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

REQUEST for EX PARTE
REEXAMINATION
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I.  **INTRODUCTION**


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 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 straightforward: 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.
The 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.


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

<table>
<thead>
<tr>
<th>The SOFIA patent, claim 1</th>
<th>The ‘444 patent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A method for reducing the incidence and severity of epileptic seizures</td>
<td>anti-convulsant activity, <em>see</em> 1:17; preventing the occurrence of seizures, <em>see e.g.</em>, 1:18, 2:26-30</td>
</tr>
<tr>
<td>which comprises administering to a warm-blooded animal in need of such treatment</td>
<td>Testing in warm-blooded animals such as mice, <em>see</em> 2:26-30</td>
</tr>
<tr>
<td>a therapeutic amount of</td>
<td>Doses that produce sleep, <em>see</em> 2:36; doses that protect from seizures, <em>see</em> 2:37</td>
</tr>
<tr>
<td>2-phenyl-1,3-propanediol dicarbamate</td>
<td>2-phenyl-1,3-propanediol dicarbamate. <em>See e.g.</em>, 1:19.</td>
</tr>
</tbody>
</table>
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 polynoxy 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 does 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 anticonvulsant” 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 intended purpose, however, it is as a matter of law *prima facie* 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.

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...

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.
THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS

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PHARMACEUTICAL PATENT ATTORNEYS LLC
55 MADISON AVENUE, 4TH FLOOR
MORRISON, NJ 07960

EX PARTE  REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO  90/007991
PATENT NO.  4,978,680
ART UNI  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)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the ex parte reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).
Office Action in Ex Parte Reexamination

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

- Responsive to the communication(s) filed on 31 October 2006.
- This action is made FINAL.
- 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 rejected 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: _______
DETAILED ACTION: Reexamination: Final Rejection

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-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-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-3-propanediol dicarbamate is 2300 mg.
Withdrawn Objection(s) and/or Rejection(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 carbamazepines 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.

    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 carbamazepines 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.


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 \textit{teaching toward} administration of 2-phenyl-1,3 propanediol dicarbamate alone as encompassed by the instantly claimed invention \textit{if} "consisting essentially of" is interpreted to be equivalent to "consisting of".

\textbf{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".

\textbf{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, \textit{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." \textit{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 Correspondeces

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).

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