CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-033

CHEMISTRY REVIEW(S)

CMC BRANCH CHIEF MEMORANDUM

To: NDA 22-033
From: Ramesh Sood, Branch Chief, ONDQA
Date: 13-Feb-2008
Subject: **"Approval"** recommendation for NDA 22-033

Luvox CR (fluvoxamine maleate) extended-release capsules are indicated for the treatment of generalized social anxiety disorder and obsessive compulsive disorder (OCD) in adults. The capsules will be available in 100 mg and 150 mg strengths. The capsules are packaged in 30-count bottles

The only CMC pending issue at the end of the previous review cycle was non conformity of the drug product release and shelf-life stability data for the primary registration batches with respect to the dissolution specification at the 6 hour time point. During an internal meeting on January 22, 2008, with members of the clinical pharmacology team and clinical review team, it was decided that an acceptance limit at 6 hour time point was not critical to the performance of the product. Therefore, the company was allowed to drop the 6 hour drug release limit from the dissolution specification. The final dissolution acceptance limit is as follows:

Time	% Released
2h	
4h	
8h	
12h	

An expiration date of 24 months has been assigned for this product based on the provided drug product stability data. All manufacturing sites have been found acceptable by the Office of Compliance.

Recommended action: The application is recommended as **"Approval"** from CMC perspective.

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

/s/

Ramesh Sood
2/13/2008 02:19:22 PM
CHEMIST

NDA 22-033

LUVOX CR
fluvoxamine maleate extended release capsules

Solvay Pharmaceuticals, Inc.

David J. Claffey, Ph.D.
ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-033

2. REVIEW #3

3. REVIEW DATE: 7 FEB 2008

4. REVIEWER: David J. Claffey, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Initial Application	28-APR -2006
Resubmission	21 JUN 2007
Amendment	21 JUN 2007
Amendment	20 JUL 2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission	28 DEC 2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Solvay Pharmaceuticals, Inc.
Address:	901 Sawyer Road, Marietta, GA 30062

Chemistry Review Data Sheet

Representative: Michael F. Hare

Telephone: (770) 578 5620

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: LUVOX CR
b) Non-Proprietary Name (USAN): Fluvoxamine maleate
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3 (new formulation)
- Submission Priority: S (standard)

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Treatment of Generalized Social Anxiety Disorder and Obsessive Compulsive Disorder (OCD) in Adults

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 100 mg and 150 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

____x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

this review cycle. The applicant states that [redacted] ; are manufactured by [redacted] (DMF [redacted] The [redacted] are transported to [redacted] where they are [redacted] All CMC information relating to the drug substance and [redacted] are referenced to their respective DMFs. The initial submission contained information pertaining to the commercial product packaging and labels and the environmental assessment.

The drug substance, fluvoxamine maleate, is currently marketed as immediate release tablets. It is a white to off-white crystalline powder [redacted] It is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether. [redacted] of the compound; a drug substance specification in place for the [redacted] Within the capsules are [redacted] beads [redacted] the capsules was designed to provide fluvoxamine release over 12 hours. The DMFs detailing the manufacture of the drug product capsules was found to be acceptable to support this Application with respect to the drug product specifications at time of review.

In the course of the previous two review cycles the acceptance criterion for the six-hour time point for the drug product dissolution specification has been an on-going issue for the OCP review team (for details refer to the Review Notes below). However during a recent in-house meeting (22 JAN 2008) the Clinical Division Director determined that it would be appropriate to delete the six-hour time point from the drug product dissolution specification (ref: Meeting Cancellation Form 31 JAN 2008). A revised drug product specification reflecting this change was submitted by the Applicant (see below). This resolves this issue and removes all barriers to an approval recommendation from a CMC perspective. It should be noted that the recommendation of the OCP review team remains unchanged *i.e.* that the dissolution specification needs to include a six-hour time point with a [redacted] acceptance criterion (Review dated 4 FEB 2008, Drs Noory and Baweja).

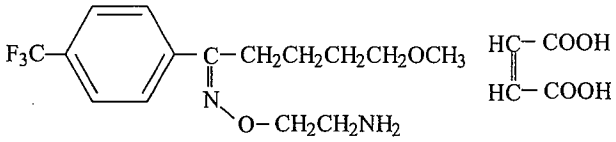
In conclusion, an approval recommendation is being made from a CMC perspective with a drug product expiry period of 24 months.

Chemistry Review Data Sheet

USAN Name: 5-Methoxy-4'-(trifluoromethyl)-valerophenone (*E*)-*O*-(2-aminoethyl)oxime, maleate (1:1)

Molecular Formula: $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$

Molecular Weight: 434.41



Fluvoxamine maleate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
5169	II	Solvay	Fluvoxamine maleate drug substance	1	Adequate	10 DEC 2007	
—	II	—		1	Adequate	10 DEC 2007	Drug product release spec will be updated with the deletion of the 6-hour dissolution time point.
—	II	—		1	Adequate	10 DEC 2007	
—	III	—		3	Adequate	32 MAY 2003	
—	III	—		3	Adequate	25 OCT 2004	
—	III	—		3	Adequate	15 SEP 2000	
—	III	—		3	Adequate	12 AUG 1999	

		Plastics group	Closures				

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND	

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	15 NOV 2007	C. Cruz
Biopharm	None	4 FEB 2008	Carol Noory, PhD
Methods Validation			
DMETS	Pending		
EA	N/A		
Microbiology	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-033

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend that this application be approved from a CMC perspective. No new CMC data was provided during this review cycle, however the revision of drug product dissolution specification on the recommendation of the Clinical Division Director (ref: meeting cancellation form of 31 JAN 2008) removes any final barriers to an overall approval recommendation from a CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Note: Very limited information can be provided in this review document as the bulk of the drug substance and drug product information is referred to drug master files.

Note: this same drug product was [redacted]

This application proposes the marketing of fluvoxamine maleate extended release capsules of two strengths (100 mg and 150 mg) for the treatment of generalized social anxiety disorder and obsessive compulsive disorder (OCD) in adults. The capsules will be packaged in [redacted] 30-count [redacted] bottles [redacted] The [redacted] proposed the use of a single source of drug substance, Solvay Pharmaceuticals B.V., The Netherlands (DMF 5169). The prior resubmission was amended with a proposed alternate drug substance manufacturing site at [redacted] (DMF [redacted], this DMF was found to be adequate to support this Application during

B. Description of How the Drug Product is Intended to be Used

The recommended starting dose for LUVOX CR Capsules in adult patients is 100 mg, administered as a single daily dose at bedtime. It is recommended to increase the dose in 50 mg increments every week, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day. As this product will need to carry a MedGuide, appropriate unit of use packaging is proposed.

C. Basis for Approvability or Not-Approval Recommendation

An approval recommendation is being made from a CMC perspective. The Office of Compliance found the manufacturing/testing sites to be acceptable. The cross-referenced DMFs, in particular, those of the drug product and drug substance manufacturing sites (5169, [redacted]) were found to be adequate to support this application. The Applicant's recent deletion of the six-hour drug product dissolution time point on the recommendation of the Clinical Division Director removes any final barriers to an overall approval recommendation from a CMC perspective.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

DClaffey/Date: Same date as draft review
RSood/Date
SGoldie/Date

C. CC Block

7 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

David Claffey
2/13/2008 12:33:51 PM
CHEMIST

Ramesh Sood
2/13/2008 01:40:54 PM
CHEMIST

CMC BRANCH CHIEF MEMORANDUM

To: NDA 22-033
From: Ramesh Sood, Branch Chief, ONDQA
Date: 17-Dec-2007
Subject: **"Approvable"** recommendation for NDA 22-033

Introduction: Luvox CR (fluvoxamine maleate) extended-release capsules are indicated for the treatment of generalized social anxiety disorder and obsessive compulsive disorder (OCD) in adults. The capsules will be available in 100 mg and 150 mg strengths. The capsules are packaged in [redacted] 30-count [redacted] bottles [redacted]. A sister application NDA 21-519 by the same applicant for the immediate release tablets of fluvoxamine maleate is also being recommended for approval.

Drug Substance: One source of drug substance described in DMF 5169 was proposed prior to this review cycle. It was found to be deficient in the previous review cycles and these issues were resolved in the course of this review cycle. [redacted] An amendment (18 JUN 2007) to the current resubmission proposed the use of an alternate drug substance supplier, [redacted] (referenced to DMF [redacted]). This involved the use of a very different synthetic route to fluvoxamine maleate, the most significant feature of which was the use of [redacted]. This [redacted] is a suspected genotoxin and being a [redacted] it carries a significant risk of being carried forward in the synthetic process to the final drug substance. The issues related to the control of this impurity were resolved during this review cycle. This source of drug substance was found to be acceptable for the manufacture of the drug product. Fluvoxamine maleate is a white to off-white crystalline powder [redacted] It is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether. It is the [redacted] of the compound; a drug substance specification is in place for the [redacted]. The quality of the drug substance is controlled by having appropriate in-process and final specifications that ensure its identity, quality and purity.

Drug Product: The extended-release capsules contain [redacted] beads. [redacted]

The OCP reviewer recommended that the company agree to the following dissolution acceptance criteria.

Time	% Released
2h	
4h	
6h	
8h	
12h	

The applicant's original proposal differed from the OCP recommendation for drug released at 6 hours time point (where applicant had proposed ——, released at 6 hour). The company agreed to the dissolution acceptance criteria recommended by OCP reviewer. However, the primary stability data submitted to support the expiration period for the product show that 4 out of 12 primary batches would not meet this acceptance criteria even at release (product tested to L2 stage) and the data also show several failures under intermediate storage conditions. Therefore, the CMC reviewer is unable to assign any expiration date for this product based on the provided stability data. Even though the stability data seem to comply with an acceptance criterion of —— at 6h, the OCP reviewer confirmed at an internal meeting on December 13, 2007, that this limit would not be acceptable based on the data submitted in the clin/pharm section. The OCP will elaborate on the additional information needed to support applicant's original proposed dissolution acceptance criteria. The company will have to resolve this issue before an expiration date can be assigned to this product.

All manufacturing sites have been found acceptable by the Office of Compliance.

Recommended action: The application is recommended as "Approvable" from CMC perspective.

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

/s/

Ramesh Sood
12/17/2007 01:21:24 PM
CHEMIST

NDA 22-033

LUVOX CR
fluvoxamine maleate extended release capsules

Solvay Pharmaceuticals, Inc.

David J. Claffey, Ph.D.
ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-033

2. REVIEW #: 2

3. REVIEW DATE: 14 DEC 2007

4. REVIEWER: David J. Claffey, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Initial Application	28-APR -2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission	21 JUN 2007
Amendment	21 JUN 2007
Amendment	20 JUL 2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Solvay Pharmaceuticals, Inc.
Address:	901 Sawyer Road, Marietta, GA 30062
Representative:	Michael F. Hare
Telephone:	(770) 578 5620

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: LUVOX CR
b) Non-Proprietary Name (USAN): Fluvoxamine maleate
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3 (new formulation)
- Submission Priority: S (standard)

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Treatment of Generalized Social Anxiety Disorder and Obsessive Compulsive Disorder (OCD) in Adults

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 100 mg and 150 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

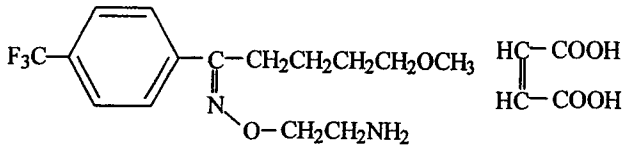
____x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN Name: 5-Methoxy-4'-(trifluoromethyl)-valerophenone (*E*)-*O*-(2-aminoethyl)oxime, maleate (1:1)

Molecular Formula: $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$

Molecular Weight: 434.41



Fluvoxamine maleate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
5169	II	Solvay	Fluvoxamine maleate drug substance	1	Adequate	10 DEC 2007	
[redacted]	II	[redacted]	[redacted]	1	Adequate	10 DEC 2007	
[redacted]	II	[redacted]	[redacted]	1	Adequate	10 DEC 2007	
[redacted]	III	[redacted]	[redacted]	3	Adequate	32 MAY 2003	
[redacted]	III	[redacted]	[redacted]	3	Adequate	25 OCT 2004	
[redacted]	III	[redacted]	[redacted]	3	Adequate	15 SEP 2000	
[redacted]	III	[redacted]	[redacted]	3	Adequate	12 AUG 1999	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF

3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND	

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	15 NOV 2007	C. Cruz
Biopharm	Revisions to the dissolution specification recommended	4 DEC 2007	Carol Noory, PhD
Methods Validation			
DMETS	Pending		
EA	N/A		
Microbiology	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-033

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend that this application is approvable from a CMC perspective, as an expiry period can not be assigned to the drug product at this time. This is due to the more restrictive drug product dissolution acceptance criteria accepted by the Applicant on 11 DEC 2007 on the recommendation of the Office of Clinical Pharmacology (OCP).

Recommend that the following comment be added to the action letter:

1. *At this time an expiry period can not be assigned as the primary stability data do not support the recently amended (11 DEC 2007) drug product dissolution acceptance criteria. This issue will need to be appropriately addressed. If this issue is to be addressed through the drug product manufacturers DMF —— , we remind you to inform the DMF Holder of this point.*

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Note: Very limited information can be provided in this review document as the bulk of the drug substance and drug product information is referred to drug master files.

This application proposes the marketing of fluvoxamine maleate extended release capsules of two strengths (100 mg and 150 mg) for the treatment of generalized social anxiety disorder and obsessive compulsive disorder (OCD) in adults. The capsules will be packaged in —— 30-count —— bottles —————————— The initial NDA submission proposed the use of a single source of drug substance, Solvay Pharmaceuticals B.V., The Netherlands (DMF 5169). The current resubmission was amended with a proposed alternate drug substance manufacturing site at

(DMF [redacted]; this DMF was found to be adequate to support this Application during this review cycle. The applicant states that t [redacted] are manufactured by [redacted] (DMF [redacted]). The [redacted] are transported to [redacted] where they are [redacted] All CMC information relating to the drug substance and [redacted] s are referenced to their respective DMFs. This NDA application contains information pertaining to the commercial product packaging and labels and the environmental assessment.

The drug substance, fluvoxamine maleate, is currently marketed as immediate release tablets. It is a white to off-white crystalline powder [redacted] It is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether. It is the [redacted] of the compound; a drug substance specification in place for the [redacted] Within the capsules are [redacted] beads [redacted] the capsules was designed to provide fluvoxamine release over 12 hours. The DMFs detailing the manufacture of the drug product capsules was found to be acceptable to support this Application with respect to the drug product specifications at time of review. However, a drug product expiry period can not be assigned due to the narrower (from [redacted] to [redacted]) drug product dissolution acceptance criterion at the 6-hour time point accepted by the Applicant on 11 DEC 2007 on the recommendation of the Office of Clinical Pharmacology. All lots met the initial acceptance criterion [redacted] through the proposed 24-month expiry period at 25°C/60%RH and 12 months at 30°C/65%RH. However four out of the 12 pivotal stability lots were outside the recently revised range [redacted] at release; several more failed through the proposed expiry period under long-term stability storage conditions and most did not remain within the modified limits through 12 months at 30°C65%RH. The following chart summarizes these data:

	Percentage released at 6-hour time point		
	25oC (thru' 24 M)	30oC (thru' 12 M)	40oC (thru' 6 M)

*outside recently-accepted acceptance criterion

It should be noted that during the previous review cycle (Jan-Feb 2007) that this reviewer made the OCP review team aware that their recommended range —— would not be acceptable from a CMC viewpoint (personal communication and memo of 12 FEB 2007). The OCP review team did not involve the CMC review team in these most recent negotiations with the Applicant. The OCP review team were again made aware that a —— range would be more acceptable from a CMC perspective, as it is more reflective of the registration stability lots at release and through the proposed 24 month expiry period (internal meeting 13 DEC 2007). Further, the ——limit would meet the 20% range recommended by the Agency for drug products in which an IVIVC had not been established. The OCP review team determined that this range did not meet their requirements.

B. Description of How the Drug Product is Intended to be Used

The recommended starting dose for LUVOX CR Capsules in adult patients is 100 mg, administered as a single daily dose at bedtime. It is recommended to increase the dose in 50 mg increments every week, as tolerated, until maximum therapeutic benefit is

achieved, not to exceed 300 mg per day. As this product will need to carry a MedGuide, appropriate unit of use packaging is proposed.

C. Basis for Approvability or Not-Approval Recommendation

An approvable recommendation is made from a CMC perspective. The Applicant will need to resolve the outstanding issues with OCP, as a drug product expiry period can not be established based on the drug product dissolution acceptance criterion that the Applicant agreed to on the recommendation of OCP. The remainder of the Application was found to be adequate. OC found the sites to be acceptable. The cross-referenced DMFs especially those of the drug product and drug substance manufacturing sites (5169, ~~[redacted]~~ were found to be adequate to support this application.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

DClaffey/Date: Same date as draft review
RSood/Date
SGoldie/Date

C. CC Block

29 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

David Claffey
12/17/2007 11:10:10 AM
CHEMIST

Ramesh Sood
12/17/2007 11:11:58 AM
CHEMIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 12, 2007

FROM: David J. Claffey, PhD

SUBJECT: **Chemistry issues related to NDA 22-033**
NDA 22-033, LUVOX CR Fluvoxamine Maleate Extended Release Capsules

Note: should this document be released to the Applicant, the portions relating to the cross referenced DMFs may need to be redacted.

Introduction: Several factors complicated the review of this application. The actual NDA contained little CMC data, and consisted mostly of packaging information. Details of the drug substance were referenced to DMF 5169 and of the drug product to DMF ——. Three main issues related to the acceptance criteria for impurities (DP), particle size (DS) and the dissolution (DP) remain to be resolved. Resolution of these issues was complicated by this applications' lack of a drug product specification. These issues are recounted in this document and are followed by recommended comments for the action letter. It should be noted that, as of this date, the Office of Compliance recommendation on the acceptability of the drug product manufacturing site is still pending.

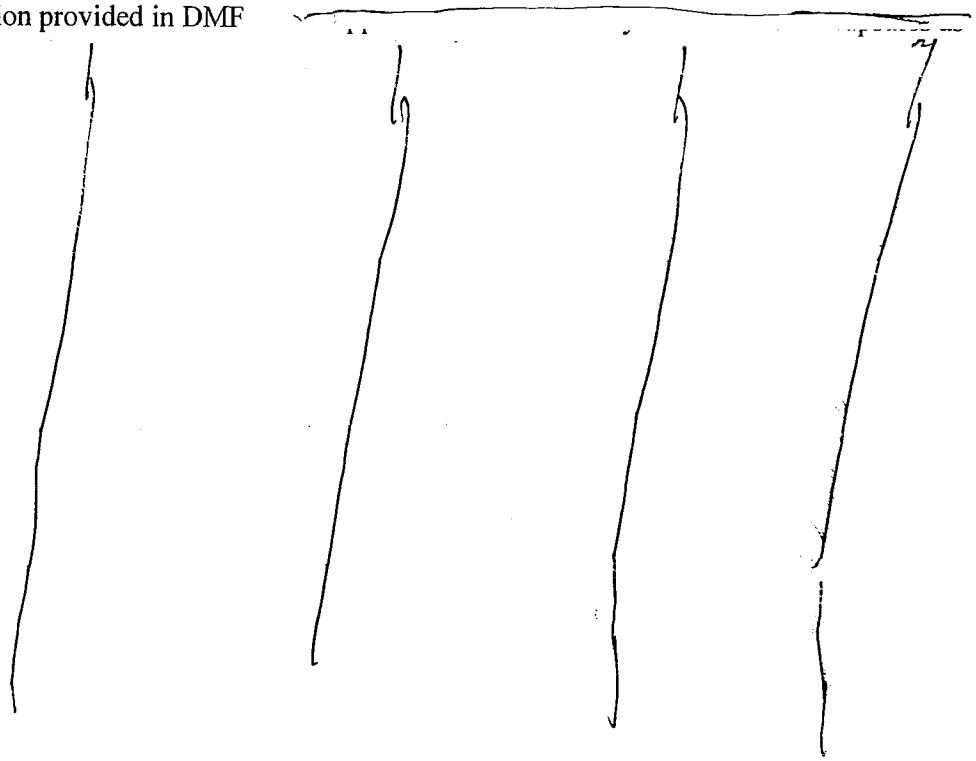
Inadequate Impurity Specification: Deficiencies were sent to the Applicant (Solvay) and the drug product manufacturer (— DMF —) in December 2006. Several of the deficiencies involving the drug product specification that were forwarded to — were deliberately not forwarded to the applicant (Solvay), as there was no indication in the NDA submission that the applicant had access to this information (NDA contained no drug product specification or drug product CoAs). Therefore in order to protect the — intellectual property, it was thought inappropriate to inform the applicant, at that time, of these particular deficiencies. In order to resolve this issue an IR was sent to the applicant that included requests to provide the proposed drug product release specification and CoAs of the final drug product. They failed to respond to this request. On 5 FEB a request was made of the applicant to at least provide the drug product specification to the Agency (it was thought that this was the minimum information that was required to assure the Agency that they had access to this information so that it could be evaluated and any deficiencies forwarded). They responded on 5 FEB 2007 (via email) with a partial response to the DEC 2006 information request and stated that the NDA would be amended "with a full response as soon

as all items are available". This information again contained no drug product specification but did include representative CoAs for some of the drug product batches. This provided assurance that the Applicant was using the same drug product specification as that of the drug product manufacturer.

It should be noted that as the NDA did not contain drug product impurity specification, this reviewer provided this information to the pharm/tox reviewer (Dr Linda Fossom) from information submitted in [redacted] DMF. Dr. Fossom used data from another Solvay NDA for Luvox (IR) tablets (21-519) to determine if the proposed limits were adequately qualified. The [redacted] and [redacted] impurities were subsequently determined to be not adequately qualified based on the toxicological information provided in NDA 21-519. However Dr. Fossom could not communicate with the Applicant what data was required to qualify these impurities, as no drug product specifications were provided in [redacted] This information could not be forwarded to the DMF holder either, as [redacted] did not have access to Solvays toxicological data. It was therefore found to be critical that the NDA Applicant provide their proposed drug product specifications to the Agency.

Although this issue regarding the drug product specification might seem trivial, and that the applicant should obviously have access to the same drug product specification as the manufacturer; this was not entirely as clear-cut in this case. For example, the drug substance specification differed in some very critical respects between that described in DMF 5169 (drug substance manufacturer), DMF [redacted] (drug product manufacturer) and that which was provided in [redacted]

Lack of Drug Product Specification for the Packaged Product: The drug product specification provided in DMF [redacted]

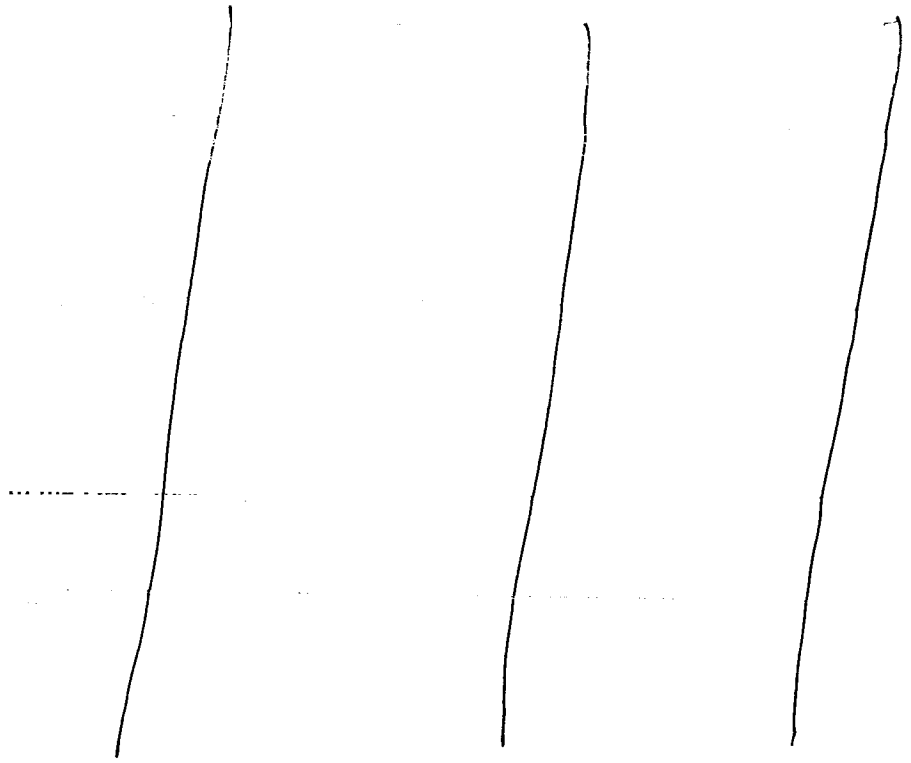


1 Page(s) Withheld

1 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process



Recommended Changes to Dissolution Specification: The Clin/Pharm reviewer (Dr. Andre Jackson) assumed responsibility for the evaluation of the drug product dissolution specification. This reviewer sought Dr Jacksons assurance during the review cycle of the acceptability of the dissolution specification. As late as 29-30 January 2007 in a personal communication with Dr. Jackson, he assured me that the specification was acceptable. However on 8 February 2007 I noticed that the Clin/Pharm review was finalized in DFS with an apparent recommendation that the dissolution specification be tightened. It should be noted that should this revised acceptance criterion be adopted, that substantial portions of my evaluation and conclusions especially that of the drug product will need to be revised, as the dissolution specifications recommended by Dr Jackson will cause some of the primary drug product lots to be outside the specified limits at release and during the stability studies under the long-term storage conditions. Dr Jackson was asked whether he considered revising the range at the six-hour time point from — % to — , instead of the recommended — — as many of the lots have released a mean (n=12) ca. 65±2% of the drug at six hours. Additionally this reviewer is recommending that the Applicant and drug product DMF holder be advised that any revision of the dissolution acceptance criteria will require them to provide a complete re-evaluation of the acceptability of the results of the drug product dissolution data used to support the primary lots and the various stability studies.

Recommend that the following comments be added to the action letter:

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

2. Note that the drug product acceptance criteria for two drug product impurities ([redacted]) are unacceptable and will need to be revised (Refer to the P/T comments).

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

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

2 Page(s) Withheld

/ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

David Claffey
2/12/2007 02:24:18 PM
CHEMIST

Ramesh Sood
2/12/2007 02:43:01 PM
CHEMIST

NDA 22-033

Fluvoxamine Maleate 'Controlled'-Release Capsules

Solvay Pharmaceuticals, Inc.

David J. Claffey, Ph.D.
ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-033

2. REVIEW #: 1

3. REVIEW DATE: 29 JAN 2007

4. REVIEWER: David J. Claffey, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Initial Application	28-APR -2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Solvay Pharmaceuticals, Inc.
Address:	901 Sawyer Road, Marietta, GA 30062
Representative:	Michael F. Hare
Telephone:	(770) 578 5620

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: LUVOX CR
b) Non-Proprietary Name (USAN): Fluvoxamine maleate
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3 (new formulation)
- Submission Priority: S (standard)

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Treatment of Generalized Social Anxiety Disorder and Obsessive Compulsive Disorder (OCD) in Adults

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 100 mg and 150 mg

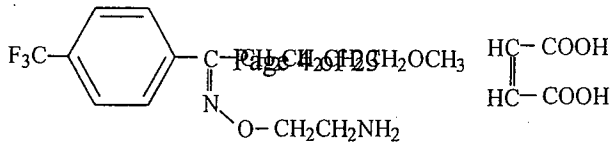
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

____x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
USAN Name: 5-Methoxy-4'-(trifluoromethyl)-valerophenone (*E*)-*O*-(2-aminoethyl)oxime, maleate (1:1)
Molecular Formula: $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$
Molecular Weight: 434.41



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
5169	II	Solvay	Fluvoxamine maleate	3	Inadequate	4 Nov 2006	
				1	Inadequate	25 JAN 2007	
	III			3	Adequate	32 MAY 2003	
	III			3	Adequate	25 OCT 2004	
	III			3	Adequate	15 SEP 2000	
	III			3	Adequate	12 AUG 1999	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND —	

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending. Awaiting OC decision on — site; 483 was issued after Dec 2006 inspection.		
Pharm/Tox	Pending. Determined that limits for some impurites needed to be lowered (refer to IR).		Linda Fossom, PhD
Biopharm	Pending. Dissolution specification is acceptable (personal communications)		Andre Jackson, PhD
LNC			
Methods Validation	N/A		
DMETS	Pending		
EA	N/A		
Microbiology	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-033

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is Approvable from a CMC perspective pending:

1. Resolution of the deficiencies in the drug master files for both the drug substance (DMF 5169) and the drug product (DMF —— .
2. Adequate responses to the IR of 22 DEC 2006.
3. Receipt from the Office of Compliance of an acceptable recommendation for the capsule manufacturing site (Elan, Athlone, Ireland).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

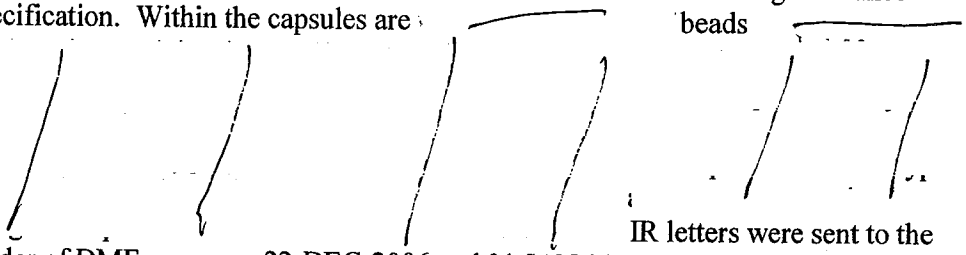
II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

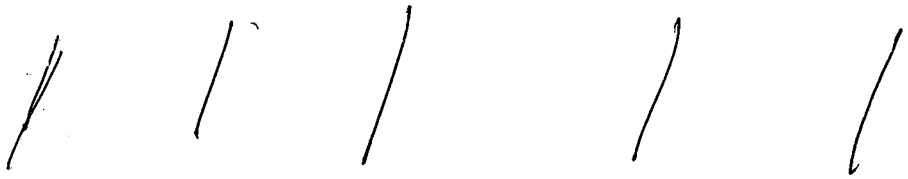
Note: Very limited information can be provided in this review document as the bulk of the drug substance and drug product information is referred to drug master files.

This application proposes the marketing of fluvoxamine maleate extended release capsules of two strengths (100 mg and 150 mg) for the treatment of generalized social anxiety disorder and obsessive compulsive disorder (OCD) in adults. The capsules will be packaged in —— 30-count —— bottles ———— The drug substance (fluvoxamine maleate) is manufactured by Solvay Pharmaceuticals B.V. in The Netherlands then shipped to ———— for drug product manufacture. ———— All CMC information relating to the drug substance and ———— are referenced to two DMFs, (5169 and —— respectively). This NDA application contains information pertaining to the commercial product packaging and labels and the environmental assessment. The drug substance, fluvoxamine maleate, is currently marketed as immediate release tablets. It is a white to off-white crystalline powder ———— It is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether. It is the ———— of the compound; a drug substance specification in place for the ———— The drug

substance specification is similar to that provided in DMF 5169; this was found to be inadequate by this reviewer and a deficiency letter stating this was sent to the DMF holder on 20 NOV-2006. The drug substance specification lacked appearance and particle size tests, the applicant was asked to include these in the drug substance specification. Within the capsules are beads



IR letters were sent to the holder of DMF on 22-DEC-2006 and 31 JAN 2007. Approval of this application awaits adequate responses to these letters.



B. Description of How the Drug Product is Intended to be Used

The recommended starting dose for LUVOX CR Capsules in adult patients is 100 mg, administered as a single daily dose at bedtime. It is recommended to increase the dose in 50 mg increments every week, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day. As this product will need to carry a MedGuide, appropriate unit of use packaging is proposed.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable from a CMC perspective on receipt of a satisfactory EER report for the manufacturing sites and once the deficiencies relating to this application and DMFs 5169 and have been adequately addressed.

Recommend that the following comment be added to the action letter:

-

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

DClaffey/Date: Same date as draft review
RSood/Date
SGoldie/Date

C. CC Block

14 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

David Claffey
1/31/2007 03:25:16 PM
CHEMIST

Ramesh Sood
1/31/2007 04:24:51 PM
CHEMIST

Initial Quality Assessment
Branch I

OND Division:	Division of Psychiatry Products
NDA:	**22-033**
Applicant:	Solvay Pharmaceuticals, Inc.
Letter Date:	28-APR-06
Stamp Date:	01-MAY-06
PDUFA Date:	01-MAR-07
Trademark:	Luvox® CR
Established Name:	fluvoxamine maleate
Dosage Form:	controlled release capsules (100 mg and 150 mg)
Route of Administration:	Oral
Indications:	Generalized Social Anxiety Disorder and Obsessive Compulsive Disorder (OCD)
Assessed by:	**Thomas F. Oliver, Ph.D.**

Summary
Fluvoxamine maleate is a small molecule that is being developed by Solvay Pharmaceuticals as an extended release capsule for once daily administration in the treatment of Generalized Social Anxiety Disorder and OCD. Fluvoxamine maleate has been approved in more than 80 countries for the treatment of Obsessive Compulsive Disorder (OCD) and depression.

Solvay Pharmaceuticals Inc. [redacted]

[redacted] DMF [redacted] has now been reactivated.

Luvox® (fluvoxamine maleate) Tablets were approved in NDA 20-243 on December 5, 1994 for OCD. In September 1997, Solvay Pharmaceuticals was placed under the Application Integrity Policy (AIP). As a result of an agreement between the FDA and Solvay, NDA 20-243 was withdrawn. On April 11, 2003 the FDA removed Solvay from AIP, allowing scientific review of their pending NDA 21-519 [Luvox® (fluvoxamine maleate) Tablets], which was submitted June 28, 2002. NDA 21-519 was found approvable (February 10, 2004). Solvay has not filed a complete response to this letter. As a result, there are no approved Luvox products on the US market (it should be noted there are a number of approved generic fluvoxamine maleate products on the US market).

A Pre-NDA meeting (September 22, 2004) for fluvoxamine maleate controlled release capsules focused on the differences between the original and the proposed manufacturing processes, compatibility of the drug product excipients, [redacted] in [redacted], and on the stability data package. Minutes for the meeting can be found in DFS.

Drug Substance

Fluvoxamine maleate is a white to off-white crystalline powder [redacted] ie [redacted] Fluvoxamine maleate contains no chiral centers [redacted] Solvay Pharmaceuticals (Weesp, Netherlands) manufactures the drug substance. The sponsor references DMF 5169 (fluvoxamine maleate, Solvay) for all information in support of the drug substance. A Deficiency Letter was sent to the DMF holder on October 30, 2003 as part of the NDA 21-519 (Luvox® Tablets) review.

Drug Product

The sponsor references DMF [redacted] fluvoxamine maleate controlled released capsules, Elan Pharmaceutical Research Corp.) for all information in support of the drug product. Luvox® CR (fluvoxamine maleate) capsules will be available in two strengths: 100 and 150 mg. The recommended starting dose is 100 mg administered as a single daily dose at bedtime. The maximum daily dose should not exceed 300 mg. [redacted] manufactures the drug product. The drug release is controlled by utilizing Elan's SODAS™ (Spheroidal Oral Drug Absorption System) technology, which involves [redacted] . The drug product will be packaged in [redacted] bottles [redacted]

Critical Issues for Review

- The sponsor does not appear to have an appearance test as part of the drug substance specifications (only *appearance of solution*).

- Since a number of the drug substance impurities have limits higher than those outlined in ICH Q3a(R), the adequacy of these limits should be discussed with the pharm/tox reviewer.

- Safety and efficacy studies were conducted with batches from the original drug product manufacturing process. As the proposed drug product manufacturing process has differences from the original process, equivalence of the proposed and original batches will need to be determined. Any differences in the drug substance batches (used in the original safety and efficacy DP batches and the current DP batches) should also be identified and evaluated.

- The compatibility of the excipients in the drug product should be evaluated.

- The adequacy of the [redacted] in place for batch to batch consistency.

• The discriminatory nature of the dissolution method should be evaluated and any modifications of the method over time should be identified and evaluated, as the equivalence of batches used in the safety and efficacy studies and the proposed batches will need to be determined.

• Information to support the size of the sugar spheres should be evaluated, including the controls in place to ensure proper size within a batch and from batch to batch.

• The sponsor uses the language " [redacted] ' capsules as part of their labeling. As this dosage form designation is not accepted by CDER, the sponsor will need to change their designation to "extended release" capsules.

Comments and Recommendation:

The NDA appears to be fileable from a CMC perspective. All establishments have been entered into EES (May 11, 2006), however, the reviewer should verify the entered establishments. As Dr. Chhagan Tele participated in the pre-NDA meeting for this product and has reviewed at least one other SODAS™ designed product, he would be a prudent choice as the chemistry reviewer. There does not appear to be any manufacturing issues that would warrant a consult, as the SODAS™ technology is utilized in other approved products. However, due to the history of the product, the NDA should be assigned to an experienced reviewer and I would strongly recommend that the assigned reviewer accompany the Field investigator on any DP manufacturing inspections.

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

/s/

Thomas Oliver
5/12/2006 08:40:20 AM
CHEMIST

Ramesh Sood
5/12/2006 09:00:57 AM
CHEMIST