Patent Application
Attorney Docket No. PC9838B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

William J. Curatolo, et al.

Examiner: **To be assigned**

APPLICATION NO.: **To be assigned**

FILING DATE: **Concurrently herewith**

Group Art Unit: **To be assigned**

TITLE: **Gelatin Encapsulated Solution Dosage Forms of Sertraline**

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

RESPONSE UNDER RULE 1.121

In response to the Office Action of June 5, 2002, reconsideration and reexamination of this application are requested in view of the following amendments and comments.

Please amend this application as follows:

1. (amended once) A dosage form comprising a gelatin-encapsulated solution comprising sertraline, or a pharmaceutically acceptable salt thereof, dissolved in a water-immiscible vehicle wherein complete precipitation does not occur when said sertraline solution is diluted ten fold into 0.1N HCl or phosphate buffered saline pH5.8.

11. (amended once) A dosage form as defined in claim 1, wherein said vehicle comprises a vegetable oil.

Please add the following new claims:

23. A dosage form comprising a gelatin-encapsulated solution comprising sertraline, or a pharmaceutically acceptable salt thereof, dissolved in a water-immiscible vehicle wherein complete precipitation does not occur when said sertraline

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solution is diluted ten fold into 0.1N HCl or phosphate buffered saline pH 5.8 and wherein the solubility of sertraline in said water-immiscible vehicle is at least 1.6 mg/ml per mg. dose.

24. A dosage form as defined in claim 23, which decreases T_{max} by at least 0.5 hr.

25. A dosage form as defined in claim 24, which decreases T_{max} by at least one hour.

26. A dosage form as defined in claim 23, containing 10 mgA to 300 mgA of sertraline.

27. A dosage form as defined in claim 26, containing 10 mgA to 250 mgA of sertraline.

28. A dosage form as defined in claim 27, containing 10 mgA to 100 mgA of sertraline.

29. A dosage form as defined in claim 23, wherein said vehicle comprises a mono-, di-, or triglyceride, or a mixture thereof.

30. A dosage form as defined in claim 29, wherein the acyl chain(s) of said mono-, di-, or triglyceride are 4-18 carbons in length.

31. A dosage form as defined in claim 30, wherein the acyl chain(s) of said mono-, di-, or triglyceride are 6-14 carbons in length.

32. A dosage form as defined in claim 23, wherein said vehicle is liquid at 37°C.

33. A dosage form as defined in claim 23, wherein said vehicle comprises a vegetable oil.

34. A dosage form as defined in claim 33, wherein said vegetable oil comprises corn oil, peanut oil, sesame oil, olive oil, castor oil, coconut oil, cottonseed oil, soybean oil, or safflower oil.

35. A dosage form as defined in claim 23, wherein said vehicle comprises a surfactant or emulsifier.

36. A dosage form as defined in claim 35, wherein said surfactant or emulsifier comprises polysorbate 80, nonylphenoxypolyoxyethylene, dioctyl sodium sulfosuccinate, PEG-6-glycerylmono-oleate, or PEG-6-glyceryllinoleate.

37. A dosage form as defined in claim 23, wherein said dosage form comprises a fatty acid.

38. A dosage form as in claim 37, wherein said fatty acid comprises caprylic acid, capric acid, lauric acid, oleic acid, or linoleic acid.

39. A dosage form as in claim 23, wherein said dosage form comprises a liquid ester of short chain alcohol and acid.

40. A dosage form as in claim 39, wherein said ester is selected from the propylene glycol esters of caprylic and/or capric acids.

41. A dosage form as in claim 23, wherein said vehicle additionally comprises an alcohol.

42. A dosage form as in claim 41, wherein said alcohol is polyethyleneglycol, glycerin, ethanol, or propylene glycol.

43. A dosage form as defined in claim 23, which decreases precipitation of sertraline in a choloride ion containing use environment relative to a comparison dosage form made with a water-miscible vehicle.

44. A method of treating an illness amenable to treatment with sertraline, comprising administering to a person in need of such treatment a dosage form as defined in claim 23.

Marked-up version showing changes made:

1. A dosage form comprising a gelatin-encapsulated solution comprising sertraline, or a pharmaceutically acceptable salt thereof, dissolved in a water-immiscible vehicle wherein complete precipitation does not occur when said sertraline solution is diluted ten fold into 0.1N HCl or phosphate buffered saline pH5.8.

11. A dosage form as defined in claim 1, wherein said vehicle comprises a [vegtable] vegetable oil.

Remarks

This application is directed to a dosage form comprising a gelatin-encapsulated solution comprising sertraline, or a pharmaceutically acceptable salt thereof, dissolved in a water-immiscible vehicle.

After the present amendments, the claims in this case number 1 to 44.

Claim 1 has been amended to stipulate that complete precipitation does not occur when the sertraline solution is diluted ten-fold into 0.1N HCl or phosphate buffered saline pH 5.8. Support for the amendment may be found at page 9, line 18 of the specification. Claims 23 through 44 are newly added to more fully round out the present claims of the invention. Claims 23 to 44 are fully supported throughout the specification, particularly at page 3, lines 18 to 31. Other amendments are formal. It is believed no new matter has been added by the present amendments.

The claims, in a broad aspect, are directed to a dosage form comprising a gelatin encapsulated composition comprising sertraline, or a pharmaceutically acceptable salt thereof, and a water-immiscible vehicle. The dosage form exhibits one or more of the following advantages: (1) exhibiting a T_{max} which is decreased relative to the T_{max} exhibited by currently known immediate release sertraline tablet dosage forms; or (2) decreasing one or more GI side effects; and/or (3) decreasing, relative to a comparison dosage form made with a water-miscible vehicle, precipitation of sertraline in a chloride ion-containing use environment, such as the stomach, small intestine, or in vitro test fluid which simulates such an in vivo environment. The invention is surprising in that encapsulated solution dosage forms are typically formulated for drugs and vitamins, which have very low solubilities. Since sertraline has an excellent aqueous solubility (3 mg/ml) and its salts (e.g., acetate, aspartate and lactate) have even higher aqueous solubilities, there would be no inclination to prepare gelatin-encapsulated formulations, i.e., because sertraline is not a low solubility drug.

Claims 1 and 13-20 have been rejected under 35 U.S.C. 103(a)

as being unpatentable over Noble, U.S. 6,001,848 ('848). The rejection is respectfully traversed.

Initially, Applicant notes that Noble '848 is newly cited as basis for a rejection in this application and respectfully submits that the finality of the Office Action in the parent case was premature in view of such rejection.

In contrast to the present application, which is directed to a dosage form comprising a gelatin encapsulated composition comprising sertraline, or a pharmaceutically acceptable salt thereof, and a water-immiscible vehicle, the disclosure of Noble is directed to a method of identifying alcoholics who are suitable for treatment using dopaminergic or opioidergic compounds.

Noble contains no specific or general teachings, which would render obvious the concept of a composition comprising sertraline and a water-immiscible vehicle in a gelatin capsule. By the Examiner's own admission at the bottom of page 2 of the Office Action, Noble discloses sertraline in a *list* of other active agents. The Examiner's opinion is that since sertraline is a well-known serotonin reuptake inhibitor, it would have been obvious to one skilled in the art to select sertraline with the expectation of a similar result. "The expected result would be a gelatin capsule comprising sertraline for oral administration useful in pharmaceutical art." With due respect, the Examiner misses the point of the present invention which is a composition comprising sertraline and *a water-immiscible vehicle* in a gelatin capsule.

The recitation of sertraline in the list of agents disclosed by Noble cannot seriously be said to make the instant invention obvious to a skilled artisan. Withdrawal of the rejection in view of Noble is requested.

Claims 1-13, 15, 17-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Shannon et al. USPN 5,945,416 ('416), in view of Bacopoulos USPN 5,130,338 ('338).

The rejection is traversed on the basis that it is based on hindsight. It is well accepted that for two references to be combined in order to establish *prima facie* obviousness, there must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of

ordinary skill in the art. In re Jones, 21 USPQ2d 1941, at 1943-44 (Fed Cir 1992). Neither Shannon nor Bacopoulos contains any language which could be construed as such a suggestion, however. Neither Shannon nor Bacopoulos teaches any reason for making such a combination, or even hints at any benefit or advantage to be derived from doing so.

Shannon teaches a method of treating pain by administering the drug olanzapine with one or more other drugs useful in the treatment of pain. Shannon lists a litany of such other pain killer drugs, including sertraline (column 5, line 21). Shannon also lists a myriad of routes of administration (column 6, lines 47-49), several types of dosage forms (column 7, lines 36-37 and 41-42), and numerous vehicles (column 7, lines 39 et seq). As carriers/diluents, Shannon lists solids, semi-solids, and liquids the carriers being both water soluble and water-immiscible. A gelatin capsule containing sertraline in a water immiscible vehicle is no more suggested or obvious from Shannon than any of the other, essentially infinite number of dosage form combinations that could be imagined by taking any member from any of the long lists of dosage forms, vehicles and drugs, and permuting and combining them randomly. Shannon simply contains no specific or general teachings, which would render obvious the concept of a composition comprising sertraline and a water-immiscible vehicle in a gelatin capsule. Shannon contains no disclosure, teaching, or even the slightest shred of guidance, which could be combined with Bacopoulos to render Applicants' gelatin encapsulated composition of sertraline and a water immiscible vehicle obvious.

Bacopoulos, although being directed to sertraline, discloses a myriad of dosage forms (tablets, capsules, lozenges, troches, hand candies, powders, sprays, elixirs, syrups, aqueous suspensions, injectable solutions, and the like). The only mention of gelatin capsules is capsules containing solid compositions ("of a similar type", referring to the solid compositions previously reviewed for use in capsules). Bacopoulos contains no suggestion to put sertraline and a water immiscible vehicle in a gelatin capsule.

Thus, as between Bacopoulos (who discloses gelatin capsules containing solid, tablet-like compositions) and the general

disclosure of Shannon, there is no disclosure, which, even when combined, could be regarded as a suggestion to combine sertraline and a water-immiscible vehicle in a gelatin capsule. Only Applicants own disclosure, which of course is not prior art against Applicants, does that.

To re-iterate, Bacopoulos and Shannon are not combinable because there is no motivation or any suggestion to do so grounded in either reference itself. For example, in Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 37 USPQ2d 1626, 1629 (Fed. Cir. 1996) the court stated "It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion or motivation to combine those references." Clearly, neither Bacopoulos nor Shannon provides any such suggestion or motivation to make the combination.

Claims 1, and 3-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas 5,741,807 ('807), in view of Bacopoulos ('338).

The rejection is again traversed. The references are not combinable unless one uses Applicants' own specification, in hindsight fashion, as a template for piecing the invention together. Neither reference contains any guidance for doing so.

Applicants' statements and comments from above relating to Bacopoulos are incorporated by reference in this regard. That is, it is submitted that Bacopoulos, although relating to sertraline, contains no suggestion, which would render obvious the concept of gelatin encapsulating sertraline in a water-immiscible vehicle.

Thomas suffers the same defects as Shannon. Thomas names sertraline, among many drugs and classes of drugs, as a drug suitable for use in his invention. Where sertraline is disclosed, it is mentioned only in a long list and in the context of naming drugs that can give rise to diarrheal episodes as a side effect (column 5, lines 16-19 and 41). Thomas names numerous routes of administration (column 7, line 16 et seq), dosage forms, and carriers (column 8, line 16 et seq). Though capsules are mentioned generally (e.g., column 8, line 30 and line 42), there is no mention or even the remotest suggestion of a gelatin encapsulated formulation comprising sertraline and a water-

immiscible vehicle, and there is no guidance otherwise which would suggest such a formulation/dosage form. When disclosing oral dosage forms, and even though he refers generally to liquid as well as solid carriers, Thomas discusses and names only solid form preparations and carriers. The concept of sertraline in a water immiscible vehicle is never even remotely addressed.

Thus, as between Thomas and Bacopoulos, there is no reason or basis for combining teachings. Nether makes any suggestion, which would render the concept of sertraline in a water-immiscible vehicle obvious. Though capsules are mentioned generally there is no guidance otherwise which would suggest such Applicants' formulation/dosage form. No advantage of a dosage form comprising sertraline encsapsulated in a water-immiscible vehicle is even remotely hinted at. Without some reason or advantage for making a dosage form, there does not appear to be any teachings otherwise which would motivate one of ordinary skill to make Applicants' claimed dosage forms.

To summarize, Applicants' submit there is no way one of ordinary skill in the art would find their invention obvious from any combination of Shannon, Bacopoulos, and Thomas. The mere fact that the prior art could be modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. In re Gordon, 221 USPQ 1125 (Fed Cir 1984). There is no such suggestion here. Applicants' respectfully submit that the only way one of ordinary skill in the art would find their invention obvious from any combination of the references is by hindsight. And, the law is emphatic that hindsight is an improper standard. The Federal Circuit has explained the proper test:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Cir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016.

1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Again, none of Shannon, Bacopoulos, and Thomas, or any combination thereof, comes even close to suggesting Applicants' invention, let alone providing any expectation of success.

The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of active ingredients after administration to the patient by employing procedures well known in the art

The Examiner is respectfully urged to reconsider the rejections in this application as it is submitted that, for the reasons stated above, they simply are not tenable and/or are otherwise based on hindsight.

Accordingly, in view of the present amendments and comments, the rejections under 35 USC 103 have been obviated. Withdrawal of such rejections and allowance to issue are earnestly requested.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§ 1.16 and 1.17, or to credit any overpayment to Deposit Account No. 16-1445.

Respectfully submitted,

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Carmella A. O'Gorman

Carmella A. O'Gorman
Attorney for Applicant(s)
Reg. No. 33,749

Pfizer Inc.
Patent Department, MS8260-1611
Eastern Point Road
Groton, CT 06340
(860) 686-1847