CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-033

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-033 SUPPL # HFD # HFD-130

Trade Name Luvox CR

Generic Name fluvoxamine maleate

Applicant Name Solvay

Approval Date, If Known February 28, 2008

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

505b1

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.

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?

3 years

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?

No

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# 20-243 Luvox (fluvoxamine maleate) Immediate Release Tablets; AP Date 9-3-03; WD by Solvay due to AIP violations

NDA# 21-519 Luvox (fluvoxamine maleate) Immediate Release Tablets; AP Date 12-20-07; Sponsor relied on data from NDA 20-243 to support approval

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:

Social Anxiety Disorder (SAD): Trial 3107 & Trial 3108
Obsessive Compulsive Disorder (OCD): Trial 3103

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"):

Social Anxiety Disorder (SAD): Trial 3107 & Trial 3108
Obsessive Compulsive Disorder (OCD): Trial 3103

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 # 57,838	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 57,838	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 ☐ ! NO ☐
Explain: ! Explain:

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

Name of person completing form: Renmeet Grewal, Pharm.D.
Title: Senior Regulatory Project Manager
Date: 2/28/08

Name of Office/Division Director signing form: OND/ODE1/DPP, Mitchell Mathis, M.D.
Title: Deputy Division Director

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

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/s/

Mitchell Mathis
2/29/2008 04:36:00 PM
For Dr. Laughren

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-033 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: December 31, 2007 **PDUFA Goal Date:** February 29, 2008

HFD 130 **Trade and generic names/dosage form:** Luvox CR (fluvoxamine maleate) extended release capsules)

Applicant: Solvay Pharmaceuticals **Therapeutic Class:** Anti Anxiety

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

X **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: Generalized Social Anxiety Disorder

Is this an orphan indication?

☐ **Yes. PREA does not apply. Skip to signature block.**

X **No. Please proceed to the next question.**

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

☐ **Yes: Please proceed to Section A.**

X **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._0____ 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**
- X **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._17____ 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**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): 3 years from the date of approval

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.

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)

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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/s/

Renmeet Grewal
2/29/2008 04:00:24 PM

For Internal Use Only

Meeting Cancellation Form

(Use this form to cancel a meeting that was granted and scheduled after which time the sponsor or FDA has subsequently cancelled.)

Please remember to update the Meeting Status field in IMTS for this cancellation.

Complete the information below and check form into DFS.

Application Type	NDA
Application Number	22-033
DATE Meeting Cancelled (per communication with requester)	Tuesday, January 22, 2008
Scheduled Meeting Date	Thursday, January 24, 2008
Reason for Cancellation	The agency let the sponsor know the 6 hour time point for the dissolution specs could be dropped. Therefore the meeting was no longer needed.
Project Manager	Renmeet Grewal, Pharm.D.

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/s/

Renmeet Grewal
1/31/2008 03:05:27 PM

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:

We acknowledge receipt of your resubmission dated December 28, 2007, received December 31, 2007 to your new drug application for Fluvoxamine maleate extended release tablets.

We consider this a complete, class 1 response to our December action letter. Therefore, the user fee goal date is February 29, 2008.

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

Sincerely,

{See appended electronic signature page}

Renmeet Grewal, Pharm.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Renmeet Grewal
1/31/2008 11:57:32 AM

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Monday, December 10, 2007 2:19 PM
To: 'Hare, Michael'
Cc: Grewal, Renmeet
Subject: NDA 22-033 dissolution specification

Importance: High

Hi Michael,
Please respond to my email stating you agree to the following specifications regarding NDA 22-033 Luvox CR (fluvoxamine) Capsules which are the same specifications relayed to you in the February 27, 2007 Approvable Letter:

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:	

Please respond to this email by COB today.

Thank you,
Rimmy

Renmeet Grewal, Pharm.D., LCDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838

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/s/

Renmeet Grewal
12/10/2007 02:33:01 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-033

INFORMATION REQUEST LETTER

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

Dear Mr. Hare:

Please refer to your June 21, 2007, correspondence to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luvox CR(fluvoxamine maleate) extended release capsules.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response as soon as possible in order to continue our evaluation of your NDA:

1. Based on the particle size distribution data for the drug substance lots which you listed in Attachment 20 of the 21 JUN 2007 submission, we recommend the following acceptance criteria for the drug substance particle size distribution specification:

   These ranges bracket the proven acceptable ranges and are within the 99% confidence interval described in the Application.

2. Revise the drug product label as below so that the dosage form designation (extended release capsules) follows 'fluvoxamine maleate' in the carton labels. For example:

LuvoxCR (fluvoxamine maleate) extended release capsules	Or	Luvox CR (Fluvoxamine maleate) extended release capsules

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
11/21/2007 11:07:29 AM

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Friday, November 16, 2007 9:47 AM
To: 'Hare, Michael'
Cc: Bender, William
Subject: NDA 21-519 and NDA 22-033; request for final reports for PT studies

Good Morning Michael,

In your response to our Approvable Letters for NDA 21-519 and NDA 22-033, you submitted audited draft reports for 4 nonclinical studies to be used to support qualification of impurities/degradants in your drug substance and/or drug products (your submissions: NDA 21-519, N-000, AZ, letter-dated 6/20/07; and NDA 22-033, N-000, AZ, letter-dated 6/21/07).

We cannot complete our reviews of those submissions without consulting the final study reports. If you have already provided these final reports, please let us know where and when they were submitted; otherwise you must submit them immediately. You are reminded that you should also provide a list of all differences between the audited draft and final versions.

Sincerely,
Rimmy

Renmeet Grewal, Pharm.D., LCDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838

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/s/

Renmeet Grewal
11/16/2007 01:31:34 PM
CSO

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Wednesday, October 24, 2007 11:57 AM
To: 'Hare, Michael'
Subject: NDA 22-033

Dear Michael,

We have identified the following discrepancies between the adverse reactions reported in the CRFs, the JMP AE listing and the narratives as presented in the table below.

1. Please reconcile the differences in reported AEs between the 3 types of documentation, and for each patient, provide explanations for the discrepancies observed between what has been reported in CRFs, the JMP AE lists and the narratives included in this application.

2. Please review the remaining CRFs, narratives and AE lists related to identify any additional inconsistencies that are clinically meaningful.

3. Please provide a general explanation for the disparities that we have discovered in the audit of your application, as the accuracy of the safety data is of the utmost concern to us as the review process is being completed.

As you alluded to in your voicemail left today, it is in your best interest to provide the data required as expeditiously as possible to finalize the review of your application. Please send us a complete response to these questions by Wednesday, 31 October 2007.

Patient ID	Case Report Form AE's	Narrative Summary	JMP AE Listing
3104-69123	**SINUS ARRHYTHMIA BRADYCARDIA, ST-WAVE DEPRESSION** URINARY TRACT INFECTION,	OK	**ADDED:** ANOREXIA INSOMNIA
3104-69138	**INTERMITTENT LETHARGY,** URI, **DYSPNEA, LETHARGY,**	**ADDED:** SEXUAL DYSFUNCTION	**ADDED:** DRY MOUTH, HEADACHE, NAUSEA, SEXUAL DYSFUNCTION
3104-69152	NAUSEA, DIARRHEA, INDIGESTION, DECREASED APPETITE, **BURNING IN STOMACH**	OK	**ADDED:** CYST, HEADACHE, PAIN, LETHARGY, SKIN ULCER, WORSENING HYPERTENSION
3104-69166	**DELAYED EJACULATION,** DECREASED APPETITE, LIGHTHEADEDNESS, **INSOMNIA,** SOMNOLENCE	OK	**ADDED:** MIGRAINE, HEADACHE

3104-69242	**TINGLING IN BOTH ARMS, LIGHTHEADEDNESS, DECREASED APPETITE, NAUSEA**	OK	**ADDED: INCREASED APPETITE**
00020	LOOSE STOOL, PRESSURE TO BOTH EARS, **HIGH BLOOD PRESSURE**, HEADACHE, CHEST PAINS	Ok	?
3109-84-70161	Sore throat, **tonsillectomy**, headache.	OK	**Added still there**
3103-20-69015	Diarrhea, nausea, nightmares, pain (right flank), **suicidal ideation w/plan.**	**Entirely different AE's: dizziness, syncope**	**Same listing Entirely different AE's: dizziness, syncope**
3104-07-69215	**Hot and cold flashes, feeling disoriented, dizziness, tremor, nausea, decreased concentration, photophobia**, loss of sexual interest.	OK	**Added still there**
3104-19-69034	**Weight gain, increased anxiety.**	**Submitted OK**	**Added sore throat**
3109-29-70074	**Fatigue**, weariness.	OK	**Added:** Tachycardia, dry mouth, rash.

Renmeet Grewal, Pharm.D., LCDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838

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/s/

Renmeet Grewal
10/24/2007 05:12:45 PM
CSO

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: January 10, 2007

TO: Renmeet Grewal, Pharm.D., Regulatory Project Manager
June Cai, M.D., Clinical Reviewer
Division of Psychiatry Products, HFD-130

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Sherbet Samuels, R.N., M.P.H.

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-033

APPLICANT: Solvay Pharmaceuticals, Inc.

DRUG: Luvox (Fluvoxamine) CR capsules

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of Obsessive Compulsive Disorder and Generalized Social Anxiety Disorder.

CONSULTATION REQUEST DATE: September 11, 2006

DIVISION ACTION GOAL DATE: January 11, 2007

PDUFA DATE: March 1, 2007

I. BACKGROUND:

Luvox (Fluvoxamine) is currently marketed for the treatment of Obsessive Compulsive Disorder and Depression. The sponsor, Solvay Pharmaceuticals, Inc. submitted a New Drug Application (NDA # 22-033) for the use of Luvox (Fluvoxamine) in the treatment of Obsessive Compulsive Disorder and Generalized Social Anxiety Disorder.

Drs. Mohammed Bari, Robert Dupont, Jon Heiser, and Peter Londborg sites were selected for inspection due to large enrollment. The goals of the inspections were to assess adherence to FDA regulatory requirements; specifically, investigator oversight, protocol compliance, validity of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare. Protocol S1143103 entitled "A Multicenter, Double-Blind, Randomized, Parallel Group Study of the Efficacy and Safety of a Flexible Dose Regimen of Fluvoxamine CR versus Placebo in Outpatients with Obsessive Compulsive Disorder" and protocols S1143107 and S1143108 both entitled "A Twelve-Week, Randomized, Double-blind, Placebo Controlled, Flexible Dose Study of Fluvoxamine CR in the Treatment of Generalized Social Anxiety Disorder" were inspected. Dr. Dupont's conduct of protocol S1143107 was inspected in 2001 in support of NDA 21-309 submitted by the applicant, which was later withdrawn.

Summary Report of U.S. Inspections

II. RESULTS (by protocol/site):

Name of CI and site #	City, State	Protocol	Insp. Date	EIR Received Date	Final Classification
Mohammed Bari, M.D./1	National City, CA	S1143103	Nov.7-16, 2006	Nov. 30, 2006	VAI
Robert Dupont, M.D./8	Rockville, MD	S1143107	May 1-7, 2001	May 25, 2001	VAI
Jon Heiser, M.D./13	New Port Beach, CA	S1143107	Nov. 16-21, 2006	EIR Pending	EIR Pending
Robert Dupont, M.D./92	Rockville, MD	S1143108	Nov. 30-Dec. 5, 2006	EIR Pending	EIR Pending
Jon Heiser, M.D./94	New Port Beach, CA	S1143108	Nov. 16-21, 2006	EIR Pending	EIR Pending
Peter Londborg, M.D./95	Seattle, WA	S1143108	Nov. 15-Dec. 4, 2006	EIR Pending	EIR Pending

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations from regulations. Data unreliable.

A. Protocol # S1143103

1. Mohammed Bari, M.D. (Site Number 1)
   Synergy Clinical Research Center
   11908 Sweetwater Road,
   National City, CA 91950

a. What was inspected: Dr. Bari enrolled 23 subjects. The inspection encompassed an audit of 15 subjects' records. Primary endpoint efficacy data were verified for 15 subjects.

b. Limitations of inspection: Our investigator was unable to copy requested electronic case report forms (e-CRFs) because the dedicated computer used to retrieve the e-CRFs did not allow printing.

c. General observations/commentary: The inspection found inadequate and inaccurate case histories. Specifically:

1. For Subject 69058, the source dosing compliance and accountability record for Day 85, return date 9/16/99, indicates that two capsules were lost with four remaining. However, the e-CRF indicates that six capsules remain with none lost.

2. For Subject 69059, a note to file, dated 8/17/99, indicates that the patient did not return the blister card at the Day 22 visit on 8/17/99 and would return the card on 8/24/99. However, the source dosing compliance/accountability record and e-CRF list 8/17/99 as the date of return.

3. For Subject 69141, the source dosing compliance and accountability record for Day 29, return date 9/24/99, indicates that two capsules were lost. However, the e-CRF accountability record indicates that none were lost while an e-CRF comment section states that two capsules were lost.

4. For Subject #69170:

i. The source dosing compliance and accountability record for Day 8, return date 10/5/99, indicates that one capsule was lost with five remaining and a photocopy of the associated blister card indicates that five remain. However, a note to file and the e-CRF indicates that six remain with none lost.

ii. The source accountability record for Day 15, return date 10/12/99, indicates that one capsule was lost with five remaining and a photocopy of the associated blister card indicates that five remain. However, the e-CRF indicates that six remain with none lost.

d. Data from this site are acceptable.

B. Protocol # S1143107

1. Robert Dupont, M.D. (Site Number 8)
   Institute for Behavior & Health, Inc.
   6191 Executive Boulevard
   Rockville, MD 20852

Observations noted below for this clinical investigator are based on the inspection conducted in May 2001 in support of [redacted]

a. What was inspected: Dr. Dupont enrolled 33 subjects. The inspection encompassed an audit of 28 subjects' records. Primary endpoint efficacy data were verified for 28 subjects.

b. Limitations of inspection: none

c. General observations/commentary: The inspection found that a subject was terminated due to an adverse event, but there was no documentation to indicate that the subject was followed up as required by the protocol. The inspection also found that there was no documentation for 5 out of 431 study kits that were returned to the sponsor.

d. Data from this site are acceptable.

2. Jon Heiser, M.D. (Site Number 13)
   Pharmacology Research Institute
   1000 Dove Street, Suite 200
   Newport Beach, CA 92660-2814

Observations noted below for this clinical investigator are based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. What was inspected: Dr. Heiser enrolled 23 subjects. The inspection encompassed an audit of 12 subjects' records. Primary endpoint efficacy data were verified for 12 subjects.

b. Limitations of inspection: none

c. General observations/commentary: No significant deviations from FDA regulations were observed.

d. Data from this site are acceptable.

C. Protocol S1143108

Observations noted below for all three clinical investigators are based on communications from field investigators. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

1. Robert Dupont, M.D. (Site Number 92)
   Institute for Behavior & Health, Inc.
   6191 Executive Boulevard
   Rockville, MD 20852

a. What was inspected: Dr. Dupont enrolled 10 subjects. The inspection encompassed an audit of 8 subjects' records. Primary endpoint efficacy data were verified for 10 subjects.

b. Limitations of inspection: none

c. General observations/commentary: No significant deviations from FDA regulations were observed. However, it was noted that for subject 70240, an adverse event description at Week 10, reads "stopped breathing, while dreaming, woke self up". The clinical investigator noted it probably meant sleep apnea. This adverse event was not noted in the data line listings. In addition, for subject 70290, an adverse event description at the Final Visit noted "side pain" off and on for 3 days. The data line listing did not note any description related to "side pain".

d. Data from this site are acceptable.

2. Jon Heiser, M.D. (Site Number 94)
   Pharmacology Research Institute
   1000 Dove Street, Suite 200
   Newport Beach, CA 92660-2814

a. What was inspected: Dr. Heiser enrolled 11 subjects. The inspection encompassed an audit of 9 subjects' records. Primary endpoint efficacy data were verified for 9 subjects.

b. Limitations of inspection: none

c. General observations/commentary: No significant deviations from FDA regulations were observed. Data listings provided by the sponsor for subject 69831, Liebowitz Social Anxiety Scale (LSAS), dated 10/28/99, did not match the CRF.

d. Data from this site are acceptable.

3. Peter Londborg, M.D. (Site Number 95)
   Seattle Research Center
   901 Boren Avenue, Suite 1800
   Seattle, WA 98104

a. What was inspected: Dr. Londborg enrolled 10 subjects. The inspection encompassed an audit of all subjects' records. Primary endpoint efficacy data were verified for 10 subjects.

b. Limitations of inspection: none

c. General observations/commentary: The inspection found inaccurate record keeping. Specifically:

CGI global improvement for subject #70304 at visit 4 (2/3/00) is documented as "4" in the source documents. However, it is reported as "5" (minimally worse) in the CRF and data listings.

CGI Severity for subject #70304 at visit 4 (2/3/00) is documented as "5" in the source documents. However it was reported as "4" (moderately ill) in the CRF and data listings.

An adverse event with start date of 2/10/00 for subject 70363 was reported as "decreased appetite" in the source documents, but the CRF noted the adverse event as "increased appetite".

d. Data from this site are acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As noted above, inspection of Drs. Bari and Londborg found inadequate and inaccurate record keeping. The inspection of Dr. Dupont's site for protocol S1143107 found failure to adhere to protocol and failure to maintain adequate records of the disposition of the drug. The inspection of Drs. Dupont (protocol S1143108) and Heiser revealed that these investigators appear to have conducted the studies noted in accordance with FDA regulations. Data from these four clinical investigators are acceptable in support of NDA 22-033.

As previously mentioned, observations noted above regarding Drs. Dupont (protocol S1143108), Heiser, and Londborg sites are based on communications from the field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Sherbet Samuels, R.N., M.P.H.

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Sherbert Samuels
1/12/2007 11:22:53 AM
CSO

Constance Lewin
1/12/2007 11:29:49 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-033

INFORMATION REQUEST LETTER

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

Dear Mr. Hare:

Please refer to your May 1, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luvox (fluvoxamine maleate) extended release capsules.

We also refer to your submissions dated October 5, 2006 and October 9, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response as soon as possible in order to continue our evaluation of your NDA.

1. Please note that a deficiency letter has been sent to DMF [redacted] December 22, 2006). These deficiencies will need to be resolved before this application can be approved.
2. Provide a letter of authorization to access DMF 5169.
3. The term [redacted] for the dosage form is not acceptable, we recommend that it be replaced with 'extended-release'.
4. Provide information about the [redacted] Who is responsible for the release testing of the final commercial product packaged in marketed packaging? Provide release specification and representative CoAs for the final commercial product.
5. Please lower the specified limit for the [redacted] impurity in drug substance specification to the recommended ICH Q3A qualification level [redacted]. Similarly the limit for individual unidentified substances should be lowered from [redacted] o the ICH Q3A recommended identification limit of 0.10%.
6. An appearance test and particle size test and [redacted] i acceptance limit that appropriately defines the particle size distribution based on the lots used for manufacture of clinical batches should be added to the drug substance specification.
7. The drug product label needs to reflect regulatory requirement with respect to the inclusion of a manufactured by/for designation (21 CFR 201.1)
8. Please provide updated mockups of the proposed drug product labels.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

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 April 28, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luvox CR (fluvoxamine maleate) Controlled-Release 100 mg &150 mg capsules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on June 30, 2006 in accordance with 21 CFR 314.101(a).

Clinical:
Please provide the following information:

1) For the pool of all Phase 3 studies with Luvox CR, please provide a table enumerating all patients by their total duration of exposure to Luvox CR and their mean dose of Luvox CR. This should be in the format shown below. Each cell should contain the number of patients who had the specified duration of exposure and a mean dose over that period of exposure in the specified range. Please note that patients should be enumerated only once in this table so that the sum of all cells equals the total number of unique patients in Phase 3 studies who were treated with Luvox CR.

Duration	Mean Daily Luvox CR Dose			
	<100mg	100-200mg	201-300mg	>300mg
0-4 wks.				
5-12 wks.				
13-26 wks.				
27-52 wks.				
>52 wks.				

2) Also for the pool of all Phase 3 studies with Luvox CR, please provide the total number of patient-exposure years for both Luvox CR and placebo. This should be computed by summing the total durations of exposure to Luvox CR (or placebo) for all patients in this study pool.

3) For studies 3103, 3107, and 3108 separately, please provide the mean daily dose of Luvox CR for all Luvox CR patients in-study for each study visit.

4) Kindly integrate analyses regarding mean change from baseline and outlier data for laboratory values, vital sign measures, and ECG parameters for the three pivotal studies (3107, 3108, and 3103). For example, please combine data from the following pages (of Studies 3107 and 3108) from volumes 31 with those of Study 3103 from Volume 30 of your submission altogether:

Laboratory Analyses
• page 23 and page 161 of volume 31 and page 24 of volume 30

Vital Sign Analyses
• page 80 and page 300 of volume 31 with page88 of volume 30

ECG Analyses
• page 106 and page 334 of volume 31 with page 124 of volume 30

Office of Clinical Pharmacology & Biopharmaceutics:
As requested in an e-mail communication from Dr. Andre Jackson, of this Agency, on June, 6, 2006, please provide the following information for studies Biostudy 1098001; Study 1098002; Study S1141106; Study 0398002; Study 0798005; Study 0698001; Study 0300002; Study S1141109 and Study S1141107:

1. Dates samples were collected.
2. Dates samples were analyzed.
3. QC -amount added -amount found-precision and accuracy
4. Calibrators-amount added -amount found-precision and accuracy

Be sure that each study has all of the above information.

Please confirm you will perform an analysis on the suicide data on the studies conducted using the fluvoxamine controlled release capsules.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission. If you have any questions, call Renmeet Gujral, 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

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/s/

Thomas Laughren
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MEETING MINUTES
IND ?

Date:	September 22, 2004
Location:	Conference Room E; WOC2
Time:	1:00 – 2:00 PM EST
Firm:	Solvay and Elan Pharmaceuticals
Type:	Face-to-Face
Meeting:	Type C-Pre-NDA Meeting
Drug:	Luvox CR (fluvoxamine maleate) Controlled-Release Capsules
Indication:	Obsessive Compulsive Disorder and Generalized Anxiety Disorder
Meeting Chair:	Thomas Oliver, Ph.D., CMC Psychopharm Team Leader, DNDP, HFD-120
Meeting Recorder:	Paul David, R.Ph., Senior Regulatory Project Manager

Participants:

FDA:

Drs. Thomas Oliver, Chhagan Tele, Andre Jackson, Sally Yasuda, and Mr. Paul David

Solvay Pharmaceuticals:

Willem J. Bolink, Ch.E.,	Vice-President of Chemical and Pharmaceutical Development, Weesp, The Netherlands
C. Rob van den Akker, M.S., R.Ph.,	CMC Project Leader, Weesp, The Netherlands
Karen D. Quinn, Ph.D.,	Manager Regulatory Affairs-CMC, Baudette, MN

Elan Pharmaceuticals:

Roger Wayne Wiley, R.Ph.,	Senior Director, Regulatory Affairs, Gainesville, GA
Mairead Fogarty, B.Sc,	Director, Technical Services, Athalone, Ireland
Geraldine Carr, M.Sc.,	Associate Director, Regulatory Affairs, Athalone, Ireland

Meeting Objective

The sponsor requested a meeting with the office of clinical pharmacology and biopharmaceutics (OCPB) and chemistry review teams to discuss 2 questions related to their NDA resubmission.

Background

The sponsor requested this Type C meeting in a submission dated July 14, 2004. The meeting briefing packages were submitted on September X and X, 2004.

Purpose:

The sponsor has the following 2 questions:

1. Does the Agency agree that the equivalence data presented for the pivotal clinical lots and the lots representing the final proposed manufacturing process are adequate to support resubmission of the NDA?
2. Does the Agency agree the overall stability data package is sufficient to support the resubmission of the NDA for the proposed commercial product? The stability data package includes — months of pivotal stability from the original process and 12 months of supportive stability data fro product produced by the final manufacturing process.

Solvay was informed, prior to the meeting that the briefing package did not contain sufficient information to respond to their two questions. Both Solvay and the Agency agreed that the purpose of this meeting would be to discuss what information should be provided in order for the Agency to respond to their questions.

Discussion:

- Solvay made a presentation of the manufacturing process and how it differs from the originally proposed manufacturing process.
- The Agency replied that Solvay should submit component composition comparisons between the previous manufacturing method and the current manufacturing method. This would delineate all of the differences between the clinical lots used in the pivotal studies and the batches targeted for commercial distribution.
- The sponsor should submit information (comparisons between the previous manufacturing method and the current manufacturing method) on the [redacted] equipment and particle size.
- The sponsor had no release and/or stability data for the [redacted] beads. The NDA will need to contain release/stability data on [redacted] beads. The sponsor acknowledged they would be following ICHQ7A guidelines.
- [redacted] contains [redacted]. Your NDA should provide information how you control [redacted] suspected mutagens) in [redacted]
- Provide information about the compatibility studies of the excipients used in the drug product formulations.
- Provide information about the characterization of potential impurities in the drug product.
- The sponsor proposes to market two capsule strengths, i.e., 100 mg and 150 mg. To date, the sponsor only has release data on two batches of 100 mg strength. Typically, the NDA would contain data from three batches of each strength. This issue will be discussed in the near future, after the component/composition data mentioned above is received by the Agency.
- The Agency noted that there have been [redacted] of capsules in the new manufacturing process. The sponsor should address these [redacted] issues and provide photostability data in the NDA.
- The Agency stressed that they would consider the stability data generated from the to be marketed commercialization process to be the primary data. Data from previous manufacturing processes would be considered as supportive data.
- The Agency recommended that the NDA, at submission, contain 12 months of stability data. Stability updates received within 3 months of the PDUFA date, would be reviewed within that cycle. Updates received after that 3-month date, would receive no such guarantee for that cycle.
- The Agency stated that this product would carry a MedGuide based upon the PDAC's recent recommendations regarding this class of drug. As such, the sponsor would be obligated to submit unit of use packaging. The sponsor replied that they intend to package this drug as unit of use [redacted]
- The sponsor will need to submit individual capsule data consistent with the USP description of analysis for controlled release formulations. The information requested in the USP can not be obtained from the mean data submitted by the firm.
- The sponsor stated that they will submit the entire NDA at the time of resubmission.

Conclusions:

1. Solvay will submit the additional information so that the Agency could respond to their questions.
2. Minutes will be provided to sponsor within 30 days from the date of this meeting in accordance with MAPP 4512.1.

Minutes Preparer

Concurrence, Chair (or designated authority)

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

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/s/

Thomas Oliver
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