CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-519

CHEMISTRY REVIEW(S)

CMC BRANCH CHIEF MEMORANDUM

To: NDA 21-519
From: Ramesh Sood, Branch Chief, ONDQA
Date: 10-Dec-2007
Subject: Approval recommendation for NDA 21-519

Introduction: Luvox (fluvoxamine maleate) tablets are indicated for the treatment of obsession and compulsions in adults and in pediatric (8-17 years) patients with Obsessive Compulsive Disorder (OCD). The tablets are available in 25 mg, 50 mg and 100 mg strengths. The tablets are packaged in 100-count bottles for commercial distribution and [redacted] b(4)

The proposed drug product (LUVOX) was previously approved by the Agency under NDA 20-243 by the same applicant in 1994. In 1997 this application was placed under AIP (Application Integrity Policy) because of issues related to the reliability of their stability data. This resulted in the 2002 withdrawal of NDA 20-243 and the submission of this application. Substantive scientific review of this application was initiated in June 2003 after removal of the AIP. The applicant stated in the initial submission that the proposed drug product has an identical composition to that previously submitted in NDA 20-243, and that it is manufactured in an identical manner and at the same sites as previous product. This application was found to be approvable in Feb 2004. A list of CMC approvability issues was sent to the applicant in the action letter. The responses to these deficiencies were provided in the previous submission and resulted in several deficiencies which were forwarded to the sponsor during the previous review cycle. The response to these deficiencies was reviewed in this review cycle.

Drug Substance: Prior to this review cycle just one source of drug substance described in DMF [redacted] was proposed. It was found to be deficient in the previous review cycles; these issues were resolved in the course of this review cycle. An amendment (18 JUN 2007) to the current resubmission proposed the use of an alternative 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 involved the use of [redacted] as an [redacted] This reagent is a suspected genotoxin and being a [redacted] the drug substance 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. b(4)

Drug Product: LUVOX® (fluvoxamine maleate) Tablets 25 mg, 50 mg and 100 mg are manufactured as elliptical, film-coated tablets with a unique color for each strength (25 mg, white; 50 mg, yellow;100 mg, beige). Tablets are debossed with "LT25", "LT50" or "LT100" for 25 mg, 50 mg and 100 mg strength, respectively. The 50 mg and 100 mg strength tablets are scored on the opposing side. The tablets are manufactured using excipients which are USP/NF grade, and tablet colorants [redacted] All strengths of drug product are b(4)

manufactured by [redacted] (tablet size differs). The sponsor maintains a sampling plan which assures that each lot of raw material (i.e., inactive ingredient and packaging components) is tested for identity, sampled, acceptance tested and released. In-process testing is performed on the [redacted] tablets, coated tablets and packaged finished product. A 36-month and [redacted] for the product packaged in bottles and [redacted] respectively, are assigned based on the provided stability data. b(4)

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

Recommended action: The application is recommended as "Approval" from CMC perspective pending agreement on the labeling.

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/s/

Ramesh Sood
12/10/2007 01:55:22 PM
CHEMIST

NDA 21-519

LUVOX® (fluvoxamine maleate) Tablets

Solvay Pharmaceuticals, Inc.

David J. Claffey Ph.D.
ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-519

2. REVIEW NUMBER: 3

3. REVIEW DATE: 7 DEC 2007

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	28 June 2002
Amendment	07 May 2003
Amendment	29 May 2003
Amendment	05 June 2003
Amendment	05 September 2003
Amendment	24 May 2006
Amendment	25 Oct 2006

6. SUBMISSION BEING REVIEWED:

Submission Reviewed	Document Date
Amendment BL	20 JUN 2007
Amendment BC	21 JUN 2007

Chemistry Review Data Sheet

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Solvay Pharmaceuticals, Inc.
Address:	901 Sawyer Road Marietta, GA 30062
Representative:	Michael F. Hare, Assistant Director Regulatory Affairs
Telephone:	770-578-5620

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: LUVOX®
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)

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

10. PHARMACOL. CATEGORY: Obsessive Compulsive Disorder (OCD)

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 25 mg, 50 mg, 100 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

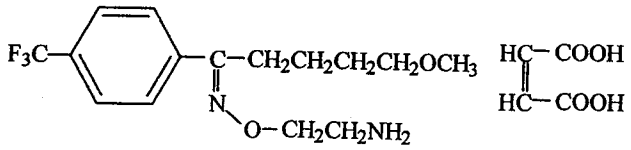
__X__Not a SPOTS product

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
[redacted]	II	Solvay	Fluvoxamine drug substance	1	**Adequate**	**Dec 7, 2007**	
[redacted]	II	[redacted]	Fluvoxamine drug substance	1	***Adequate***	***Dec 10, 2007***	
[redacted]	III	[redacted]	[redacted]	3	Adequate	Sept. 26, 2000	b(4)
[redacted]	III	[redacted]	[redacted]	3	Adequate	Sept. 1, 1999	
[redacted]	III	[redacted]	[redacted]	3	Adequate	Sept. 1, 1999	
[redacted]	III	[redacted]	[redacted]	3	Adequate	Sept. 11, 2003	

Chemistry Review Data Sheet

	III		3	Adequate	August 6, 2001	
	III		3	Adequate	March 14, 2002	b(4)
	III		3	Adequate	June 3, 2003	

[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
NDA	20-243	LUVOX® Tablets (Withdrawn 13 May 2002)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	All Site Acceptable	14 JUN 2006	Office of Compliance (Establishment Report Appended)
Pharm/Tox			
Biopharm			
LNC	USAN Available	N/A	N/A
Methods Validation			
OPDRA	N/A	N/A	N/A
EA	Categorical Exclusion Granted	1/28/04	Lorenzo Rocca, Ph.D.
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-519

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend that this Application be approved from a CMC perspective.

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

II. Summary of Chemistry Assessments

Regulatory background: The proposed drug product (LUVOX) was previously approved by the Agency under NDA 20-243 by the same applicant in 1994. In 1997 this application was placed under AIP (Application Integrity Policy) because of issues related to the reliability of their stability data. This resulted in the 2002 withdrawal of NDA 20-243 and the submission of this application. Substantive scientific review of this application was initiated in June 2003 after removal of the AIP. The applicant stated in the initial submission that the proposed drug product has an identical composition to that previously submitted in NDA 20-243, and that it is manufactured in an identical manner and at the same sites as previously. This application was found to be approvable in Feb 2004. A list of CMC approvability issues was sent to the applicant in the action letter. The responses to these deficiencies were provided in the previous submission and resulted in several deficiencies which were forwarded to the sponsor during the previous review cycle.

A. Description of the Drug Product and Drug Substance

LUVOX® (fluvoxamine maleate) Tablets 25 mg, 50 mg and 100 mg are manufactured as elliptical, film-coated tablets with a unique color for each strength (25 mg, white; 50 mg, yellow;100 mg, beige). Tablets are debossed with "LT25", "LT50" or "LT100" for 25 mg, 50 mg and 100 mg strength, respectively. The 50 mg and 100 mg strength tablets are scored on the opposing side. The original submission lists the following as the proposed packaging configurations:

25 mg and 50 mg strength tablets:

[redacted] b(4)

100 mg tablets:

[redacted] b(4)

The current submission proposes the use of 100-count bottles for commercial distribution and [redacted] for each tablet strength.

LUVOX® (fluvoxamine maleate) Tablets 25 mg, 50 mg and 100 mg are manufactured using excipients which are USP/NF grade, and tablet colorants [redacted] b(4)

[redacted]. All strengths of drug product are manufactured by [redacted] using the identical [redacted] (tablet size differs). The sponsor maintains a sampling plan which assures that each lot of raw material (i.e., inactive ingredient and packaging components) is tested for identity, sampled, acceptance tested and released. In-process testing is performed on the [redacted] coated tablets and packaged finished product. The sponsor's sampling and testing assures that critical parameters such as [redacted] are monitored during manufacture, and that the final product is release tested accorded to the regulatory release specifications.

The drug product formulation for the LUVOX® Tablets 25 mg, 50 mg and 100 mg provided for in this application (NDA 21-519) is identical to the formulation under NDA 20-243, and the sponsor has demonstrated by data previously submitted to the FDA in NDA 20-243 the bioequivalence of LUVOX® Tablets to the clinical materials used in pivotal efficacy and safety trials. Therefore, differences between the commercial formulation proposed in NDA 21-519, and the clinical formulations were not found to be an issue from a chemistry standpoint (review #1).

Prior to this review cycle just one source of drug substance described in DMF [redacted] was proposed. It was found to be deficient in the previous review cycles; these issues were resolved in the course of this review cycle. An amendment (18 JUN 2007) to the current resubmission proposed the use of an alternative 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 involved the use of [redacted] b(4)

This [redacted] is a suspect genotoxin and being a [redacted] it carries a significant risk of being carried forward in the synthetic process to the final drug substance. The DMF holder [redacted] agreed to include a specification in the drug substance to control this impurity to a level within [redacted] (reflected in drug substance specification in DMF [redacted]).

Note that no drug product has been manufactured with drug substance from the proposed additional site (5 DEC 2007 Telecon). Although this would generally be considered unacceptable for a new drug application, in this case it was found to be acceptable (though not ideal), when the following were considered:

- The Applicant committed to placing the first three commercial distributed lots of each dosage strength and package size on stability studies (p. 72, Review #1).
- The drug substance from both sites/processes were found to be comparable (DMF ——). b(4)
- Initial stability data from the extended-release drug product manufactured with drug substance from the —— site was comparable to that from the original Solvay site/process (DMF ——). Although the excipients differ with the product proposed in this application, it can be considered to be of lower risk of future quality failures due to its immediate-release nature. b(4)
- The drug product manufactured with drug substance from the initial site/process was found to be generally stable and fluvoxamine maleate drug product
- Its stability to-date together with its relatively long marketing history both as an innovator product and as a generic product.
- The Applicant stated that the proposed synthetic process has been used in Europe for the production of fluvoxamine maleate immediate release tablets since 2002.
- There is a precedent to allowing such an action - such as in a post approval action, where data from drug product manufactured from a new site/process of drug substance is not always required.

***Issues encountered in second from last review cycle*:** The executive summary of the previous review details issues encountered with discrepancies involving the specified impurity levels. These issues in particular that of the —— impurity have now been resolved. b(4)

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

This application proposes the use of LUVOX® (fluvoxamine maleate) Tablets 25 mg, 50 mg and 100 mg for oral administration to treat obsessions and compulsions in adults and pediatric (8-17 years) patients with Obsessive Compulsive Disorder (OCD). The 150 mg dose strength is not proposed as a commercial product in this application as was the case in the original NDA (20-243). The recommended starting dose for LUVOX® tablets in adult patients is 50 mg, administered as a single daily dose at bedtime. The dose can be increased in 50 mg increments every 4 to 7 days, as tolerated, not to exceed 300 mg per day. The recommended starting dose for LUVOX® Tablets in the pediatric population is 25 mg, administered as a single daily dose at bedtime. Age and gender differences impact dosing pediatric patients. The maximum dose in children up to age 11 should not exceed 200 mg/day. Therefore dose adjustments in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit. The dose should be increased in 25 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved. It is advisable that a total daily dose of more than 100 mg should be given in two divided doses. The stability data support the b(4)

Applicant's proposed 36 month expiration dating for all strengths packaged in bottles and [redacted]. Drug product should be protected from high humidity and stored at controlled room temperature, 15°-30°C (59°-86°F). b(4)

C. Basis for Approvability or Not-Approval Recommendation

- The outstanding issues with the acceptance criteria for the impurities have been resolved. Additionally, DMF [redacted] and DMF [redacted] were found to be adequate to support this application. The remainder of the application was generally found to be adequate and an acceptable recommendation was received from OC on the manufacturing and testing sites. b(4)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

18 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

David Claffey
12/10/2007 02:01:00 PM
CHEMIST

Ramesh Sood
12/10/2007 02:03:17 PM
CHEMIST

draft for chemistry review
(Dec 2007) signature page

NDA 21-519

LUVOX® (fluvoxamine maleate) Tablets

Solvay Pharmaceuticals, Inc.

David J. Claffey Ph.D.
ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-519

2. REVIEW NUMBER: 2

3. REVIEW DATE: 1 NOV 2006

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	28 June 2002
Amendment	07 May 2003
Amendment	29 May 2003
Amendment	05 June 2003
Amendment	05 September 2003

6. SUBMISSION BEING REVIEWED:

Submission Reviewed	Document Date
Amendment	24 May 2006
Amendment	25 Oct 2006

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Solvay Pharmaceuticals, Inc.
Address:	901 Sawyer Road Marietta, GA 30062
Representative:	Judy Tian., Manger, Assistant Director Regulatory Affairs
Telephone:	770-578-5782

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: LUVOX®
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)

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

10. PHARMACOL. CATEGORY: Obsessive Compulsive Disorder (OCD)

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 25 mg, 50 mg, 100 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

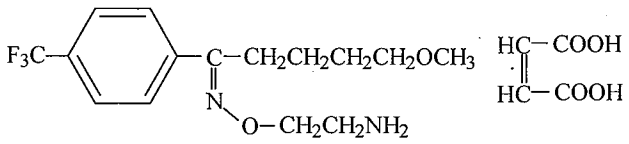
__X__Not a SPOTS product

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
[redacted]	II	Solvay	Fluvoxamine drug substance	1	Inadequate	Nov 2, 2006	
[redacted]	III	[redacted]	[redacted]	3	Adequate	Sept. 26, 2000	
[redacted]	III			3	Adequate	Sept. 1, 1999	
[redacted]	III			3	Adequate	Sept. 1, 1999	
[redacted]	III			3	Adequate	Sept. 11, 2003	
[redacted]	III			3	Adequate	August 6, 2001	
[redacted]	III			3	Adequate	March 14, 2002	

b(4)

Chemistry Review Data Sheet

[redacted]	III	[redacted]	3	Adequate	June 3, 2003	

b(4)

[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
NDA	20-243	LUVOX® Tablets (Withdrawn 13 May 2002)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	All Site Acceptable	14 JUN 2006	Office of Compliance (Establishment Report Appended)
Pharm/Tox			
Biopharm			
LNC	USAN Available	N/A	N/A
Methods Validation			
OPDRA	N/A	N/A	N/A
EA	Categorical Exclusion Granted	1/28/04	Lorenzo Rocca, Ph.D.
Microbiology	N/A	N/A	N/A

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On Original

The Chemistry Review for NDA 21-519

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended to be approval from a CMC perspective. The chief unresolved issue is the acceptance criterion for the [redacted] degradant in the drug product specification; the applicant did not qualify this impurity after being recommended to do so by the Agency in the previous review cycle. The proposed limit is [redacted] whereas the ICH Q3B qualification limit is 0.2%. The most recent stability data do not support the lowering of this limit, and the clinical division does not appear likely to accept the applicant's proposal to carry out qualification studies in Phase IV. b(4)

In addition the following issues need to be addressed by the applicant:

1. Provide drug substance and drug product specifications that list both the common and chemical names of the impurities with the previously agreed upon limits. The footnotes regarding the [redacted] impurity in the drug product specification will also need to be revised to reflect the revised limit. In particular, we note that the the [redacted] impurity remains specified at the [redacted] limit in the drug substance specification, although you repeatedly committed to lowering this limit to 0.15%. b(4)
2. For clarification purposes please provide a complete list of all the proposed packaging configurations. If this application provides for a [redacted] for commercial distribution, provide mock-ups of these carton and [redacted] labels. b(4)
3. Provide an explanation for the fluctuating levels of the [redacted] in the stability studies for drug product lots #92994, 92995 and 92996. b(4)
4. The deficiencies that were recently forwarded to the holder of DMF [redacted] need to be adequately resolved before this application can be approved. b(4)

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

N/A

II. Summary of Chemistry Assessments

Regulatory background: The proposed drug product (LUVOX) was previously approved by the Agency under NDA 20-243 by the same applicant in 1994. In 1997 this application was placed under AIP (Application Integrity Policy) because of issues relating to the reliability of their stability data. This resulted in the 2002 withdrawal of NDA 20-243 and the submission of this application. Substantive scientific review of this application was initiated in June 2003 after removal of the AIP. The applicant stated in the initial submission that the proposed drug product has an identical composition to that

previously submitted in NDA 20-243, and that it is manufactured in an identical manner and at the same sites as previously. This application was found to be approvable in Feb 2004. A list of CMC approvability issues was sent to the applicant in the action letter. Their responses to these deficiencies were provided in this submission and are evaluated in this review. Note also that the drug substance information is contained in DMF this was found to be inadequate in the previous review cycle. b(4)

A. Description of the Drug Product and Drug Substance

LUVOX® (fluvoxamine maleate) Tablets 25 mg, 50 mg and 100 mg are manufactured as elliptical, film-coated tablets with a unique color for each strength (25 mg, white; 50 mg, yellow;100 mg, beige). Tablets are debossed with [redacted] on one side for 25 mg, 50 mg and 100 mg strength, respectively. The 50 mg and 100 mg strength tablets are scored on the opposing side. The original submission lists the following as the proposed packaging configurations: b(4)

25 mg and 50 mg strength tablets:

1) [redacted] (100 count) [redacted] Bottles.
2) [redacted]

100 mg tablets: b(4)

1) [redacted] (100 count) [redacted] Bottles
2) [redacted]

Container labeling was provided in the 25 OCT 2006 amendment. No details on the commercial [redacted] configuration was received, therefore the applicant will be asked to provide an updated list of all the proposed packaging configurations together with mock-ups of all labels.

The fluvoxamine maleate drug substance is described in Type II DMF [redacted] DMF [redacted] was reviewed in support of NDA 21-519 and was previously found to be deficient. Deficiencies were found in the amended DMF, a deficiency letter was sent to the holder.

LUVOX® (fluvoxamine maleate) Tablets 25 mg, 50 mg and 100 mg are manufactured using excipients which are USP/NF grade, and tablet colorants [redacted] All strengths of drug product are manufactured by [redacted] using the identical [redacted] (tablet size differs). The sponsor maintains a sampling plan which assures that each lot of raw material (i.e., inactive ingredient and packaging components) is tested for identity, sampled, acceptance tested and released. In-process testing is performed on the [redacted] coated tablets and packaged finished product. The sponsor's sampling and testing assures that critical parameters such as [redacted] b(4)

[redacted] are monitored during manufacture, and that the final product is release tested accorded to the regulatory release specifications.

The drug product formulation for the LUVOX® Tablets 25 mg, 50 mg and 100 mg provided for in this application (NDA 21-519) is identical to the formulation under NDA 20-243, and the sponsor has demonstrated by data previously submitted to the FDA in NDA 20-243 the bioequivalence of LUVOX® Tablets to the clinical materials used in pivotal efficacy and safety trials. Therefore, differences between the commercial formulation proposed in NDA 21-519, and the clinical formulations were not found to be an issue from a chemistry standpoint (review #1).

Issues encountered in this review cycle: The applicant responded adequately to the deficiencies related to them in the previous action letter (see review notes), with the exception of IR#1 concerning DMF [redacted], which remains inadequate. It should be noted that in the initial review cycle the reviewer found that the stability data supported the proposed 36 month expiry period for all strengths packaged in bottles [redacted] However the resulting action letter recommended that the specified limits for the unqualified drug product impurities be lowered to ICH recommended levels. In this submission the applicant stated that they had done so. However on review of the drug product specifications it appeared that the specified limit for one of the drug product impurities, the [redacted], remained at [redacted] higher than the ICH Q3B recommended level of 0.2% (given the recommended daily dose). In addition the specified level of the [redacted] impurity remained above ICH Q3A recommended levels in the drug substance specification. The applicant was notified of these discrepancies in the course of this review cycle; they agreed to lower the specified level of the [redacted] impurity in the drug substance to ICH Q3A recommended levels (0.15%), however the drug substance specification provided in the 25 OCT 2006 again fails to reflect the recommended changes. Additionally the applicant proposed to retain the specified level of the [redacted] impurity at [redacted] and to carry out qualification studies on this impurity within one year of approval of this application (Attachment 3). They went on to state that the [redacted] impurity "has most likely been in the marketed product and demonstrated many patient-years of favorable clinical experience". No data was provided to substantiate this claim, however it appears that contrary to this claim the specified limit of this drug product impurity in the first Luvox application was [redacted]. The applicant went on to state that "the drug product specifications cannot be tightened for [redacted] based on our review of the stability data and the historical performance of the drug product". Updated stability data was requested and was submitted in the 25 Oct 2006 amendment. It did appear that historically (since 1998) [redacted] levels remained generally at or below [redacted] through the proposed expiry period, with the exception of three sequential lots manufactured in 1998 (#89817, 89818 and 89819) where the [redacted] levels increased gradually from [redacted] over 36 months. Of particular note were the most recent (2004) series of lots (#92994, 92995 and 92996) which were studied for the purpose of qualifying "Raw Material (corn starch NF)". These lots had an initial level of [redacted] which appeared to increase over time with levels of up to [redacted] being observed thus-far (24 months data is

b(4)

Initial Quality Assessment
Branch I

OND Division:	Division of Psychiatry Products
NDA:	**21-519**
Applicant:	Solvay Pharmaceuticals, Inc.
Letter Date:	16-MAY-06
Stamp Date:	17-MAY-06
PDUFA Date:	Not determined yet
Trademark:	Luvox®
Established Name:	fluvoxamine maleate
Dosage Form:	Tablets (25, 50, and100 mg)
Route of Administration:	Oral
Indications:	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 immediate release tablet in the treatment of Obsessive Compulsive Disorder (OCD). Fluvoxamine maleate has been approved in more than 80 countries for the treatment of Obsessive Compulsive Disorder (OCD) and depression.

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 now filed a response to this letter.

Solvay Pharmaceuticals Inc. (via their US agent, Quintiles, Inc) first submitted fluvoxamine maleate controlled release capsules (Luvox® CR) as NDA [redacted] in December 1, 2000. After encountering drug product manufacturing difficulties, [redacted] withdrew DMF [redacted] (fluvoxamine maleate controlled released capsules). As a result, Solvay withdrew NDA [redacted] DMF [redacted] has now been reactivated and NDA 22-033 for Luvox® CR has been submitted April 28, 2006 and is under review. b(4)

As a result, there are no currently approved Luvox products on the US market.

Comments and Recommendation:
The sponsor has responded to each of the issues detailed in the February 9, 2004 AE letter. All establishments have been entered into EES (May 24, 2006), however, the reviewer should verify the entered establishments. As Dr. David Claffey has been assigned to the recently submitted NDA 22-033 (Luvox® CR Capsules, fluvoxamine maleate), he would be a good choice to review this application, since both applications share the same drug substance DMF [redacted]. The PDUFA date has not been determined at this time. b(4)

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/s/

Thomas Oliver
5/25/2006 10:16:44 AM
CHEMIST

Ramesh Sood
5/25/2006 10:28:01 AM
CHEMIST

NDA 21-519

LUVOX® Tablets

Solvay Pharmaceuticals

Lorenzo A. Rocca, Ph.D.
HFD-120

Table of Contents

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Chemistry Review Data Sheet

1. NDA: 21-519

2. REVIEW NUMBER: 1

3. REVIEW DATE: January 28, 2003

4. REVIWER: Lorenzo A. Rocca, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	28 June 2002
Amendment	07 May 2003
Amendment	29 May 2003
Amendment	05 June 2003
Amendment	05 September 2003

6. SUBMISSION BEING REVIEWED:

Submission Reviewed	Document Date
Original NDA	28 June 2002

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Solvay Pharmaceuticals, Inc.
Address:	901 Sawyer Road Marietta, GA 30062
Representative:	Karen D. Quinn, Ph.D., Manger, Regulatory Affairs-CMC
Telephone:	770-578-5868

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: LUVOX®
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)

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

10. PHARMACOL. CATEGORY: Obsessive Compulsive Disorder (OCD)

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 25 mg, 50 mg, 100 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

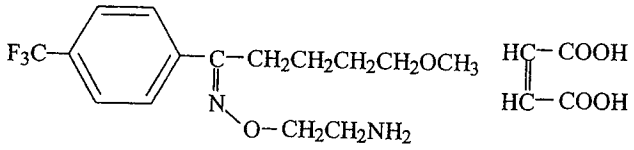
__X__Not a SPOTS product

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
[redacted]	III	[redacted]	[redacted]	3	Adequate	Sept. 26, 2000	
[redacted]	III			3	Adequate	Sept. 1, 1999	
[redacted]	III			3	Adequate	Sept. 1, 1999	
[redacted]	III			3	Adequate	Sept. 11, 2003	
[redacted]	III			3	Adequate	August 6, 2001	
[redacted]	III			3	Adequate	March 14, 2002	
[redacted]	III			3	Adequate	June 3, 2003	

b(4

[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
NDA	20-243	LUVOX® Tablets (Withdrawn 13 May 2002)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	All Site Acceptable	8/11/03	Office of Compliance (Establishment Report Appended)
Pharm/Tox	Approvable	1/28/04	Linda Fossom, Ph.D.
Biopharm	Approved	11/24/03	Andre Jackson, Ph.D.
LNC	USAN Available	N/A	N/A
Methods Validation	Pending	N/A	Lorenzo Rocca, Ph.D.
OPDRA	N/A	N/A	N/A
EA	Categorical Exclusion Granted	1/28/04	Lorenzo Rocca, Ph.D.
Microbiology	N/A	N/A	N/A

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The Chemistry Review for NDA 21-519

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing and Controls (CMC) section of NDA 21-519 is approvable from a chemistry review perspective. Before NDA 21-519 can be approved for CMC, the applicant needs to adequately respond to the following CMC deficiency.

- The Type II DMF [redacted] describing the manufacture of fluvoxamine maleate drug substance was reviewed in support of NDA 21-519 and was found deficient. A Deficiency Letter has been sent to the DMF holder. Before NDA 21-519 can be approved for CMC the DMF holder needs to adequately address all the deficiencies noted in their Type II DMF [redacted] A Deficiency Letter (dated October 30, 2003) was sent to the DMF [redacted] holder. b(4)

The Biopharm review of NDA 21-519 was completed November 24, 2003. The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has no issues related to the approval of NDA 21-519, and finds the sponsor's proposed dissolution conditions and specifications (same as for the original NDA (20-243)) acceptable. The Pharm/Tox review of NDA 21-519 is awaiting submission to DFS. The Pharm/Tox reviewer is recommending that NDA 21-519 is approvable because of inadequate tox data to support the sponsor's proposed levels for the identified impurities (i.e., Related Substances) in the drug substance and drug product. Approval of NDA 21-519 for CMC must await the sponsor adequately addressing the issues raised by the Pharm/Tox reviewer. Because LUVOX® Tablets are a non-sterile solid oral dosage no microbiological issues were reviewed for NDA 21-519.

The Office of Compliance has found acceptable, from a cGMP standpoint, both the supplier of fluvoxamine maleate drug substance and the manufacturer of LUVOX® Tablets 25 mg, 50 mg and 100 mg. The FDA CDER Establishment Evaluation System (EES) Detail Report is appended to this review.

Submission of the NDA 21-519 methods validation package, to the appropriate FDA testing laboratory, is pending.

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

N/A

II. Summary of Chemistry Assessments

Solvay Pharmaceuticals Inc. (SPI) (Marietta, GA) NDA 20-243 for LUVOX® (fluvoxamine maleate) Tablets, 25 mg, 50 mg and 100 mg was approved on December 5, 1994 for the

indication of Obsessive Compulsive Disorder (OCD) for use in adults and for use in children and adolescents since March 25, 1997. In September 1997, SPI, the owner/applicant for LUVOX® Tablets, was placed under Application Integrity Policy (AIP). As a result of an agreement between the FDA and SPI, NDA 20-243 was withdrawn in a letter dated May 13, 2002. On April 11, 2003 the FDA removed SPI from API (effective April 9, 2003) because the validity assessment of the firm has been completed. The FDA's April 11, 2003 action allowed substantive scientific review of data to be resumed, and pending applications returned to the review queue. Pursuant to 21 CFR314.50 SPI submitted on June 28, 2002, NDA 21-519 for LUVOX® (fluvoxamine maleate) Tablets, 25 mg, 50 mg and 100 mg for the treatment of OCD in adults and pediatric patients.

On May 7, 2003 SPI answered the FDA's September 5, 2002 IR Letter (NDA 21-519/N-BZ Response to Request for Information dated May 7, 2003). The sponsor responded to one of three CMC Questions in the following manner:

There are no CMC differences between the drug product and drug substance filed in NDA 20-243 and in NDA 21-519, except as noted below in Questions #3 concerning the correction of the calculation of the specification levels for the degradation products in the drug product. For your convenience, we have provided copies of the formulations for the drug product from NDA 20-243 (Attachment 6 in NDA 21-519/N-BZ Response to Request for Information dated May 7, 2003) and from NDA 21-519 (Attachment 7 in NDA 21-519/N-BZ Response to Request for Information dated May 7, 2003).

On September 5, 2003 SPI responded to a request from the FDA's Office of Clinical Pharmacology and Biopharmaceutics (OCPB) requesting a confirmation on several issues related to NDA 21-519. The sponsor responded in the following manner to OCPB's questions about the composition, manufacture and dissolution method/specifications for the LUVOX® Tablet formulation described in NDA 21-519.

- *Solvay confirms that qualitatively and quantitatively the formulations for the 25 mg, 50 mg and the 100 mg filed in the current NDA, 21-519, are identical to that approved in NDA 20-243. The formulations for the 25 mg, 50 mg and 100 mg tablets submitted in NDA 20-243 and in NDA 21-519 are provided in Attachment 1 (Attachment 1 in NDA 21-519/N-BZ Response to Request for Information dated September 5, 2003) and Attachment 2 (Attachment 2 in NDA 21-519/N-BZ Response to Request for Information dated September 5, 2003), respectively.*

- *Solvay confirms that the manufacturing procedures and the site location for the manufacture of the 25 mg, 50 mg and 100 mg tablets in the current NDA 21-519 are identical to the manufacturing procedures and site location for the formulations approved under NDA 20-243. The manufacturing procedures and site location submitted in NDA 20-243 and in NDA 21-519 are provided in Attachment 3 (Attachment 3 in NDA 21-519/N-BZ Response to Request for Information dated September 5, 200) and Attachment 4 (Attachment 4 in NDA 21-519/N-BZ Response to Request for Information dated September 5, 2003), respectively.*

- *Solvay confirms that the dissolution method and specification for the 25 mg, 50 mg and 100 mg tablets in current NDA 21-519 are and will be identical to those in the approved NDA 20-243. The dissolution method and specifications for the 25 mg, 50 mg and 100 mg tablets submitted and approved in NDA 20-243 (from the Amendment of 9 September 1994 response to approvable letter) and submitted in NDA 21-519 are provided in Attachment 5 (Attachment 5 in NDA 21-519/N-BZ Response to Request for Information dated September 5, 2003) and Attachment 6 (Attachment6 in NDA 21-519/N-BZ Response to Request for Information dated September 5, 2000), respectively.*

SPI's NDA 21-519 for LUVOX® (fluvoxamine maleate) 25 mg, 50 mg and 100 mg Tablets has been reviewed for CMC with the goal of confirming the sponsor's claim that there are no CMC differences between the drug product and drug substance filed in NDA 20-243 and the drug product and drug substance described in NDA 21-519 (except as noted above).

A. Description of the Drug Product and Drug Substance

LUVOX® (fluvoxamine maleate) Tablets 25 mg, 50 mg and 100 mg are manufactured as elliptical, film coated tablets with a unique color for each strength (25 mg (white), 50 mg (yellow) and 100 mg (beige)). Tablets will be debossed with [redacted] and either [redacted] on one side for 25 mg, 50 mg and 100 mg strength, respectively. The 50 mg and 100 mg strength tablets are scored on the side opposite debossing. LUVOX® Tablets 25 mg and 50 mg will be packaged in the following package configurations: [redacted] (100 count) [redacted] Bottles with [redacted] LUVOX® Tablets 100 mg will be packaged in following configurations: [redacted] (100 count) [redacted] Bottles with [redacted] The sponsor also lists in the product insert for the 50 mg and 100 mg strength under the **HOW SUPPLIED** section bottles of [redacted] tablets, but does not provide a description of this container/closure system in NDA 21-519. The sponsor will be asked to either remove the [redacted] count package configuration from the product labeling or provide a description of the [redacted] count packaging configuration and include this configuration in their drug product stability protocol. b(4)

The fluvoxamine maleate drug substance is described in Type II DMF [redacted] DMF [redacted] was reviewed in support of NDA 21-519 and was found deficient. A Deficiency Letter (October 30, 2003) was sent to the DMF holder. Before NDA 21-519 can be approved for CMC the DMF holder needs to adequately address all DMF deficiencies. b(4)

LUVOX® (fluvoxamine maleate) Tablets 25 mg, 50 mg and 100 mg are manufactured using excipients which are USP/NF grade, and tablet colorants [redacted] b(4)

[redacted] The tablet colorants are composed of components which are CFR referenced color additives or acceptable food additives permitted for human consumption. The sponsor needs to certify that LUVOX® Tablets 25 mg, 50 mg and 100 mg meets 21 CFR 73.1200(c) for *uses and restrictions* for synthetic iron oxides. All strengths of drug product are manufactured by [redacted] The individual strengths are created by varying the size of the tablets. The sponsor maintains a sampling plan which assures that each lot of raw material (i.e., inactive ingredient and packaging components) is tested for identity, sampled, acceptance tested and released. In process testing is performed on the [redacted] coated tablets and packaged finished product. The latter are sampled for release, stability and retain. The sponsors sampling and testing assures that critical parameters such as [redacted] are monitored during manufacture, and that the final product is release tested accorded to the regulatory release specifications. While testing is performed at various stages of the manufacturing process the sponsor's in-process testing [redacted] However, sufficient sampling and testing (i.e., [redacted] testing) is performed to assure the identity, strength, quality and purity of the final product.

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b(4)

The drug product formulation for the LUVOX® Tablets 25 mg, 50 mg and 100 mg provided for in this application (NDA 21-519) is identical to the formulation under NDA 20-243, and the sponsor has demonstrated by data previously submitted to the FDA in NDA 20-243 the bioequivalence of LUVOX® Tablets to the clinical materials used in pivotal efficacy and safety trials. Therefore, differences between the commercial formulation proposed in NDA 21-519, and the clinical formulations are not an issue from a chemistry standpoint and comparability studies are not needed.

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

LUVOX® (fluvoxamine maleate) Tablets 25 mg, 50 mg and 100 mg are being developed for oral administration to treat obsessions and compulsions in adults and pediatric (8-17 years) patients with Obsessive Compulsive Disorder (OCD). Please note the 150 mg dose strength is not proposed as a commercial product in NDA 21-519 as was the case in the original NDA (20-243). The recommended starting dose for LUVOX® tablets in adult patients is 50 mg, administered as a single daily dose at bedtime. The dose can be increased in 50 mg increments every 4 to 7 days, as tolerated, not to exceed 300 mg per day. The recommended starting dose for LUVOX® Tablets in the pediatric population is 25 mg, administered as a single daily dose at bedtime. Age and gender differences impact dosing pediatric patients. The maximum dose in children up to age 11 should not exceed 200 mg/day. Therefore dose adjustments in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit. The dose should be increased in 25 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved. It is advisable that a total daily dose of more than 100 mg should be given in two divided doses. The sponsor is

b(4)

proposing a 36 month expiration dating for all strengths packaged in bottles and [redacted] Drug product should be protected from high humidity and stored at controlled room temperature, 15°-30°C (59°-86°F). The sponsor will be asked to use the following labeling statement: b(4)

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F)
[see USP Controlled Room Temperature]

When SPI was placed on AIP in September of 1997 it was discovered that some stability data, acquired at Solvay prior to 1998, could not be reliably substantiated. SPI subsequently instituted procedures in their stability program to assure the FDA that reliable stability data is acquired. On April 11, 2003 the FDA removed SPI from API (effective April 9, 2003) because the validity assessment of the firm has been completed. The FDA's April 11, 2003 action allowed substantive scientific review of data to be resumed and pending applications returned to the review queue. Stability data generated at SPI since the time control procedures were in force (January 1998) are presented in NDA 21-519, and cover drug product stored up to 36 months under ICH conditions. In addition, in late 1998, SPI contracted [redacted] to perform additional stability studies at accelerated conditions (40°C/75%RH) and room temperature (25°C/60%RH) of three batches of each strength drug product in both bottle and [redacted] has been found acceptable by the Office Compliance as a finished dosage release tester of LUVOX® Tablets. The FDA CDER Establishment Evaluation System (EES) Detail Report is appended to this review. The [redacted] data are presented in NDA 21-519 and cover drug product stored up to 30 months under ICH conditions. The stability data presented in NDA 21-519 support the sponsor's proposed drug product expiry. In addition, SPI contracted [redacted] an outside consultant to perform independent statistical analysis of room temperature stability data generated by [redacted] and SPI. [redacted] results are presented in NDA 21-519 and support the sponsor's proposed 36 month expiration dating for all strengths packaged in bottles and [redacted] The sponsor also lists in the product insert for LUVOX® Tablets 50 mg and 100 mg, bottles of 1000 tablets but provides no stability data for this packaging in NDA 21-519. The sponsor will be asked to either remove the [redacted] configuration from the product labeling or provide the appropriate stability data for their proposed [redacted] packaging configuration and include this configuration in their drug product stability protocol. SPI has provided the appropriate post-approval stability commitments for future lots of drug product. The sponsor's proposed 36 month expiration dating for all strengths packaged in bottles and [redacted] b(4)

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-519 is **approvable** for CMC. The approvable recommendation is based on the following major chemistry issues:

- The Type II DMF [redacted] describing the manufacture of fluvoxamine maleate drug substance was reviewed in support of NDA 21-519 and was found deficient. Before NDA 21-519 can be approved for CMC the DMF holder needs to adequately address all the deficiencies noted in their Type II DMF [redacted]. A Deficiency Letter (dated October 30, 2003) was sent to the DMF [redacted] holder. b(4)
- Solvay Pharmaceuticals needs to adequately respond to several CMC deficiencies, which are described under **Chemistry Assessment** Section VIII titled **DRAFT DEFICIENCY LETTER.**

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

LRocca/Date:
TOliver(TL)/Date:
JWare(PM)/Date:

C. CC Block

Orig NDA 21-519
HFD-120/Division File
HFD-120/LRocca
HFD-120/TOliver
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