CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-033

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-033

Solvay Pharmaceuticals, Inc.
Attention: Michael F. Hare
Manager, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Hare:

Please refer to your new drug application dated April 28, 2006, received May 1, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fluvoxamine maleate [redacted]100mg, 150mg controlled release capsules

We acknowledge receipt of your submissions dated May 10, 2006, July 13, 14, 2006, October 5, 9, 25, 31, 2006 and February 13, 2007.

We completed our review of this application, as submitted, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies and respond to our requests listed below:

Clinical

- Discrepancies in CRFs, narrative summaries, and common AE listing need to be corrected and reanalyzed.

- Additionally, the demographic analysis of AEs needs to be conducted properly by analyzing each common, drug-related adverse event incidence for each demographic variable, specifically by calculating the odds ratios of the event in each subgroup as well as the common odds ratio for the event across subgroups followed by use of the Breslow-Day Chi-Square test to test for homogeneity of the odds ratios across the subgroups, with determination of the *p*-value for this test. Furthermore, given the age distribution of these events, the following age subgroups are recommended in lieu of the multiple age categories utilized by you: age 50 years or younger versus age 51 years or older.

Pharmacology/Toxicology

- There are several impurities/degradants in the drug substance and/or CR drug product with specifications above the threshold(s) for qualification. Although you have not addressed this issue in your current NDA, you did attempt to address similar issues under your NDA 21-519 for Luvox IR tablets. Based on the toxicology studies available for review under that NDA, we have determined that only the specifications for the [redacted]r (i.e. [redacted]) and [redacted]

(i.e., ' —) have been set too high in the CR product and cannot be considered to be qualified by nonclinical studies that have previously been submitted. Consequently, you will need to qualify these 2 impurities/degradants, as described below, prior to approval.

- Only an additional (adequate) Ames test will be required to qualify the ——— to its higher specification in the CR drug product (— compared with —— for the IR product under NDA 21-519 and a threshold for qualification of — ,. It should be noted that you were informed, in the AE letter for NDA 21-519 dated 11/16/06, that the Ames tests that had been submitted up to that that time (with ——— at concentrations up to ——— would be considered adequate to qualify the specification of — proposed for the IR product, but not higher specifications.

- No studies that could serve to qualify ——— have been provided (under NDA 21-519 or the current NDA). Qualification of ——— will require: 1) a general toxicology study in one species of 14-90 days duration, which should include microscopic, as well as macroscopic, evaluation of the standard battery of tissues; 2) *in vitro* genotoxicity studies (*in vitro* gene mutation in bacteria and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay [with colony sizing]); and 3) an embryofetal development study in one species.

Chemistry, Manufacturing & Controls

- Provide justification for the proposed acceptance criteria for the ——— particle size specification alluded to in the recent communication via email from Rex Horton to Scott Goldie on February 5, 2007. This justification should be based on scientific arguments and/or particle size data from clinical drug product batches. Please note that this deficiency has also been sent to DMF 5169.

- Note that the drug product acceptance criteria for two drug product impurities ——— and — , are unacceptable and will need to be revised.

- Note that any revision of the dissolution acceptance criteria will require you to provide a complete re-evaluation of the acceptability of the results of the drug product dissolution data used to support the pivotal lots and the various stability studies. If this information is to be communicated to the Agency through the drug product manufacturers DMF (—— ,, we remind you to inform the DMF Holder of this point.

- We remind you that the deficiencies sent to you on 22 December 2006 need to be resolved before this application can be approved.

Dissolution Method and Specification

We ask that you agree to the following final dissolution method and specification for fluvoxamine maleate 100 mg and 150 mg CR capsules:

Dosage Form:	Capsule
Strength:	100mg and 150mg
Apparatus Type:	USP Apparatus II (Rotating Paddles)
Media:	Phosphate Buffer pH 6.8

Volume:	900ml
Speed of Rotation:	50rpm
Sampling Times:	2,4,6,8 and 12 hours

Specifications:

Time	Criteria (Per Cent Released)
2 hr	
4 hr	
6 hr	
8 hr	
12 hr	

Post Marketing Commitments

Pediatric Studies

We request that you commit to conducting studies to assess the safety and effectiveness of Fluvoxamine maleate as a treatment for Social Anxiety Disorder in adolescent patients ages 12 to 17. There should be a reasonable distribution of both sexes.

We request that you commit to conducting and submitting the results of these studies no later than 3 years after the date of approval of this NDA.

Long Term Efficacy Studies

Since OCD and Social Anxiety Disorder are chronic illnesses, you are required to assess the longer-term effectiveness and safety of fluvoxamine CR in OCD and Social Anxiety Disorder.

Labeling
Please submit the revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling text for the package insert.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Proprietary Name and Container Label
The Division of Medication Errors and Technical Support (DMETS) finds the proprietary name "Luvox CR" acceptable. However, approval of the proprietary name is tentative based upon the final date of NDA approval. We remind you that this proprietary name will need to be re-evaluated approximately three months (90 days) prior to the expected approval of this application.

Additionally, we have the following recommendations pertaining to the carton and container label:

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Foreign Regulatory Update/Labeling
We require a review of the status of all Fluvoxamine Maleate actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If Fluvoxamine Maleate has been approved by any non-US regulatory bodies, we ask that you provide us any approved labeling for Fluvoxamine Maleate along with English translations when needed.

Request for Safety Update and World Literature Update
When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
    - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Prior to an approval action, we require an updated report on the world's archival literature pertaining to the safety of Fluvoxamine Maleate. Please provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries. This report should include only literature not covered in your previous submissions. We will need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of Fluvoxamine Maleate. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Promotional Material
In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Renmeet Grewal, Pharm.D., Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
2/27/2007 12:12:11 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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NDA 22-033

Solvay Pharmaceuticals, Inc.
Attention: Michael F. Hare
Manager, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Hare:

Please refer to your new drug application dated April 28, 2006, received May 1, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luvox CR (fluvoxamine maleate) 100mg and 150mg Extended-Release Capsules.

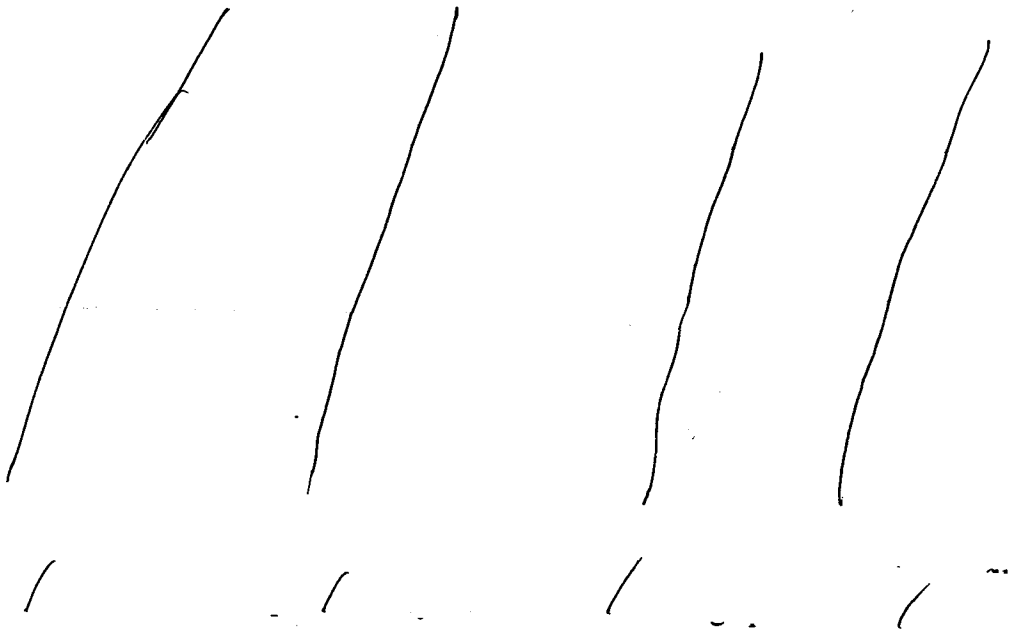
We acknowledge receipt of your submissions dated April 11, June 21, July 20, August 8, November 1, and December 10, 2007.

The June 21, 2007 submission constituted a complete response to our February 27, 2007 action letter.

This NDA proposes the use of Luvox CR in the treatment of social anxiety disorder (SAD) and obsessive compulsive disorder (OCD).

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies:

Office of Clinical Pharmacology



2. Dissolution: The dissolution method and specifications for both 100 mg and 150 mg capsules are as follows:

USP Apparatus 2:	Paddle Method
RPMs:	50 rpm
Volume:	900 mL
Medium:	pH 6.8 Phosphate Buffer
Sampling Times:	2, 4, 6, 8, and 12 hours

Time	% Released
2 hours	
4 hours:	
6 hours:	
8 hours:	
12 hours:	

Chemistry Control & Manufacturing

At this time an expiry period can not be assigned as the primary stability data do not support the recently amended (December 10, 2007) drug product dissolution acceptance criteria. This issue will need to be appropriately addressed. If this issue is to be addressed through the drug product manufacturer's DMF , we remind you to inform the DMF Holder of this point.

Post Marketing Commitment

1. Pediatric Studies

   We request that you commit to conducting studies to assess the safety and effectiveness of fluvoxamine maleate as a treatment for social anxiety disorder in pediatric patients ages 12 to 17. There should be a reasonable distribution of both sexes. We request that you commit to conducting and submitting the results of these studies no later than 3 years after the date of approval of this NDA.

2. Microscopic Examination of the Standard Battery of Tissues used in the General Toxicity Study

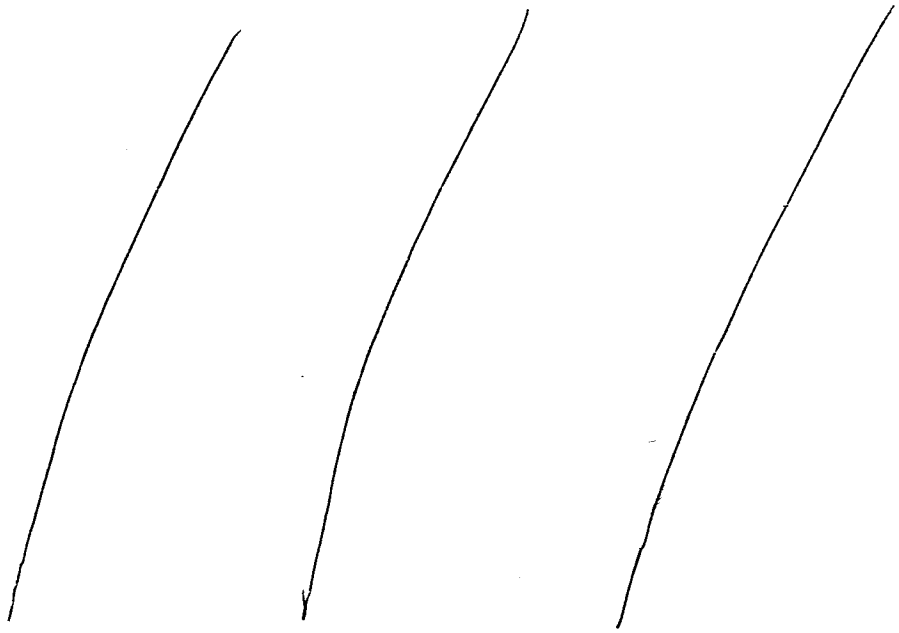
You did not conduct microscopic examination of the standard battery of tissues in the general toxicity study entitled "Fluvoxamine Maleate: 14-Day Oral (Gavage) Administration Comparative Toxicity Study in the Rat with Fluvoxamine Maleate and Fluvoxamine Maleate Spiked with _____. You will need to address this issue by conducting complete microscopic assessment on tissues from that study or, if that is not possible, by conducting another general toxicity study to qualify fluvox ketone, and including microscopic examination of the standard battery of tissues. [We recognize that a request for this same post-marketing commitment was made for your NDA 21-519 for Luvox IR, and that under that NDA you have already committed to having the remaining tissues from the general toxicity study in question processed and evaluated histopathologically.] Please provide us with an estimated date in which the Agency could expect to receive this supplemental report.

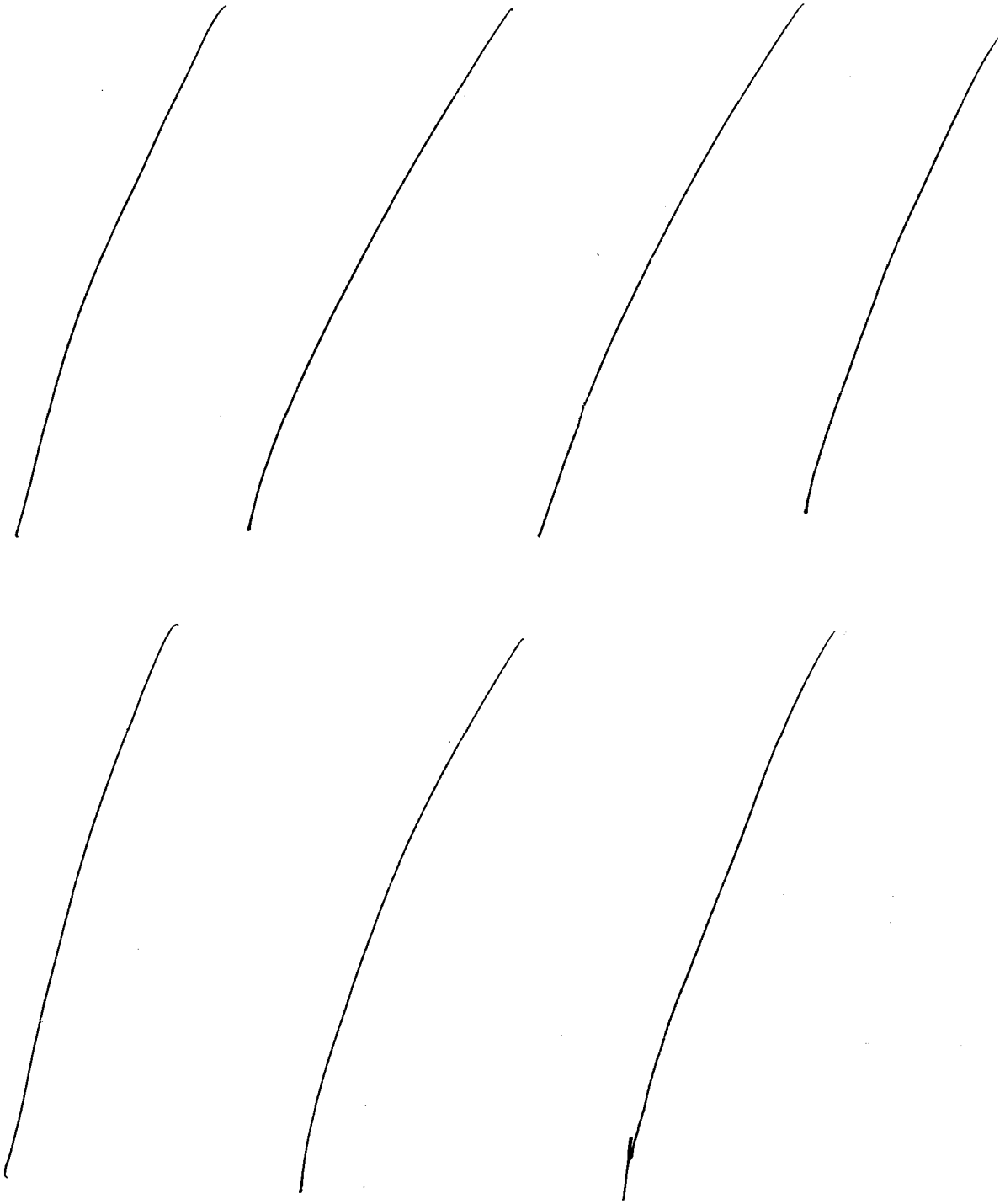
Labeling
Please submit the revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling text for the package insert.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Proprietary Name and Container Label
The Division of Medication Errors and Technical Support (DMETS) finds the proprietary name "Luvox CR" acceptable. However, approval of the proprietary name is tentative based upon the final date of NDA approval. We remind you that this proprietary name will need to be re-evaluated approximately three months (90 days) prior to the expected approval of this application.

Additionally, we have the following recommendations pertaining to the carton and container label:





Foreign Regulatory Update/Labeling
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5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Promotional Material
In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

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Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Labeling

36 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

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/s/

Thomas Laughren
12/20/2007 11:42:51 AM