

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203479Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

To: NDA 203-479
From: Thomas M. Wong, Ph.D., Chemist
Date: Feb 6, 2013
Drug: Versacloz (Clozapine) Oral Suspension
Route of administration: Oral
Strength: 50 mg/mL
Subject: “Approval” recommendation for NDA (b) (4)

The pending issues on the final overall recommendation from EES on the manufacturing sites and the pending data demonstrating the accuracy of the mass delivered dose conducted on the oral syringes have been resolved.

EES: On Feb 6, 2013, the Office of Compliance provided an overall Acceptable recommendation for the manufacturing sites.

Accuracy of the mass delivered dose conducted on the oral syringes:

The sponsor provided the results of the accuracy of mass delivered dose conducted on the 1 mL and 10 mL oral syringes in the Amendment #25 dated 10/17/2012. Clozapine Suspension USP, 50 mg/mL, Lot# 7805.001A was used for the study. The EP criterion for The Uniformity of Mass of Delivered Doses from Multiple Dose Containers is used to evaluate the study results. The results met the acceptance criterion.

Oral Syringe:	1 mL Oral Syringe		10 mL Oral Syringe				
	0.25 mL	1.0 mL	1.5 mL	3.0 mL	6.0 mL	8.0 mL	9.0 mL
Average mass of 20 samples	0.27262	1.09102	1.61455	3.26278	6.50216	8.68330	9.68677
% RSD	1.6	0.3	1.3	0.7	0.6	0.7	0.4
Average mass, in Volume, of 20 samples (Density: 1.09 g/mL)	0.25011	1.00094	1.48124	2.99337	5.96529	7.96633	8.88695
% Diff from Theoretical Volume	0.04	0.09	1.25	0.22	0.58	0.42	1.26

Pending consult review: Microbiology has provided an approval recommendation to this NDA.

CMC Recommendation:

The application is recommended for “Approval” from CMC perspective. Attached is the final EES summary report.

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 203479/000	Sponsor:	DOUGLAS PHARMS
Org. Code:	130		1775 WEST OAK PKY STE 800
Priority:	3		MARIETTA, GA 30062
Stamp Date:	29-DEC-2011	Brand Name:	CLOZAPINE ORAL SUSPENSION, 50 MG/ML
PDUFA Date:	29-OCT-2012	Estab. Name:	CLOZAPINE ORAL SUSPENSION, 50 MG/ML
Action Goal:		Generic Name:	
District Goal:	07-SEP-2012	Product Number; Dosage Form; Ingredient; Strengths	001; SUSPENSION; CLOZAPINE; 50MG

FDA Contacts:	T. BOUIE	Project Manager		3017961649
	T. WONG	Review Chemist	(HFD-810)	3017961608
	C. TELE	Team Leader		3017961762

Overall Recommendation:	ACCEPTABLE	on 06-FEB-2013	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 05-FEB-2013	by EES_PROD		
	PENDING	on 19-DEC-2012	by EES_PROD		
	WITHHOLD	on 19-DEC-2012	by EES_PROD		
	WITHHOLD	on 02-NOV-2012	by EES_PROD		
	PENDING	on 17-OCT-2012	by EES_PROD		
	PENDING	on 16-OCT-2012	by EES_PROD		
	PENDING	on 01-FEB-2012	by EES_PROD		
	PENDING	on 01-FEB-2012	by EES_PROD		

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)



DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	20-MAR-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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/s/

THOMAS M WONG
02/06/2013

RAMESH K SOOD
02/06/2013



Date: February 6, 2013

From: Linda Ng, Ph.D., Senior Policy Advisor
New Drug Manufacturing Assessment Branch
Division of Good Manufacturing Practice Assessment

Subject: Concurrence with Baltimore District Office (BAL-DO) Approval Recommendation for NDA 203-479, Versacloz (clozapine oral suspension), 50 mg/mL

Thru: Tara Goen, Acting Branch Chief
New Drug Manufacturing Assessment Branch
Division of Good Manufacturing Practice Assessment

To: Ramesh Sood, Ph.D., Branch Chief, CDER/OPS/ONDQA/DNDQAI/BI

Applicant: Douglas Pharmaceuticals America Ltd
c/o Versapharm Inc
1775 West Oak Pky Ste 800
Marietta, Georgia 30062

Manufacturer: Pharmaceutics International Inc
10819 Gilroy Rd
Hunt Valley, MD 21031-8213
FEI: 1000513101

Pharmaceutics International Inc (PII) has been inspected for pre-approval and surveillance of drug products manufactured at their facility. A Form 483 has been issued to cover multi-products. This memo will only discuss the pre-approval inspection for Versacloz (clozapine oral suspension), 50 mg/mL. A concurrence memo to support the BLT-DO withhold recommendation for PII was issued by CDER/OC/OMPQ/NDMAB on November 2, 2012. CDER/OND/DPP extended the review clock to February 6, 2013 based on the expectation of a response to the FDA form 483.

CDER/OC/OMPQ/DGMPA/NDMAB's previous withhold recommendation was issued due to a lack of complete manufacturing and control instructions as well as a lack of assurance of manufacturing process understanding, including the drug suspension mixing and hold time, mixing tank fill volume, and mixing ^{(b) (4)} speed and position.

Pharmaceutics International Inc had submitted an engineering study proposal dated October 18, 2012 for Versacloz to evaluate the process characterization of bulk hold studies and ^{(b) (4)} during bottle filling at their facility. The final report and the results of the engineering study were submitted in response to the 483 to ^{(b) (4)} on January 28, 2013. An updated batch record demonstrating adequate manufacturing and control instructions was submitted to ^{(b) (4)} on February 6, 2013.

The following documents were submitted and reviewed by BLT-DO and CDER/OC/OMPQ/DGMPA/NDMAB in response to the deficiencies observed in the manufacturing of Versacloz. These documents are listed in the order they were provided to BLT-DO.

January 28, 2013 - The completed report for the engineering study.

January 31, 2013 – Additional attachments:

- QE1736- to explain low assay
- Feasibility record Page 34 of 40 to show how the composite sample was taken for the assay.
- TR12-2258 for 0 hour sampling for the hold study from stratified sampling points – as part of the engineering protocol.
- TR12-2263 for 24 hours sampling for the hold study from stratified sampling points at storage at static conditions – as part of the engineering protocol.
- TR13-3359 for the assay testing of the composite sample from the bulk container – as part of the normal batch record.
- TR13-2271 for the filled bottles – as part of the engineering protocol.

February 6, 2013 – The updated batch record and related documents:

- Cover Letter
- Change control with summary and effective date for the manufacturing record.
- 3. batch record changed pages that were referenced in the change control and the signature approval page.
- Change control with summary and effective date for the packaging record.
- All pages for the revised packaging record with signature approval pages.

CDER/OC/OMPQ/DGMPA/NDMAB has completed its review of responses submitted to BLT-DO related to the manufacturing operations of Versacloz at PII, Hunt Valley, MD. CDER/OC/OMPQ/DGMPA/NDMAB finds the amendments to sufficiently address the deficiencies observed during the pre-approval inspection and concurs with BLT-DO's recommendation for approval of the PII drug product manufacturing facility relating to Versacloz.

If you have questions, please contact Linda Ng, Ph.D., at 301-796-1426.

cc: HFR- CE2545 District Pre-Approval Manager (PAM) Brooke Higgins
HFD-323 Shared Drive\\cdnas\OCS1\OC_320\HFD-323\Domestic PAI Case
Management
ONDQA/DNDQAI/BI, Thomas Wong, Product Quality Reviewer
OND/DPP, Sharonjit Sagoo, OND Project Manager

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/s/

LINDA L NG
02/06/2013

MAHESH R RAMANADHAM
02/06/2013
Signing as Acting Branch Chief on behalf of Tara Gooen

NDA 203-479

Clozapine Oral Suspension

Douglas Pharmaceuticals America Limited

Thomas M. Wong, Ph.D.

Division of New Drug Quality Assessment I

Office of New Drug Quality Assessment

Division of Psychiatry Products

Review of Chemistry, Manufacturing, and Controls

Table of Contents

The Executive Summary	6
I. Recommendations	6
A. Recommendation and Conclusion on Approvability	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	6
II. Summary of Chemistry Assessments	6
A. Description of the Drug Product(s) and Drug Substance(s)	6
B. Description of How the Drug Product is Intended to be Used	7
C. Basis for Approvability or Not-Approval Recommendation	8
III. Administrative	8
A. Reviewer’s Signature	8
B. Endorsement Block	8
C. CC Block	8
Chemistry Assessments	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	9
S DRUG SUBSTANCE	9
P DRUG PRODUCT	16
A APPENDICES	92
R REGIONAL INFORMATION	92
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	93
A. Labeling & Package Insert	93
Bottle Labels	95
Carton Labels	95
B. Environmental Assessment Or Claim Of Categorical Exclusion	96
III. List Of Deficiencies To Be Communicated:	97

Chemistry Review Data Sheet NDA 203-479

Chemistry Review Data Sheet

1. NDA 203-479
2. REVIEW #: 1
3. REVIEW DATE: Aug 23, 2012
4. REVIEWER: Thomas M. Wong, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

IND (b) (4)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original submission	6-Jan-2012
Amendment #001	14-Feb-2012
Amendment #004	23-Mar-2012
Amendment #0015	1-Aug-2012
Amendment #0016	22-Aug-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Douglas Pharmaceuticals America Limited

Address: Central Park Drive,
Lincoln, Auckland, New Zealand
John Franolic, Ph.D., Vice President of Regulatory Affairs

U.S. Regulatory Agent: VersaPharm Incorporated

Contact: 1775 West Oak Parkway, Suite 800
Marietta, GA 30062

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: To be determined
- b) Non-Proprietary Name: Clozapine USP
- c) Code Name/#: None

Chemistry Review Data Sheet NDA 203-479

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

10. PHARMACOL. CATEGORY: Treatment of resistant schizophrenia

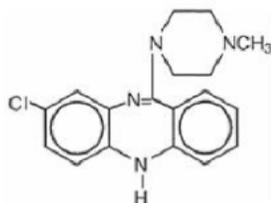
11. DOSAGE FORM: Oral suspension

12. STRENGTH/POTENCY: 50 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

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

USAN Name: Clozapine USP**CAS Name:** 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[*b,e*][1,4]diazepine**CAS registry #:** 5786-21-0**Molecular weight:** 326.83**Molecular formula:** C₁₈H₁₉ClN₄**Structure:**

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet NDA 203-479

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Drug substance	3	Adequate		Last reviewed by Dr. Dominick Roselle dated Jun 12, 2012
	IV		(b) (4)	4			
	III			4			
	III			4			
	III			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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		Office of Compliance
Pharm/Tox	N/A		
Biopharm	Pending		Dr. Deepika A. Lakhani
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Acceptable/categorical exclusion	As per this review	Thomas M. Wong, Ph.D.
Microbiology	Recommended approval	22-Aug-2012	Dr. Vinayak B. Pawar

Executive Summary Section

The Chemistry Review for NDA 203-479

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

NDA 203-479 for clozapine oral suspension, 50 mg/mL, can not be approved from the CMC perspective due to the following pending issues:

- The Office of Compliance has not issued a final overall recommendation regarding the cGMP inspections.
- Awaiting study results from the applicant on the accuracy of delivered dose conducted on the oral syringes.

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

None at this time.

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)****Introduction**

Clozapine is an atypical antipsychotic marketed in the U.S. as Clozaril® and generic tablets in strengths of 12.5 mg, 25 mg, 50 mg, 100mg, and 200 mg, and as FazaClo® orally disintegrating tablets in strengths of 12.5 mg, 25 mg, 100 mg, 150 mg, and 200 mg. It is approved for the treatment of resistant schizophrenia and to reduce the risk of recurrent suicidal behavior in patients with schizophrenia and schizoaffective disorder. The current NDA is submitted as a 505(b)(2) application. The applicant developed an oral suspension in the strength of 50 mg/mL for the treatment of resistant schizophrenia. There are currently no liquid/suspension dosage forms of clozapine in the U.S. and the applicant believes the proposed product will meet an unmet medical need by providing a suspension formulation for those patients with swallowing difficulties. Clozapine Oral Suspension, 50 mg/mL is currently approved in New Zealand and Australia as Clopine™, and also approved in the United Kingdom, Ireland, and Germany under various company names (the EU formulation containing a higher level of (b) (4) than the US formulation). The U.S. suspension is reformulated to match the performance of the Clozaril® 100 mg tablets (U.S.) by changes in the EU formulation inactive ingredients.

Drug Substance

Clozapine, USP, is an atypical antipsychotic drug. It is a tricyclic dibenzodiazepine derivative and chemically, clozapine is 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[*b,e*][1,4]diazepine. It is a yellow, crystalline powder and is almost insoluble in water. There is no polymorphic form of clozapine found or described in the chemical literature. The

Executive Summary Section

drug substance is manufactured by (b)(4). Douglas as well as the drug product manufacturer, Pii, who will release the drug substance prior to use proposed specification for clozapine included all test items listed in the current USP monograph for clozapine. In addition, the proposed specification also includes testing and control for particle size and (b)(4). The applicant refers to DMF (b)(4) for detailed information on the drug substance. Detailed information in DMF # (b)(4) has been reviewed previously by Dr. Gil Kang on Feb 15, 2012 and all subsequent submissions by Dr. Dominick Roselle on Jun 12, 2012 and the current status of this DMF is adequate.

Drug Product

The proposed product is an immediate oral suspension in strength of 50 mg/mL. The clozapine oral suspension is packaged into a (b)(4) amber glass bottle. Each bottle contains 100 mL (b)(4). The prescribed quantity of suspension is withdrawn from the bottle by means of a graduated 1 mL or (b)(4) oral dispenser through a press-in bottle adaptor. The maximum daily dose will be 900 mg. Adequate information on the components and compositions of the oral suspension is provided. All the excipients in the formulation are common, compendial grades, and are widely used in the pharmaceutical industry. The manufacturing of the oral suspension consists of (b)(4). Limits for particle size of clozapine in the suspension is in place in the specification. Mixing of the suspension prior to filling is required. The drug product specification includes test and acceptable limits for appearance, viscosity, specific gravity, pH, identification of clozapine (UV spectrum and HPLC), and identification of sodium methylparaben and sodium propylparaben (HPLC), assay of clozapine and the parabens (HPLC), uniformity of dosage units (HPLC), impurities (HPLC), deliverable volume, dissolution, microbiological purity and particle size. Stability data support a twenty-four months expiry dating as proposed by the applicant when packaged into the commercial packaging configuration and stored at room temperature of 25°C (77 °F); protect from light. The package insert, container label and carton label has a statement of “shake well before use”.

Additional Items

DMFs: All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Methods Validation: The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the biopharmaceutical industry; revalidation by Agency laboratories will not be requested.

EES: **As of Aug 23, 2012, the Office of Compliance has not yet provided an overall acceptable recommendation for the manufacturing sites.**

Post-Approval Agreements: None.

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

The applicant developed an oral suspension in the strength of 50 mg/mL for the treatment of resistant schizophrenia. The trade name has not yet been finalized. The maximum daily dose is

Executive Summary Section

900 mg. The oral suspension is administered to the mouth by the oral syringes provided (1 mL or 9 mL).

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Douglas Pharmaceuticals American Limited has submitted sufficient and appropriate information to support the approval of the drug product, clozapine oral suspension. **However, this NDA cannot be approved from CMC perspective for the reasons mentioned in the Executive Summary of this review.**

III. Administrative**A. Reviewer's Signature**

See DARRTS

B. Endorsement Block

See DARRTS

C. CC Block

See DARRTS

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/s/

THOMAS M WONG
08/23/2012

RAMESH K SOOD
08/23/2012