

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203479Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA # 203479  
Product Name: Versacloz (clozapine) oral suspension

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PMR/PMC Description: Requirement to conduct an actual use human factors study in the U.S. in patients with schizophrenia. The study should include patients who are new to clozapine and patients who are stabilized on clozapine. The study should assess patients' ability to correctly measure doses using the approved Instructions for Use and packaging components.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/30/2013</u>
	Study/Trial Completion:	<u>08/30/2013</u>
	Final Report Submission:	<u>10/31/2013</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The applicant was originally instructed to conduct a Human Factors study to validate the usability of the dispensing syringes and Instructions For Use (IFU) for clozapine oral suspension during the IND process. The applicant experience delays due to the Agency's request for this study to be conducted in the United States, and the applicant's difficulty in <sup>(b) (4)</sup> during the review phase. This was not identified as an approval issue, and therefore this is an appropriate PMC.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the study is to validate the usability of the dispensing syringes and Instructions For Use (IFU) for clozapine oral suspension.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
Human Factors Validation Study
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other  
Human Factors Validation Study
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

505(b)(2) ASSESSMENT

Application Information		
NDA # 203479	NDA Supplement #: S- 000	Efficacy Supplement Type SE- N/A
Proprietary Name: Versacloz Established/Proper Name: Clozapine Dosage Form: Oral suspension Strengths: 50 mg/mL		
Applicant: Douglas Pharmaceuticals America LTD		
Date of Receipt: January 6, 2012		
PDUFA Goal Date: February 6, 2012		Action Goal Date (if different):
Proposed Indication(s): Treatment resistant schizophrenia; prevention of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES  NO

*If "YES "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. (*If not clearly identified by the applicant, this information can usually be derived from annotated labeling.*)

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Clozaril NDA 19758	Pharmacokinetic data

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

BE study in rate and extent of absorption to the listed drug product Clozaril (clozapine tablets)

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO,” proceed to question #5.*

*If “YES,” list the listed drug(s) identified by name and answer question #4(c).*

Clozaril (clozapine) tablets

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Clozaril	NDA 19758	Y

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph: Clozaril tablets

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

N/A YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in dosage form (from an oral tablet to an oral suspension), as well as for a change in strength (from 100 mg to 50 mg).

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

If "**NO**" to (a) proceed to question #11.  
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?  
YES  NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO   
If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?  
YES  NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

*the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):  
NDA 21590 Fazaclo  
ANDA: Multiple generic tablets

**PATENT CERTIFICATION/STATEMENTS**

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): Clozaril NDA 19758 / None

No patents listed 0 *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

**Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHARONJIT K SAGOO  
02/06/2013

## SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

<b>Product Title</b>	<b>VERSACLOZ (clozapine) oral suspension</b>
Applicant	Douglas Pharmaceuticals America Ltd
Application/Supplement Number	NDA 203479
Type of Application	Original Submission
Indication(s)	For the treatment of treatment-resistant schizophrenia and reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder.
Established Pharmacologic Class <sup>1</sup>	Atypical antipsychotic
Office/Division	ODEI/DPP
Division Project Manager	Sharon Sagoo
Date FDA Received Application	January 6, 2012
Goal Date	February 6, 2013
Date PI Received by SEALD	January 30, 2013
SEALD Review Date	January 31, 2013
SEALD Labeling Reviewer	Debra Beitzell
SEALD Division Director	Laurie Burke

PI = prescribing information

<sup>1</sup> The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item (**deficiency**).
- **YES:** The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A (not applicable):** This item does not apply to the specific PI under review.

## **Selected Requirements of Prescribing Information**

## Selected Requirements of Prescribing Information

### Highlights (HL)

#### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:** DPP to grant waiver of 1/2 page HL limit in approval letter.

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- NO** 4. White space must be present before each major heading in HL.

**Comment:** Insert one line of white space above Dosage Forms and Strengths heading and Drug Interactions heading in HL.

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:** BW, 3<sup>rd</sup> bulleted item, correct cross reference from "2.3" to "2.2".

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI

## Selected Requirements of Prescribing Information

• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

**Comment:**

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

**Comment:**

#### Product Title

- YES** 10. Product title in HL must be **bolded**.

**Comment:**

#### Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning

- YES** 12. All text must be **bolded**.

**Comment:**

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

## Selected Requirements of Prescribing Information

Comment:

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

### Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

### Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

**YES**

## Selected Requirements of Prescribing Information

24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

### Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: Change revision date to "February 2013" and bold date.

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: TOC subsection number for "Interference with Cognitive and Motor Performance" needs changed to "5.14." Correct TOC subsection heading 5.16 to read "Cerebrovascular Adverse Reactions"; correct 5.17 heading to read "Recurrence of Psychosis and Cholinergic Rebound after Abrupt Discontinuation of VERSACLOZ"; and correct 8.6 heading to read "Patients with Renal or Hepatic Impairment."

- NO** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

## Selected Requirements of Prescribing Information

***Comment:*** The BW title in the TOC does not match the BW title in HL. Add "PATIENTS" to BW title in HL (i.e., "Increased Mortality in Elderly Patients with Demetia-Related Psychosis").

**YES** 32. All section headings must be **bolded** and in UPPER CASE.

***Comment:***

**YES** 33. All subsection headings must be indented, not bolded, and in title case.

***Comment:***

**YES** 34. When a section or subsection is omitted, the numbering does not change.

***Comment:***

**NO** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS**" must be followed by an asterisk and the following statement must appear at the end of TOC: "\*Sections or subsections omitted from the Full Prescribing Information are not listed."

***Comment:*** Capitalize the first letters of "Full Prescribing Information" in the following statement "\*Sections or subsections omitted from the Full Prescribing Information are not listed."

## Full Prescribing Information (FPI)

### GENERAL FORMAT

**YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION**".

***Comment:***

**YES** 37. All section and subsection headings and numbers must be **bolded**.

***Comment:***

**YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>

## Selected Requirements of Prescribing Information

9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

**Comment:**

**NO**

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

**Comment:** *Attach Patient Information and Instructions for Use to the end of the PI.*

**NO**

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

**Comment:** *BW, last sentence, correct cross reference to read “[see Warnings and Precautions, (5.6)]”; subsection 2.8, last sentence, correct cross reference to read “[see Use in Specific Populations (8.6, 8.7)]”; subsection 7.1, last sentence of 4<sup>th</sup> paragraph, correct cross reference to read “[see Dosage and Administration (2.7)]”.*

**N/A**

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

**YES**

42. All text is **bolded**.

**Comment:**

**NO**

43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:** *Center BW title and change case of letters to upper-case for the entire title.*

**YES**

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

#### Contraindications

## Selected Requirements of Prescribing Information

- N/A** 45. If no Contraindications are known, this section must state “None”.

**Comment:**

### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

**Comment:**

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

**Comment:**

### Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

**Comment:**

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/s/  
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DEBRA C BEITZELL  
01/31/2013

LAURIE B BURKE  
01/31/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Consumer Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** November 1, 2012

**To:** Sharonjit Sagoo, PharmD  
Regulatory Project Manager  
Division of Psychiatry Products (DPP)

**From:** Susannah K. Hubert, MPH  
Regulatory Review Officer  
Division of Consumer Drug Promotion (DCDP)

**Subject:** **NDA 203479 VERSACLOZ™ (clozapine) oral suspension**

---

DCDP has reviewed the draft Medication Guide (MG) and Instructions for Use (IFU) for VERSACLOZ™ (clozapine) oral suspension as requested in the consult from DPP dated January 11, 2012.

DCDP's comments on the draft MG and IFU, which are based on the version provided by Robin Duer, DMPP, on October 26, 2012, are provided below.

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at [Susannah.Hubert@fda.hhs.gov](mailto:Susannah.Hubert@fda.hhs.gov).

DCDP appreciates the opportunity to provide comments on these materials. Thank you!

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/s/  
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SUSANNAH HUBERT  
11/01/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: October 25, 2012

To: Thomas Laughren, M.D., Director  
**Division of Psychiatry Products (DPP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Melissa Hulett, MSBA, BSN, RN  
Team Leader, Patient Labeling Team  
**Division of Medical Policy Programs**

From: Robin Duer, MBA, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs**

Subject: DMPP Review of Patient Labeling (Patient Information and Instructions for Use)

Drug Name (established name): VERSACLOZ (clozapine)

Dosage Form and Route: Oral Suspension

Application Type/Number: NDA 203479

Applicant: Douglas Pharmaceuticals America LTD

## 1 INTRODUCTION

On December 28, 2011, Douglas Pharmaceuticals submitted for the Agency's review a 505(b)(2) new drug application (NDA) for VERSACLOZ (clozapine) Oral Suspension. The reference listed drug for VERSACLOZ is CLOZARIL (clozapine) Tablets, NDA 19-758.

VERSACLOZ (clozapine) Oral Suspension is an atypical antipsychotic indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia. VERSACLOZ is indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state.

This review is written in response to a request by the Division of Psychiatry Products (DPP) for the Division of Medical Policy Programs (DMPP) to provide a review of the Applicant's proposed Patient Information (PPI) and Instructions for Use (IFU) for VERSACLOZ (clozapine) Oral Suspension. DMPP provided DNP with high level comments for the patient labeling on February 14, 2012 and March 27, 2012.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DPP under separate cover.

## 2 MATERIAL REVIEWED

- Draft VERSACLOZ (clozapine) Oral Suspension Patient Information (PPI) and Instructions for Use (IFU) received on October 15, 2012, and received by DMPP on October 16, 2012
- Draft VERSACLOZ (clozapine) Oral Suspension Prescribing Information (PI) received December 28, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on October 15, 2012

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We have reformatted the PPI and IFU document using the Verdana font, size 11.

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated version of the PPI and IFU are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/  
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ROBIN E DUER  
10/25/2012

MELISSA I HULETT  
10/25/2012

LASHAWN M GRIFFITHS  
10/26/2012

**MEMORANDUM**  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Drug Promotion

**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** October 19, 2012

**To:** Sharonjit Sagoo, PharmD  
Regulatory Project Manager  
Division of Psychiatric Products (DPP)

**From:** Jessica Cleck Derenick, PhD  
Regulatory Review Officer  
Division of Professional Promotion (DPP)  
Office of Prescription Drug Promotion (OPDP)

**Subject: NDA 203479**  
DPDP labeling comments for Versacloz™ (clozapine) oral solution

---

DPDP has reviewed the draft product labeling (PI) for Versacloz™ (clozapine) oral solution (Versacloz) as requested in the consult from DPP dated January 1, 2012.

DPDP's comments on the labeling, which are based on the draft version of the PI emailed by Sharonjit Sagoo on October 15, 2012, are provided below.

If you have any questions, please feel free to contact us:

Jessica Cleck Derenick: 301-796-0390; [Jessica.Cleck-Derenick@fda.hhs.gov](mailto:Jessica.Cleck-Derenick@fda.hhs.gov)

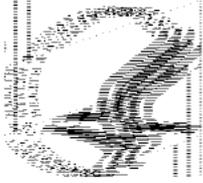
Thank you! DPDP appreciates the opportunity to provide comments on these materials.

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/s/  
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JESSICA N CLECK DERENICK  
10/19/2012



**DEPARTMENT OF HEALTH & HUMAN SERVICES**      Public Health Service

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Pediatric and Maternal Health Staff  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-0700  
FAX 301-796-9744

**Maternal Health Team Review**

**Date:** October 1, 2012                      **Date Consulted:** March 6, 2012

**From:** Upasana Bhatnagar, M.D.  
Medical Officer, Maternal Health Team  
Pediatric and Maternal Health Staff

**Through:** Melissa S. Tassinari Ph.D.  
Acting Team Leader, Maternal Health Team  
Pediatric and Maternal Health Staff

**Through:** Lynne P. Yao, M.D.  
Acting Associate Director, Office of New Drugs  
Pediatric and Maternal Health Staff

**To:** Division of Psychiatry Products (DPP)

**Drug:** Clozapine (FazaClo NDA 21590; (b) (4) NDA 203479)

**Sponsor:** Azur Pharma International III Limited (FazaClo)  
Douglas Pharmaceuticals America ( (b) (4) )

**Subject:** Pregnancy and Nursing Mothers Labeling

**Materials Reviewed:** Pregnancy and Nursing Mothers subsections of labeling, Published literature about clozapine in pregnancy and about infant exposure through ingestion of breast milk

**Consult Question:** Please review the Pregnancy and Nursing Mothers subsections of clozapine labeling and develop standard language for all clozapine labeling.

## INTRODUCTION

On June 14, 2011, Azure Pharmaceuticals International submitted a prior approval labeling supplement to the Division of Psychiatry Products (DPP) for FazaClo (clozapine), which is an orally disintegrating tablet indicated for the treatment of resistant schizophrenia. Clozapine was initially approved on February 9, 2004. Subsequently, on December 28, 2011, Douglas Pharmaceuticals America submitted a 505(b)(2) application for (b) (4) (clozapine oral suspension) indicated for the treatment of resistant schizophrenia; this is a new form (from tablet to oral suspension) and a change in strength from 100 mg to 50 mg from the listed drug Clozaril (clozapine).

DPP consulted the Pediatric and Maternal Health Staff's Maternal Health Team for both FazaClo and (b) (4) to develop labeling recommendations for the Pregnancy and Nursing mothers sections of labeling that can be applied to all clozapine products. This review provides PMHS-MHT recommendations for the Pregnancy and Nursing Mothers sections for all clozapine products.

## BACKGROUND

Clozapine is an antipsychotic agent indicated for the management of schizophrenic patients who have failed other antipsychotic treatment options. Clozapine's profile of binding to dopamine receptors (transient occupation of the D<sub>2</sub> receptor followed by rapid dissociation to allow normal function) results in a decreased risk for extrapyramidal symptoms such as seen with typical antipsychotic drugs.<sup>1</sup> Serious adverse reactions associated with clozapine include risk of agranulocytosis and seizure. Additionally, patients using clozapine have an increased risk of hyperglycemia.<sup>2</sup>

The incidence of schizophrenia peaks in women at age 25 to 35 years old, which coincides with peak reproductive age.<sup>3</sup> Women with schizophrenia have an increased risk of unplanned pregnancy and in some women, symptoms worsen during pregnancy and the postpartum period.<sup>4</sup> Therefore, female patients with schizophrenia have the potential to be exposed to clozapine during pregnancy and lactation.

## REVIEWED MATERIALS

### **Sponsors Proposed Pregnancy and Nursing Mothers Labeling for FazaClo**

*FazaClo labeling is provided as an example since the approved labeling is the same for all clozapine products in these sections.*

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<sup>1</sup> Einarson A, Boskovic R. Use and safety of antipsychotic drugs during pregnancy. J of Psychiatric Practice. 2009;15(3):183-192.

<sup>2</sup> Clozaril (clozapine) labeling, approved 10/19/2011

<sup>3</sup> Einarson A, Boskovic R. Use and Safety of Antipsychotic Drugs During Pregnancy. Journal of Psychiatric Practice. 2009;15(5):183-192.

<sup>4</sup> Solari H, Dickson KE, Miller L. Understanding and treating women with schizophrenia during pregnancy and postpartum-Motherisk Update 2008. Can J Clin Pharmacol.2009;16(1):e23-32.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

FazaClo (clozapine, USP) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### **Pregnancy Category B**

Reproduction studies have been performed in rats and rabbits at doses of approximately 2-4 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to clozapine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

#### **Non-teratogenic Effects**

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

### **8.3 Nursing Mothers**

Animal studies suggest that clozapine may be excreted in breast milk and have an effect on the nursing infant. Therefore, women receiving FazaClo (clozapine, USP) should not breast feed.

## **17 PATIENT COUNSELING INFORMATION**

- Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should not breast feed an infant if they are taking FazaClo (clozapine, USP).

## **REVIEW OF LITERATURE**

### **Pregnancy**

A PubMed literature search was conducted with the query “pregnancy and clozapine” which resulted in thirteen case reports of schizophrenic patients treated with clozapine during pregnancy. There were 18 pregnancies and 19 infants (one set of twins) with reported outcomes, and one neonatal death occurred after being delivered to mother who attempted suicide by an overdose of clozapine. These studies are summarized in Appendix A and including any data regarding infant exposure during lactation provided in the case reports.

#### *Reviewer Comments*

*The case reports are varied in regards to the amount of data reported and follow up of infants and therefore do not provide sufficient data to inform labeling. Although most of the infants with known outcomes were noted to have normal development, two infants had a*

*diagnosis of “Floppy Infant Syndrome” or FIS; one child had a speech delay; and one neonatal demise was reported in a mother who had overdosed. Karukala et al.<sup>5</sup> reported one infant with FIS after a preterm delivery at 28 weeks gestation due to fetal arrhythmia. The neonatal course included findings of an abnormal heart shape on x-ray, seizures, and a diagnosis of encephalopathy. Details of the cardiac anomaly were not provided, but the authors concluded that the complications were due to exposure to clozapine. However, it is not evident from the case report whether the outcomes were a result of drug exposure or a complication of severe prematurity. Similarly, the report by Di Michele et al.<sup>6</sup> of another infant with FIS also does not have a clear association with clozapine exposure since the mother took both lorazepam and clozapine during the pregnancy.*

*Mendhekar et al.<sup>7</sup> reported a child who had significant delay in development of speech. However, the child had no congenital anomalies contributing to the speech delay and after therapy had normal speech by age 5 years old. Lastly, Klys et al<sup>8</sup> reported a birth resulting in neonatal demise after a maternal suicide attempt with an overdose with clozapine. The neonate had poor cardiac and respiratory status upon delivery and could not be resuscitated. Although the demise was likely related to medication exposure, the death likely resulted from a toxic exposure since the mother took 200 tablets of 100mg clozapine.*

Reis and Kallen<sup>9</sup> published data from the Swedish Medical Birth Register to describe birth outcomes after use of antipsychotic medications in early pregnancy, including clozapine. 18 patients with exposure to clozapine in the first trimester were included in the study. One of the infants with exposure to clozapine had a ectopic anus. The study found an overall increase in all malformations with use of antipsychotic medications in pregnancy, but no increase in risk with a specific antipsychotic was found.

#### *Reviewer comments*

*Data regarding the drug dosage and gestational age at exposure were not known. Additionally, some of the patients treated with clozapine also used other medications concomitantly so the effects cannot be definitively associated with exposure to clozapine.*

#### **Lactation**

Although clozapine has been approved since 1989, there is little data regarding its use during breastfeeding. A PubMed and Lactmed search was performed with the query “clozapine and lactation,” and the reports in literature are summarized below.

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<sup>5</sup> Karakula H, Szajer K, Spila B. et al. Clozapine and Pregnancy. *Pharmacopsychiatry*.2004;37:303-304.

<sup>6</sup> DiMichele V, Ramenghi LA, Sabatino G. Clozapine and lorazepam administration in pregnancy. *Eur Psychiatry*. 1996;11:214.

<sup>7</sup> Mendhekar DN. Possible delayed speech acquisition with clozapine therapy during pregnancy and lactation. *J Neuropsychiatry Clin Neurosci*.2007;19(2).196-97.

<sup>8</sup> Klys M, Rojek S, Rzepecka-Wozniak E. Neonatal death following clozapine self-poisoning in late pregnancy. *Forensic Science International*.2007;171.e5-e10.

<sup>9</sup> Reis M, Kallen Bengt. Maternal Use of Antipsychotics in Early Pregnancy and Delivery Outcome. *J of Clin Psychopharmacology*. 2008;28(3).279-287.

Barnas et al.<sup>10</sup> published a case in which breast milk from a post-partum patient treated with clozapine was sampled one day and one week after delivery. In this patient, the concentration of clozapine in the breast milk was higher than the plasma concentration both one day (plasma 14.7 ng/ml, breast milk 63.5 ng/ml) and one week after delivery (plasma 41.4 ng/ml and breast milk 115.6 ng/ml). The authors attributed this to the lipophilic properties of clozapine.

In the case report, noted above, by Mendhekar et al.<sup>11</sup>, the infant was breast fed for one year. A speech delay was noted in this child which resolved by 5 years of age. The author could not attribute the delay in speech to exposure to clozapine or possibly related to maternal mental illness.

Dev and Krupp<sup>12</sup> reported four cases of infants that were breast fed by mothers treated with clozapine. Two out of four infants had adverse event that were potentially related to exposure to clozapine. One infant had agranulocytosis and one infant experienced drowsiness. The authors did not include details regarding these cases including the dose or duration of exposure to breast milk.

#### *Reviewer comments*

*These studies indicated that clozapine is present in breast milk of treated women, and may be present in higher concentrations in the breast milk than plasma in some patients. Additionally, although the reported data are minimal, some reports suggest that adverse events can be associated with infant exposure to clozapine through breast milk.*

## **DISCUSSION**

Clozapine is an atypical antipsychotic agent whose mechanism of action is mediated through dopamine (D<sub>2</sub>) receptors. Clozapine is indicated for the treatment of patients who have failed other antipsychotic therapy. The Division of Psychiatry Products (DPP) consulted the Pediatric and Maternal Health Staff's Maternal Health Team (PMHS-MHT) to review labeling in the pregnancy and nursing mothers sections of labeling clozapine products and specifically for FazaClo (clozapine) and (b) (4) (clozapine).

Because embryofetal studies in animals do not indicate adverse developmental effects with exposure to clozapine and data regarding clozapine use in pregnancy are limited, the PMHS-MHT recommends maintaining the current pregnancy category B for clozapine products. The small number of case reports in the literature are difficult to interpret because of the variations in the dosage used, timing of exposure, and variability of pregnancy outcome data. No specific pattern of adverse events in the fetus is evident from these reports. Thus, the available human data from these reports are not sufficient to inform labeling. Providers treating patients with schizophrenia during pregnancy must balance the potential for

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<sup>10</sup> Barnas C, Bergant A, Hummer M et al. Clozapine Concentrations in Maternal and Fetal Plasma, Amniotic Fluid, and Breast Milk. *Am J Psychiatry*.1994;151(6):945

<sup>11</sup> Mendhekar DN. Possible delayed speech acquisition with clozapine therapy during pregnancy and lactation. *J Neuropsychiatry Clin Neurosci*.2007;19(2).196-97.

<sup>12</sup> Dev VJ, Krupp P. Adverse event profile and safety of clozapine. *Rev Contemp Pharmacother*.1995;6:197-208.

worsening psychosis in the untreated mother with the potential for deleterious effects on the fetus.

In addition, because of the increased risk for hyperglycemia with clozapine treatment, PMHS-MHT recommends that clinicians consider monitoring of pregnant women taking clozapine for persistent hyperglycemia. Persistent hyperglycemia as is seen in gestational diabetes pregnancy is associated with adverse pregnancy outcomes such as congenital malformations and birth injury.<sup>13</sup>

PMHS-MHT recommends that nursing mothers be advised to discontinue clozapine or discontinue breastfeeding. Available case reports indicate that clozapine is present in the breast milk of lactating patients receiving clozapine, and may be actively secreted into breast milk. Serious adverse effects of exposure to clozapine through breast milk have been reported although the data are extremely limited. Because this data are insufficient to determine the long-term effects on infants exposed to clozapine through breast milk, providers must counsel patients about the potential risks to the infant balanced with the risk of stopping treatment in the mother.

### **Pregnancy and Nursing Mothers Labeling**

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

### **RECOMMENDATIONS**

- Clozapine should continue to be labeled as pregnancy category B due to negative animal studies and limited available human data.
- PMHS-MHT notes that hyperglycemia is a known adverse reaction associated with clozapine. The presence of persistent hyperglycemia during pregnancy may result in adverse pregnancy outcomes. Therefore, PMHS-MHT recommends additional labeling to advise providers to monitor pregnant women treated with clozapine for the development of gestational diabetes.

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<sup>13</sup> Gabbe S, Neiby JR, Simpson JL eds. *Obstetrics Normal & Problem Pregnancies*. 3<sup>rd</sup> ed, New York, 1996:1037-81.

- Nursing mothers should be advised to discontinue nursing or discontinue treatment with clozapine because the drug is present in the breast milk of treated patients and inadequate data are available regarding infant exposure to clozapine.

## **PMHS – Maternal Health Labeling Recommendations for clozapine products**

### **-----USE IN SPECIFIC POPULATIONS-----**

- Nursing mothers: Discontinue drug or discontinue nursing, taking into consideration importance of the drug to mother. (8.3)

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category B

#### Risk Summary

There are no adequate or well-controlled studies of clozapine in pregnant women. Reproduction studies have been performed in rats and rabbits at doses of approximately 2-4 times the human dose and have shown no evidence of impaired fertility or harm to the fetus due to clozapine. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

#### Clinical Considerations

Consider the risk of exacerbation of psychosis when discontinuing or changing treatment with antipsychotic medications during pregnancy and postpartum.

Consider early screening for gestational diabetes for patients on antipsychotic medications because of the risk of persistent hyperglycemia. [*see 5.X Metabolic Adverse Reactions*]

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Monitor neonates for symptoms of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding difficulties. The severity of complications can vary from self-limited symptoms to some neonates requiring intensive care unit support and prolonged hospitalization.

#### Animal Data

*[Pharm Tox to revise this section]*

### **8.3 Nursing Mothers**

Clozapine is present in human milk. Because of the potential for serious adverse reactions in nursing infants from clozapine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

## **17 PATIENT COUNSELING INFORMATION**

### **17.1 Information for Patients**

- Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should not breast feed an infant if they are taking clozapine.

## Appendix A [Summary Table of Case Reports]

Summary of Case Reports						
Author	Dose Clozapine	Number cases	Pregnancy Course	Delivery	Neonatal outcome	Other
Waldman <sup>14</sup> 1993		1 case	Gestation Diabetes	Vaginal Delivery Shoulder Dystocia	8lb 2oz, healthy	
Barnas <sup>15</sup> 1994	9w- 50 mg/day, raised to 100 mg/day 3 days post delivery	1 case	Normal pregnancy course x 25 kg wt gain	41 wks VAVD		Levels Maternal plasma, Amniotic fluid, Breast milk
DiMichele <sup>16</sup> 1996	200 mg/day increased to 300 mg/3 times day	1 case	Normal pregnancy course	37 weeks Normal APGARS	Developed tachypnea and mild Floppy Infant Syndrome admitted to NICU. Hyptonia resolved in five days. Cerebral ultrasound, EEG, abdominal ultrasound, chest x-ray all normal	Treatment with Lorazepam 2.5 mg >3 to 5 times/day
Stoner <sup>17</sup> 1997	(1) 350 mg/day (2) 600-635 mg/day	2 cases	Both with intensified psychotic symptoms during pregnancy	(1) VAVD 39 wks (2) FAVD 40wks	(1) 3800g, Resolved cephalohematoma, seizure 8days of age but negative evaluation, normal development at age 2 years old (2) 2510g mild post-partum fever that resolved	
Dickson <sup>18</sup> 1998	1 <sup>st</sup> trimester 450 mg/day 2 <sup>nd</sup> -200- 250mg/day 3 <sup>rd</sup> 150mg/day	1 case	Diabetes-treated with insulin Intermittent exacerbations of symptoms of fatigue/hypersomnolenc e, doses reduced	Mid Forceps Delivery Shoulder Dystocia	Healthy infant	

<sup>14</sup> Waldman D, Safferman AZ. Pregnancy and clozapine. *The American Journal of Psychiatry*. 1993;150(1):168-169.

<sup>15</sup> Barnas C, Bergant A, Hummer M et al. Clozapine Concentrations in Maternal and Fetal Plasma, Amniotic Fluid, and Breast Milk. *Am J Psychiatry*. 1994;151(6):945

<sup>16</sup> DiMichele V, Ramenghi LA, Sabatino G. Clozapine and lorazepam administration in pregnancy. *Eur Psychiatry*. 1996;11:214.

<sup>17</sup> Stoner SC, Sommi RW, Marken PA et al. Clozapine use in two full-term pregnancies. *J Clin Psychiatry*. 1997;58(8):364-65.

Summary of Case Reports						
Author	Dose Clozapine	Number cases	Pregnancy Course	Delivery	Neonatal outcome	Other
Yogev <sup>19</sup> 2002		1 case	Decreased fetal heart rate variability noted at 34 wks, other testing normal	SVD 37wks Decreased fetal heart rate variability	3420 g Discharged with mother	
Nguyen <sup>20</sup> 2003	350 mg/day	1 patient- 2 pregnancies	1 <sup>st</sup> -Gestational Diabetes (GDM), insulin treatment 2 <sup>nd</sup> - normal pregnancy course no GDM	2 children	Normal development at 2 and 5 yrs old, respectively	Abstract only-article in French
Gupta <sup>21</sup> 2004	(1) 200mg/day (2) 100mg/day	1 patient- 2 pregnancies	(1) PIH at 38wks (2) PIH at 30 wks	(1) SVD 39wk (2)C section for breech 39 wks	(1)3000g, normal development until 20 months (2) 2800g, normal development until 6 months	
Karakula <sup>22</sup> 2004	200 mg/day	1 case	Preterm labor at 28wks	Cesarean section due to fetal arrhythmia	4000g NICU admission due to seizures, apnea, lockjaw, encephalopathy, respiratory insufficiency, abnormal heart shape, "Floppy infant syndrome" 7 months age- Delayed development, absent left testicle, hernia linea alba	Father alcoholic
Sethi <sup>23</sup> 2006	250 mg/day	1 case	Uncomplicated	No complications	Normal development until 2 years old	
Klys <sup>24</sup> 2007	Off clozapine after first trimester until took 4 boxes	1 case- Suicide attempt	In patient hospitalization for suicidal ideation	VAVD after labor while patient unconscious, meconium stained	4050g, poor cardiac and respiratory status, coded but not able to be resuscitated, Autopsy performed-levels of	OVERDOSE Neonatal demise

<sup>18</sup> Dickson RA, Hogg L. Pregnancy of a patient treated with clozapine. Psychiatry online. August 1, 1998. accessed 7/26/12.

<sup>19</sup> Yogev Y, Ben-Haroush A, Kaplan B. Maternal clozapine treatment and decreased heart rate variability. International Journal of Gynecology and Obstetrics.2002;79:259-60.

<sup>20</sup> Nguyen HN, Lalonde P. Clozapine and pregnancy [abstract, article in French].Encephale.2003;29(2):119-24.

<sup>21</sup> Gupta N, Grover S. Safety of clozapine in 2 successive pregnancies.Can J Psychiatry. 2004.49(12):863.

<sup>22</sup> Karakula H, Szajer K, Spila B. et al. Clozapine and Pregnancy. Pharmacopsychiatry.2004;37:303-304.

<sup>23</sup> Sethi S. Clozapine in Pregnancy. Indian J of Psychiatry. 2006;48(3):196-197.

### Summary of Case Reports

Author	Dose Clozapine	Number cases	Pregnancy Course	Delivery	Neonatal outcome	Other
	each with 50 tablets/100mg			fluid	clozapine and metabolites in fetal blood and tissues noted	
Mendhekar <sup>25</sup> 2007	100mg/day	1case	Unremarkable	SVD at 9 months, 2950g	Speech delay-normal speech by age 5 years old. Normal Ear Nose and Throat exam, normal hearing, other milestones met	Breastfed infant x 1year
Duran <sup>26</sup> 2008	(1a &1b) 200mg/day (2) 400mg /day to 200mg/day	2 patients • 1 with 2 deliveries (a &b) • 1 with twin delivery	(1a) uncomplicated (1b) uncomplicated (2) non compliant with prenatal care, only seen last month pregnancy	(1a) SVD term, 2900g (1b) SVD term, 3000g (2) SVD term, twins 3100g, 2940g		

SVD-spontaneous vaginal delivery, C section-Cesarean section, VAVD-Vacuum assisted vaginal delivery, FAVD-Forceps assisted vaginal delivery, NICU-neonatal intensive care unit

<sup>24</sup> Klys M, Rojek S, Rzepecka-Wozniak E. Neonatal death following clozapine self-poisoning in late pregnancy. *Forensic Science International*.2007;171.e5-e10.

<sup>25</sup> Mendhekar DN. Possible delayed speech acquisition with clozapine therapy during pregnancy and lactation. *J Neuropsychiatry Clin Neurosci*.2007;19(2).196-97.

<sup>26</sup> Duran A, Ugur MM, Tura S et al. Clozapine use in two women with schizophrenia during pregnancy. *J Psychopharmacol*.2008;22:111-12.

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/s/  
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UPASANA BHATNAGAR  
10/01/2012

MELISSA S TASSINARI  
10/01/2012

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10/09/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: August 7, 2012

Reviewer: Loretta Holmes, BSN, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS  
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, PharmD, MPH  
Division of Medication Error Prevention and Analysis

Division Director: Carol A. Holquist, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Clozapine Oral Suspension  
50 mg/mL

Application Type/Number: NDA 203479

Applicant: Douglas Pharmaceuticals America Limited

OSE RCM #: 2012-750

**\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\***

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## 1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Clozapine Oral Suspension, NDA 203479, for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

NDA 203479 for Clozapine Oral Suspension is a 505(b)(2) application. The Reference Listed Drug (RLD) is Clozaril Tablets (NDA 19758). The Applicant currently markets Clozapine Oral Suspension in New Zealand. If approved, this will be the first clozapine oral suspension marketed in the United States. Additionally, this product will have an associated Risk Evaluation and Mitigation Strategy (REMS) that references the approved Fazacllo ODT REMS.

The proposed proprietary name for this product, VersaCloz, is being evaluated under separate cover in OSE Review #2012-738. Additionally, the human factors study protocol for this product was evaluated in OSE Review #2012-379.

### 1.2 PRODUCT INFORMATION

The following product information was provided in the March 23, 2012 submission.

- Active Ingredient: Clozapine
- Indication of Use: Management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia; reducing the risk of recurrent suicidal behavior in patients with schizophrenic or schizoaffective disorder who are judged to be at chronic risk for reexperiencing suicidal behavior based on history and recent clinical state. This product is not indicated in children.
- Route of administration: Oral
- Dosage form: Oral Suspension
- Strength: 50 mg/mL
- Dose and Frequency of Administration: Begin with 12.5 mg once or twice daily. The dosing should be continued with daily dosage increases of 25 mg to 50 mg per day, if well tolerated, to achieve a target dose of 300 mg to 450 mg per day by the end of 2 weeks. Subsequent dosage increases should be made no more than once or twice weekly in increments not to exceed 100 mg. Dosing should not exceed 900 mg per day.
- How Supplied: Clozapine oral suspension will be supplied in amber bottles containing 100 mL. Each carton will contain one bottle of clozapine oral suspension, one 1 mL oral syringe, one 9 mL oral syringe, and one bottle adaptor.
- Storage: Store at or below 25°C (77°F)
- Container and Closure Systems: Each bottle will have a   (b) (4)

## 2 METHODS AND MATERIALS REVIEWED

Using the principals of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Packaging
- Container Label submitted March 23, 2012 (Appendix A)
- Carton Labeling submitted March 23, 2012 (Appendix B)
- Insert Labeling submitted May 4, 2012
- Instructions for Use submitted May 4, 2012

## 3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The Applicant proposes to co-package two different oral syringes for use with this product. The acceptability of this packaging presentation is subject to the results of the usability study that will be conducted by the Applicant (see OSE Review #2012-379).

The product will be supplied in bottles containing 100 mL. However, the amount of product dispensed by the pharmacist may be limited to less than 100 mL since the dose and frequency of WBC and ANC monitoring determines the amount that can be dispensed under the REMS, which could lead to the dispensing of partial bottles. It is not clear what is expected of the pharmacist regarding the dispensing of partial bottles, especially since the proposed product will be supplied with only one 1 mL oral syringe and one 9 mL oral syringe. The supplied bottle adaptor will be specific to the original packaged container and may not be suitable for use with other bottles provided directly by a pharmacy. Additionally, only one set of Patient Information and Patient Instructions for Use will be enclosed in the carton, which increases the likelihood that a patient is dispensed the medication without the accompanying FDA approved patient labeling. These concerns were included in our review of the human factors protocol submitted by the Applicant for this product and conveyed to the Applicant.

Additionally, we were informed by CMC that the product should be shaken for a minimum of 10 seconds in order to produce a (b) (4) suspension. Therefore, these instructions will need to be incorporated into the “Shake Well” statements on the labels and labeling.

The strength and dosage form proposed for Clozapine Oral Suspension are reasonable given the proposed indication, dosage and administration for this product. However, DMEPA identified deficiencies in the container labels, carton labeling, insert labeling and instructions for use. These deficiencies include:

- Inadequate prominence of important information

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Layout and format of information that can be optimized
- Unclear label and labeling statements
- Lack of information to the pharmacist regarding the dispensing of partial bottles
- Use of abbreviations and error-prone symbols in the insert labeling

We provide recommendations in Section 5 to correct these deficiencies and minimize the risk of medication errors.

## 4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product, to mitigate any confusion, and to clarify information.

Additionally, as currently proposed, the packaging design is not optimal since it does not allow pharmacists to easily dispense partial bottles and provide patients with the materials necessary to use the medication as labeled (i.e., extra supply of oral syringes, instructions for use, etc.). Our concerns regarding packaging have already been conveyed to the Division of Psychiatry Products (DPP) and the Applicant, and we will work with them to determine a path forward with regards to packaging.

## 5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA.

### 5.1 COMMENTS TO THE DIVISION

#### A. Insert Labeling

1. *Dosage and Administration* Sections of Highlights of Prescribing Information and Full Prescribing Information

Abbreviations (e.g. t.i.d.), error-prone symbols (e.g. hyphens) and numerical values without their corresponding unit of measure (e.g., 25-50 mg/day) are used throughout the *Dosage and Administration* sections of the insert labeling. We recommend removing these abbreviations and error-prone symbols and replace, where needed, with the spelled out meaning (e.g., 25 mg to 50 mg per day; 12.5 mg; 12.5 mg to 900 mg; and three times per day).

2. *Dosage and Administration* and *Patient Counseling Information, Information for Patients* Sections of Full Prescribing Information

It appears the term “Patient Use Instructions” is used in some instances where it appears the term “Patient Instructions for Use” is intended. We recommend the term “Patient Instructions for Use” be used consistently throughout all sections of the labeling.

3. *How Supplied/Storage and Handling* Section of Full Prescribing Information
  - a. For clarity, we recommend revising the statement “Each box contains ...” to read: “Each box contains one 1 mL oral syringe, one 9 mL oral syringe and one bottle adaptor”.
  - b. Revise the statement “Shake well before use” to read: “Shake well for 10 seconds before use”.
  - c. This section of the labeling provides information to the pharmacist regarding the amount of Clozapine Oral Suspension that can be dispensed. We recommend this information be relocated to Section 2 *Dosage and Administration* in Full Prescribing Information and placed under the main heading.
- B. Patient Information
  1. The Patient Information states that the pharmacist will instruct the patient on how to use Clozapine Oral Suspension under “How should I take VERSACLOZ?” However, there is no guarantee that the pharmacist will always instruct the patient. Therefore, we recommend this statement be deleted.
  2. Under “*How should I store VERSACLOZ?*” the statement “Do not refrigerate or freeze” is present. This statement is not on the container label, carton labeling, or in the Prescribing Information. Ensure the storage conditions statements are consistent throughout all of the labels and labeling.
  3. Under the heading “How should I store Versacloz”, revise the statement “Shake well before use” to read: “Shake well for 10 seconds before use”.
- C. Patient Instructions for Use [The following recommendations (#1 through #3) have already been conveyed to the Applicant as part of our review of the Human Factors Protocol and are reiterated here for your information. See IR correspondence dated June 21, 2012 in DARRTS and OSE Review 2012-379 dated June 5, 2012. We have one additional comment (#4) that has not yet been conveyed to the Applicant].
  1. Step 4 in the Instructions for Use (IFU) states that if the dose is lower than 50 mg (1 mL) then the 1 mL syringe should be used and if the dose is greater than 50 mg (1 mL) the larger 9 mL syringe should be used. However, the instructions do not state which syringe should be used if the dose is 50 mg (1 mL). Include instruction regarding which syringe should be used to measure a 50 mg (1 mL) dose.
  2. Some of the Figures show sweeping semicircular marks that appear to be intended to show direction (e.g., Figures A, G, and K), however, the arrows lack prominence which makes it difficult to see the direction that is being represented. Increase the prominence of the arrows.
  3. The first figure showing contents of the package and Figure D should be enlarged to clearly show the details of the oral syringes including graduation marks. As currently presented, the graduation marks cannot be easily read in

the applicable figures. The pictures of the oral syringes should accurately reflect the actual syringes that will be packaged in the carton.

4. In Step 1: Revise the statement “Shake the bottle to mix the medicine” to read: “Shake the bottle for 10 seconds to mix the medicine”.

## 5.2 COMMENTS TO THE APPLICANT

### A. General Comments for Container Label and Carton Labeling

1. Since VersaCloz is not a name that has been involved in drug name confusion or wrong drug errors, the capitalization of the letter “C” is inappropriately applied. Ensure the proprietary name, Versacloz, is presented without a capital “C”.
2. The dosage form statement (“oral suspension”) lacks prominence due to its small size and (b) (4) color which is difficult to see against the white background. The font for the dosage form statement should match the font used for the active ingredient statement (clozapine, USP) in size, typography, and color.
3. The statement of strength lacks prominence due to its small size and thin white font against the blue background. Increase the size of the statement of strength and use a heavier font weight.
4. The (b) (4) graphic above the proprietary name is distracting. Delete the graphic to minimize clutter and allow additional room for more important information on the principal display panel (PDP).
5. The net quantity statement is too prominent due to its size. Decrease the size of the net quantity statement and debold the font.
6. Add the statement “For Oral Administration Only” to the principal display panel (PDP). Postmarketing experience has demonstrated that wrong route of administration errors have occurred in the clinical setting when oral liquid products have been inadvertently administered as injections.
7. Under “*How should I store VERSACLOZ?*” in the Patient Instructions for Use, the statement “Do not refrigerate or freeze” is present. This statement is not on the container label, carton labeling, or in the Prescribing Information. Ensure the storage conditions statements are consistent throughout all of the labels and labeling.

### B. Container Label

1. The statement “Each mL contains 50 mg of clozapine” and the storage conditions are on the principal display panel (PDP). Relocate these statements to one of the side panels since they are not necessary on the PDP and add clutter to the PDP as well.
2. The statement “The prescribed amount of suspension should be drawn from the bottle using the oral dispenser provided” is located under the dispensing instructions to the pharmacist. However, this statement should be prominent

for patients. Move the statement to the principal display panel. Additionally, we recommend revising the term “oral dispenser” to read “oral syringe”.

3. According to data that you submitted to the Agency, the product should be shaken for at least 10 seconds in order to ensure a (b) (4) suspension. Therefore, revise the statement “Shake Well Before Use” to read: “Shake Well for 10 Seconds Before Use”. Additionally, change from upper case to title case lettering for improved readability. To retain prominence, maintain the bold font or consider the use of color or some other means.

### C. Carton Labeling

1. The statement “Each mL contains 50 mg of clozapine” is on the principal display panel (PDP). Delete it from the PDP since it is redundant and it adds clutter to the PDP.
2. The list of carton contents is not optimally worded for clarity. Revise to read as follows:

This Carton Contains:

One 1 mL oral syringe

One 9 mL oral syringe

One bottle adaptor

This recommendation may change based on the final packaging presentation for this product.

3. Revise the statement “Shake well before use” to read “Shake Well For 10 Seconds Before Use” and relocate the statement to the PDP. Additionally, change from upper case to title case lettering for improved readability. To retain prominence, maintain the bold font or consider the use of color or some other means.
4. Currently, the section “Dispensing Instructions—Attention Pharmacists:” precedes and is attached to the approved Patient Labeling (Patient Information and Patient Instructions for Use). The pharmacist is required to tear off this section of the labeling prior to giving the Patient Information and Instructions for Use to the patient. Having the dispensing instructions for the pharmacist inside the package is error-prone because pharmacists may not always look in the carton to find the dispensing instructions or be aware that these instructions are inside the package. Since these instructions are more detailed, replace the existing dispensing instructions on the carton with those that are attached to the Patient Labeling.

Additionally, pharmacists may be required to dispense partial bottles. Therefore, the packaged bottle of oral suspension, oral syringes, bottle adapter, and FDA approved patient labeling may not be available to dispense to all patients. Provide information on the carton labeling that instructs pharmacists on what to do in this situation.

In order to accommodate this additional information, consider moving storage information and other statements from the back panel to the side panel(s). Additionally, consider removing redundant statements.

If you have further questions or need clarifications, please contact Sandra Griffith, Project Manager, at 301-796-2445.

**APPENDICES**

**Appendix A:** Container Label



**Appendix B:** Carton Labeling



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LORETTA HOLMES  
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IRENE Z CHAN  
08/07/2012

KELLIE A TAYLOR  
08/09/2012

CAROL A HOLQUIST  
08/09/2012

MEMORANDUM

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

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DATE: July 27, 2012

TO: Thomas P. Laughren M.D.  
Director,  
Division of Psychiatry Products

FROM: Arindam Dasgupta Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGLPC)  
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, R.Ph., Ph.D.  
Chief, Bioequivalence Branch,  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

and

William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 203-479, Clozapine oral  
suspension, 50 mg/ml sponsored by Douglas  
Pharmaceuticals America Ltd.

At the request of the Division of Psychiatry Products (DPP), the Division of Bioequivalence and GLP Compliance (DBGLPC), conducted inspections of the clinical and analytical portions of the following bioequivalence study:

**Study Number:** C11-005-LBB (ZPS 411)  
**Study Title:** Multiple-dose, multi-centre, randomized, bioequivalence study of clozapine in multiples of 100 mg using 50 mg/ml Clozapine suspension (Douglas, America) in a two way crossover comparison with multiples of 100 mg using Clozaril 100 mg tablet (Novartis, USA) in stable patients under fasting and fed conditions and at steady state.

**BACKGROUND:**

This study enrolled 30 subjects, males and non-pregnant females (18-55 yrs), who were receiving treatment with multiple doses of 100 mg clozapine once daily, and stabilized (for at least 3 months after enrollment and randomization) for psychotic illnesses, but were otherwise in good health. There were no dropouts and all 30 subjects completed the study. Seventeen subjects were enrolled at the clinical site in Dunedin, New Zealand, and 13 subjects were enrolled at the clinical site in Hamilton, New Zealand.

**OBJECTIVE:**

The primary objectives of the study were to compare the bioavailability and bioequivalence of clozapine Test (Clozapine suspension, 50 mg/mL) and Reference (Clozaril® 100 mg tablets) formulations in stabilized adult patients under fasting and fed conditions. The secondary objectives were to assess the overall safety of the patients with regard to adverse events and standard laboratory evaluations.

The inspections were conducted by ORA Investigator Craig Garmendia (CG) and DBGLPC Scientist Arindam Dasgupta (AD). The inspection of the clinical site#1 and analytical Site#1 were conducted at Zenith Technology Corporation Ltd., Dunedin, New Zealand (By CG and AD). The inspection of the clinical site #2 was conducted at Waikato Hospital, Hamilton, New Zealand (by CG). The audits included a thorough review of study records, examination of facilities, equipment, and interviews and discussions with the firms' management and staff.

Following the inspection of the clinical and analytical sites, a Form FDA 483 was issued at each site (**Attachment 1-3**). Response to the inspectional observations from clinical sites 1 and 2 were received on June 7 and June 10, 2012, respectively (**Attachments 4-5**). A response to the inspectional observations from the analytical site was received on June 15, 2012 (**Attachment 6**). DBGLPC's evaluation of the inspectional observations and the firm's responses follows:

**Clinical site 1:**

**Zenith Technology Corporation Ltd., Dunedin, New Zealand**  
**(Inspection Dates: May 14-22, 2012 by CG and AD, Response to**  
**FDA-483: June 7, 2012)**

**Observation 1**

Failure to assure that reserve samples came from the same samples used in the specific bioequivalence study identified by the agency, and failure to adequately identify said samples to assure positive identification. Specifically in regards to the multi-center study Protocol ZPS-411, the Dunedin site housed reserve samples for both for the Dunedin site and the Waikato site. The samples returned from the Waikato site were commingled with the Dunedin site. Upon collection of the reserve samples by the agency, there was no positive identification on the samples that allowed the agency to identify which samples were from the Dunedin site and which samples were from the Waikato site.

Zenith acknowledged the observation and stated that this was the first multi-site study they had conducted and they did not understand the regulation for retention of reserve samples during such multi-site studies. The samples returned from the Waikato clinical site were hence comingled and not stored separately. However, Zenith pointed out that the sponsor had no role in selection of the sequence of investigational products administered to each patient on the study.

As a preventive action, Zenith has assured that during conduct of all future multi-site studies, each Principal Investigator will be responsible for drug accountability and traceability. Zenith also assures that adequate amounts of drug products would be provided to each of the study sites who will independently dispense the drug products and retain adequate amount of appropriately labeled reserve samples. If the reserve samples from a multi-center study were to be stored at Zenith, they would be adequately identified upon receipt.

**DBGLPC's Assessment of Data Integrity:** Although the reserve samples coming from the two clinical sites Zenith and Waikato were comingled, the study was not blinded and the reference and test formulations were different in appearance (suspension vs solid oral dosage form). The sponsor had sent the investigational products (reference and test drugs) for the study as one shipment to Zenith. The reference and test drugs from the same shipment were used at both clinical sites during the study. The subject case report forms clearly identified the dosage forms given to individual subjects. Hence, even though the reserve samples were comingled, they can be identified as coming from the same source used during the clinical study. The

DBGLPC reviewer is of the opinion that observation 1 should not have a significant impact on the study outcome.

**Observation 2**

**Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.**

**Specifically,**

**A. Source data does not match the data submitted to the agency. For Protocol ZPS-411, the C-SSRS questionnaires for dosed Subject 9 submitted to the agency did not match the source information available at the site, specifically the Suicidal Behavior data.**

In their response, Zenith acknowledged that one of their staff members had made additions to the C-SSRS questionnaires for subject 9 where a "0" was added to the "total number of attempts" column for suicidal behavior after the document was scanned for submission. Zenith believes that it was unnecessary as the check box was already selected for no suicide attempts for this subject and this change did not alter the data submitted to the agency. They acknowledged that they are unable to identify the reason behind the change as the staff member is no longer employed at Zenith. As corrective action, the copy was amended and forwarded to the sponsor. To prevent future occurrence, Zenith has initiated a new SOP which detailed the best practices of handling source documents. All staff handling/completing source documents were to be trained on this SOP by June 27, 2012.

**DBGLPC's Assessment of Data Integrity:** Zenith did not follow best documentation practices and they are of concern as they can raise general questions on the reliability and integrity of the study data. However, based on the response, this reviewer thinks that observation 2a, by itself, does not affect the study outcome.

**Clinical site 2:**

**Puna-A-Tarle, Puna Maatai Puawai, Waikato Hospital, Hamilton, New Zealand (Inspection Date: May 23, 2012 by CG, Response to FDA-483: June 10, 2012)**

**Observation 1**

**Failure to retain reserve samples specific to an in vivo bioequivalence study.**

**Specifically in regards to the multi-center study Protocol ZPS-411, you have not retained reserve samples for this study. All study drugs, both used and unused, were returned to the Dunedin site, which was not apart of the study protocol.**

Waikato site acknowledged the observation and stated that this study was conducted under the guidance and supervision of Staff from Zenith Technology Corp. Ltd. and the Waikato investigator, subcontracted by [REDACTED] <sup>(b) (4)</sup> was unaware of the requirement for retention of reserve samples as this was not stipulated in the Protocol for this study. However, they promised to work with Zenith for clear stipulation regarding retention of reserve samples in study protocols during future studies to prevent similar occurrences.

**DBGLPC's Assessment of Data Integrity:** Waikato clinical site did not maintain the reserve samples as required by regulation and instead sent them back to Zenith. However, as Zenith was not the sponsor, manufacturer or packager, the integrity of the reserve samples was not compromised. Furthermore, the reference and test formulations used at Waikato and Zenith clinical sites came from a single shipment and were different in appearance (Suspension vs solid oral dosage form). Zenith staff transported the study drugs to the Waikato site without involvement of the sponsor. Also, the subject case report forms clearly identified the dosage forms given to each subject. In the opinion of this reviewer, observation 2 is unlikely to affect study outcome as the subject treatments could be confirmed from other source documents.

**Observation 2**

**Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.**

**Specifically in regards to Protocol ZPS-411,**

- A. Source data from the Patient Study Record and Adverse Reactions form does not match the data submitted to the agency.**
- i. Dosed Subject 25 - Days 1, 2, and 5**
  - ii. Dosed Subject 26 -Day 4**
  - iii. Dosed Subject 29 - All Days**

In their response, Waikato site stated that all source data were scanned by Zenith for submission to the sponsor. The response included the original pages of the patient study records which matched with the records submitted to the agency. No alterations were revealed in factual information. The response also stated that the patient study records for subjects 25, 26 and 29 were transcribed for clarity, however no factual information was changed.

As corrective and preventive action, Zenith has initiated a new SOP which details the best practices of handling source documents. All staff handling/completing source documents were to be trained on this SOP by June 27, 2012.

**DBGLPC's Assessment of Data Integrity:** In the opinion of the DBGLPC reviewer, the factual information did not change between the original and the transcribed document as evident from the original documents provided for comparison by Zenith, and therefore, the above observation should not have a significant impact on the outcome of the overall study data.

**B. Post study safety labs were outside the date range specified in ProtocolZPS-411 for dosed Subjects 3, 19-25 and 27-30.**

In their response, the Waikato site stated that many subjects did not have reliable transportation and did not wish to return for the post study safety labs. Hence, the post study safety samples were collected immediately after the final study sample was collected on day 23. Due to an oversight, collection of these samples at the earlier date was not recorded as a protocol deviation. As a corrective action, the Zenith promised to generate a study record form (SRF) to record all protocol deviations during the study and notify the sponsor. These corrective actions were to be finalized by July 6, 2012.

**DBGLPC's Assessment of Data Integrity:** The above observations should not have a significant impact on the outcome of the overall study data.

**Analytical site:**

**Zenith Technology Corporation Ltd., Dunedin, New Zealand**  
**(Inspection Dates: May 14-25, 2012 by CG and AD, Response to FDA-483: June 15, 2012)**

**Observation 1**

**Failure to accurately report the bench top stability experiment conducted during pre-study method validation.**

Specifically, in the first experiment for evaluation of bench top stability for 2 and 4 hours for clozapine, data generated for 2 hours bench top stability failed to meet acceptance criteria. A second bench top stability experiment was conducted subsequently. Data for 4-hours bench top stability from the first experiment and data for 2-hours bench tap stability from the second experiment were reported together and there was no mention of the failed data in the method validation report.

In their response, Zenith acknowledged the observation and promised to report all data including failed data with reasons for failure in the validation report. In the response, they have also included the amended validation report including the data from the failed run. They believe the 2 hour bench top stability experiment failed due to possible sample processing error.

**DBGLPC's Assessment of Data Integrity:** During the validation study, the 2-hour bench top stability experiment failed to meet acceptance criteria (+/-15% of nominal concentration). However, during analysis of subject samples, clozapine QCs processed identically as subject samples were compared to freshly-prepared calibrators. This allows for evaluation of QC stability used within the run to freshly prepared calibration standards which had not undergone any degradation due to freeze-thaw (or storage at room temperature for which bench top stability needs to be demonstrated). As such, if there were stability concerns under the conditions used for subject sample processing, this would have been reflected in the precision and accuracy data of QC samples included in each run, and the runs would have been rejected. Additionally, the inspected lab had demonstrated bench-top stability up to four hours, and the study passed. It is highly improbable that stability of the same samples would fail at two hours, then pass at four. Therefore, it appears reasonable that the initial 2-hour stability study failed due to sample processing error, as the response from Zenith suggested.

This reviewer is of the opinion that observation 1 should not have a significant impact on the study data.

**Conclusions:**

Following review and evaluation of the Form FDA-483 observations and responses from the inspected sites, this DBGLPC reviewer is of the opinion that the clinical and analytical data generated for studies C11-005-LBB (ZPS 411) were not affected by the cited deficiencies.

The reviewer recommends that the data for clinical and analytical portion of study C11-005-LBB (ZPS 411) be accepted for further agency review.

Arindam Dasgupta Ph.D.  
Bioequivalence Branch, DBGLPC, OSI

**Final Classification:**

**VAI: Clinical Site #1 and Analytical**  
**Zenith Technology Corporation Ltd., Dunedin, New Zealand**  
**FEI: 3006135653**

**VAI: Clinical Site #2**  
**Waikato Hospital, Hamilton,**  
**FEI: 3004771398**

CC:  
CDER OSI PM TRACK  
OSI/DBGLPC/Taylor/Dejernett  
DBGLPC/BEB/Haidar/Dasgupta  
OND/ODEI/DPP/Laughren/Sagoo  
OCP/DCPI/Jackson  
ORA/SE-FO/FLA-DO/FLA-IB/MIAMI-FL/Garmendia  
Draft: AD 7/27/2012  
Edit: GB 7/27/2012 SH 08/07/2012  
BE File # 6301; O:\BE\EIRCOVER\203479dou.clo.doc  
ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/Electronic Archive/BEB  
FACTS: 1378670

# Attachment 1

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER Center for Drug Evaluation and Research, Office of Compliance, Office of Scientific Investigations, DBGC, Bioequivalence Branch, W051-RM5215 10903 New Hampshire Silver Spring, MD 20993 +1(301)796-3150 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 05/14 - 18/2012; 05/21 - 22/2012
	FEI NUMBER 3006135653

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED  
**TO: Dr. Cheung-Tak Hung, Managing Director**

FIRM NAME Zenith Technology Coporation Limited	STREET ADDRESS 156 Frederick Street
CITY, STATE AND ZIP CODE Dunedin 9054, New Zealand	TYPE OF ESTABLISHMENT INSPECTED Contract Research Organization

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

**Observation 1**

Failure to assure that reserve samples came from the same samples used in the specific bioequivalence study identified by the agency, and failure to adequately identify said samples to assure positive identification.

Specifically in regards to the multi-center study Protocol ZPS-411, the Dunedin site housed reserve samples for both for the Dunedin site and the Waikato site. The samples returned from the Waikato site were commingled with the Dunedin site. Upon collection of the reserve samples by the agency, there was no positive identification on the samples that allowed the agency to identify which samples were from the Dunedin site and which samples were from the Waikato site.

**Observation 2**

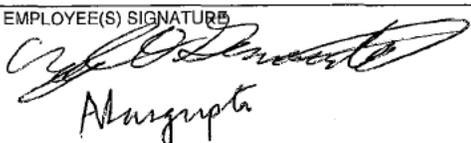
Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically,

A. Source data does not match the data submitted to the agency.

- i. For Protocol ZPS-411, the C-SSRS questionnaires for dosed Subject 9 submitted to the agency did not match the source information available at the site, specifically the Suicidal Behavior data.
- ii. For Protocol [REDACTED] (b) (4)

B. Post study safety labs were outside the range specified in Protocol ZPS-411 for dosed Subjects 7, 8, 16, 17 and 18.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURES 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Craig A. Garmendia, Investigator Arindam Dasgupta, Ph. D., Pharmacologist	DATE ISSUED 05/22/2012
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# Attachment 2

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER Center for Drug Evaluation and Research, Office of Compliance, Office of Scientific Investigations, DBGC, Bioequivalence Branch, W051-RM5215 10903 New Hampshire Silver Spring, MD 20993 +1(301)796-3150 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 05/23/2012  FEI NUMBER 3004771398
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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED  
 TO: Peter J. Dean, Clinical Investigator

FIRM NAME Puna-A-Tane, Puna Maatai Puawai, Waikato Hospital	STREET ADDRESS Selwyn Street
CITY, STATE AND ZIP CODE Hamilton, New Zealand	TYPE OF ESTABLISHMENT INSPECTED Contract Research Organization

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

**Observation 1**

Failure to retain reserve samples specific to an in vivo bioequivalence study.

Specifically in regards to the multi-center study Protocol ZPS-411, you have not retained reserve samples for this study. All study drugs, both used and unused, were returned to the Dunedin site, which was not apart of the study protocol.

**Observation 2**

Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically in regards to Protocol ZPS-411,

A. Source data from the Patient Study Record and Adverse Reactions form does not match the data submitted to the agency.

- i. Dosed Subject 25 - Days 1, 2, and 5
- ii. Dosed Subject 26 - Day 4
- iii. Dosed Subject 29 - All Days

B. Post study safety labs were outside the date range specified in Protocol ZPS-411 for dosed Subjects 3, 19 - 25 and 27 - 30.

<small>SEE REVERSE OF THIS PAGE</small>	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE ( <i>Print or Type</i> ) Craig A. Garmendia, Investigator	DATE ISSUED 05/23/2012
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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER Center for Drug Evaluation and Research, Office of Compliance, Office of Scientific Investigations, DBGC, Bioequivalence Branch, W051-RM5215 10903 New Hampshire Silver Spring, MD 20993 +1(301)796-3150 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 05/23/2012  FEI NUMBER 3004771398
---	---

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED  
 TO: Peter J. Dean, Clinical Investigator

FIRM NAME Puna-A-Tane, Puna Maatai Puawai, Waikato Hospital	STREET ADDRESS Selwyn Street
CITY, STATE AND ZIP CODE Hamilton, New Zealand	TYPE OF ESTABLISHMENT INSPECTED Contract Research Organization

Observation 3

An investigation was not conducted in accordance with the investigational plan.

Specifically in regards to Protocol ZPS-411, page 32 of version Revised 5 states that "tests will be performed by (b) (4)." for safety labs. The labs performing the safety labs for your site were the (b) (4) which are located in (b) (4) and not contained within the protocol. Furthermore, you have no documentation of the credentials for (b) (4).

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Craig A. Garmendia, Investigator	DATE ISSUED 05/23/2012
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# Attachment 3

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER Center for Drug Evaluation and Research, Division of Scientific Investigations - HFD-45 Office of Compliance, DBG, Bioequivalence Branch, W051-RM5215 10903 New Hampshire Silver Spring, MD 20993 Industry Information: <a href="http://www.fda.gov/oc/industry">www.fda.gov/oc/industry</a>	DATE(S) OF INSPECTION 05/14 -25/2012
	FEI NUMBER 3006135653

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED  
**TO: Dr. Cheung-Tak Hung, Managing Director**

FIRM NAME Zenith Technology Coporation Limited	STREET ADDRESS 156 Frederick Street
CITY, STATE AND ZIP CODE Dunedin 9054, New Zealand	TYPE OF ESTABLISHMENT INSPECTED Contract Research Organization

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:



(b) (4)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Arindam Dasgupta, Ph.D., Pharmacologist	DATE ISSUED 05/25/2012
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**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

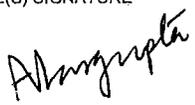
DISTRICT OFFICE ADDRESS AND PHONE NUMBER Center for Drug Evaluation and Research, Division of Scientific Investigations - HFD-45 Office of Compliance, DBGC, Bioequivalence Branch, W051-RM5215 10903 New Hampshire Silver Spring, MD 20993 Industry Information: <a href="http://www.fda.gov/oc/industry">www.fda.gov/oc/industry</a>	DATE(S) OF INSPECTION 05/14 -25/2012
	FEI NUMBER 3006135653

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED  
**TO:** Dr. Cheung-Tak Hung, Managing Director

FIRM NAME Zenith Technology Coporation Limited	STREET ADDRESS 156 Frederick Street
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CITY, STATE AND ZIP CODE Dunedin 9054, New Zealand	TYPE OF ESTABLISHMENT INSPECTED Contract Research Organization
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Specifically, in the first experiment for evaluation of bench top stability for 2 and 4 hours for clozapine, data generated for 2 hours bench top stability failed to meet acceptance criteria. A second bench top stability experiment was conducted subsequently. Data for 4-hours bench top stability from the first experiment and data for 2-hours bench top stability from the second experiment were reported together and there was no mention of the failed data in the method validation report.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE ( <i>Print or Type</i> ) Arindam Dasgupta, Ph.D., Pharmacologist	DATE ISSUED 05/25/2012
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# Attachment 4



## Zenith Technology Corporation Limited

156 Frederick St., P.O.Box 1777, Dunedin, New Zealand  
Phone 64-3-477-9669 or 0800 89 82 82,  
Fax 64-3-477-9605  
www.zenithtechnology.co.nz

7<sup>th</sup> June 2012

Dr Sam H. Haidar, Ph.D, R.Ph  
Chief, Bioequivalence Investigations Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Building 51, Room 5330  
10903 New Hampshire Ave  
Silver Spring, MD 20993  
Phone: +1 301 796 3150  
Fax: +1 301 847 8746

**Email:** [sam.haidar@fda.hhs.gov](mailto:sam.haidar@fda.hhs.gov)

Dear Dr Haidar

**FEI number: 3006135653**

Inspectors: Craig A. Garmendia, Investigator  
Arindam Dasgupta, Ph. D., Pharmacologist

Site: Zenith Technology Corporation Limited  
156 Frederick Street  
Dunedin 9054  
New Zealand

With reference to the above inspection, please find below our response to the written Observations:

### **Observation 1**

*Failure to assure that reserve samples came from the same samples used in the specific bioequivalence study identified by the agency, and failure to adequately identify said samples to assure positive identification.*

*Specifically in regards to the multi-center study Protocol ZPS-411, the Dunedin site housed reserve samples for both the Dunedin site and the Waikato site. The samples returned from the Waikato site were commingled with the Dunedin site. Upon collection of the reserve samples by the agency, there was no positive identification on the samples that allowed the agency to identify which samples were from the Dunedin site and which samples were from the Waikato site.*

### Response

We are grateful to the FDA Investigator for taking the time to explain the importance of these regulations to us. This (ZPS-411) is the first multi-center study involving

patients that Zenith has conducted for FDA registration. With regret, we acknowledge that we were not as familiar with the FDA regulations as we should have been in relation to sample retention requirements for multi-center studies.

At the conclusion of the study, all samples from the Waikato site were returned to Zenith for storage, as stated in the contract with the Sponsor, Douglas Pharmaceuticals (refer to Section 7.2 of attachment 3006135653-1). The returned samples were not distinguished according to Waikato or Dunedin site.

During the study, however, the Sponsor had no involvement with the study samples, and Zenith chose which samples were used. The integrity of the samples was not compromised.

#### Corrective Action

Not applicable.

#### Preventive Action

Zenith staff are now familiar with the appropriate regulations regarding the retention of samples for multi-centre studies. Zenith provides assurance that in the future, drug accountability and traceability will be the responsibility of the Principal Investigator at each study centre. An adequate amount of each dose formulation will be provided to each study centre. Each centre will be responsible for dispensing all of their own doses, and an adequate amount of retention samples from each centre will be selected and labelled accordingly. If the retention samples from multiple centres are to be stored by Zenith, Zenith will ensure that the samples from each centre have been clearly labelled upon receipt of the samples.

(b) (4)

## **Observation 2**

*Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.*

*Specifically,*

*A. Source data does not match the data submitted to the agency.*

*i. For Protocol ZPS-411, the C-SSRS questionnaires for doses Subject 9 submitted to the agency did not match the source information available at the site, specifically the Suicidal Behaviour data.*

#### Response

After the CRF for subject 9 was scanned to be submitted, a Zenith staff member has added "0" to the "Total number of attempts" column of the Suicidal Behaviour section of the C-SSRS questionnaires (refer to attachment 3006135653-2). Zenith is unable to identify the reason behind the action, as the staff member responsible is no longer employed.

This addition was unnecessary and does not change the information that was submitted to the FDA as it is indicated by the check-box on the questionnaires that no suicide attempts had been made by this subject.

Corrective Action

A copy of the document that has been amended will be forwarded to the Sponsor. This action was completed on 07 June 2012.

Preventive Action

At the conclusion of all future studies, once a source document has been finalised, the folder containing the document will be stamped with the following and completed by the appropriate personnel:

COMPLETED FILE

DO NOT MODIFY

Date:

Checked by:

An SOP will be issued to capture the above procedure to finalise (or effectively seal) source documents upon completion and to explain the correct procedures for working with sealed documents. All staff that complete and/or handle the completed source documents will be trained in these procedures. A draft SOP for this procedure is attached (refer to attachment 3006135653-3).

This preventive action will be finalised by (b) (4).

(b) (4)

*B. Post study safety labs were outside the range specified in Protocol ZPS-411 for dosed Subjects 7, 8, 16, 17 and 18.*

Response

Post study safety labs for ZPS-411 were scheduled to occur on Study Day 24. These samples were taken following the final study sample on Study Day 23 and

immediately prior to their release from the Clinical Site for subjects 7, 8, 16, 17 and 18.

Subjects 7 and 8 lived out of town and did not wish to commute to Zenith on the day following their release from the Clinical Site. Subjects 16, 17 and 18 had stated that they were not available to return to Zenith on Study Day 24 to provide a post study sample.

For these reasons, the post study safety lab samples were collected on Study Day 23. The sampling date should have been recorded as a protocol deviation but was overlooked during the reporting process.

#### Corrective Action

Notify the Sponsor of the unreported protocol deviation.

This action was completed on 07 June 2012.

#### Preventive Action

A study record form (SRF) will be generated for each study to record all protocol deviations occurring during a study as they are reported. Completion of this form will include revisiting the study Protocol immediately following study completion to ensure that all deviations have been recognised and recorded. A draft SRF for this action is attached (refer to attachment 3006135653-5).

This preventive action will be finalised by 06 July 2012.

**In addition to the written observations, the following items were discussed. Please find recorded below our response to the Discussion items:**

#### **Discussion Item 1**

*The times for the consumption of standard meals were not adequately recorded.*

*Specifically in regards to study Protocol [REDACTED] (b) (4)*

*[REDACTED] In regards to study Protocol ZPS-411, the time subjects began eating and the time they finished eating was not recorded.*

#### Response

Zenith staff supervised the consumption of all standard meals for [REDACTED] (b) (4) ZPS-411. Subjects were verbally instructed that the entire meal must be consumed and to consume the meals slowly, in order to achieve the required timing. Each subject was instructed about the time they should finish their meal, i.e. five minutes prior to their scheduled dosing time, as was indicated in the study Protocol. Staff members were verbally instructed to confirm the meals had been completed prior to each subject's dosing time, but this was not recorded.

The time the subjects began their meals was recorded on [REDACTED] (b) (4). This section had not been included in CRF-411 in error.

As indicated at the inspection closeout meeting, Zenith will include a section in the individual subject CRFs for all future fed studies, to record the time that the standard

meal consumption began and the time that the meal consumption was completed. A check box will be included to indicate whether the entire meal was consumed.

This action will be finalised prior to Zenith submitting the CRF for any future fed BE studies for ethics approval.

## Discussion Item 2

(b) (4)

## Discussion Item 3

*Study Protocol ZPS-411 indicates that (b) (4) in (b) (4) would conduct testing on all safety labs. All safety labs testing for subjects from the Waikato site was conducted by laboratories in (b) (4).*

### Response

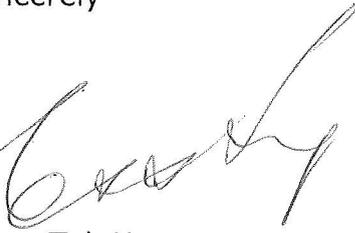
The Protocol for study ZPS-411 was approved prior to the location and details of the Hamilton study site being finalised. It was intended that the details of the site, including the laboratory would be reported in the final study report, which they were. Zenith recognises that this should also have been recorded as a protocol deviation.

As indicated in the response to 483 observation 2B, Zenith plans to generate a study record form (SRF) for each study to record all protocol deviations occurring during a study as they are reported. Completion of this form will include revisiting the study Protocol immediately following study completion to ensure that all deviations have been recognised and recorded. A draft SRF for this action is attached (refer to attachment 3006135653-5).

This preventive action will be finalised by 06 July 2012.

Please do not hesitate to contact Zenith if you require any further information.

Yours sincerely



Dr Cheung-Tak Hung  
Managing Director  
Email: [tak.hung@zenithtechnology.co.nz](mailto:tak.hung@zenithtechnology.co.nz)

**Copy to:** Craig A Garmendia, Investigator  
Email: [craig.Garmendia@fda.hhs.gov](mailto:craig.Garmendia@fda.hhs.gov)

Arindam Dasgupta, Ph.D., Pharmacologist  
Email: [Arindam.Dasgupta@fda.hhs.gov](mailto:Arindam.Dasgupta@fda.hhs.gov)

# Attachment 5



THE UNIVERSITY OF AUCKLAND  
NEW ZEALAND



Waikato Clinical School

Private Bag 3200  
Hamilton 3240  
New Zealand  
phone: +64 7 8398750  
[menkesd@waikatodhb.govt.nz](mailto:menkesd@waikatodhb.govt.nz)

8 June 2012

Dr Sam H. Haidar, Ph.D, R.Ph  
Chief, Bioequivalence Investigations Branch  
Division of Bioequivalence and GLP Compliance  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Building 51, Room 5330  
10903 New Hampshire Ave  
Silver Spring, MD 20993  
Phone: +1 301 796 3150  
Fax: +1 301 847 8746

**Email:** [sam.haidar@fda.hhs.gov](mailto:sam.haidar@fda.hhs.gov)

Dear Dr Haidar

**FEI number: 3004771398**

Inspectors: Craig A. Garmendia, Investigator  
Arindam Dasgupta, Ph. D., Pharmacologist

Site: Puna-A-Tane, Puna Maatai Puawai, Waikato Hospital  
Selwyn Street  
Hamilton  
New Zealand

With reference to the above inspection, please find below our response to the written Observations:

**Observation 1**

*Failure to retain reserve samples specific to an in vivo bioequivalence study.*

*Specifically in regards to the multi-center study Protocol ZPS-411, you have not retained reserve samples for this study. All study drugs, both used and unused, were returned to the Dunedin site, which was not a part of the study protocol.*

Response

This study was conducted under the guidance and supervision of Zenith Technology Corp. Ltd. The Waikato investigator, subcontracted by [REDACTED] <sup>(b) (4)</sup> was not aware of

the requirement to retain reserve samples for this study as this was not stipulated in the Protocol.

Protocol ZPS-411 states that "All unused study drugs, including opened and unopened labelled containers will be returned to the Sponsor by Zenith Technology". The investigator now understands that samples of the study medication must be retained and not be returned to the Sponsor after completion of the clinical phase of the investigation. We understand that return of the study medication by Zenith Technology to the sponsor is only to occur once the FDA has approved the New Drug Application (NDA) submitted by the sponsor and not before.

The investigator confirms that during the study the Sponsor had no involvement with the study samples and that the integrity of the samples has never been compromised.

Together with [REDACTED] <sup>(b) (4)</sup> the investigator aims to work with Zenith Technology to increase and complete our knowledge of the regulation requirements to ensure that these are clearly included in future study protocols.

## **Observation 2**

*Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.*

*Specifically in regards to Protocol ZPS-411,*

*A. Source data from the Patient Study Record and Adverse Reactions form does not match the data submitted to the agency.*

- i. Dosed Subject 25 – Days 1, 2 and 5.*
- ii. Dosed Subject 26 – Day 4.*
- iii. Dosed Subject 29 – All Days.*

### Response

All source data from patient study records was scanned and submitted to the Sponsor by Zenith Technology Corp. Ltd. Zenith has held all study files since the conclusion of the study. Zenith has provided the following response:

Upon review of these records, Zenith contends that the documents submitted for Dosed Subject 25-Day 5 and Dosed Subject 26-Day 4 have not been amended. During the inspection, Investigator Craig Garmendia requested copies of the source documents for Dosed Subject 25-Day 14 and Dosed Subject 26-Day 2. These pages have been included in the attachments for your record.

After the documents were scanned for submission, a Zenith staff member has rewritten pages from CRF-411-Appendix 1, Patient Study Record and Adverse Reactions for subjects 25, 26 and 29.

Zenith has compared the pages submitted with the corresponding source document pages and confirms that the data have not been changed (refer to attachment 3004771398-1 for Dosed Subject 25, 3004771398-2 for Dosed Subject 26 and 3004771398-3 for Dosed Subject 29). No additional data have been added and none of the original data has been altered to information that differs in accuracy from the original information.

This incident occurred in the copier room while the documents were being scanned.

Zenith is unable to identify the reason behind this action, as the staff member responsible is no longer with the company. Zenith believes that this action was performed in good faith to ensure the writing on these pages was legible, and that there was no malicious intent.

#### Corrective Action

A copy of the documents that have been amended will be forwarded to the Sponsor. This action was completed on 07 Jun 2012.

#### Preventive Action

At the conclusion of all future studies, once a source document has been finalised, the folder containing the document will be stamped with the following and completed by the appropriate personnel:

COMPLETED FILE

DO NOT MODIFY

Date:

Checked by:

An SOP will be issued to capture the above procedure to finalise (or effectively seal) source documents upon completion and explaining the correct procedures for working with sealed documents. All staff that complete and/or handle the completed source documents will be trained in these procedures. A draft SOP for this procedure is attached (refer to attachment 3004771398-4).

This preventive action will be finalised by 27 June 2012.

*B. Post study safety labs were outside the date range specified in Protocol ZPS-411 for dosed Subjects 3, 19-25 and 27-30.*

#### Response

Post study safety labs for ZPS-411 were scheduled to occur on Study Day 24. These samples were taken immediately following the final study sample on Study Day 23 and immediately prior to their release from the Clinical Site for subjects 3, 19-25 and 27-30.

Many of the subjects did not have reliable transport and had stated that returning to the hospital site the following day would be problematic for them. For this reason, the post study safety lab samples were collected immediately following the final study sample collection on Study Day 23. The sampling date should have been recorded as a protocol deviation but was overlooked during the reporting process.

#### Corrective Action

Zenith Technology will notify the Sponsor of this unreported protocol deviation.

This action was completed on 07 Jun 2012.

#### Preventive Action

Zenith Technology plans to generate a study record form (SRF) for each study to record all protocol deviations occurring during a study as they are reported. Completion of this form will include revisiting the study Protocol immediately following study completion to ensure that all deviations have been recognised and recorded. A draft SRF for this action is attached (refer to attachment 3004771398-5).

This preventive action will be finalised by 06 July 2012.

### Observation 3

*An investigation was not conducted in accordance with the investigational plan.*

*Specifically in regards to Protocol ZPS-411, page 32 of version Revised 5 states that "tests will be performed by (b) (4) for safety labs. The labs performing the safety labs for your site were the (b) (4) and (b) (4) both of which are located in (b) (4), and not contained within the protocol. Furthermore, you have no documentation of the credentials for (b) (4).*

#### Response

The Protocol for study ZPS-411 was approved prior to the location and details of the Hamilton study site being finalised. It was intended that the details of the site, including the use of (b) (4) for safety labs would be reported in the final study report, which they were. IANZ accreditation for this laboratory was provided to the Investigator during the inspection. We recognise that this should also have been recorded as a protocol deviation as per the corrective and preventive actions proposed under Observation 2B.

During the screening process, subjects were given request forms and instructed to provide a blood sample at (b) (4). Subject 24 misunderstood this instruction and had his sample taken at the community laboratory he frequently used when required to provide blood samples, (b) (4). Results of this testing were forwarded to (b) (4), who reprinted the results on their letterhead. Staff checking the blood results mistakenly identified the reprinted results as repeat testing conducted by (b) (4) and thus did not report it as a protocol deviation.

A copy of the IANZ accreditation from (b) (4) is attached along with a copy of their reference ranges in use at the time of the study (refer to attachment 3004771398-6).

Zenith Technology will notify the Sponsor of this unreported protocol deviation. This action was completed on 07 Jun 2012.

**In addition to the written observations, the following items were discussed. Please find recorded below our response to the Discussion items:**

#### **Discussion Item 1**

*The times for the consumption of standard meals were not adequately recorded.*

*Specifically in regards to study Protocol ZPS-411, the time subjects began eating and the time they finished eating was not recorded.*

Zenith staff supervised the consumption of all standard meals for ZPS-411. Subjects were verbally instructed that the entire meal must be consumed and to consume the meals slowly, in order to achieve the required timing. Each subject was instructed about the time they should finish their meal, i.e. five minutes prior to their scheduled dosing time, as was indicated in the study Protocol. Staff members were verbally instructed to confirm the meals had been completed prior to each subject's dosing time but this was not recorded.

Zenith plans to include a section in the individual subject CRFs for all future fed studies to record both the time the standard meal consumption was begun and the time the meal consumption was completed. A check box will be included to indicate whether the entire meal was consumed.

(b) (4) will ensure that study CRFs include this section for fed studies before agreeing to conduct fed BE studies in the future.

## Discussion Item 2

*The delegation log did not specify all individuals who worked on the study and what their delegated tasks were. The delegation log had not been signed off by the Principal Investigator.*

(b) (4) were not aware that a delegation log was required for this study. All key staff had signed a signature identification page that included a brief description of their duties during the study (refer to attachment 3004771398-7).

Zenith Technology had provided SRF-C, Staff Delegation and Instruction Form. This form was completed by staff working during the confinement periods of the study and was provided to the Investigator during the inspection (refer to attachment 3004771398-8).

(b) (4) understands the importance of having a study delegation log for the entire study maintained and approved by the Principal Investigator that includes staff involved in the recruitment and screening of subjects as well as the dispensing of study products. A delegation log will be included and completed as a standard part of the study documentation for all future BE studies.

Yours sincerely



A/Prof David B Menkes  
Principal Investigator  
Email: [David.Menkes@waikatodhb.health.nz](mailto:David.Menkes@waikatodhb.health.nz)

**Copy to:** Craig A Garmendia, Investigator  
Email: [craig.Garmendia@fda.hhs.gov](mailto:craig.Garmendia@fda.hhs.gov)

Arindam Dasgupta, Ph.D., Pharmacologist  
Email: [Arindam.Dasgupta@fda.hhs.gov](mailto:Arindam.Dasgupta@fda.hhs.gov)

# Attachment 6



## Zenith Technology Corporation Limited

156 Frederick St., P.O.Box 1777, Dunedin, New Zealand  
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www.zenithtechnology.co.nz

15 June 2012

Dr Sam H. Haidar, Ph.D, R.Ph  
Chief, Bioequivalence Investigations Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Building 51, Room 5330  
10903 New Hampshire Ave  
Silver Spring, MD 20993  
Phone: +1 301 796 3150  
Fax: +1 301 847 8746

**Email:** [sam.haidar@fda.hhs.gov](mailto:sam.haidar@fda.hhs.gov)

Dear Dr Haidar

**FEI number: 3006135653**

Inspectors: Craig A Garmendia, Investigator  
Arindam Dasgupta, Ph. D., Pharmacologist

Site: Zenith Technology Corporation Limited  
156 Frederick Street  
Dunedin  
New Zealand

With reference to the above inspection, please find below our response to the written Observations:

### Observation 1

(b) (4)

12 pages have been withheld immediately following this page as b4 (CCI/TS)

Appendix 3 Reports

VP-0412/1 issue 2 Bioanalytical method validation report for determination of clozapine (100 mg) in human plasma by LCMSMS

Yours sincerely



Dr Cheung-Tak Hung  
Managing Director  
Email: [tak.hung@zenithtechnology.co.nz](mailto:tak.hung@zenithtechnology.co.nz)

**Copy to:** Craig A Garmendia, Investigator  
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Arindam Dasgupta, Ph.D., Pharmacologist  
Email: [Arindam.Dasgupta@fda.hhs.gov](mailto:Arindam.Dasgupta@fda.hhs.gov)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ARINDAM DASGUPTA  
08/07/2012

SAM H HAIDAR  
08/07/2012

WILLIAM H TAYLOR  
08/07/2012

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 203479 BLA#	NDA Supplement #:S- 000 BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: Clozapine Oral Suspension Dosage Form: Oral Suspension Strengths: 50 mg/mL		
Applicant: Douglas Pharmaceuticals America LTD Agent for Applicant (if applicable): VersaPharm Incorporated		
Date of Application: 12-28-11 Date of Receipt: 01-06-12 Date clock started after UN: 01-06-12		
PDUFA Goal Date: 11-06-12	Action Goal Date (if different):	
Filing Date: 02-20-12	Date of Filing Meeting: 02-14-12	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3		
Proposed indication(s)/Proposed change(s): Treatment resistant schizophrenia		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>            and refer to Appendix A for further information.</i></b>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 108466				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			X	
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input checked="" type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  Check the <i>Electronic Orange Book</i> at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>	<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>															
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><b>If yes, # years requested:</b></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?			<b>X</b>	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>	X			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>			X	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>		X		
<b>Y BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>	X			
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>		X		
Is the PI submitted in PLR format? <sup>4</sup>	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>			X	
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>			X	
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent: Microbiology – 01/23/12</i>	X			
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>  <i>If yes, distribute minutes before filing meeting</i>		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> <i>If yes, distribute minutes before filing meeting</i>		X		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** February 14, 2012

**BLA/NDA/Supp #:** 203479

**PROPRIETARY NAME:** (b) (4)

**ESTABLISHED/PROPER NAME:** Clozapine

**DOSAGE FORM/STRENGTH:** Oral suspension, 50 mg/mL

**APPLICANT:** Douglas Pharmaceuticals America LTD

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Treatment resistant schizophrenia

**BACKGROUND:** Douglas has submitted the initial filing of NDA 203479 for (b) (4) (clozapine oral suspension) 50 mg/mL. This NDA is submitted in follow-up to their IND 108466 submitted December 22, 2010. Douglas is pursuing approval of a clozapine 50 mg/mL oral suspension via the 505(b)(2) pathway. There are currently no liquid dosage forms of clozapine in the US. The sponsor believes the proposed product will meet an unmet medical need by providing a suspension formulation for those patients with swallowing difficulty or patients who “cheek” their medication.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sharonjit Sagoo	Y
	CPMS/TL:	Paul David/Keith Kiedrow	
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Mark Ritter	Y
	TL:	Bob Levin	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		

Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Andre Jackson	Y
	TL:	Hao Zhu	N
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Elzbietca Chalecka-Franaszek	N
	TL:	Aisar Atrakchi	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Thomas Wong	Y
	TL:	Chhagan Tele	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Vinayak Pawar	N
	TL:	John Metcalfe	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Yelena Maslov	N
	TL:	Irene Chan	N
OSE/DRISK (REMS)	Reviewer:	Robin Duer	Y
	TL:	Melissa Hulettn	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		

	TL:		
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Bioresearch Monitoring (DSI)	Reviewer:	Arindam Dasgupta	N
	TL:	Michael Skelly	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Maternal Health	Upasana Bhatnagar	Y	
Pediatric Health	Jeanine Best	Y	
Biopharmaceutics	Deepika Lakhani	N	
Other attendees	Angelica Dorantes, Biopharmaceutics Supervisor	Y	
	Loretta Holmes, DMEPA	Y	

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul>	<input type="checkbox"/> YES Date if known:

<p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p><b>Comments:</b></p>	<input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review</u></b></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b>  Paul David, R.Ph., CPMS for RPM Filing Review  Tomas Laughren, M.D., Division Director for original NDA</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p>Comments:</p>	
<p><b>REGULATORY CONCLUSIONS/DEFICIENCIES</b></p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<p><b>ACTIONS ITEMS</b></p>	
<p><input checked="" type="checkbox"/></p>	<p>Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).</p>
<p><input type="checkbox"/></p>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).</p>
<p><input type="checkbox"/></p>	<p>If filed, and the application is under AIP, prepare a letter either granting (for signature by</p>

	Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

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Regulatory Project Manager

Date

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Chief, Project Management Staff

Date

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

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

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

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

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

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

for approval on published literature based on data to which the applicant does not have a right of reference).

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

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

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHARONJIT K SAGOO  
02/15/2012

PAUL A DAVID  
02/15/2012

# REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

**Application:** NDA 20639/N-000

**Name of Drug:** (b) (4) (clozapine) oral suspension 50 mg/mL

**Applicant:** Douglas Pharmaceuticals America LTD

## Labeling Reviewed

**Submission Date:** December 28, 2011

**Receipt Date:** January 6, 2012

## Background and Summary Description

Douglas has submitted the initial filing of NDA 203749 for (b) (4) (clozapine oral suspension) 50 mg/mL. This NDA is submitted in follow-up to their IND 108466 submitted December 22, 2010. Douglas is pursuing approval of a clozapine 50 mg/ml oral suspension via the 505(b)(2) pathway. There are currently no liquid dosage forms of clozapine in the US. The sponsor believes the proposed product will meet an unmet medical need by providing a suspension formulation for those patients with swallowing difficulty or patients who “cheek” their medication.

## Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

## Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies within one month from the date of the 74-day letter. The resubmitted labeling will be used for further labeling discussions.

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Regulatory Project Manager

Date

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Chief, Project Management Staff

Date

# Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a **Boxed Warning** is present, it must be limited to 20 lines. (**Boxed Warning** lines do not count against the one-half page requirement.)
- A horizontal line must separate the **HL** and **Table of Contents (TOC)**.
- All headings must be presented in the center of a horizontal line, in **UPPER-CASE** letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (**FPI**) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading - if no contraindications are known, it must state "None")
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

- **Highlights Limitation Statement**
  - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
  
- **Product Title**
  - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
  
- **Initial U.S. Approval**
  - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
  
- **Boxed Warning**
  - All text in the boxed warning is **bolded**.
  - Summary of the warning must not exceed a length of 20 lines.
  - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
  - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
  
- **Recent Major Changes (RMC)**
  - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) -- 2/2010.”
  - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
  - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) -- removal 2/2010.”
  
- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and bold type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in bold type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

- **General Format**
  - A horizontal line must separate the TOC and FPI.
  - The heading - **FULL PRESCRIBING INFORMATION** - must appear at the beginning in UPPER CASE and bold type.
  - The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).
- **Boxed Warning**
  - Must have a heading, in UPPER CASE, bold type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use bold type and lower-case letters for the text.
  - Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).
- **Contraindications**
  - For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

37 pages of draft labeling have been withheld immediately following this page as b4 (CCI/TS)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHARONJIT K SAGOO  
02/07/2012

PAUL A DAVID  
02/07/2012