, if required

Certification Of Service of Reply To Office Action

In compliance with 37 C.F.R. § 1.550(f), the undersigned, on behalf of the Patent Owner, hereby certifies that a copy of this paper has been served on the third-party requester by first class mail on January 22, 2007. The name and address of the party served is as follows:

Mark Pohl
Pharmaceutical Patent Attorneys, LLC
55 Madison Ave, 4th Floor
Morristown, NJ 07960-7397

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Brian J. Del Buono
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Date: January 22, 2007

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Remarks

Patent claim 1 and new claim 3 have been canceled. New claim 2 has been amended from the prior version. Specifically, claim 2 now recites the transitional term "consisting of" (in place of "comprising") as well as that "2-phenyl-1,3-propanediol dicarbamate is the sole active component administered in said method." These changes are believed to be fully supported by the specification, introduce no new matter, and do not enlarge the scope of the patent claims. Thus, claim 2 is currently pending in this reexamination. Based on the following remarks, the Patent Owner respectfully requests that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Statement of Substance of Examiner Interview

The Patent Owner's representatives thank Examiners Huang and Celsa for the telephonic interview on January 12, 2007. The date of the interview on the Interview Summary form was mistakenly dated "November 12, 2007," but the form has since been hand-corrected by the Examiner to reflect the correct interview date of January 12, 2007 and re-mailed to the undersigned. The Interview Summary reflects the substance of the interview and should be made of record. More specifically, the Patent Owner discussed several proposed amendments, such as amending the transitional term to "consisting of" and reciting that felbamate was the sole active component in the method.

Rejection Under 35 U.S.C. § 102(b) Over Wilensky et al., Epilepsia 26:602-606 (1985)("Wilensky")

At pages 3-4 of the final Office Action, the Examiner rejects claims 1 and 2 under 35 U.S.C. § 102(b) as being anticipated by Wilensky. Since claim 1 is no longer pending, the Patent Owner respectfully traverses this rejection of claim 2.

According to the Examiner, Wilensky discloses that 2-phenyl-1,3-propanediol dicarbamate (alternatively called "W-554" or "felbamate"), has antiepileptic activity in animals and further reports on results in human epileptic patients with respect to the control and severity of seizures. The Examiner states that in the Wilensky human clinical study, patients receiving phenytoin (PHT) or carbamazepine (CBZ), who were then administered felbamate (as an "add on" or adjunctive drug) in dosages of 200, 400, 800, 1200, and 1600 mg/day, experienced a reduction in seizure frequency and severity.

The Examiner contends that the coadministration of PHT or CBZ with felbamate falls within the scope of the claimed method that "consists essentially of" administering felbamate, because PHT or CBZ allegedly have the same basic and novel anti-epileptic properties as felbamate. Also, the Examiner contends that there is no evidence of record that the presence of PHT or CBZ would materially affect the basic and novel anti-epileptic characteristics of felbamate especially since Wilensky's clinical data allegedly demonstrates that coadministration of felbamate with PHT or CBZ resulted in an improvement in the seizure control in patients already receiving PHT or CBZ.

Without acquiescing to the propriety of the rejection, but solely to expedite allowance or at least place the claims in better condition for appeal, claim 1 has been canceled and claim 2 has been amended. Claim 2 now recites the transitional term "consisting of" (in place of "comprising") as well as that "2-phenyl-1,3-propanediol

dicarbamate is the sole active component administered in said method." For the reasons below, it is believed that these amendments will obviate the current rejection.

It is well-established in patent law that the transitional phrases -- "comprising," "consisting essentially of," and "consisting of" -- define the scope of the claim with respect to what unrecited additional components or steps, if any, are excluded from the scope of the claim. The transitional term "consists of" *excludes* any element, step, or ingredient not specified in the claim. *See*, M.P.E.P. 2111.03.

As acknowledged by the Examiner, Wilensky discloses the use of felbamate as an adjunctive or "add on" medication in patients taking either of two standard anti-convulsants -- PHT or CBZ. *See*, Wilensky, Table 1, Abstract, lines 1-6, and page 602, right col., lines 10-12. Thus, since Wilensky discloses the use of felbamate, *together with one of two standard anti-convulsants*, Wilensky does not disclose, or even suggest, the use of felbamate as the sole anti-convulsant (or sole active component) for reducing the incidence and severity of epileptic seizures in humans.

Further, since the use of felbamate on its own is not disclosed in Wilensky, the proper therapeutic dose or dosage range of this compound for independent use in humans is not disclosed either. In fact, Wilensky discusses the drug interactions between W-554 and CBZ and W-554 and PHT, cautioning that the addition of W-554 can increase serum phenytoin levels and decrease serum carbamazepine levels. *See,* Wilensky, page 605, left column, first paragraph. That is, there is no guidance of the proper dosage in patients taking felbamate alone for the treatment of their epileptic seizures. Thus, not only does Wilensky not teach or even suggest the sole use of felbamate for treating epileptic seizures, it also does not teach a proper therapeutic dosage of felbamate when used independently of PHT and CBZ.

Accordingly, Wilensky does not anticipate currently pending claim 2. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection Under 35 U.S.C. § 103 Over Wilensky

At pages 5-7 of the Office Action, the Examiner rejects claims 1-3 under 35 U.S.C. § 103 as being obvious over Wilensky. Without acquiescing to the propriety of the rejection, but solely to expedite allowance or at least place the claims in better condition for appeal, claims 1 and 3 have been cancelled. The Patent Owner respectfully traverses this rejection of claim 2.

The Examiner characterizes Wilensky as above for the § 102 rejection. Again, regarding claim 2, the Examiner states that the coadministration of PHT or CBZ with felbamate is within the scope of the claimed method that "consists essentially of" administering felbamate and that there is allegedly no evidence of record that the presence of PHT or CBZ would materially affect the basic and novel anti-epileptic characteristics of felbamate. Office Action, paragraph bridging pages 5-6.

As mentioned above in connection with the § 102 rejection, claims 1 and 3 have been canceled and claim 2 has been amended. Claim 2 now recites the transitional term "consisting of" (in place of "comprising") as well as that "2-phenyl-1,3-propanediol dicarbamate is the sole active ingredient administered in said method." For the reasons below, it is believed that these amendments also obviate the current obviousness rejection.

Although this is an obviousness rejection over Wilensky alone, the Examiner appears to reiterate the same rationale for this rejection as for the anticipation rejection. However, the Examiner does not articulate why, for method claim 2, it would have been

obvious to go from Wilensky's use of felbamate as an add-on or adjunctive medication to treat epileptic seizures, to the use of felbamate as the sole active component. No motivation or reasonable expectation of success in making this change from Wilensky's approach has been provided by the Examiner. If this § 103 rejection over Wilensky is maintained for current claim 2, it is respectfully requested that the basis for this rejection be more particularly articulated.

Accordingly, Wilensky does not render obvious current claim 2. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection Under 35 U.S.C. § 103 Over Wilensky Alone or in View of Swinyard et al., Epilepsia 27:27-34 (1986)("Swinyard")

At pages 7-10 of the Office Action, the Examiner rejects claims 1-3 under 35 U.S.C. § 103 as obvious over Wilensky alone[1] or in view of Swinyard. Since claims 1 and 3 are no longer pending, the Patent Owner respectfully traverses this rejection of claim 2.

For claim 2, the Examiner starts with the presumption that "consists essentially of" equals "consists of" (essentially the current claim 2), and acknowledges that Wilensky does not teach the sole administration of felbamate. Office Action, pages 7-8. The Examiner contends, however, that Wilensky provides motivation for one skilled in the art to solely administer felbamate in order to (1) reduce PHT or CBZ associated side-effects; and (2) in light of the study evidence of efficacy attributed to felbamate in controlling epileptic seizures.

[1] The § 103 rejection over Wilensky alone appears to be redundant to the § 103 rejection above. Clarification is respectfully requested.

The Examiner also states that Swinyard provides additional motivation to modify Wilensky to utilize felbamate alone since Swinyard allegedly discloses that felbamate possesses a wider range of anticonvulsant activity than other prototype anti-epileptic drugs. Office Action, page 9, last paragraph. Thus, the Examiner concludes that it would have been obvious to use felbamate alone and not as an adjunct to PHT or CBZ therapy.

To establish a *prima facie* case of obviousness, (1) the combined references must teach or suggest all of the claim limitations, (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references, and (3) there must be a reasonable expectation of success. *See,* M.P.E.P. § 706.02(j) and cases cited therein. The Examiner has the burden of establishing a *prima facie* case of obviousness.

Further, a *prima facie* case of obviousness can be rebutted if the applicant can show that the art in any material respect taught away from the claimed invention. See *In re Haruna*, 58 U.S.P.Q.2d 1517, 1522 (Fed. Cir. 2001). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 52 U.S.P.Q.2d 1294,1298 (Fed. Cir. 1999).

The Patent Owner respectfully submits that based on the legal standard for obviousness, the Examiner has not set forth a legally sufficient *prima facie* case of obviousness and, in any event, any *prima facie* case of obviousness that *may* have been established has been rebutted, for at least the following reasons.

Wilensky is a self described pharmacokinetic and toxicity study of felbamate as an adjunctive medication (*i.e.*, felbamate + CBZ or felbamate + PHT). *See*, Abstract, line 4. One of the main objectives of the Wilensky study was "to determine the effect of W-554 on seizure frequency when given as an add-on medication." *See*, page 602, left column. Despite Wilensky's discussion of toxicity associated with increased levels of PHT or CBZ, Wilensky fairly discloses only adjunctive use of these medications. In fact, while Wilensky states that subject 1 felt that his seizure control was improved on W-554, Wilensky states that this "may have been the result of his increased PHT level." See page 604, right column. Further, Wilensky states that "the reductions in seizure frequency [from W-554] are not definitive . . . and further controlled studies are indicated." Thus, it is only with improper hindsight that the Examiner concludes that there was motivation to have used felbamate as a monotherapy, *i.e.*, in the absence of PHT and/or CBZ.

At best, in view of Wilensky, one skilled in the art might have found it "obvious to try" felbamate as the sole active component. However, it is well-established law that whether or not something would have been "obvious to try" is not a proper standard for obviousness under 35 U.S.C. § 103. *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see also Amgen v. Chugai*, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991); *In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988); *In re Fine*, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988).

The Examiner contends that Swinyard provides additional motivation to use felbamate alone since Swinyard allegedly discloses that felbamate possesses a wider range of anti-convulsant activity than other prototype anti-epileptic drugs. The Patent Owner respectfully disagrees.

First, the Patent Owner would like to clarify that Swinyard's analysis and conclusions regarding a "wider range of anti-convulsant activity" for felbamate were based on studies in *experimental* animal models with *experimental* anti-convulsant activity. It is not a foregone conclusion that this broad general statement in Swinyard of an alleged "wider range of anti-convulsant activity" would necessarily translate to a reduction in the incidence and severity of epileptic seizures in human patients.

Further, Swinyard can actually be viewed as teaching away from the currently claimed method of using felbamate as the sole active component for treating epileptic seizures in humans. For example, Swinyard states:

- "Felbamate exhibits a somewhat more restricted range than either phenobarbitol or valproate." (Abstract);
- "Felbamate is a less potent anticonvulsant agent than either phenytoin or phenobarbitol. . . ." page 32, left column;
- "Felbamate is ineffective against Bic-induced seizures." page 32, right column; and
- [Felbamate] is inferior to the prototype agents in terms of its absorption ratio by the s.c. PTZ test. . . . page 33, left column.

The above statements, on balance to the Examiner's statements, do not provide one skilled in the art with the requisite motivation to have used felbamate as a sole active component in treating epileptic seizures in humans, and in fact more likely would have taught away from doing so.

Accordingly, Wilensky alone or in view of Swinyard does not render obvious currently pending claim 2. Reconsideration and withdrawal of this rejection are respectfully requested.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. The Patent Owner therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

The Patent Owner believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present reexamination proceeding is in condition for a Notice of Intent to Issue a Reexamination Certificate. If the Examiner believes, for any reason, that a personal communication will expedite prosecution of this reexamination, the Examiner is invited to telephone the undersigned directly at (202) 772-8525.

Prompt and favorable consideration of this Response is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Brian J. Del Buono
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623972v1

Amendments to the Patent Claims (37 C.F.R. §§ 1.530(d)(2) and (f))

Please cancel patent claim 1 and new claim 3.

Please add new claim 2:

2. A method for reducing the incidence and severity of epileptic seizures in a human, said method consisting of:

administering 2-phenyl-1,3-propanediol dicarbamate to said human in a daily dosage of from about 100 milligrams to about 5 grams, wherein said 2-phenyl-1,3-propanediol dicarbamate is the sole active component administered in said method.

Status of Claims and Support for Claim Changes (37 C.F.R. § 1.530(e))

Status

Patent claim 1 and new claim 3 have been canceled.

New claim 2 is pending.

Support

Support for new claim 2 can be found in the '680 patent specification at *e.g.*, col. 1, lines 5-16; and col. 2, lines 9-11 and 27-29.

A.NE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re third party reexam request of:

U.S. Patent 4,978,680 (Sofia)

Reexam Control No.: 90/007,991

Filed: March 30, 2006

For: **Method for the Prevention and Control of Epileptic Seizure**

Confirmation No.: 9538

Art Unit: 3991 **(Central Reexam)**

Examiner: Bennett Celsa

Atty.Dkt: 2286.019REX0/BJD/KRM

Amendment and Reply to final Office Action in *Ex Parte* Reexamination

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Mail Stop Ex Parte Reexam

Sir:

In reply to the final Office Action in *Ex Parte* Reexamination dated November 21, 2006, the Patent Owner submits the following Amendments and Remarks, in accordance with 37 C.F.R. §§ 1.530(d)-(j) and 1.550(b).

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Re-ex

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Art Unit 3991

Attn: Mail Stop Ex Parte Reexam

Re: *Ex Parte* Reexamination of U.S. Patent No. 4,978,680
Control No. 90/007,991; Filed: March 30, 2006
For: **Method for the Prevention and Control of Epileptic Seizure**
Patentee: Robert D. Sophia
Our Ref: 2286.019REX0/BJD/KRM

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Amendment and Reply to Final Office Action in *Ex Parte* Reexamination along with a Certification of Service; and

2. Return postcard.

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier.

In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Brian J. Del Buono
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BJD/KRM/pcd
Encls.

632939_1.DOC

In the United States Patent Office

In re Application of Robert Duane SOFIA,	Serial No. 90/007,991 Art Unit: Central Reexam Examiner Bennett CELSA, Esq.
	RULE 535 RESPONSE

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THIS RESPONSE IS
AUTHORIZED BY RULE 535

A patent owner is not required to submit a response under Rule 530. If, however, the patent owner does so, then the third party requestor has a right to respond under Rule 535.

In the immediate case, the patent owner filed an After-Final Amendment on 22 January 2007. That amendment was made pursuant to Rule 530. *See* 37 C.F.R. § 1.121(j) ("Any proposed amendment to the description and claims in patents involved in reexamination proceedings must be made in accordance with § 1.530"); Amendment (22 January 2007) at page 1 (asserting that "the Patent Owner submits the following Amendments and Remarks, in accordance with 37 C.F.R. §§ 1.530(d)-(j) and 1.550(b)").

The third-party requestor accordingly has a right under Rule 535 to respond. *See* 37 C.F.R. § 1.535.

This Response is accordingly submitted pursuant to Rule 535. This Response being submitted within two months of the patent owner's Rule 530 amendment, this Response is respectfully believed timely filed.

RULE 116(B) PROHIBITS ENTRY OF THE AFTER-FINAL AMENDMENT

Reexamination procedure is expedited. It therefore requires issues to be raised *early* in the reexamination process. Office procedure thus says that prosecution should be conclude *before* a final office action, not *after*:

> It is intended that prosecution before the examiner in a reexamination proceeding will be concluded with the final action. Once a final rejection that is not premature has been entered in a reexamination proceeding, the patent owner no longer has any right to unrestricted further prosecution.

Manual Pat. Exam. Proc. § 2272.

In the immediate case, the final action was not premature. Thus, the patent owner no longer has a right to unrestricted further prosecution. To the contrary, for an amendment to be entered after final, the amendment must comply with the "strict standards" of Rule 116. *Id*.

Rule 116 requires the amendment to be accompanied by an evidentiary showing of facts establishing "good and sufficient reasons why the amendment was not earlier presented." *See* 37 C.F.R. § 1.116(b).

In the instant case, the patent owner's late-raised amendment fails to provide the required evidentiary showing. To the contrary, the amendment ignores this requirement entirely. The patent owner failed to comply with the "strict standards" of Rule 116. Because the patent owner has not even attempted to

comply with Rule 116, the Office lacks legal authority to enter the after-final amendment.

Further, the patent owner appears to withhold the required evidence because that evidence would show that the amendment is not permissible. Rule 116 prohibits entering an amendment which could have been presented earlier. *See* 37 C.F.R. § 1.116(b). In the immediate case, the Office's 26 April 2006 Office Action invited the patent owner to file a Rule 530 response not later than June, 2006.

The patent owner could have filed its amendment at that time. The patent owner, however, refused to do so. To the contrary, the patent owner refused to respond to the Office Action *at all*. The patent owner could have filed its amendment on time, but simply refused to do so. The patent owner cannot belatedly raise it now. *See* 37 C.F.R. § 1.116(b).

NEW CLAIM 2 IS NOT SUPPORTED BY THE ORIGINAL DISCLOSURE

Where the originally filed disclosure does not provide support for each claim limitation, the claim must be rejected under 35 U.S.C. § 112, first paragraph as lacking adequate written description. *See e.g., In re Wright*, 866 F.2d 422 (Fed. Cir., 1989).

The sole pending claim is newly-added claim 2. Claim 2 recites the new claim limitations "the sole active component administered" and "in a human."

Adding these new limitations is prohibited because they are not taught in the original disclosure. *See* 35 U.S.C. § 112, first paragraph.

Applicant alleges that the new limitations are supported in the Specification at 1:5-16; 2:9-11; and 2:27-29. None of these sections, however, even mentions "human" use, and the cited sections indeed say that the invention *does not* use felbamate as the sole active component.

For example, the Specification says, "The present invention relates to pharmaceutical compositions containing 2-phenyl-1,3-propanediol dicarbamate as ***an*** active component." *See* Specification at 1:5-7 (emphasis mine). Similarly, the Specification says, "the present invention further relates to … therapeutic compositions which contain as ***an*** active ingredient 2-phenyl-1,3-propanediol dicarbamate." *Id*. at 1:10-16. The Specification thus says that Sofia's alleged invention relates to add-on compositions wherein felbamate is ***an*** active ingredient – *i.e.*, one among several – rather than ***the only*** ingredient.

The patent owner may argue that proposed new claim 2 simply adds new limitations to a previously-presented claim. This statement, however, while true, fails to make the amendment allowable, because adding a narrowing limitation which is not supported by the original disclosure violates the written description requirement. *See e.g., In re Ruschig*, 379 F.2d 990, 995 (C.C.P.A., 1967) (while the new claim limitation is a simple change from the original

disclosure, the new limitation was not disclosed and thus cannot be used); *Ex parte Ohshiro*, 14 U.S.P.Q.2d 1750 (B.P.A.I., 1989); *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996).

Claim 2 is thus barred under both 35 U.S.C. 112, first paragraph and under 37 C.F.R. § 1.530(j) (no amendment may introduce new matter into the claims).

THE PATENT OWNER PROVIDES NO EVIDENCE THAT THE CLAIMED INVENTION IS "MATERIALLY CHANGED" FROM THE PRIOR ART

The patent owner concedes that WILENSKY teaches administering felbamate together with another known anti-epileptic medicine(s). The patent owner has therefore amended claim 2 to limit it to a one-ingredient drug product. The patent owner explains that claim 2 "now recites the transitional term 'consisting of' (in place of 'comprising') as well as that '2-phenyl-1,3-propanediol dicarbamate is the sole active component administered." *See* Amendment (22 Jan. 2007) at 4. The patent owner explains that this amendment is intended to exclude the multiple-ingredient methods taught by WILENSKY.

Where an applicant contends that the additional materials taught by the prior art are excluded by the transitional phrase "consisting of," the applicant bears the burden of introducing into the record factual evidence showing that the introduction of those additional materials would materially change the

characteristics of the claimed invention. *See In re De Lajarte*, 337 F.2d 870 (C.C.P.A., 1964); *see also* Manual Pat. Exam. Proc. § 2111.03 (2006).

In the instant case, the Examiner correctly notes that the patent owner has failed to provide this evidence. *See* Final Office Action at 5-6 (21 Nov. 2006). Claim 2 must therefore be rejected because the patent owner has not bothered to provide the Examiner with the required factual evidence.

Further, the patent owner has apparently withheld this factual evidence because this evidence shows that prior-art anti-epileptics *do not* materially affect the basic and novel anti-epileptic characteristics of felbamate. *See* Walter E. KOZACHUK, Declaration (February, 2007). This evidence thus *contradicts* the patent owner.

THE PRIOR ART TEACHES THE INVENTION OF NEW CLAIM 2

The patent owner concedes that WILENSKY teaches administering felbamate together with other known anti-epileptic medicines. The patent owner attempts to avoid WILENSKY by limiting claim 2 in two ways: by limiting it to a felbamate-only method, and by limiting claim 2 to specific dosage amounts. These amendments, however, fail to save claim 2 because claim 2 nonetheless still reads on the prior art.

The Prior Art Teaches Felbamate-Only Methods

WILENSKY Teaches Felbamate-Only Methods

WILENSKY teaches that felbamate was, in 1985, already known in the art to be effective to treat epilepsy when used alone. WILENSKY says felbamate "has broad-spectrum anti-epileptic activity." *See* Abstract. WILENSKY also says that the felbamate "chemical structure is similar to that of the antianxiety agent meprobamate. However, in contrast to meprobamate, [felbamate] exhibits broad-spectrum anti-epileptic activity in pre-clinical animal models." *Id*. at 602, col. 1, *citing* E.A. Swinyard *et al., The Profile of Anticonvulsant Activity And Acute Toxicity* …, (1982) (Nat. Inst. Of Health, publ.) WILENSKY thus teaches that at the time of his study, it was already widely-known to use felbamate alone.[1]

WILENSKY thus does not investigate the already-known safety and utility of felbamate monotherapy. Rather, WILENSKY thus investigates whether felbamate would be safe and effective as an add-on medication. *Id*. at 602, col. 1 (noting that an objective of the study is "to determine the effect of [felbamate] on seizure frequency when given as an add-on medication.").

[1] Felbamate mono-therapy is also taught by SWINYARD (1986) at page 27, col. 1.; BERGER (1959) at col. 1; BERGER (1953) at col. 2.

While WILENSKY investigates add-on use, his investigation does not negate the already-known utility as mono-therapy. To the contrary, WILENSKY found that add-on therapy requires monitoring for toxic drug interations.

WILENSKY found that administering felbamate together with phenytoin or carbamazepine caused toxic drug interactions. WILENSKY noted, "Most of the toxicity recorded during the study was associated with increased levels of [phenytoin] or [carbamazepine]. Subjects 1, 3, and 4 experienced [phenytoin] toxicity when their serum levels rose from baseline levels." *Id*. at 604, col. 2. WILENSKY concluded that phenytoin "levels rose dramatically in three of four subjects when W-544 was added; in two of these, the [phenytoin] dose had to be reduced because of intolerable toxicity. … The increases in [phenytoin] levels in subjects 1 and 3 cannot be explained by changes in compliance; rather, they appear to reflect a true drug interaction." *Id*. at 605, col.1.

Notably, WILENKSY found toxic drug interactions in three of the patients tested. The entire study, however, involved only eight patients. Thus, WILENSKY found toxic adverse drug interactions in ***38% of patients*** using add-on therapy. This is an extremely high frequency of toxicity.

Thus, while WILENSKY reiterates the known efficacy of felbamate monotherapy, WILENSKY teaches the danger of using felbamate as add-on therapy.

The Alleged Inventor Concealed
Information on Toxic Drug Interactions
From The Food & Drug Administration

WILENSKY's research is somewhat unusual in the rarified world of patent jurisprudence because his research had a quite tragic real-world aspect.

The patent owner undoubtedly knew of the WILENSKY study, because the patent owner *sponsored* it, and because the alleged patent inventor is a named *co-author*. When the patent owner asked the F.D.A. for permission to sell felbamate, however, it had a choice: the patent owner could have filed a more expensive application to sell felbamate as monotherapy, or a less expensive application to sell felbamate as an add-on therapy.

Despite WILENSKY teaching a 38% risk of toxic drug interaction, the patent owner pursued the less expensive application to sell felbamate as add-on therapy.

The results were predictable - and horrific. In 1993, the Food & Drug Administration granted the patent owner permission to sell felbamate as an add-on therapy. Within a year, felbamate add-on use was associated with over seventy reported cases of aplastic anemia or liver damage, including nearly twenty reported deaths. *See Monica Valentino v. Carter-Wallace, Inc.*, slip op. 95-15935 (9th Cir., Oct. 7, 1996).

The patent owner nonetheless continued to aggressively advertise felbamate for add-on use:

> Prior to and during the publication of the advertisements, Carter-Wallace learned that some patients taking Felbatol were developing illnesses. Pursuant to FDA regulation, drug manufacturers must relay to the FDA reports from doctors describing illnesses developed by patients using the manufacturer's product, regardless of whether there is a known or perceived causal connection between the drug and the illness. See 21 C.F.R. § 314.80 (1999). Among the most serious illnesses reported to Carter-Wallace was aplastic anemia, a frequently fatal form of acquired bone marrow failure. According to the complaint, from October 1993 until July 1994, Carter-Wallace received and was aware of at least fifty- seven adverse medical reports relating to Felbatol, including at least six deaths and six cases of aplastic anemia. In July 1994, Carter-Wallace received four additional reports of aplastic anemia, along with reports of other illnesses and deaths. On August 1, 1994, Carter-Wallace, in association with the FDA, sent a letter to doctors warning of an association between Felbatol and aplastic anemia. The letter recommended the immediate withdrawal of patients from treatment with Felbatol.

In re Carter-Wallace Inc. Securities Litigation, slip op. 99-9475 (2nd Cir., Aug. 7, 2000). The Food & Drug Administration became involved and, in August 1994, severely restricted the patent owner's ability to further market felbamate. A follow-up study investigating these patient deaths found that while monotherapy appeared safe, every patient death occurred when felbamate was combined with another antiepileptic drug. *See e.g.*, Walter E. Kozachuk, Declaration (Feb. 2007), *citing* D.W. KAUFMAN *et al., Evaluation of Case Reports of Aplastic Anemia Among Patients Treated With Felbamate*, 38 Epilepsia 1265 (1997) (WEK001055 *et seq*.).

Patient deaths are unfortunate. *Avoidable* patient deaths are tragic. Deaths caused by concealing known risks from the F.D.A. are ***inexcusable***.

In this case, the patent owner began to sell felbamate for add-on use in 1993. Several years earlier, however, WILENSKY had clearly showed that such add-on use entails a high likelihood of toxic drug interactions. The patent owner undoubtedly knew of the WILENSKY study, because the patent owner *sponsored* it (*see* WILENSKY at the Acknowledgements section), and because the patent owner's alleged inventor (Robert Duane SOFIA) is a named *co-author* of WILENSKY.

The alleged inventor knew of WILENSKY, yet concealed it from the Patent Office during prosecution of the patent in suit. Frighteningly, the patent owner gave this same executive responsibility for forewarning the Food & Drug Administration of potential toxic drug interactions. *See* Walter E. KOZACHUK, Declaration (February 2007). Had that executive candidly explained the WILENSKY study findings to the F.D.A., a number of patient deaths could have been easily avoided.

SWINYARD and WILENSKY Teach Felbamate Monotherapy

The Examiner correctly asserts that WILENSKY combined with SWINYARD suggest the use of felbamate alone.

In response, the patent owner's attorney alleges that WILENSKY teaches away from using felbamate alone. One of skill in the art, however, would

read WILENSKY and SWINYARD to each suggest monotherapy. *See* Walter E. KOZACHUK, Declaration (Feb., 2007).

The Claimed Dosage Range Reads on The Prior Art Dosage Ranges

WILENSKY teaches a daily dosage of 200 to 1,600 milligrams. *See* WILENSKY at, *e.g.*, Abstract. WILENSKY does not teach an actual reduction to practice of dosages above 1,600 milligrams. WILENSKY does, however, teach that one of skill in the art would know to "titrate," or gradually adjust, the daily dosage of anti-seizure medication to suit the individual patient. WILENSKY teaches that his group in fact actually did titrate daily dosages to increase them. *See id*. at 602, col. 2 ("On day 9, upward titration of the W-544 dose began.").

In predicting the effect of increased dosage on serum concentration of drug, WILENSKY notes that "the dose-level relationship was linear, with doses of 400 – 1,600 mg/day producing [serum] levels of ~5-20 mg/L." *Id*. at 604, col. 1. Given the linear relationship and the lack of toxicity, WILENSKY thus concludes, "the maximum tolerated dose is greater than 1,600 mg/day." *Id*. at 605, col. 2.

Thus, while WILENSKY fails to teach an actual reduction to practice of dosages greater than 1,600 mg, WILENSKY expressly suggests that such greater dosages will be safe, and will produce a predictable, linear rise in plasma levels of drug. WILENSKY thus renders obvious dosages grater than 1,600 milligrams.

Claim 2 claims "a daily dosage of from about 100 milligrams to about 5 grams." The claimed dosage range overlaps the prior art dosage range. The claimed dosage range is therefore obvious in light of WILENSKY. *See e.g., In re Wertheim*, 541 F.2d 257 (C.C.P.A., 1976); *In re Woodruff*, 919 F.2d 1575 (Fed. Cir., 1990); *In re Geisler*, 116 F.3d 1465 (Fed. Cir., 1997).

The patent owner's attorney alleges that WILENSKY does not teach "the proper therapeutic dose" for felbamate monotherapy. See Amendment (22 Jan. 2007) at 6. This argument, however, is a red herring. The issue is not whether WILENSKY teaches "proper" dosages; rather, the issue is whether WILENSKY teaches the *claimed* dosages. Here, the patent owner does not dispute that WILENSKY teaches the claimed dosage.

THE EXAMINER SHOULD ISSUE AN ADVISORY ACTION REFUSING ENTRY OF THE AFTER-FINAL AMENDMENT

The after-final amendment should be refused entry because it is prohibited by Rule 116(b) and because it fails to place the claim in condition for allowance. The Examiner should therefore issue an Advisory Action advising that the amendment will not be entered, and reminding the patent owner of the non-extendible deadline for filing for an appeal. *See* Manual Pat. Exam. Proc. § 2272 (2006) ("The period for response may not, however, be extended to run past 6 months from the date of the final rejection.").

Respectfully submitted on behalf of the Third-Party Requestor by its attorneys,

PHARMACEUTICAL PATENT ATTORNEYS, LLC

/mark pohl/
J. Mark POHL, Reg. No. 35,325
22 February 2007

55 Madison Avenue, 4th floor
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Affidavit Of Service

I hereby certify that on Thursday, February 22, 2007 I served the patent lawyer of record by postage prepaid First Class Mail with Delivery Confirmation:

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In the United States Patent Office

In re Application of Robert Duane SOFIA,	Serial No. 90/007,991 Serial No. 90/007,992 Art Unit: Central Reexam Examiner Bennett CELSA, Esq.
	DECLARATION

1) I am a medical doctor. I am a specialist in neurology. I have several decades of experience in researching felbamate and in treating epileptic patients with felbamate and with other anti-convulsive medicines. I therefore respectfully believe that I am one of skill in the art.

2) I have read and understand the captioned patents, A.J. WILENSKY *et al., Pharmacokinetics of W-544 (ADD 03055) In Epileptic Patients*, Epilepsia v. 26, pp. 602-606 (1985) and Ewart A. SWINYARD *et al., Compariative Anticonvulsant Activity and Neurotoxicity of Felbamate*…, Epilepsia v. 27, pp. 27-34 (1986), and the Frank BERGER '444 patent.

A.J. WILENSKY *et al., Pharmacokinetics of W-544 (ADD 03055) In Epileptic Patients*, Epilepsia v. 26, pp. 602-606 (1985)

WILENSKY Teaches That Felbamate Monotherapy is Effective

3) One of skill in the art would read WILENSKY to teach that felbamate monotherapy is effective to treat epileptic seizures.

4) WILENSKY teaches that felbamate was, in 1985, already known in the art to be effective to treat epilepsy when used alone. WILENSKY says felbamate "has broad-spectrum anti-epileptic activity." *See* Abstract. WILENSKY also says that the felbamate "chemical structure is similar to that of the antianxiety agent meprobamate. However, in contrast to meprobamate, [felbamate] exhibits broad-spectrum anti-epileptic activity in pre-clinical animal models." *Id*. at 602, col. 1, *citing* E.A. Swinyard *et al., The Profile of Anticonvulsant Activity And Acute Toxicity* …, (1982) (Nat. Inst. Of Health, publ.) WILENSKY thus teaches that at the time of his study, it was already widely-known to use felbamate alone.[1]

5) WILENSKY teaches that felbamate is effective. WILENSKY nowhere suggests that felbamate is effective *only* if administered with phenytoin or carbamazepine. Thus, one of skill in the art would read WILENSKY to teach that felbamate is effective, regardless of whether it is used alone, or

[1] Felbamate mono-therapy is also taught by SWINYARD (1986) at page 27, col. 1.; BERGER (1959) at col. 1; BERGER (1953) at col. 2.

together with phenytoin, or with carbamazepine, or with some other anti-seizure medication.

6) WILENSKY notes that "the results with respect to efficacy are promising, and further controlled studies are indicated." One of skill in the art would not read this to discourage use of felbamate monotherapy. To the contrary, one of skill in the art would read this to encourage it, by suggesting that felbamate is efficacious.

7) WILENSKY notes that his results are not definitive. One of skill in the art, however, does not need "definitive" results to appreciate WILENSKY's teaching of monotherapy as useful.

8) WILENSKY teaches dosages of 200 to 1,600 milligrams of felbamate per day. Based on my clinical experience prescribing felbamate, these dosages would indeed be correct felbamate monotherapy dosages for certain patients.

WILENSKY Teaches That Adjunct Therapy
May Create Drug Interaction Toxicity

9) Felbamate shares the same novel anti-epileptic properties as phenytoin and carbamazepine. Neither phenytoin nor carbamazepine materially affect the basic and novel anti-epileptic characteristics of felbamate. One may administer felbamate alone (as monotherapy) or together with one or more other anti-epileptic medicines (adjunct therapy or "add-on therapy").

Combining felbamate with phenytoin or carbamazepine does not materially affect the basic and novel anti-epileptic characteristics of felbamate.

10) WILENSKY confirms this. WILENSKY teaches results obtained by administering felbamate together with phenytoin or carbamazepine, two anti-convulsant drugs in use at the time. One of skill in the art would therefore read WILENSKY to teach that joint administration of felbamate with phenytoin or carbamazepine results in the retention of the anti-seizure activity of both felbamate and the other administered drug.

11) WILENSKY investigates whether felbamate would be safe and effective as an add-on medication. *Id*. at 602, col. 1 (noting that an objective of the study is "to determine the effect of [felbamate] on seizure frequency when given as an add-on medication.").

12) While WILENSKY investigates add-on use, his investigation does not discourage use of felbamate's already-known utility as monotherapy.

13) To the contrary, WILENSKY found that add-on therapy entailed potentially dangerous drug interactions. WILENSKY found that administering felbamate together with phenytoin or carbamazepine caused toxic and potentially-dangerous drug interactions. WILENSKY noted, "Most of the toxicity recorded during the study was associated with increased levels of [phenytoin] or [carbamazepine]. Subjects 1, 3, and 4

experienced [phenytoin] toxicity when their serum levels rose from baseline levels." *Id*. at 604, col. 2. WILENSKY concluded that phenytoin "levels rose dramatically in three of four subjects when W-544 was added; in two of these, the [phenytoin] dose had to be reduced because of intolerable toxicity. … The increases in [phenytoin] levels in subjects 1 and 3 cannot be explained by changes in compliance; rather, they appear to reflect a true drug interaction." *Id*. at 605, col.1. Notably, WILENKSY found toxic drug interactions in three of the patients tested. The entire study, however, involved only eight patients. Thus, WILENSKY found toxic adverse drug interactions in ***38% of patients*** using add-on therapy.

14) Thus, while WILENSKY reiterates the known efficacy of felbamate monotherapy, WILENSKY cautions that when combining felbamate with other antiepileptic medicines, it may be necessary to titrate down the level of the non-felbamate drug to avoid the risk of adverse drug interactions. Read as a whole, one of skill in the art would read WILENSKY to confirm the efficacy of felbamate monotherapy.

15) On information and belief: Robert Duane SOFIA worked at Wallace Laboratories. Mr. SOFIA was the Director of Toxicology responsible for reviewing clinical research on felbamate before Wallace Laboratories began to commercially sell felbamate. As such, Mr. SOFIA was responsible for

investigating possible adverse drug interactions, and for reporting any such interactions to the United States Food & Drug Administration.

D.W. KAUFMAN *et al., Evaluation of Case Reports of Aplastic Anemia Among Patients Treated With Felbamate*, 38 Epilepsia 1265 (1997) (WEK001055 *et seq*.)

16) WILENSKY teaches that felbamate combined with another antiepileptic drug may create a toxic drug interaction. This finding was confirmed by later research. For example, I attach here a copy of D.W. KAUFMAN *et al., Evaluation of Case Reports of Aplastic Anemia Among Patients Treated With Felbamate*, 38 Epilepsia 1265 (1997). KAUFMAN at Table 3 lists the universe of incidences of aplastic anemia studied. Table 3 shows that there was no information on whether or not patient #15 was taking other epilepsy medications. Each and every other adverse drug event, however, was shown to be associated with the combination of felbamate and at least one other epilepsy drug.

Ewart A. SWINYARD *et al., Compariative Anticonvulsant Activity and Neurotoxicity of Felbamate*…, Epilepsia v. 27, pp. 27-34 (1986)

17) SWINYARD actually used felbamate monotherapy. He found that it works quite well. *See e.g.,* page 32, col. 2 (monotherapy with "felbamate increases seizure threshold and prevents seizure spread."). One of skill in

the art would thus read SWINYARD to teach that felbamate monotherapy is effective.

18) One of skill in the art would read the animal results in SWINYARD to predict efficacy in humans. This is, after all, why SWINYARD had done his studies; he was not searching for a drug to treat sick laboratory rats, but sick human beings.

19) The patent owner's attorney alleges that SWINYARD teaches away from the claimed invention because SWINYARD says, "Felbamate exhibits a somewhat more restricted range than either phenobarbitol or valproate" and "Felbamate is a less potent anticonvulsant agent than either phenytoin or phenobarbitol" and "Felbamate is ineffective against Bic-induced seizures" and that Felbamate has an inferior absorption ratio (as measured by the s.c. PTZ test) compared to certain prototype anticonvulsants.

20) One of skill in the art would not, however, read these phrases in isolation, nor read these phrases to discourage the use of felbamate (as monotherapy or adjunct herapy). To the contrary, one of skill would read these phrases in the context of the broad teachings of SWINYARD to indicate that felbamate is "a relatively non-toxic antiepileptic" with a "unique spectrum of antiepileptic activity." which, as with all drugs, differs from other drugs in toxicity, potency, absorption, and the like. Such

differences do not *discourage* the use of felbamate (alone nor as adjunct therapy); rather, these differences simply inform more fully the appropriate clinical circumstances for felbamate use.

21) One of skill in the art would read the animal results in BERGER to predict efficacy in humans. This is, after all, why BERGER had done his studies; he was not searching for a drug to treat sick laboratory rats, but sick human beings. Similarly, BERGER uses electroshock induced seizures; one of skill in the art would infer that epileptic seizures in humans would likely react similarly to felbamate treatment. This is indeed why from BERGER used electroshock seizures in laboratory mice in the first place; BERGER was investigating a treatment for human epilepsy, not electroshock-induced seizures in mice; if electroshock seizures in mice were not predictive of epileptic seizures in humans, then BERGER would not have used that model.

The Patents In Suit

22) The patents in suit do not reasonably communicate to one of skill in the art that the invention at issue involves monotherapy.

23) The particular form of oral dosage, whether tablet or gelatin capsule or liquid, does not appear to materially affect the basic and novel anti-epileptic characteristics of felbamate. To the contrary, commercially-

available Felbatol® felbamate is available in both liquid and solid dosage forms, and both provide antiepileptic activity.

24) I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United State Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon or any patent to which this verified statement is directed.

_____

Walter E. KOZACHUK, M.D.
Kensington, Maryland
Dated as of 20 February 2007

UNITED STATES COURT OF APPEALS

August Term, 1997

(Argued: October 20, 1997 Decided:July 13, 1998)

Docket No. 97-7345

In re CARTER-WALLACE, INC. SECURITIES LITIGATION.

JOAN T. BRUNJES, on behalf of herself and all others similarly situated,
***Plaintiff-Appellant*,**

EUGENE HONEYMAN, individually and on behalf of all others similarly situated,
***Consolidated Plaintiff-Appellant*,**

v.

HENRY H. HOYT, JR., DANIEL J. BLACK, PAUL A. VETERI and CARTER-WALLACE, INC.,
***Defendants-Appellees*,**

JOSEPH S. HARUN,
***Consolidated-Defendant-Appellee*.**

B e f o r e: WINTER, Chief Judge, MESKILL, Circuit Judge,

and MARTIN, District Judge.*

Appeal from the United States District Court for the Southern District of New York (Kevin T. Duffy, Judge), which dismissed this securities-fraud action pursuant to Rule 12(b)(6). The court held that, as a matter of law, technical and detailed advertisements for drugs in sophisticated medical journals are not made "in connection with" a securities transaction as required by Section 10(b) of the Exchange Act. It also held that other statements and omissions alleged in appellants' complaint were not materially misleading. We hold that advertisements in sophisticated medical journals may be "in connection with" a securities transaction and reverse on this narrow ground. Otherwise, we affirm.

ROBERT P. SUGARMAN, Milberg, Weiss, Bershad, Hynes & Lerach, LLP, New York, New York (Ralph M. Stone, Milberg, Weiss, Bershad, Hynes & Lerach, LLP, New York, New York, Richard J. Kilsheimer, Frederic S. Fox and Joel B. Strauss, Kaplan, Kilsheimer &

Fox, LLP, New York, New York, Jules Brody, Stull, Stull & Brody, New York, New York, Joseph H. Weiss, Weiss & Yourman, New York, New York, of counsel), for Plaintiffs-Appellants.

ERIC M. NELSON, Whitman, Breed, Abbott & Morgan, New York, New York, for Defendants-Appellees.

WINTER, Chief Judge:

Joan T. Brunjes and Eugene Honeyman appeal from Judge Duffy's dismissal pursuant to Fed. R. Civ. P. 12(b)(6) of their securities-fraud action. Their complaint alleged that Carter-Wallace, Inc. violated Section 10(b) of the Securities Exchange Act of 1934, 15 U.S.C. § 78j(b), and Rule 10b-5, 17 C.F.R. § 240.10b-5 (1971), by: (i) making materially false statements in the advertisements it ran in two medical journals, Neurology and Archives of Neurology, (ii) failing to disclose information that would correct misleading representations in its financial statements, and (iii) violating Generally Accepted Accounting Principles ("GAAP"). The district court held that, as a matter of law, Carter-Wallace's advertisements in medical journals were not made "in connection with" a securities transaction and that the other omissions and statements identified in the complaint were not materially misleading. We do not agree that detailed drug advertisements in sophisticated medical journals can, as a matter of law, never be statements made "in connection with" a securities transaction. We affirm the dismissal of appellants' other claims.

BACKGROUND

We of course accept the allegations of the complaint as true. See Jaghory v. New York State Dept. of Educ., 131 F.3d 326, 329 (2d Cir. 1997). In July 1993, Felbatol, a new anti-epileptic drug produced by Carter-Wallace was approved by the Food and Drug Administration ("FDA") for sale as prescription medication. In August 1993, Carter-Wallace commenced selling Felbatol, hailing it as the first major anti-epileptic drug to be introduced in the United States in over fifteen years.

To promote Felbatol, Carter-Wallace ran a sixteen-page advertisement in the January 1994 issue of Neurology. The advertisement recited Felbatol's safety record and stated that "no life-threatening liver toxicities or blood dyscrasias have been attributed to Felbatol monotherapy." An identical advertisement appeared in the January 1994 issue of Archives of Neurology. Five-page advertisements containing the same statement appeared in the February, March, April, May, June, and July 1994 issues of Neurology and Archives of Neurology.

During this period, Carter-Wallace issued other statements that are the subject of appellants' complaint. Specifically, in June 1994, Carter-Wallace filed with the Securities Exchange Commission a Form 10-K in which it stated, pursuant to Section 13(a) of the Securities Exchange Act of 1934, 15 U.S.C. § 78m(a), that its sales were higher as a result of "greater than planned introductory sales of Felbatol." In its annual "Report to Shareholders," included in the Form 10-K, Carter-Wallace also represented that "Felbatol sales have exceeded expectations," that "[t]his rate of growth is expected to continue," and that the company expected "to receive royalties, which could be significant" from licensing Felbatol.

The present action concerns information received by Carter-Wallace in 1994 indicating that Felbatol caused,

in some patients, a fatal form of acquired bone-marrow failure known as aplastic anemia. Carter-Wallace received the first report of a Felbatol-related aplastic-anemia death in January 1994. A report of another such death was received in March and reports of two deaths were received in each of April and May. On August 1, 1994, after four additional deaths were reported in July -- amounting to a total of ten deaths -- Carter-Wallace and the FDA issued a "Dear Doctors" letter, recommending that most patients be withdrawn from Felbatol treatment.

Appellants purchased shares of Carter-Wallace stock in June and July 1994. They allege that Carter-Wallace's advertisements in the medical journals were false and that its statements regarding Felbatol in the Form 10-K were misleading in the absence of disclosure of the reports of death due to aplastic anemia. They further allege that the advertisements and the Form 10-K misled the market and distorted the price of Carter-Wallace stock, thereby violating Section 10(b). In addition, appellants contend that Carter-Wallace violated GAAP, and, in turn, Section 10(b) by overstating the value of its Felbatol inventory when it knew the drug would not be commercially viable.

The district court dismissed the complaint under Rule 12(b)(6). With respect to appellants' claims based on the advertisements in the medical journals, the district court found that the advertisements in stating that no reports of life-threatening effects had been received were false. See In re Carter-Wallace Sec. Litig., No. 94 Civ. 5704 (S.D.N.Y. Feb. 11, 1997). Nevertheless, it held that the advertisements were not actionable under Section 10(b) because, as a matter of law, drug advertisements in medical journals "[a]re not made in connection with the purchase or sale of securities, but [a]re directed at a technical audience intimately familiar with the potential adverse side effects of new drugs." Id. With regard to appellants' other claims, the district court held that Carter-Wallace's representations in its Form 10-K and "Report to Shareholders" did not place the company under a duty to disclose prior to August 1, 1994, the Felbatol-associated deaths, because the company "justifiably went about accumulating more evidence regarding the possible adverse side effects in order to dissect the merits of the incoming reports." Id.

DISCUSSION

We review de novo a district court's dismissal of a complaint pursuant to Rule 12(b)(6). See Harsco Corp. v. Segui, 91 F.3d 337, 341 (2d Cir. 1996). To state a claim under Section 10(b), "a plaintiff must plead that 'in connection with the purchase or sale of securities, the defendant, acting with scienter, made a false material representation or omitted to disclose material information and that plaintiff's reliance on defendant's action caused [plaintiff] injury.'" In re Time Warner Inc. Sec. Litig., 9 F.3d 259, 264 (2d Cir. 1993) (quoting Bloor v. Carro, Spanbock, Londin, Rodman & Fass, 754 F.2d 57, 61 (2d Cir. 1985)). We turn now to the disputed issues concerning the advertisement in the medical journals and the statements in Carter-Wallace's Form 10-K.

A. The Advertisements in Medical Journals

The crux of this issue involves whether Carter-Wallace's Felbatol advertisements may constitute statements made "in connection with" a securities transaction, as required by Section 10(b). Appellants' precise allegation is that Carter-Wallace's false advertisements in Neurology and Archives of Neurology "had an impact on the market price of Carter-Wallace common stock."

We have broadly construed the phrase "in connection with," holding that Congress, in using the phrase "intended only that the device employed, whatever it might be, be of a sort that would cause reasonable

investors to rely thereon, and, in connection therewith, so relying, cause them to purchase or sell a corporation's securities," SEC v. Texas Gulf Sulphur Co., 401 F.2d 833, 860 (2d Cir. 1968) (en banc) ("TGS"); see also In re Ames Dep't Stores Inc. Stock Litig., 991 F.2d 953, 965 (2d Cir. 1993). Moreover, when, as here, a claim is based on the fraud-on-the-market theory, a "straightforward cause and effect" test is applied, In re Ames, 991 F.2d at 967, under which it is sufficient that "statements which manipulate the market are connected to resultant stock trading." Id. at 966.

Under the "cause and effect" test, we cannot say that, as a matter of law, detailed drug advertisements using technical jargon and published in sophisticated medical journals can never constitute statements made "in connection with" a securities transaction. As the Supreme Court has noted, "market professionals generally consider most publicly announced material statements about companies, thereby affecting stock market prices." Basic Inc. v. Levinson, 485 U.S. 224, 247 n.24 (1988). Technical advertisements in sophisticated medical journals detailing the attributes of a new drug could be highly relevant to analysts evaluating the stock of the company marketing the drug. See In re Time Warner, 9 F.3d at 265 (discussing analysts' use of information).

That the market can absorb technical medical information is neither novel nor surprising. See Wielgos v. Commonwealth Edison Co., 892 F.2d 509, 514-15 (7th Cir. 1989) (finding generally that market absorbs complex scientific data). Technical information about the medical efficacy of new drugs, whether found in advertisements or elsewhere, has an obvious bearing on the financial future of a drug company. In an economy that produces highly sophisticated products, technical information is of enormous importance to financial analysts, whether such companies are producing drugs, as here, or nuclear power plants, as in Weiglos. The fact that such information is found in a specialized medical journal, as here, rather than in a statement addressed to participants in financial markets, as in TGS, seems to us irrelevant, so long as the journals are used by analysts studying the prospects of drug companies. In fact, an analyst might consider such an advertisement more informative than a non-technical but corresponding statement to financial market professionals.

We are aware that Ross v. A. H. Robins Company, [1978 Transfer Binder] Fed. Sec. L. Rep. (CCH) ¶ 96,388 (S.D.N.Y. April 6, 1978), held that false product advertisements in medical journals are not actionable under Section 10(b). However, Ross pre-dated Basic Incorporated supra, and considered only the nexus between advertisements and individual investments; it did not consider the fraud-on-the-market theory, which provides a broader framework in which to analyze the "in connection with" requirement. See In re Ames, 991 F.2d at 967.

We hold, therefore, that false advertisements in technical journals may be "in connection with" a securities transaction if the proof at trial establishes that the advertisements were used by market professionals in evaluating the stock of the company. We leave it to the district court on remand to decide whether the appellants' complaint with respect to the advertisements sufficiently alleges the other elements of a Section 10(b) claim.

B. Carter-Wallace's Financial Statements

Appellants also argue that the district court's dismissal of their remaining claims was improper. In particular, appellants maintain that Carter-Wallace had a duty to disclose before August 1, 1994 the Felbatol-related deaths having reported in its Form 10-K an increase in sales attributable to Felbatol, significant royalties from

licensing the drug, and the expectation of increased Felbatol sales in the future.

We disagree that Carter-Wallace had a duty under Section 10(b) to disclose the Felbatol-related deaths prior to August 1, 1994. The statements in Carter-Wallace's Form 10-K and its "Report to Shareholders" did not become materially misleading until Carter-Wallace had information that Felbatol had caused a statistically significant number of aplastic-anemia deaths and therefore had reason to believe that the commercial viability of Felbatol was threatened. Cf. San Leandro Emergency Med. Group Profit Sharing Plan v. Philip Morris Cos., 75 F.3d 801, 811 (2d Cir. 1996). Drug companies need not disclose isolated reports of illnesses suffered by users of their drugs until those reports provide statistically significant evidence that the ill effects may be caused by -- rather than randomly associated with -- use of the drugs and are sufficiently serious and frequent to affect future earnings. In the present case, four of the ten reported deaths occurred in July -- the disclosure was on August 1 -- and the earlier reports are not by themselves sufficient to support inferences of either actual knowledge or recklessness. See Chill v. General Elec. Co., 101 F.3d 263, 269 (2d Cir. 1996) (stating that reckless conduct is "conduct which is highly unreasonable and which represents an extreme departure from the standards of ordinary care"). We therefore affirm the district court's dismissal of the appellants' claims based on these statements.

Finally, appellants allege that Carter-Wallace's financial statements violated GAAP by overstating the value of Carter-Wallace's inventory. Specifically, appellants allege that Carter-Wallace should have discounted the value of its Felbatol inventory "given its obviously impaired value." However, one cannot state a claim for securities fraud merely by alleging a GAAP violation; the allegation must be accompanied by a statement of fraudulent intent. See Chill, 101 F.3d at 270. In this case, no such intent can be inferred because, for the reasons stated above, Carter-Wallace had no sound reason to doubt the commercial viability of Felbatol or the value of its inventory until the reports of Felbatol-associated deaths became statistically significant.

CONCLUSION

In conclusion, we reverse the holding that technical drug advertisements in sophisticated medical journals cannot, as a matter of law, be "in connection with" a securities transaction. Otherwise, we affirm.

FOOTNOTE

***** The Honorable John S. Martin, Jr., of the United States District Court for the Southern District of New York, sitting by designation.

U.S. 2nd Circuit Court of Appeals

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UNITED STATES COURT OF APPEALS
FOR THE SECOND CIRCUIT

August Term, 1999

(Argued June 6, 2000 Decided: August 07, 2000)

Docket No. 99-9475

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IN RE: CARTER-WALLACE, INC. SECURITIES LITIGATION

* * * * * * * * * * * *

EUGENE HONEYMAN, individually and on behalf of all others similarly situated,

Consolidated-Plaintiff-Appellant,

JOAN T. BRUNJES, on behalf of herself and all others similarly situated,

Plaintiff-Appellant,

v.

HENRY H. HOYT, JR.; DANIEL J. BLACK; PAUL A. VETERI; CARTER-WALLACE, INC.,

Defendants-Appellees,

JOSEPH S. HARUN,

Consolidated-Defendant-Appellee.

Before: MESKILL and WALKER, Circuit Judges, and HADEN, District Judge[*].

Appeal from a dismissal pursuant to Fed. R. Civ. P. 12(c) of plaintiffs- appellants' securities fraud class action.

The United States District Court for the Southern District of New York, Duffy, J., held that the complaint failed to allege scienter.

Affirmed.

RICHARD J. KILSHEIMER, New York City (Frederic S. Fox, Joel B. Strauss, Kaplan, Kilsheimer & Fox, New York City),

David J. Bershad, William C. Fredericks, Milberg Weiss Bershad Hynes & Lerach, New York City,

Co-Lead Counsel for Appellants.

Joseph H. Weiss, Weiss & Yourman, New York City,

Jules Brody, Stull, Stull & Brody, New York City,

for Appellants.

ERIC M. NELSON, New York City (Matthew D. Griffin, Whitman Breed Abbott & Morgan, New York City, of counsel),

for Appellees.

MESKILL, Circuit Judge:

Appellants Joan T. Brunjes and Eugene Honeyman, co-lead plaintiffs in this securities fraud class action, appeal the dismissal of their claim pursuant to Fed. R. Civ. P. 12(c). See In re Carter-Wallace, Inc. Sec. Litig., No. 94 Civ. 5704, 1999 WL 1029713, at *3-6 (S.D.N.Y. Nov. 10, 1999). The appellants alleged that defendants-appellees Carter-Wallace, Inc., and members of its Board of Directors (collectively "Carter-Wallace") violated Section 10(b) of the Securities Exchange Act of 1934, 15 U.S.C. § 78j(b), and Rule 10b-5, 17 C.F.R. § 240.10b-5, by running advertisements in medical journals stating that Carter-Wallace's new epilepsy drug, Felbatol, had an "unprecedented safety profile" and that "no life-threatening liver toxicities or blood dyscrasias have been attributed to Felbatol monotherapy," even though Carter-Wallace was aware of medical reports that some patients using Felbatol had developed severe or fatal illnesses. On remand from an earlier appeal, In re Carter-Wallace, Inc. Sec. Litig., 150 F.3d 153 (2d Cir. 1998) (Carter-Wallace I), the United States District Court for the Southern District of New York, Duffy, J., granted Carter- Wallace's motion to dismiss on the ground that the appellants failed to allege scienter. We agree and affirm the decision of the district court.

BACKGROUND

On a motion to dismiss, we accept the factual allegations contained in the complaint as true. See Jaghory v. New York State Dep't of Educ., 131 F.3d 326, 329 (2d Cir. 1997). In July 1993, Carter-Wallace's new epilepsy drug, Felbatol, was approved for sale by the Food and Drug Administration (FDA). At the time, Felbatol was considered a major advance in epilepsy treatment. It was thought to be unburdened by the risk of serious side effects, which plagued other epilepsy drugs. To promote Felbatol, Carter-Wallace ran advertisements in medical journals. A sixteen page advertisement appeared in the January 1994 issues of Neurology and Archives of Neurology. The advertisement stated that Felbatol had an "unprecedented safety

profile" and that "no life-threatening liver toxicities or blood dyscrasias have been attributed to Felbatol monotherapy." The same statements were made in shorter advertisements running monthly in the same journals through July 1994.

Prior to and during the publication of the advertisements, Carter-Wallace learned that some patients taking Felbatol were developing illnesses. Pursuant to FDA regulation, drug manufacturers must relay to the FDA reports from doctors describing illnesses developed by patients using the manufacturer's product, regardless of whether there is a known or perceived causal connection between the drug and the illness. See 21 C.F.R. § 314.80 (1999). Among the most serious illnesses reported to Carter-Wallace was aplastic anemia, a frequently fatal form of acquired bone marrow failure. According to the complaint, from October 1993 until July 1994, Carter-Wallace received and was aware of at least fifty- seven adverse medical reports relating to Felbatol, including at least six deaths and six cases of aplastic anemia. In July 1994, Carter-Wallace received four additional reports of aplastic anemia, along with reports of other illnesses and deaths. On August 1, 1994, Carter-Wallace, in association with the FDA, sent a letter to doctors warning of an association between Felbatol and aplastic anemia. The letter recommended the immediate withdrawal of patients from treatment with Felbatol. That day, following disclosure of the letter, Carter-Wallace's common stock fell $4.875 per share, almost 33 percent, from $15.625 to $10.75 on heavy trading.

Shortly after the plunge in Carter-Wallace's stock price, two class actions were filed with Joan T. Brunjes and Eugene Honeyman serving as lead plaintiffs of classes of investors who bought stock during a period beginning January 20, 1994 and ending July 31, 1994. The class actions were consolidated into the present suit. The second amended class action complaint alleged three claims: (1) that the advertisements in the medical journals were materially false and misleading, (2) that Carter-Wallace failed to disclose information (the adverse medical reports) that made representations in its financial statements misleading, and (3) that Carter-Wallace violated Generally Accepted Accounting Principles (GAAP) by overvaluing its inventory of Felbatol when it allegedly knew that Felbatol would not be commercially viable. Carter-Wallace moved for dismissal pursuant to Fed. R. Civ. P. 12(b)(6). The district court found that the advertisements in the medical journals were not made "in connection with" the purchase or sale of securities. The district court dismissed the other claims as well, reasoning that Carter-Wallace was under no duty to disclose the adverse reports or re- value its inventory because prior to August 1, 1994 there was no statistically significant link between Felbatol and any side effect. On appeal, we affirmed the district court's dismissal of the financial statements claim and the GAAP claim. With respect to the medical advertisement claim, however, we disagreed with the district court's determination that advertisements in medical journals could not, as a matter of law, be made "in connection with" a securities transaction. We remanded to the district court to determine, in the first instance, "whether the appellants' complaint with respect to the advertisements sufficiently alleges the other elements of a Section 10(b) claim." Carter- Wallace I, 150 F.3d at 157.

On remand, Carter-Wallace moved for judgment on the pleadings on the ground that the complaint had failed to allege scienter. The district court agreed and dismissed the claim.

DISCUSSION

A district court's grant of judgment on the pleadings is reviewed de novo. See Williams v. Apfel, 204 F.3d 48, 49 (2d Cir. 2000). The standards governing this case are not disputed by the parties.[1] "[A] plaintiff must plead that `in connection with the purchase or sale of securities, the defendant, acting with scienter, made a false material representation or omitted to disclose material information and that plaintiff's reliance on defendant's

action caused [plaintiff] injury.'" In re Time Warner Inc. Sec. Litig., 9 F.3d 259, 264 (2d Cir. 1993) (quoting Bloor v. Carro, Spanbock, Londin, Rodman & Fass, 754 F.2d 57, 61 (2d Cir. 1985)) (second alteration in original). "The scienter needed in connection with securities fraud is intent `to deceive, manipulate, or defraud,' or knowing misconduct." Press v. Chemical Inv. Servs. Corp., 166 F.3d 529, 538 (2d Cir. 1999) (quoting SEC v. First Jersey Sec., 101 F.3d 1450, 1467 (2d Cir. 1996)). For purposes of its motion, Carter-Wallace has conceded all of the elements of the appellants' claim except scienter. Thus, the sole issue on appeal is whether the complaint sufficiently alleges scienter. For the reasons that follow, we conclude that it does not.

Fed. R. Civ. P. 9(b) requires that allegations of fraud be pled with specificity. Although Rule 9(b) raises the pleading standard in fraud cases, it provides that "[m]alice, intent, knowledge, and other condition of mind of a person may be averred generally." However, "the relaxation of Rule 9(b)'s specificity requirement for scienter must not be mistaken for license to base claims of fraud on speculation and conclusory allegations." Shields v. Citytrust Bancorp, 25 F.3d 1124, 1128 (2d Cir. 1994) (internal quotation marks omitted). In order to plead scienter, we require the complaint "to allege facts that give rise to a strong inference of fraudulent intent." Id.; see also Mills v. Polar Molecular Corp., 12 F.3d 1170, 1176 (2d Cir. 1993). A "strong inference of fraudulent intent" may be established either "(a) by alleging facts to show that defendants had both motive and opportunity to commit fraud, or (b) by alleging facts that constitute strong circumstantial evidence of conscious misbehavior or recklessness." Shields, 25 F.3d at 1128 (citing In re Time Warner, 9 F.3d at 268-69).

The appellants argued both the "conscious misbehavior" and "motive and opportunity" theories before the district court. On appeal, they have abandoned the "motive and opportunity" theory. To survive dismissal under the "conscious misbehavior" theory, the appellants must show that they alleged reckless conduct by the appellees, which is "at the least, conduct which is highly unreasonable and which represents an extreme departure from the standards of ordinary care to the extent that the danger was either known to the defendant or so obvious that the defendant must have been aware of it." Rolf v. Blyth, Eastman Dillon & Co., 570 F.2d 38, 47 (2d Cir. 1978) (internal quotation marks and alterations omitted). "An egregious refusal to see the obvious, or to investigate the doubtful, may in some cases give rise to an inference of recklessness." Chill v. General Elec. Co., 101 F.3d 263, 269 (2d Cir. 1996) (internal quotation marks and alterations omitted). It is sufficient for appellants to allege "defendants' knowledge of facts or access to information contradicting their public statements." Novak v. Kasaks, 2000 WL 796300, at *7 (2d Cir. 2000).

Appellants' theory of "conscious misbehavior" is based solely on the allegation that Carter-Wallace touted Felbatol's safety while it was receiving adverse medical reports. They argue that Carter-Wallace was recklessly, if not intentionally, perpetrating fraud by allowing the advertisements to continue when it was aware of reports that undermined the accuracy of the advertisements. Fatal to their argument, however, is our determination in Carter-Wallace I that the medical reports did not demonstrate a statistically significant link between Felbatol and any illness until August 1, 1994, when Carter-Wallace recommended the withdrawal of patients from Felbatol treatment.

In holding that Carter-Wallace had no duty to disclose the Felbatol-related deaths prior to August 1, 1994, we reasoned that the financial statements

> did not become materially misleading until Carter-Wallace had information that Felbatol had caused a statistically significant number of aplastic-anemia deaths and therefore had reason to believe that the commercial viability of Felbatol was threatened. Drug companies need not disclose isolated reports of illnesses suffered by users of their drugs

> until those reports provide statistically significant evidence that the ill effects may be caused by -- rather than randomly associated with -- use of the drugs and are sufficiently serious and frequent to affect future earnings. In the present case, . . . the [pre-July 1994] reports are not by themselves sufficient to support inferences of either actual knowledge or recklessness.

Carter-Wallace I, 150 F.3d at 157 (citations omitted) (emphasis added). Our determination that the reports of aplastic anemia were not statistically significant prior to August 1, 1994 is the law of this case and we will adhere to it, "absent cogent or compelling reasons." Doe v. New York City Dep't of Soc. Servs., 709 F.2d 782, 789 (2d Cir. 1983) (internal quotation marks omitted); see also United States v. Adegbite, 877 F.2d 174, 178 (2d Cir. 1989) ("[W]e will generally adhere to our own earlier decision on a given issue in the same litigation."). As discussed below, we do not find any compelling reason for deviating from our prior conclusion.

The appellants argue that their complaint alleges that the causal connection between Felbatol and aplastic anemia was made before August 1, 1994. However, "conclusory allegations" do not satisfy the pleading requirements of Rule 9(b). See Acito v. Imcera Group, 47 F.3d 47, 53 (2d Cir. 1995). The appellants must provide "at least a minimal factual basis" for their allegations of scienter. Chill, 101 F.3d at 267 (internal quotation marks omitted). The complaint describes the adverse reports received by Carter-Wallace and concludes that the "adverse effects from Felbatol were extremely serious and the number of incidents was . . . statistically unacceptable." This allegation is based, like much of the appellants' arguments, on the sheer number of adverse reports -- 57 before July 1994.

We do not believe that the existence or the number of such reports is problematic. FDA regulations require that all "adverse drug experience information" be reported to the FDA. 21 C.F.R. § 314.80(c) (1999). Drug manufacturers receive these reports from several sources, including treating physicians. An "adverse drug experience" is defined broadly to include "[a]ny adverse event associated with the use of a drug in humans, whether or not considered drug related." 21 C.F.R. § 314.80(a) (1999) (emphasis added); see also 21 C.F.R. § 314.80(k) (1999) ("A report or information submitted by an applicant under this section . . . does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse effect."). Carter-Wallace received reports when patients on Felbatol became ill, regardless of whether or not the illness had anything to do with Felbatol. Contrary to the appellants' assertions throughout their complaint, the receipt of an adverse report does not in and of itself show a causal relationship between Felbatol and the illness mentioned in the report. On this record, the only illness eventually attributed to Felbatol was aplastic anemia. The other illnesses, although serious and even fatal in some instances, were never linked to Felbatol. Therefore, it was not reckless for Carter-Wallace to believe that these reports were random and statistically insignificant before August 1, 1994. The eventual linking of aplastic anemia to Felbatol cannot relate back to the time of the statements in the medical journals and reflect on Carter-Wallace's reasonable belief that the reports were random. Felbatol was a popular drug. Some adverse events may be expected to occur randomly, especially with a drug designed to treat people that are already ill. Carter-Wallace's actual awareness of adverse reports while touting Felbatol's safety does not, on its own, constitute "strong circumstantial evidence of conscious misbehavior or recklessness." The advertisements never guaranteed a total absence of unrelated illnesses. The appellants' pleading arguments, based on the same complaint we reviewed in Carter-Wallace I, are unpersuasive in altering our earlier opinion that the link between aplastic anemia and Felbatol was not made before August 1, 1994.

The appellants argue that our reversal of the dismissal of the medical advertisement claim in Carter-Wallace I supports their position. However, the portion of Carter-Wallace I dealing with the medical advertisements was limited to the proposition that, as a matter of law, these statements could be made "in connection with" a securities transaction. We remanded in order to develop the record, which in no way reflected on whether we believed the appellants had adequately pled the scienter element of their claim. See Carter-Wallace I, 150 F.3d at 156-57.

We are also unpersuaded by the appellants' argument that Carter-Wallace I can be distinguished on the ground that it concerned omissions, while the medical journal advertisements were affirmative statements. Actually, the GAAP claim involved an affirmative statement, namely, an overstatement of inventory, not an omission. Our reasoning in Carter-Wallace I applies with equal force here. There, we held that the adverse reports did not need to be disclosed in order to correct the financial statements because, until August 1, 1994, it was not reckless for Carter-Wallace to consider the adverse reports to be random. Not only were the financial statements not materially misleading before the link could be made, but any inference of scienter was negated as well. As we explained in affirming the dismissal of the GAAP claim, "no such intent can be inferred because . . . Carter-Wallace had no sound reason to doubt the commercial viability of Felbatol or the value of its inventory until the reports of Felbatol-associated deaths became statistically significant." Id. at 157. Contrary to the appellants' argument, this reasoning is not distinguishable on the ground that it involved Felbatol's commercial viability because Felbatol's commercial success was directly tied to its safety. We do not see any basis for distinguishing Carter-Wallace I or deviating from our conclusion that, before August 1, 1994, the connection between Felbatol and aplastic anemia was not statistically significant.

The appellants rely on Cosmas v. Hassett, 886 F.2d 8 (2d Cir. 1989), to argue that they have sufficiently pled scienter. Cosmas is readily distinguishable. In Cosmas, the defendants represented that sales to China would be "an important new source of revenue" even though import restrictions, of which the defendants were presumably aware, belied the statement. Id. at 10, 12-13. Here, by contrast, there can be no presumption that Carter-Wallace was aware of a statistically significant connection between Felbatol and aplastic anemia before August 1, 1994. This case is closer to Shields. In Shields, we explained that, even if the defendants turned out to be wrong about predicted financial performance, "misguided optimism is not a cause of action, and does not support an inference of fraud." Shields, 25 F.3d at 1129. We held that "nothing alleged indicates that management was promoting a fraud. People in charge of an enterprise are not required to take a gloomy, fearful or defeatist view of the future." Id.; see also Chill, 101 F.3d at 268-71 (dismissing the plaintiffs' allegations that the defendant failed to heed "red warning flags" that signaled the defendant's subsidiary's falsification of profits). Here, the early medical reports may have indicated a potential problem, but until a connection between Felbatol and any illness could be made, we would not expect Carter-Wallace to abandon its product on what, at the time, would have been speculation. The complaint here cannot support an inference that Carter-Wallace turned a blind eye to the reports of adverse side effects. There is no indication that Carter- Wallace knew, or should have known, of the connection between Felbatol and aplastic anemia before August 1, 1994. Although this connection was subsequently made, the allegations do not support the inference that Carter-Wallace was reckless in failing to have made it earlier.

Because there was no statistical link between Felbatol and any adverse side effect before August 1, 1994, the pleadings do not "give rise to a strong inference of fraudulent intent." As argued by Carter-Wallace, the pleadings represent an impermissible attempt to plead "fraud by hindsight." Denny v. Barber, 576 F.2d 465, 470 (2d Cir. 1978). While it may now seem clear that Felbatol was not as safe as advertised, at the time the

advertisements ran, it was not reckless for Carter-Wallace to believe the assertions to be true. Indeed, before August 1, 1994, no adverse side effect had been attributed to Felbatol. Carter-Wallace's awareness of medical reports that could have been random cannot lead to the conclusion that Carter-Wallace was reckless in permitting the advertisements to continue. Felbatol had, after all, survived the extensive testing process required by the FDA. See generally 21 C.F.R. §§ 312, 314 (1999). Carter-Wallace acted reasonably once the linkage was established between aplastic anemia and Felbatol. Immediately after receiving four adverse reports of aplastic anemia in July 1994, Carter-Wallace, in conjunction with the FDA, recommended the withdrawal of patients from Felbatol. We are satisfied that the pleadings do not allege scienter as required to survive this motion for judgment on the pleadings. Carter-Wallace's actions -- touting Felbatol's safety in medical journals in light of what were then random adverse medical reports -- did not constitute recklessness.

Finally, the appellants argue that the district court impermissibly made findings of fact, requiring reversal. We do not believe that the district court's discussion of the involvement of the FDA in the development and regulation of Felbatol, to the extent it involved disputed factual assumptions, contributed to its decision. In any event, we have reached the same conclusion on de novo review and do not believe that reversal is warranted.

CONCLUSION

Because the appellants have failed adequately to plead reckless behavior on Carter-Wallace's part, they have failed to allege scienter. The district court correctly granted Carter-Wallace's motion for judgment on the pleadings pursuant to Fed. R. Civ. P. 12(c) and its decision is affirmed.

FOOTNOTES

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[*]

Honorable Charles H. Haden II, Chief Judge of the United States District Court for the Southern District of West Virginia, sitting by designation.

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[1]

As this case was filed in August 1994, it is not subject to the Private Securities Litigation Reform Act of 1995.

10/07/96 MONICA VALENTINO; MICHAE v. CARTER-WALLACE, INC.; WA

1996.C09.775 (http://www.versuslaw.com) United States Court of Appeals for the Ninth Circuit, No. 95-15935 ; October 7, 1996

BLUE BOOK CITATION FORM: 1996.C09.775 (http://www.versuslaw.com) [Editor's note: footnotes (if any) trail the opinion]
FOR PUBLICATION

[1] UNITED STATES COURT OF APPEALS FOR THE NINTH CIRCUIT

[2] MONICA VALENTINO; MICHAEL A. HACKARD; HUGO S. JENNINGS; WANDA S. O'CONNOR, individually and on behalf of all others similarly situated,

[3] Plaintiffs-Appellees,

v.

[4] CARTER-WALLACE, INC.; WALLACE LABORATORIES, a division of Carter-Wallace, Inc.,

[5] Defendants-Appellants.

[6] No. 95-15935

[7] D.C. No. CV-94-02867-EFL

[8] OPINION

[9] Appeal from the United States District Court for the Northern District of California

[10] Eugene F. Lynch, District Judge, Presiding

[11] Argued and Submitted January 8, 1996 -- San Francisco, California

[12] Filed October 7, 1996

[13] Before: Mary M. Schroeder and Stephen S. Trott, Circuit Judges, and Edward C. Reed, *fn* District Judge.

[14] Opinion by Judge Schroeder

[15] OPINION

[16] SCHROEDER, Circuit Judge:

[17] This is an interlocutory appeal from a district court order under Fed. R. Civ. P. 23 conditionally certifying a nationwide plaintiff class and subclass in a products liability case against the manufacturer of a drug used for the treatment of epilepsy. The jurisdiction of the district court was grounded on diversity, and our jurisdiction is pursuant to certification under 28 U.S.C. 1292(b).

[18] The drug in question, known as Felbatol, is manufactured by defendants Carter-Wallace, Inc. and Wallace Laboratories (Carter-Wallace). Carter-Wallace began marketing the drug in August 1993 without giving any special warning of serious side effects. Between January 1994 and July 1994, Carter-Wallace received reports that some patients had developed aplastic anemia following use of the drug.*fn1 In August 1994, Carter-Wallace mailed letters to the physician community warning them of this risk. By September 1994, Carter-Wallace had also received reports of liver failure in connection with use of the drug. Again, Carter-Wallace mailed letters to the physician community warning them of this risk.

[19] The district court determined that the prerequisites of Fed. R. Civ. P. 23(a) had been met.*fn2 The district court conditionally

certified a plaintiff class consisting of "all persons who began using Felbatol prior to August 1, 1994." The district court also certified a "serious injury" subclass, defined as "all persons within the Felbatol user class who have developed or will develop aplastic anemia or liver failure, as a result of using Felbatol."

[20] Pursuant to Fed. R. Civ. P. 23(c)(4)(A), the district court limited class certification to the issues of strict liability, negligence, failure to warn, breach of implied and express warranty, causation in fact, and liability for punitive damages. The district court stated that "[w]ith respect to these particular issues, common questions of law and/or fact predominate over any questions affecting only individual members and a class action is superior to other available methods for adjudication of the controversy." The court's order thus echoed the preponderance and superiority requirements of Fed. R. Civ. P. 23(b)(3).*fn3 The court specifically excluded the individual issues of proximate causation, compensatory damages, and the amount of punitive damages from certification.

[21] In its certification order, the court did not discuss whether the adjudication of the certified issues would significantly advance the resolution of the underlying case, thereby achieving judicial economy and efficiency. Nor did the court discuss any alternative methods for adjudicating these claims.

[22] According to the named plaintiffs, during the brief period involved in this litigation the drug was prescribed to over 100,000 patients, who were told that the drug was unlike other anti-epilepsy drugs in that this one had few adverse side effects. Plaintiffs claim that over 3,000 people have reported some adverse reactions from the drug to the United States Food & Drug Administration, and there have been over seventy reported cases of aplastic anemia or liver damage, including nearly twenty reported deaths. Withdrawal from the drug has also been difficult for many patients.

[23] Plaintiffs contend, with considerable justification, that because the case involves only one manufacturer, only one product, only one marketing program, and a relatively short period of time, the case is more manageable for class action purposes than cases that involve multiple manufacturers, multiple products, multiple marketing programs, and a long period of time. It appears undisputed that the claims of all members of the class will raise some common issues concerning the knowledge and conduct of Carter-Wallace. Apparently, in recognition of these common issues, the Judicial Panel on Multidistrict Litigation (JPML) has consolidated pretrial proceedings in all federal Felbatol cases and transferred them to the Northern District of California.

[24] Carter-Wallace argues, with at least equal justification, that the existence of common issues of law or fact is a necessary but not the sole requirement for class certification, and that the class certified here does not meet other Rule 23 requirements. Carter-Wallace places particular stress on the Rule 23(b)(3) requirements that the common issues of fact predominate over individual issues and that the class action be superior to other methods of adjudicating the claims. Specifically, Carter-Wallace contends that the numerous adverse reactions of each plaintiff are intertwined with the certified liability issues, and that the law on each liability theory varies widely from state to state. Additionally, Carter-Wallace notes that the problems with the numerous adverse reactions affect the Rule 23(a) prerequisites of typicality and adequacy of representation in that the drug has had a variety of different effects on different people and further, that the class does not contain any representative who has allegedly developed aplastic anemia from taking the drug. Carter-Wallace also contends that class adjudication will be unmanageable and inefficient and that alternative, superior methods of adjudication exist.

[25] [1] Carter-Wallace's threshold contention in this appeal is, however, even more sweeping. It is that, regardless of any specific problems with this particular certification, class certification is never appropriate for multi-state plaintiffs asserting personal injury claims against manufacturers of drugs and medical devices. Carter-Wallace cites this circuit's opinion in In re Northern Dist. of California, Dalkon Shield IUD Prods. Liab. Litig. (Dalkon Shield), 693 F.2d 847, 854-55 (9th Cir. 1982), cert. denied, 459 U.S. 1171 (1983), and recent cases from other circuits to support its broadside attack. See, e.g., Castano v. American Tobacco Co., 84 F.3d 734 (5th Cir. 1996); In re American Medical Sys., 75 F.3d 1069 (6th Cir. 1996); In re **Rhone-Poulenc Rorer**, Inc., 51 F.3d 1293 (7th Cir.), cert. denied, 116 S. Ct. 184 (1995). Our review of the record suggests that a principal reason why the district court entered twin certifications, first to create class litigation, and then to secure appellate review of that creation, was to obtain a ruling from this court on whether the law of this circuit supports Carter-Wallace's threshold position.

[26] [2] We hold that the law of this circuit, and more specifically our leading decision in Dalkon Shield, does not create any absolute bar to the certification of a multi-state plaintiff class action in the medical products liability context. We decline to hold, at least at this early stage of the litigation, that there can never be a plaintiff class certification in this particular case. We do hold, however, on the basis of the record before us, that we must vacate this class certification order, because there has been no demonstration of how this class satisfies important Rule 23 requirements, including the predominance of common issues over individual issues and the superiority of class adjudication over other litigation alternatives.

[27] ANALYSIS

[28] I. Class Actions in Products Liability Litigation

[29] The history of class action certifications and products liability cases in this circuit and elsewhere has not been luminous. Indeed the Advisory Committee on Civil Rules for the 1966 revision to Rule 23 cast doubt on the availability of class actions in mass tort cases. See Fed. R. Civ. P. 23, advisory committee's notes to 1966 amendment, Subdivision (b)(3) ("[a] `mass accident' resulting in injuries to numerous persons is ordinarily not appropriate for a class action"). Nevertheless, courts have generally proceeded on a case-by-case basis and considered the appropriateness of class action treatment under the particular circumstances presented. See 7B Charles Alan Wright et al., Federal Practice and Procedure: Civil 2d, 1783 at 74-75 (2d ed. 1986); see also 3 Herbert B. Newberg & Alba Conte, Newberg on Class Actions, 17.05 (3d ed. 1992) (noting modern trend has been to expand use of class action litigation in mass tort context). The lead decision in this circuit was handed down in 1982 and vacated a nationwide punitive damages class and a statewide compensatory liability class of persons who had used allegedly defective intrauterine contraceptive devices. In re Northern Dist. of California, Dalkon Shield IUD Prods. Liab. Litig., 693 F.2d 847 (9th Cir. 1982), cert. denied, 459 U.S. 1171 (1983).

[30] In rejecting the nationwide class certification under Rule 23(b)(1)(B), we were clearly troubled in Dalkon Shield by the problems that would arise in endeavoring to apply the varying punitive damage standards of fifty different jurisdictions. We did not, however, hold this commonality obstacle fatal. Id. at 850. There was in Dalkon Shield the added problem that no plaintiff, and no plaintiff's lawyer, had agreed to represent the class so that the requirements of typicality and adequacy of representation could not be satisfied. Id. at 850-51.

[31] In considering the certification of the California liability class under Rule 23(b)(3), we commented in Dalkon Shield on the problems presented by products liability actions where, unlike the mass tort involving a single catastrophic event such as an airplane crash or cruise ship food poisoning,"[n]o single happening or accident occurs to cause similar types of physical harm or property damage." Id. at 853. We also discussed the inherent difficulties of proving proximate cause and a breach of a duty of care under a negligence theory, where there are different types of injuries and multiple defendants. Id. at 854-55. We were further troubled by the requirement that common issues predominate over individual issues in a certification of an entire case for class treatment; it appeared that only the underlying facts raised a common nucleus of issues, while the liability questions included highly individualized issues of damages and proximate cause. Id. at 856. Finally, we held that class adjudication would not be superior to individualized litigation given: first, the lack of any showing that class adjudication would save time or expense, and second, the management difficulties caused by the complexity and multiplicity of issues as well as the plaintiffs' hostility to the class action. Id.

[32] We were careful in Dalkon Shield, however, not to preclude the future certification of more limited classes or subclasses pursuant to Rule 23(b)(3), or to rule out the possibility of broader class action certification in other products liability cases. See id. at 852-54, 856. Although Dalkon Shield pointed out many of the problems common to products liability litigation in meeting Rule 23's class certification requirements, we cannot conclude that Dalkon Shield creates an absolute bar to such certification in this circuit. As leading commentators have pointed out, the case was unusual in that there was simply no plaintiff or plaintiff's counsel ready, willing, and able to represent the class. See, e.g., 3 Newberg & Conte, supra, 17.12 at 17-31. In addition, Dalkon Shield involved multiple defendants and multiple marketing schemes, unlike the present case where a single manufacturer marketed one drug over a limited period of time. Compare Dalkon Shield, 693 F.2d at 856 (holding district court erroneously certified class where manufacturer advertised in various medical journals and trade-show advertisements to different doctors), with In re Copley Pharmaceutical, 158 F.R.D. 485, 487, 491-93 (D. Wyo. 1994) (certifying class where one manufacturer marketed four contaminated batches of one prescription drug).

[33] The leading cases in other circuits in which class certifications have been approved are the "Agent Orange" litigation in the Second Circuit and the "School Asbestos" litigation in the Third Circuit. See In re Agent Orange Prods. Liab. Litig., 818 F.2d 145 (2d Cir. 1987), cert. denied, 484 U.S. 1004 (1988); In re School Asbestos Litig., 789 F.2d 996 (3d Cir.), cert. denied, 479 U.S. 852, and cert. denied, 479 U.S. 915 (1986). Those cases also had some unique features.

[34] In Agent Orange, the Second Circuit made it quite clear that the common issue in that case that caused class litigation to be both appropriate and superior to other forms of litigation was the common existence of a government contractor defense. [35] In our view, class certification was justified under Rule 23(b)(3) due to the centrality of the military contractor defense. First, this defense is common to all of the plaintiffs' cases, and thus satisfies the commonality requirement of Rule 23(a)(2). Second, because the military contractor defense is of central importance . . . this issue is governed by federal law, and a class trial in a federal court is a method of adjudication superior to the alternatives. If the defense succeeds, the entire litigation is disposed of. If it fails, it will not be an issue in the subsequent individual trials. In that event, moreover, the ground for its rejection, such as a failure to warn the government of a known hazard, might well be dispositive of relevant factual issues in those trials.

[36] Agent Orange, 818 F.2d at 166-67 (citations omitted).

[37] In School Asbestos, the plaintiffs were school districts seeking compensation for property damages, not for personal injuries. The Third Circuit viewed that class action as much more manageable than a personal injury case would have been because, in essence, the effect of asbestos in different buildings is the same and the effect of asbestos on different people is not. See School Asbestos, 789 F.2d

at 1010-11.

[38] A leading decision in the Seventh Circuit has recently cast a pall on the future of class action certifications in products liability cases in that circuit. See In re Rhone-Poulenc Rorer, Inc., 51 F.3d 1293 (7th Cir.), cert. denied, 116 S. Ct. 184 (1995); see also Castano v. American Tobacco Co., 84 F.3d 734 (5th Cir. 1996) (decertifying national class of all nicotine-dependent persons, and expressing approval of Rhone-Poulenc). The Seventh Circuit in Rhone-Poulenc issued a writ of mandamus ordering the district court to decertify a class of plaintiff hemophiliacs who were allegedly infected by the human immunodeficiency virus (HIV) as a result of using blood solids manufactured by the defendants. The Seventh Circuit majority was heavily influenced by at least three factors.

[39] First, the majority expressed a general distaste for requiring defendants to place high economic stakes in the hands of a single jury. See Rhone-Poulenc, 51 F.3d at 1299. The majority also noted that there was a great likelihood that plaintiffs' legal claims lacked merit, given that twelve of thirteen individual suits had resulted in verdicts favorable to the defendants. See id. at 1299-1300. This concern does not appear to be in line with the law of this circuit that has not looked favorably upon granting extraordinary relief to vacate a class certification. See, e.g., Arthur Young & Co. v. United States Dist. Court, 549 F.2d 686, 698 (9th Cir.), cert. denied, 434 U.S. 829 (1977). There is also authority disapproving a separate hearing to consider the merits of the plaintiffs' claims when determining class certification. See Eisen v. Carlisle & Jacquelin, 417 U.S. 156, 177-78 (1974); Blackie v. Barrack, 524 F.2d 891, 901 (9th Cir. 1975), cert. denied, 429 U.S. 816 (1976); see also 7B Wright et al., supra, 1785 at 125 (discussing Eisen and the Court's express rejection of a preliminary hearing to determine the merits of the litigation).

[40] Second, the Rhone-Poulenc majority found that the class action would require a jury to determine "the negligence of the defendants under a legal standard that does not actually exist anywhere in the world." Id. at 1300. The court expressed concern with the ability of the district court to condense the law of the fifty states and the District of Columbia into a single jury instruction on negligence. See id. at 1300-02. The court thus focused on the district court's decision to create a hypothetical negligence standard. The district court in this case did not create such a hypothetical standard.

[41] Third, the Rhone-Poulenc court perceived Seventh Amendment problems in the district court's bifurcation of class issues from individual issues, such as comparative negligence and proximate causation. See id. at 1302-03. The court determined that the district court's plan was inconsistent with the principle that the findings of one jury are not to be reexamined by a different jury. See id. at 1303. This constitutional concern of the Rhone-Poulenc court may not be fully in line with the law of this circuit, and constitutional issues were never squarely presented to the district court. See Arthur Young, 549 F.2d at 696.

[42] We therefore do not accept Carter-Wallace's invitation in this case to adopt the principles of Rhone-Poulenc as the law of this circuit.

[43] We are more sympathetic to the approach taken by the Sixth Circuit in In re American Medical Sys., 75 F.3d 1069 (6th Cir. 1996). American Medical rejected class certification involving ten different models of penile implants that were implanted over a twenty-two year period. The court granted mandamus to decertify a nationwide class where the district court failed to identify common issues, explain why common issues predominate over individual issues, or make a finding of superiority. The court held that district courts must conduct a "rigorous analysis" into whether the prerequisites of Rule 23 are met before certifying a class. See id. at 1078-79. The Sixth Circuit has also recognized, however, that in the mass tort context, class adjudication of certain issues may be more efficient and expeditious than individualized litigation. See Sterling v. Velsicol Chem. Co., 855 F.2d 1188 (6th Cir. 1988).

[44] [3] Our reluctance to close the door on class action litigation in products liability cases is reinforced by current legal developments that could make class litigation more manageable. There has, for example, been discussion of federal class action legislation. See, e.g., Thomas D. Rowe, Jr., Beyond the Class Action Rule: An Inventory of Statutory Possibilities to Improve the Federal Class Action, 71 N.Y.U. L. Rev. 186 (1996) (discussing several areas in which legislation might enhance federal class actions); William W. Schwarzer et al., Judicial Federalism: A Proposal to Amend the Multidistrict Litigation Statute to Permit Discovery Coordination of Large-Scale Litigation Pending in State and Federal Courts, 73 Tex. L. Rev. 1529 (1995) (proposing amendments to the multidistrict litigation statute, 28 U.S.C. 1407(a), to include state court cases). Further, the American Law Institute is now concluding its work on products liability in the Restatement of the Law of Torts. See Restatement (Third) of Torts: Products Liability (Tent. Draft No. 3, 1996); see also James A. Henderson, Jr. et al., Optimal Issue Separation in Modern Products Liability Litigation, 73 Tex. L. Rev. 1653, 1661-67 (1995) (discussing new Restatement as a reflection of current state of products liability law).

[45] [4] In addition, the Advisory Committee on Civil Rules is in the process of modifying Rule 23, and has proposed authorizing the possible certification of settlement classes that need not meet the requirements of Rule 23(b)(3). See Fed. R. Civ. P. 23(b)(4) (Draft Aug. 15, 1996); see also Samuel Estreicher, Foreword, Federal Class Actions After 30 Years, 71 N.Y.U. L. Rev. 1, 6 & n.26 (1996) (noting that proposed (b)(4) category would allow trial courts to certify class actions for purposes of settlement, even though the requirements of subdivision (b)(3) might not be met for trial); Edward H. Cooper, Rule 23: Challenges to the Rulemaking Process, 71 N.Y.U. L. Rev. 13 (1996) (discussing proposed changes to Rule 23). We observe that this idea has met with substantial opposition

from a number of quarters. See, e.g., In re General Motors Corp. Pick-Up Truck Fuel Tank Prods. Liab. Litig., 55 F.3d 768, 786-94 (3d Cir.) (holding that under present rule settlement class must meet all Rule 23 requirements and expressing concern about dangers of overrewarding attorneys and undercompensating class members), cert. denied, 116 S. Ct. 88 (1995); see also Georgine v. Amchem Prods., 83 F.3d 610, 624-25 (3d Cir. 1996), petition for cert. filed, 65 U.S.L.W. 3159 (Aug. 19, 1996) (No. 96-270); John C. Coffee, Jr., Class Wars: The Dilemma of the Mass Tort Class Action, 95 Colum. L. Rev. 1343 (1995); John C. Coffee, Jr., Understanding the Plaintiff's Attorney: The Implications of Economic Theory for Private Enforcement of Law Through Class and Derivative Actions, 86 Colum. L. Rev. 669 (1986). It is to be hoped that the debate on the proposed rule modification will add to our understanding of the appropriate role of class litigation in tort litigation.

[46] For these reasons, we reject Carter-Wallace's position that the law of this circuit should prohibit any class certifications in products liability litigation. We therefore turn to the appropriateness of this particular certification order.

[47] II. The Class Certification Order in This Case

[48] [5] This court reviews a district court's decision to grant class certification for abuse of discretion. See Six (6) Mexican Workers v. Arizona Citrus Growers, 904 F.2d 1301, 1304 (9th Cir. 1990). In order for a class action to be certified, the plaintiffs must establish the four prerequisites of Fed. R. Civ. P. 23(a) and at least one of the alternative requirements of Fed. R. Civ. P. 23(b). See Fed. R. Civ. P. 23(b). An action may be maintained as a class action if the court finds that: (1) common questions of law and fact predominate over questions affecting individual members, and (2) a class action is superior to other available methods for the fair and efficient adjudication of the controversy. Fed. R. Civ. P. 23(b)(3); Dalkon Shield, 693 F.2d at 855-56.

[49] [6] The certification order which we review is brief and conclusory. The record reflects that it was entered with the express hope on the part of the district judge of encouraging settlement, and to trigger a ruling from this court on the more general issue of the viability of class certification in this circuit. The order is provisional and contemplates the possibility of future modifications, additions, or refinements of sub-classes. The order was entered at an early stage in the proceedings, and the record simply does not reflect any basis for us to conclude that some key requirements of Rule 23 have been satisfied.

[50] [7] It is not clear that Plaintiffs have met either the typicality or adequacy of representation requirement. See Fed. R. Civ. P. 23(a)(3) and (4). The plaintiff-class representatives include two individuals who have had difficulty withdrawing from Felbatol and returning to prior medications, one alleging liver failure and one some unspecified type of liver damage. No named plaintiff has experienced aplastic anemia as a result of taking the drug, even though this condition is one of the most serious of the alleged adverse consequences. The named plaintiffs thus may not be able to provide adequate representation for those who have suffered different injuries. See Dalkon Shield, 693 F.2d at 854-55.

[51] [8] Additionally, notice may be problematic. The number of known users who have reportedly suffered actual injuries from the drug is relatively small in comparison with all the users of the drug, so that many potential members of the classes cannot yet know if they are part of the class. We therefore have serious due process concerns about whether adequate notice under Rule 23(c)(2) can be given to all class members to enable them to make an intelligent choice as to whether to opt out. See 7B Wright et al., supra, 1786 at 197-98.

[52] [9] The first requirement of Rule 23(b)(3) is predominance of common questions over individual ones. Implicit in the satisfaction of the predominance test is the notion that the adjudication of common issues will help achieve judicial economy. See 1 Newberg & Conte, supra, 4.25 at 4-86. Even if the common questions do not predominate over the individual questions so that class certification of the entire action is warranted, Rule 23 authorizes the district court in appropriate cases to isolate the common issues under Rule 23(c)(4)(A) and proceed with class treatment of these particular issues. See Dalkon Shield, 693 F.2d at 856; see also Copley, 158 F.R.D. at 491; 7B Wright et al., supra, 1790 at 276; 1 Newberg & Conte, supra, 4.25 at 4-81.

[53] [10] Here, the certification order merely reiterates Rule 23(b)(3)'s predominance requirement and is otherwise silent as to any reason why common issues predominate over individual issues certified under Rule 23(c)(4)(A). There has been no showing by Plaintiffs of how the class trial could be conducted. See e.g., Castano, 84 F.3d at 741-44. The district court abused its discretion by not adequately considering the predominance requirement before certifying the class. See Dalkon Shield, 693 F.2d at 856; cf. Agent Orange, 818 F.2d at 163-67; School Asbestos, 789 F.2d at 1010-11.

[54] [11] Last, but certainly not least, the district court must find that a class action is superior to other methods of adjudication. Fed. R. Civ. P. 23(b). Where classwide litigation of common issues will reduce litigation costs and promote greater efficiency, a class action may be superior to other methods of litigation. See Dalkon Shield, 693 F.2d at 856. A class action is the superior method for managing litigation if no realistic alternative exists. See Fed. R. Civ. P. 23(b)(3); 7A Wright et al., supra, 1779 at 552. But here, as in Dalkon Shield, there has been no showing why the class mechanism is superior to alternative methods of adjudication, particularly when coupled with the discovery coordination that is made possible by the JPML consolidation. See Dalkon Shield, 693 F.2d at 856. Again,

the certification order merely reiterates Rule 23(b)(3)'s superiority requirement but contains no discussion of alternatives or why class adjudication is superior.

[55] [12] The deficiencies in this certification are quite like those that caused the Sixth Circuit to reject the certification in American Medical, 75 F.3d at 1080-86. We similarly conclude that the district court abused its discretion by certifying particular issues for class adjudication. The district court's order is VACATED and the case is REMANDED for further proceedings.

[56] VACATED AND REMANDED.

***** BEGIN FOOTNOTE(S) HERE *****

[57] *fn* Honorable Edward C. Reed, Senior United States District Judge for the District of Nevada, sitting by designation.

[58] *fn1 Aplastic anemia is a disease which interferes with the bone marrow's ability to produce blood cells, resulting in a decrease in blood cell counts.

[59] *fn2 Rule 23(a) states:

[60] One or more members of a class may sue or be sued as representative parties on behalf of all only if (1) the class is so numerous that joinder of all members is impracticable, (2) there are questions of law or fact common to the class, (3) the claims or defenses of the representative parties are typical of the claims or defenses of the class, and (4) the representative parties will fairly and adequately protect the interests of the class.

[61] *fn3 Rule 23(b)(3) states, in pertinent part, that a class action may be maintained if:

[62] . . . the court finds that the questions of law or fact common to the members of the class predominate over any questions affecting only individual members, and that a class action is superior to other available methods for the fair and efficient adjudication of the controversy.

[63] Rule 23(c)(4)(A) states that when appropriate:

[64] an action may be brought or maintained as a class action with respect to particular issues . . .

***** END FOOTNOTE(S) HERE *****

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EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. *90/007,991*.

PATENT NO. *4978680*.

ART UNIT *3991*.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

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Examiner's Amendment

Patent owner's failure to timely file an appeal brief results in the following Notice of Intent to Issue an Ex parte Reexamination Certificate which cancels claim 1 as issued in U.S. Pat. No. 4,978,680.

In the Claims:

Please cancel claim 1.

Future Correspondences

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

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