

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-519**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 21-519

SUPPL # 000

HFD # 130

Trade Name Luvox

Generic Name Fluvoxamine maleate

Applicant Name Solvay Pharmaceuticals, Inc.

Approval Date, If Known 12-20-07

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Luvox was approved on December 5, 1994. It was voluntarily withdrawn from the market as a result of a consent decree (AIP) on September 24, 1997. The sponsor was removed from AIP on April 9, 2003. The sponsor re-submitted their application and was approved on December 20, 2007. This application provided only chemistry and bioequivalence data; no clinical data.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### **1. Single active ingredient product.**

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # YES  ! NO   
! Explain:

Investigation #2 !  
IND # YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES   
Explain:

!  
! NO   
! Explain:

Investigation #2

YES   
Explain:

!  
!  
! NO   
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

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Name of person completing form: CDR William Bender  
Title: Senior Regulatory Project Manager  
Date: 12-20-07

Name of Office/Division Director signing form: ODE1/DPP/Thomas Laughren, M.D.  
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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William Bender  
12/20/2007 01:40:48 PM

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-519 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: N000

Stamp Date: June 21, 2007 PDUFA Goal Date: December 20, 2007

HFD-130 Trade and generic names/dosage form: Luvox (fluvoxamine maleate) 25mg, 50mg and 100mg tablets

Applicant: Solvay Pharmaceuticals Inc. Therapeutic Class: Obsessive Compulsive Disorder

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

- Yes. Please proceed to the next question.  
 No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): \_\_\_\_\_

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): \_\_\_\_\_

Indication #1: \_\_\_\_\_

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.  
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.  
 No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population  
 Disease/condition does not exist in children  
 Too few children with disease to study  
 There are safety concerns  
 Other: \_\_\_\_\_

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

NDA 21-519

Page 3

**This page was completed by:**

*{See appended electronic signature page}*

William H. Bender  
**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH  
STAFF at 301-796-0700**

**(Revised: 10/10/2006)**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: \_\_\_ Partial Waiver \_\_\_ Deferred \_\_\_ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below)::

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is*

complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below)::

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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this page is the manifestation of the electronic signature.**  
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/s/

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William Bender

12/13/2007 08:41:16 AM

## ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 21-519	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Luvox Established Name: Fluvoxamine Dosage Form: 25mg, 50mg & 100mg tablets		Applicant: Solvay Pharmaceuticals, Inc.
RPM: Bill Bender		Division: Psychiatry Products    Phone # 301-796-2145
NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):  Provide a brief explanation of how this product is different from the listed drug.  <input type="checkbox"/> If no listed drug, check here and explain:  <b>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</b>  <input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date:
❖ User Fee Goal Date		12/20/2007
❖ Action Goal Date (if different)		
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions ( <i>specify type and date for each action taken</i> )		<input type="checkbox"/> None AP 12-5-94; AIP 9-24-97; removed from AIP on 4-9-03; AE 02-09-04 and 11-16-06
❖ Advertising ( <i>approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed ( <i>indicate dates of reviews</i> )		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):  NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2  <input type="checkbox"/> Orphan drug designation  NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies  NDAs and NDA Supplements: <input type="checkbox"/> OTC drug  Other:  Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP                             <ul style="list-style-type: none"> <li>Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)</li> <li>OC clearance for approval (<i>file communication in Administrative Documents section</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other



notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)</p>	<p>Division Director memorandum, 2/4/04; 11/16/06</p>
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)</p>	
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	<p>12/12/2007</p>
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	<p>N/A</p>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<p>Yes</p>
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	<p>Yes</p>
<p>❖ Patient Package Insert</p>	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	<p>N/A</p>
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
<p>➤ Medication Guide</p>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	<p>Yes</p>
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	
<p>❖ Labels (full color carton and immediate-container labels)</p>	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labels (only if generated after latest applicant submission)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	<p>June 20, 2007</p>
<p>❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)</p>	<p><input checked="" type="checkbox"/> DMETS  <input type="checkbox"/> DSRCS  <input type="checkbox"/> DDMAC  <input type="checkbox"/> SEALD  <input type="checkbox"/> Other reviews  <input type="checkbox"/> Memos of Mtgs</p>

❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) ( <i>indicate date of each review</i> )	
❖ NDA and NDA supplement approvals only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> <li>• Center Director's Exception for Review memo</li> <li>• If AP: OC clearance for approval</li> </ul>	
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. ( <i>Include certification.</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
• Outgoing Agency request for post-marketing commitments ( <i>if located elsewhere in package, state where located</i> )	In AP letter
• Incoming submission documenting commitment	06-28-02 submission
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	AE letter, 2-9-04 and 11/16/06
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference ( <i>indicate date; approvals only</i> )	
• Pre-NDA/BLA meeting ( <i>indicate date</i> )	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting ( <i>indicate date</i> )	<input checked="" type="checkbox"/> No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
❖ CMC/Product review(s) ( <i>indicate date for each review</i> )	CMC review, 11/08/06; 12/10/07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• <input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	
• <input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
• <input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

<ul style="list-style-type: none"> <li>❖ BLAs: Facility-Related Documents                             <ul style="list-style-type: none"> <li>• Facility review (<i>indicate date(s)</i>)</li> <li>• Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>)</li> </ul> </li> </ul>	N/A <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
<ul style="list-style-type: none"> <li>❖ NDAs: Methods Validation</li> </ul>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
(continued on form 101)	
<ul style="list-style-type: none"> <li>❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)</li> </ul>	Pharm/tox review, 11/13/06; 12/14/07
<ul style="list-style-type: none"> <li>❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No carc
<ul style="list-style-type: none"> <li>❖ ECAC/CAC report/memo of meeting</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Nonclinical inspection review Summary (DSI)</li> </ul>	<input checked="" type="checkbox"/> None requested
<ul style="list-style-type: none"> <li>❖ Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	Clinical review, 09/29/06; 8/31/07
<ul style="list-style-type: none"> <li>❖ Financial Disclosure reviews(s) or location/date if addressed in another review</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)</li> </ul>	<input checked="" type="checkbox"/> Not needed
<ul style="list-style-type: none"> <li>❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)</li> </ul>	<input checked="" type="checkbox"/> Not needed
<ul style="list-style-type: none"> <li>❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)                             <ul style="list-style-type: none"> <li>• Clinical Studies</li> <li>• Bioequivalence Studies</li> <li>• Clin Pharm Studies</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> None requested
<ul style="list-style-type: none"> <li>❖ Statistical Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None      10-02-06 and 8/13/2007

Comment [11]

## Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) And no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) And all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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this page is the manifestation of the electronic signature.**  
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/s/

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William Bender  
12/17/2007 09:59:18 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-519

Solvay Pharmaceuticals, Inc.  
Attention: Judy Tian  
Assistant Director, Regulatory Affairs  
901 Sawyer Road  
Marietta, GA 30062

Dear Dr. Tian:

We acknowledge receipt on May 17, 2006 of your May 16, 2006 resubmission to your new drug application for Luvox (fluvoxamine maleate) 25 mg, 50 mg and 100 mg tablets.

We consider this a complete, class 2 response to our February 9, 2004 action letter. Therefore, the user fee goal date is November 17, 2006.

If you have any question, call Bill Bender, Regulatory Project Manager, at (301) 796-2145.

Sincerely,

*{See appended electronic signature page}*

CAPT Paul A. David, R.Ph., CPMS  
Division of Psychiatry Products  
Office of Drug Evaluation  
Center for Drug Evaluation and Research

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/s/

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Paul David

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

OCT 30 2003

DMF —

b(4)

Solvay Pharmaceuticals, Inc.  
Attention: Robert A. Pollock  
Director, Regulatory Affairs  
901 Sawyer Road  
Marietta, Georgia 30062

Dear Mr. Pollock:

Your letter dated May 21, 2002, authorizes us to reference Drug Master File (DMF) — in support of Solvay Pharmaceuticals drug product application NDA 21-519 LUVOX® (fluvoxamine maleate) Tablets 25 mg, 50 mg and 100 mg.

b(4)

Your communication dated February 20, 2001 was reviewed in support of this NDA. Since approval of Solvay Pharmaceuticals drug product application NDA 21-519 is contingent upon adequate information being provided in a supporting DMF, please submit the following information as soon as possible:

- The FDA notes that the latest DMF — Annual Update is dated February 20, 2001. The holder is reminded that they should provide an annual report on the anniversary date of the original submission. If the subject matter of the DMF is unchanged, the DMF holder should provide a statement that the subject matter of the DMF is current.
- Please provide the current COAs for each analytical reference standard used in the development and analysis of fluvoxamine maleate.
- Please provide the FDA with the current regulatory release and retest specifications for fluvoxamine maleate drug substance.
- The FDA recommends that the DMF Holder lower the release and retest specifications for the identified impurities in fluvoxamine maleate drug substance so as to be consistent with the ICH Q3A(R) *Impurities in New Drug Substances* (i.e., NMT 0.15%) Guidance. Alternatively, please provide the FDA with data or references to the data that qualifies the fluvoxamine maleate drug substance impurities as listed in the current release and retest specifications.
- Please correct the fluvoxamine maleate drug substance COAs to show the current regulatory release specification for each release test.
- Please provide the FDA with the current fluvoxamine maleate drug substance stability protocol.

b(4)

This information should be provided as an amendment to your Drug Master File. Please forward two (2) copies to:

b(4)

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
12229 Wilkins Avenue  
Rockville, Maryland 20852

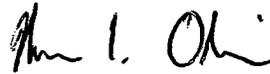
Solvay Pharmaceuticals will be notified that the information in your DMF is inadequate to support their NDA. When you amend your DMF — please notify Solvay Pharmaceuticals in accordance with 21 CFR 314.420(c) and notify the review chemist at the address below that your DMF has been amended. Please do not provide a copy of the amendment to the review chemist.

b(4)

Lorenzo Rocca  
1451 Rockville Pike  
Rockville, MD 20852

If you have any questions, call Jacqueline H. Ware, Regulatory Project Manager, at (301) 594-5533.

Sincerely,



Thomas F. Oliver, Ph.D.  
Chemistry Team Leader, Psychiatric Drugs for the  
Division of Neuropharmacological Drug Products,  
HFD-120  
DNDC DNDC I, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

DMF —  
Page 3

b(4)

CC:

Original DMF (2 copies) —

HFD-120/Division File for NDA 21-519

HFD-120/Chemist/ROCCAL *dr/10-30-03*

b(4)

HFD-120/RPM/WAREJ

HFD-120/Team Leaders/OLIVERT TO 10/30/03

HFD-120/PharmTox/FOSSOML

Drafted by: lr/October 30, 2003

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**DMF DEFICIENCY**

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## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

## Memorandum

Date APR 11 2003

From Director  
Division of Manufacturing and Product Quality, HFD-320

Subject Resumption of Application Review

To Directors  
Office of New Drugs, HFD-020  
Office of Pharmaceutical Science, HFD-003  
Office of Drug Evaluation I, HFD-101  
Office of Drug Evaluation II, HFD-102  
Office of Drug Evaluation III, HFD-103  
Office of Drug Evaluation IV, HFD-104  
Office of Drug Evaluation V, HFD-105  
Office of New Drug Chemistry, HFD-800  
Office of Generic Drugs, HFD-600  
Office of Epidemiology and Biostatistics, HFD-700  
Office of Clinical Pharmacology and Biopharmaceutics, HFD-850

On September 10, 1991, FDA published the "Application Integrity Policy" in the Federal Register (FR 5646191: "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities"). As you know, for each affected firm, we will generally defer substantive scientific review of data in each pending application or supplement, until a validity assessment determines the reliability of the submissions.

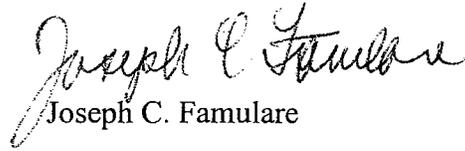
Attached is the current listing of the applicants affected by the Application Integrity Policy. This revised list reflects the **deletion of Solvay Pharmaceuticals Inc. (SPI)** (effective April 9, 2003) because the validity assessment of the firm has been completed. Unless otherwise noted, all facilities of each applicant are affected.

Substantive scientific review of data of Solvay's applications should be resumed and pending applications returned to the review queue in accordance with your Office's policy.

The attached list should be provided to those individuals responsible for reviewing applications. This list is not intended for public dissemination or discussion by the Agency personnel.

SPI has been notified of this decision to resume review. The firm has been requested to address questions to my office, however, they may contact your staff concerning review of its applications.

Please contact Albinus D'Sa at 301-827-9044, if you have any questions. Your cooperation is appreciated.

  
Joseph C. Famulare

Attachment

HFD-1  
HFD-2  
HFD-3  
CGF-1  
HFC-1  
HFC-1  
HFC-210  
HFC-230  
HFD-003  
HFD-007  
HFD-020  
HFD-030  
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HFD-820  
HFD-830  
HFD-850  
HFA-224  
HFV-230  
HFS-200  
HFS-225  
HFM-610  
HFZ-310  
HFZ-400

Chron  
Firm File

All pages are accounted for in this document.  
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**Attachment:**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Below are the firms that the Center for Drug Evaluation and Research has notified that FDA has deferred substantive scientific review of their applications pending a validity assessment**

<b>Firm</b>	<b>Location</b>	<b>Central File No./FEI No.</b>
Biochimica Opos SpA	Agrate Brianza, Italy	9611856/3002806473
Biopharmaceutics Inc.*	Bellport, NY	2434267/2434267
Solopak Pharmaceuticals, Inc.	1. Elk Grove Village, IL	1. 1450942 (Tonne Rd.)/1450942
Solopak Pharmaceuticals, Inc.	2. Franklin Park, IL	No current CFN or FEI number
Superpharm Corp.*	Bayshore, NY	2434256/2434256



## Memorandum

APR 9 2003

Dr. Harold Shlevin,  
President and CEO  
Solvay Pharmaceuticals, Inc.  
901 Sawyer Road  
Marietta, GA 30062

Dear Dr. Shlevin:

We refer to our letter dated September 24, 1997, advising Solvay Pharmaceuticals Inc. (SPI), that the Center for Drug Evaluation and Research (CDER) had suspended substantive scientific review of all applications involving SPI in Marietta, GA and Baudette, MN pending satisfactory completion of validity assessment of all marketed and investigational drug product applications. Your firm has conducted an internal review of its operations to identify and correct the circumstances that gave rise to the submission of false and misleading information. SPI has prepared and implemented a Corrective Action Operating Plan, which appears to provide sufficient safeguards to preclude future wrongful acts and non-compliance with regulatory requirements. Since then, SPI has withdrawn a large number of applications that were determined to be tainted, and recalled the affected products from the market. FDA's Minneapolis and Atlanta Districts have conducted validity assessment inspections at Baudette, MN and Marietta, GA and have determined that SPI is currently in compliance with regulatory requirements.

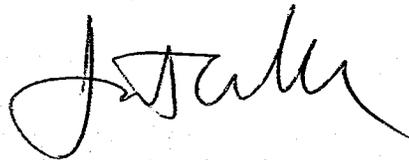
Therefore, I have directed my staff to resume substantive review of all of your company's applications. Applications that were withdrawn by SPI during this process may not be re-filed unless your firm can demonstrate to FDA's satisfaction the reliability of the supporting data. However, your firm is not precluded from filing new applications for those products if it so chooses.

Resumption of substantive review by FDA of your company's applications is not to be construed as an approval of any condition that may become known in the future. Be advised that FDA expects SPI's continuing adherence to the commitments made in its Corrective Action Operating Plan and the agency will evaluate continued compliance.

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If you have any questions, please do not hesitate to contact the appropriate reviewing office or Dr. Albinus D'Sa at the CDER Office of Compliance at 301 827 9044.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Woodcock', written in a cursive style.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research

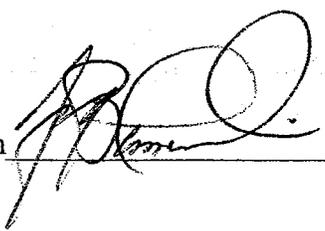
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HFD-102  
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HFD-820  
HFD-830  
HFA-224  
HFV-230  
HFS-200  
HFS-225  
HFM-610  
HFZ-310  
HFZ-400

Concurrence: Frederick Blumenschein  
Final: AD'Sa



Date: 4/11/2003



NDA 21-519

**INFORMATION REQUEST LETTER**

Solvay Pharmaceuticals, Inc.  
Attention: Judy Tian, M.S.  
Manager, Regulatory Affairs, CNS  
901 Sawyer Road  
Marietta, GA 30062

Dear Ms. Tian:

Please refer to your June 28, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luvox (fluvoxamine) Tablets.

We also refer to your original Luvox NDA (20-243), which was approved on December 5, 1994 and withdrawn by you on May 13, 2002 as result of an AIP audit and part of an agreement between Solvay and the Agency.

We have completed our filing review of your application and have determined that the application is fileable. However, because this application is subject to the provisions of the Application Integrity Policy (AIP), we will not continue our review of this application until you are notified by the Director, Center for Drug Evaluation and Research, that the AIP has been revoked, unless we determine that the AIP no longer applies to this application or that the product is medically necessary.

During our filing review, several questions arose. Therefore, we have the following requests related to your submission. Please respond in writing to these requests.

Biopharmaceutics

1. We cannot determine from your submission if the drug product formulation for the 50-mg film coated Luvox tablet (NDA 21-519) provided for in this application is identical to the formulation that was approved under NDA 20-243. Please confirm that the formulations are identical and submit a comparison of the formulations (qualitative and quantitative) for the proposed 50-mg film coated Luvox tablet (NDA 21-519) and the original 50-mg film coated Luvox tablet (NDA 20-243).
2. If the drug product formulations are different (question #1), please provide dissolution data comparing the original and proposed Luvox formulations using the original NDA dissolution conditions and specifications.

3. We note that your submission does not contain any requests for waiver of in vivo bioavailability (BA) and/or bioequivalence (BE) studies for the 25-mg and 100-mg strengths of Luvox. Therefore, we ask that you submit these waiver requests and list the formulations for all strengths of Luvox you wish to market.
4. The 5 biopharmaceutics studies provided in your submission do not contain specific information needed for review. Please provide complete assay validation data for each study, in particular assay dates, sample storage times, long term plasma stability, freeze-thaw, bench top stability and assay recovery.

Chemistry, Manufacturing, and Controls (CMC)

1. We note that your submission does not contain either an environmental assessment or a request for categorical exclusion. Please submit one or the other.
2. We are unable to easily identify CMC differences for Luvox drug product and fluvoxamine drug substance between the proposed Luvox NDA (21-519) and the original Luvox NDA (20-243). Therefore, we ask that you identify and summarize all CMC changes for drug substance and drug product that have occurred between the proposed NDA 21-519 and NDA 20-243. For ease of review, we recommend that you use a comparative format (e.g., proposed vs. original) that easily distinguishes the differences in CMC information in the two applications.
3. Several of your proposed specifications for Luvox drug product exceed the 0.2% threshold for qualification of degradation products as described in the "*Guidance for Industry - Q3B Impurities in New Drug Products*". Provide a rationale and justification for your selection of these degradation product limits.

Pharmacology/Toxicology

We remind you that, on September 9, 1994 (as a component of the original Luvox NDA approval), you committed, as a Phase IV commitment, to either repeat the Segment I and II reproduction studies in the rat or provide adequate justification for the doses which were used. Further communication on this point was made in our letter of August 12, 1998 to NDA 20-243. Your proposed Luvox NDA 21-519 does not contain any information regarding this issue. Please provide an update on your progress in addressing this issue.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-5533.

Sincerely,

Russell G. Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Center for Drug Evaluation and Research

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/s/

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Russell Katz  
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NDA 21-519

Solvay Pharmaceuticals, Inc.  
Attention: Suzanne LoGalbo  
Vice President, Regulatory Affairs  
901 Sawyer Road  
Marietta, GA 30062

Dear Ms. LoGalbo:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Luvox (fluvoxamine) Tablets

Review Priority Classification: Standard (S)

Date of Application: June 28, 2002

Date of Receipt: July 1, 2002

Our Reference Number: NDA 21-519

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 30, 2002 in accordance with 21 CFR 314.101(a). However, this application is subject to the provisions of the Application Integrity Policy (AIP). If filed, review will not begin until you are notified by the Director, Center for Drug Evaluation and Research, that the AIP has been revoked, unless we determine that the AIP no longer applies to this application or that the product is medically necessary.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the

application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neuropharmacological Drug  
Products, HFD-120  
Attention: Division Document Room 4008  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neuropharmacological Drug  
Products, HFD-120  
Attention: Division Document Room 4008  
1451 Rockville Pike  
Rockville, Maryland 20852-1420

If you have any questions, call me at (301) 594-5533.

Sincerely,

*{See appended electronic signature page}*

Jacqueline H. Ware, Pharm.D.  
Regulatory Management Officer  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Jackie Ware  
7/16/02 02:02:02 PM

**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**MEDICAL NECESSITY DETERMINATION**

**PRODUCT(S)**

*Trade Name(Generic Name) (Formulation (s) in shortage*

LUVOX® (fluvoxamine maleate) tablets 25/50/100-mg

**MANUFACTURING FIRM NAME and ADDRESS**

*Single Source Product or multiple source product*

This product is available from multiple sources

*Associated NDA numbers*

20-243

*Name of Firm*

Solvay Pharmaceuticals Inc.

*Address of firm*

901 Sawyer Road

Marietta, Georgia

30062

*Phone number*

770/578-5864

**NATURE OF PROBLEM**

- *A brief background statement of when CDER was notified of the shortage and by what mechanism. A statement of what the company indicates the shortage is due to and any additional background information. One paragraph is sufficient.*

There is no shortage of fluvoxamine at this time. There are eleven generic drug applications for fluvoxamine that are currently approved. Luvox NDA 20-243 was withdrawn from the market in a letter dated 13 May 2002. This was part of an agreement with the Agency and Solvay Pharmaceuticals Inc. after an Applications Integrity Policy (AIP) audit revealed instances where inaccurate or unsubstantiated chemistry, manufacturing and controls data had been submitted to the FDA.

- Please evaluate the medical need for this product by answering the questions below. Keep in mind that a medically necessary product is a product that is used to treat or prevent a serious disease or medical condition, and there is no other available source of that product or alternative drug that is judged by medical staff to be an adequate substitute. Patient "inconvenience" alone is an insufficient basis to classify a product as medical necessity.

**1. Is the product used to treat a serious disease or medical condition?**

**[A Serious Disease or Medical condition involves such a condition in a specific population, associated with morbidity that has substantial impact on day-to-day functioning]**

No

Yes – Explain

OCD is a debilitating anxiety disorder that, by some estimates, effects 2-3% of the population over lifetime. Suicide is a risk for patients with OCD.

**2. Are there alternative products available?**

No

Yes – Explain and state usefulness of specific products

There are eleven generic forms of fluvoxamine available.

If the nature of the shortage problem described above is related to manufacturing difficulties and/or a compromised product or bulk drug substance, please answer question three. Otherwise, proceed to question four.

**3. Risk - Benefit Comparison:**

**A. Explain the comparison of the risks of using the product to its benefits with regard to the identified serious disease or medical condition.**

There are no alternate risks in using generic forms of fluvoxamine.

**B. Explain the comparison of the risks and benefits of the product to those of each alternative product.**

Alternate forms of fluvoxamine are bioequivalent to Luvox®

**4. From the above assessment, is this product medically necessary?**

No

Yes

**5. Additional comments regarding this shortage situation:**

There is a shortage of the brand name Luvox® but there is not a shortage of the drug product fluvoxamine in appropriate dosage forms.

**6. Signature of person performing this medical necessity determination.**

*{See appended electronic signature page}*

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Paul J. Andreason, MD  
Medical Officer

Date

*{See appended electronic signature page}*

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Thomas Laughren, MD  
Medical Officer, Team Leader

Date

*{See appended electronic signature page}*

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Russell G. Katz, MD  
Division Director

Date

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this page is the manifestation of the electronic signature.**  
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/s/

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Paul Andreason  
7/15/02 10:50:19 AM  
MEDICAL OFFICER

Thomas Laughren  
7/15/02 12:29:28 PM  
MEDICAL OFFICER

Russell Katz  
7/17/02 03:48:50 PM  
MEDICAL OFFICER



# SOLVAY PHARMACEUTICALS

Suzanne E. LoGarbo, R.Ph., J.D.  
Vice President  
Regulatory Affairs

28 June 2002



RECEIVED  
JUL 01 2002  
HFD-120/CDER

Russell G. Katz, M.D.  
Director, Division of Neuropharmacological  
Drug Products, HFD-120  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Woodmont Office Complex II, Room 4037  
1451 Rockville Pike  
Rockville, MD 20852

Dear Dr. Katz:

**RE: LUVOX® (fluvoxamine maleate) Tablets, 25, 50 and 100 mg  
New Drug Application 21-519**

Pursuant to 21 CFR 314.50, Solvay Pharmaceuticals, Inc., is submitting this New Drug Application (NDA) for LUVOX® (fluvoxamine maleate) Tablets for the treatment of Obsessive Compulsive Disorder (OCD) in adults and pediatric patients.

### Background

LUVOX® (fluvoxamine maleate) 25 mg, 50 mg, and 100 mg Tablets were originally approved as NDA 20-243 on 05 December 1994 for the indication of Obsessive Compulsive Disorder (OCD) for use in adults and for use in children and adolescents since 25 March 1997. Fluvoxamine is currently registered in more than 80 countries and has been administered to over — patients for the treatment of Obsessive Compulsive Disorder (OCD) and depression. More than 46,000 patients have been exposed to fluvoxamine in clinical trials worldwide. Since December 2000, the Food and Drug Administration has approved eleven generic drug applications using the safety and efficacy of the LUVOX® Tablets NDA as the basis for approval.

b(4)

In September 1997, Solvay Pharmaceuticals, Inc., the owner/applicant for the product, was placed under the Application Integrity Policy (AIP). As a result of the AIP, a thorough audit and validity assessment of the LUVOX® Tablets application was conducted. The AIP audit revealed instances where inaccurate or unsubstantiated chemistry, manufacturing and controls data had been submitted to the Food and Drug Administration. As a result of this audit and as part of an agreement between the Agency and Solvay Pharmaceuticals, Inc., NDA 20-243 was withdrawn in a letter dated 13 May 2002.

## Contents of this application

Solvay Pharmaceuticals hereby requests that all nonclinical pharmacology and toxicology, human pharmacokinetics and bioavailability and clinical safety and efficacy information contained in NDA 20-243, including supplements S-006 and S-021, be included by reference in this New Drug Application for LUVOX® Tablets.

### Chemistry, Manufacturing and Controls

Solvay Pharmaceuticals, Inc. is submitting, a complete, updated, and independently audited Section 4.0 - Chemistry, Manufacturing and Controls. The \_\_\_\_\_ has independently audited the data submitted in this application and a copy of the audit report is being submitted with this application and to the Office of Compliance. The findings of the audit report have been addressed in a follow-up memorandum. The independent audit report and the follow-up memorandum are provided at the beginning of Section 4.0.

b(4)

### Human Pharmacokinetics and Bioavailability

This application also references and summarizes fluvoxamine maleate human pharmacokinetics and bioavailability information submitted in NDA 20-243. The bioanalytical data associated with the pharmacokinetics and bioavailability data were subject to AIP, and as such, data validity assessments were conducted by independent auditors on behalf of Solvay Pharmaceuticals, Inc. We conclude that the issues identified by the auditors do not change the interpretation or conclusions pertaining to previously reported pharmacokinetic data.

The bioequivalence of LUVOX® Tablets to the clinical materials used in pivotal efficacy and safety trials was demonstrated by data previously submitted to the Agency in NDA 20-243. Solvay Pharmaceuticals Inc. is supplementing this application with bioequivalence data from two additional studies sponsored by Solvay Pharmaceuticals BV. of the Netherlands. One study conducted in 1992 established the bioequivalence of the capsule used in clinical safety and efficacy trials to the film-coated and enteric-coated tablets marketed in Europe and an \_\_\_\_\_. A more recent study conducted in 1999 established the bioequivalence of the LUVOX® Tablets to the film-coated tablet marketed in Europe. Taken together, these studies reconfirmed that LUVOX® Tablets are bioequivalent to the capsule formulation used in clinical trials and provide convincing evidence to support the safety and efficacy of fluvoxamine and approval of this New Drug Application for LUVOX® Tablets.

b(4)

For ease of review, we have enclosed copies of the bioequivalence studies submitted in NDA 20-243 as well as reports of the two bioequivalence studies

sponsored by Solvay Pharmaceuticals BV. Copies of relevant third party audit reports and Solvay responses, all previously submitted to the Office of Compliance, are also provided.

The data submitted in this section have been independently audited by \_\_\_\_\_ . A copy of the audit report is being submitted with this application and to the Office of Compliance. The findings of the audit report have been addressed in a follow-up memorandum. The independent audit report and the follow-up memorandum are provided at the beginning of Section 6.0.

b(4)

Furthermore, Section 2.0 Labeling has been submitted with the proposed labeling.

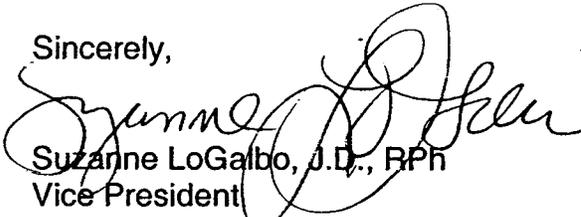
Solvay Pharmaceuticals, Inc. has mailed the user fee of \$313,320.00 on 26 June 2002, by priority overnight delivery to the FDA. Pursuant to PDUFA, Solvay Pharmaceuticals expects a standard ten-month review time.

For the convenience of the reviewer, we have included an electronic version of this submission on CD-ROM that includes the SAS datasets from the statistical analysis of the stability data. A copy of the CMC information has also been provided to the FDA District Offices. The Field Copy certification is provided.

Should you have any questions or require additional information regarding this submission, please contact Karen D. Quinn, Ph.D., Manager, Regulatory Affairs-CMC for CMC information at (770) 578-5868 or contact Don Ruggirello, Assistant Director, Regulatory Affairs-Product Liaison at (770) 578-5658 concerning any other issues.

*Judy Tian*

Sincerely,

  
Suzanne LoGalbo, J.D., RPh  
Vice President  
Regulatory Affairs

*fax 770-578-5864*

Cc: Albinus M. D'Sa, Ph.D.  
Ballard Graham, M.D.  
James Rahto  
Paul David



NDA 20-243

Solvay Pharmaceuticals, Inc.  
Attention: Suzanne LoGalbo, J.D., R.Ph.  
Vice-President, Regulatory Affairs  
901 Sawyer Road  
Marietta, GA 30062

Dear Ms. LoGalbo:

We received your May 14, 2002 correspondence on May 15, 2002 requesting withdrawal under 21 CFR 314.150(d) of approval of your new drug application (NDA) for Luvox (fluvoxamine maleate) 25 mg, 50 mg, 100 mg, and 150 mg tablets.

We have initiated withdrawal of this application. We will publish a notice in the Federal Register stating that you have voluntarily requested withdrawal of approval of this application because you have stopped marketing the drug product under the NDA.

We note that you are voluntarily withdrawing your NDA in response to audit findings indicating possible inaccuracies noted in the chemistry, manufacturing, and controls section of the application, and not due to any safety or efficacy concerns.

You can avoid being billed for a listed drug by notifying our Information Management Team (IMT) to remove your product from the approved products list by September 30 of this fiscal year. You may call the IMT at (301) 827-5467 or write to them:

Food and Drug Administration, CDER  
Division of Data Management and Services  
Information Management Team, HFD-095  
5516 Nicholson Lane, Bldg. A  
Rockville, MD 20852

If you have any questions, call Paul David, Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Russell Katz  
5/31/02 09:33:22 AM