# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 091619Orig1s000

# BIOEQUIVALENCE REVIEWS

# DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

| | | | |
|---|---|---|---|
| **ANDA No.** | 091619 | | |
| **Drug Product Name** | Disulfiram Tablets | | |
| **Strength (s)** | 250 mg and 500 mg | | |
| **Applicant Name** | Sigmapharm Laboratories, LLC | | |
| **Address** | 3375 Progress Drive<br>Bensalem, PA 19020 | | |
| **Applicant's Point of Contact** | Rakesh Grover, Ph.D. | | |
| **Contact's Phone Number** | 215-352-6636 | | |
| **Contact's Fax Number** | 215-352-6634 | | |
| **Submission Date(s)** | July 11, 2009 | | |
| **First Generic** | Yes | | |
| **Reviewer** | Deanah L. Mitchell, Ph.D. | | |
| | | | |
| **Study Number (s)** | BA08112077-02 | | |
| **Study Type (s)** | Fasting | | |
| **Strength(s)** | 500 mg | | |
| **Clinical Site** | BA Research India Ltd., | | |
| **Clinical Site Address** | 1st floor, Silver Arcade,<br>Near Ashwamegh III,<br>Samrajya, Mujmahuda Road,<br>Akota, Vadodara-390020 | | |
| **Analytical Site** | (b) (4) | | |
| **Analytical Address** | | | |
| | | | |
| **OVERALL REVIEW RESULT** | **INADEQUATE** | | |
| **DSI INSPECTION RESULT** | **ADEQUATE** | | |
| **BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT#** | STUDY/TEST TYPE | STRENGTH | REVIEW RESULT |
| **# 1** | **DISSOLUTION** | **250 MG** | **INADEQUATE** |
| **# 1** | **DISSOLUTION** | **500 MG** | **INADEQUATE** |

## I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product, but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable (at S1 level). The firm's proposed specification of NLT (b) (4) (Q) in 120 minutes is not the FDA-recommended specification of NLT (b) (4) (Q) in 90 minutes. The firm should acknowledge the FDA-recommended method and specification.

No Division of Scientific Investigations (DSI) inspection for the clinical site[1] and analytical site[2] are pending or necessary.

The DBE will review the fasting BE study and waiver request at a later date.

[1] A routine inspection was completed for the clinical site on (b) (4) for ANDA (b) (4) The outcome was Voluntary Action Indicated (VAI). The inspection was found acceptable (DARRTS, Search: ANDA (b) (4). Vehovic, David S/09-08-2009/REV-BIOEQ-03(Acceptable DSI Inspection Report Review).

[2] A routine inspection was completed for the analytical site on (b) (4) for ANDA (b) (4) The outcome was VAI. The inspection was found acceptable (DARRTS, Search: ANDA (b) (4) Solana-Sodeinde, Diana A/06-02-2009/REV-BIOEQ-01(General Review).

**Table 1: SUBMISSION CONTENT CHECKLIST**

| Information | | | YES | NO | N/A |
|---|---|---|---|---|---|
| Did the firm use the FDA-recommended dissolution method | | | ☒ | ☐ | ☐ |
| Did the firm use the USP dissolution method | | | ☐ | ☐ | ☒ |
| Did the firm use 12 units of both test and reference in dissolution testing* | | | ☒ | ☐ | ☐ |
| Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)* | | | ☒ | ☐ | ☐ |
| Did the firm conduct dissolution testing with its own proposed method | | | ☐ | ☒ | ☐ |
| Is FDA method in the public dissolution database (on the web) | | | ☒ | ☐ | ☐ |
| SAS datasets submitted to the electronic document room (edr) | Fasting BE study | PK parameters | ☒ | ☐ | ☐ |
| | | Plasma concentrations | ☒ | ☐ | ☐ |
| | Fed BE study | PK parameters | ☐ | ☐ | ☒ |
| | | Plasma concentrations | ☐ | ☐ | ☒ |
| | Other study | PK parameters | ☐ | ☐ | ☒ |
| | | Plasma concentrations | ☐ | ☐ | ☒ |
| | | | | | |
| Are the DBE Summary Tables present an in either PDF and/or MS Word Format? | | | ☒ | ☐ | ☐ |
| If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16. | | | | | |
| | | | | | |
| Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples? | | | ☒ | ☐ | ☐ |
| If the LTSS is NOT sufficient please request the firm to provide the necessary data. | | | | | |

## Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

| | | |
|---|---|---|
| **Dissolution Conditions** | **Apparatus:** | USP II (Paddle) |
| | **Speed of Rotation:** | 100 rpm |
| | **Medium:** | 2% SLS* |
| | **Volume:** | 900 mL |
| | **Temperature:** | 37˚ ± 0.5 ˚C |
| **Firm's Proposed Specifications** | Not Less Than (b) (4) (Q) in 120 minutes | |
| **Dissolution Testing Site (Name, Address)** | Sigmapharm Laboratories, Analytical Chemistry Lab<br>3375 Progress Drive, Bensalem, PA | |

| **Study Ref No.** | **Testing Date** | **Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)** | **Dosage Strength & Form** | **No. of Dosage Units** | | **Collection Times (minutes)** | | | | | | | | **Study Report Location** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | **15** | **30** | **45** | **60** | **75** | **90** | **105** | **120** | |
| DISU-DISS-PROFILE-500 | 12/29/08 | Disulfiram Tablets, USP 500 mg (Lot # BB 029 0014) | 500 mg/ Tablet | 12 | Mean | 42 | 56 | 64 | 71 | 75 | 78 | 81 | 83 | m5\53-clin-stud-rep\531-rep-biopharm-stud\5313-in-vitro-in-vivo-corr-stud-rep\ba08112077-02\500-disu-comparative-diso.pdf |
| | | | | | Range | (b) (4) | | | | | | | | |
| | | | | | %CV | 1.7 | 1.6 | 2.7 | 1.0 | 0.9 | 0.9 | 1.2 | 1.0 | |
| DISU-DISS-PROFILE-500 | 12/31/08 | Antabuse Tablets, 500 mg (Lot # 7077001SC) | 500 mg/ Tablet | 12 | Mean | 43 | 58 | 66 | 71 | 76 | 81 | 83 | 86 | |
| | | | | | Range | (b) (4) | | | | | | | | |
| | | | | | %CV | 4.0 | 3.3 | 2.4 | 1.8 | 2.4 | 4.0 | 3.7 | 2.9 | |

| | | |
|---|---|---|
| **Dissolution Conditions** | **Apparatus:** | USP II (Paddle) |
| | **Speed of Rotation:** | 100 rpm |
| | **Medium:** | 2% SLS* |
| | **Volume:** | 900 mL |
| | **Temperature:** | 37° ± 0.5 °C |
| **Firm's Proposed Specifications** | Not Less Than (b) (4) (Q) in 120 minutes | |
| **Dissolution Testing Site (Name, Address)** | Sigmapharm Laboratories, Analytical Chemistry Lab<br>3375 Progress Drive, Bensalem, PA | |

| **Study Ref No.** | **Testing Date** | **Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)** | **Dosage Strength & Form** | **No. of Dosage Units** | | **Collection Times (minutes)** | | | | | | | | **Study Report Location** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | **15** | **30** | **45** | **60** | **75** | **90** | **105** | **120** | |
| DISU-DISS-PROFILE-250 | 12/29/08 | Disulfiram Tablets, USP 250 mg (Lot #SB 028 0013) | 250 mg/ Tablet | 12 | Mean | 46 | 63 | 73 | 80 | 84 | 88 | 90 | 92 | m5\53-clin-stud-rep\531-rep-biopharm-stud\5313-in-vitro-in-vivo-corr-stud-rep\ba08112077-02\250-disu-comparative-diso.pdf |
| | | | | | Range | (b) (4) | | | | | | | | |
| | | | | | %CV | 3.3 | 1.7 | 1.9 | 1.5 | 1.7 | 1.4 | 1.7 | 1.4 | |
| DISU-DISS-PROFILE-250 | 12/31/08 | Antabuse Tablets, 250 mg (Lot # 7067004A) | 250 mg/ Tablet | 12 | Mean | 52 | 69 | 78 | 83 | 88 | 90 | 93 | 94 | |
| | | | | | Range | (b) (4) | | | | | | | | |
| | | | | | %CV | 3.7 | 2.3 | 1.5 | 1.7 | 1.9 | 1.7 | 1.4 | 2.2 | |

** SLS stands for Sodium Lauryl Sulfate, whose other names include Sodium Dodecyl Sulfate and/or Sodium Laurilsulfate. Sodium Dodecyl Sulfate is listed as the dissolution media in the FDA's Dissolution database.*

## II. COMMENTS:

1. Currently, there is no USP method for Disulfiram Tablets but there is an FDA-recommended dissolution method. The FDA-recommended dissolution method is available on the public dissolution database on the Office of Generic Drugs website, http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. The firm's dissolution testing data with the FDA-recommended method is acceptable.

2. The firm proposed a specification of NLT (b) (4)(Q) in 120 minutes, which is different from the FDA-recommended specification of NLT (b) (4)(Q) in 90 minutes[3].

3. The firm's test product meets the FDA-recommended specification at the S1 level.

## III. DEFICIENCY COMMENTS:

The firm's proposed specification is not acceptable. The firm should acknowledge and accept the following FDA-recommended dissolution method and specification for its test product, Disulfiram Tablets:

| | |
|---|---|
| **Medium** | 2% Sodium Dodecyl Sulfate (SDS) |
| **Apparatus** | USP Type II (Paddle) |
| **Speed of Rotation** | 100 rpm |
| **Temperature** | 37º ± 0.5º C |
| **Volume** | 900 mL |
| **Specification** | NLT (b) (4)(Q) in 90 minutes |

## IV. RECOMMENDATIONS

1. The in vitro dissolution testing conducted by Sigmapharm Laboratories, LLC, on its test product, Disulfiram Tablets, 250 mg (Lot #SB 028 0013) and 500 mg (Lot # BB 029 0014) comparing it to Odyssey Pharmaceuticals, Inc. Antabuse® (Disulfiram) Tablets, 250 mg (Lot # 7067004A) and 500 mg (Lot # 7077001SC), respectively, is incomplete due to the deficiency comment above.

2. The DBE acknowledges that the firm will conduct dissolution testing using the following FDA-recommended dissolution method:

| | |
|---|---|
| **Medium** | 2% Sodium Dodecyl Sulfate (SDS) |
| **Apparatus** | USP Type II (Paddle) |
| **Speed of Rotation** | 100 rpm |
| **Temperature** | 37º ± 0.5º C |
| **Volume** | 900 mL |
| **Specification** | NLT (b) (4)(Q) in 90 minutes |

[3] Internal dissolution database. Last accessed: 12/07/2009.

3. The firm should acknowledge the FDA-recommended specification of NLT (b) (4) (Q) in 90 minutes.

The firm should be informed of the above deficiency comment and recommendations.

BIOEQUIVALENCE DEFICIENCY

ANDA: 091619

APPLICANT: Sigmapharm Laboratories, LLC

DRUG PRODUCT: Disulfiram Tablets, 250 mg and 500 mg

The Division of Bioequivalence has completed its review of only the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the fasting study and waiver request will be conducted later. The following deficiency has been identified:

Your dissolution testing data are acceptable. However, the proposed specification of NLT (b) (4) (Q) in 120 minutes for your test product, Disulfiram Tablets, is not acceptable. Based on the dissolution testing data, please provide acknowledgement for your acceptance of the following FDA-recommended dissolution method and specification for your test product:

| | |
|---|---|
| **Medium** | 2% Sodium Dodecyl Sulfate (SDS) |
| **Apparatus** | USP Type II (Paddle) |
| **Speed of Rotation** | 100 rpm |
| **Temperature** | 37° ± 0.5° C |
| **Volume** | 900 mL |
| **Specification** | NLT (b) (4) **(Q) in 90 minutes** |

Sincerely yours,

*{See appended electronic signature page}*

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

## V. OUTCOME

**ANDA: 091619**

*Productivity:*

| *ID* | *Letter Date* | *Productivity Category* | *Sub Category* | *Productivity* | *Subtotal* |
|---|---|---|---|---|---|
| 9877 | 6/11/2009 | Dissolution Data | Dissolution Review | 1 | 1 |
| | | | | Bean Total: | 1 |

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| ANDA-91619 | ORIG-1 | SIGMAPHARM LABORATORIES LLC | DISULFIRAM |

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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/

DEANAH L MITCHELL
12/15/2009

APRIL C BRADDY
12/16/2009

HOAINHON N CARAMENICO on behalf of DALE P CONNER
12/17/2009

# DIVISION OF BIOEQUIVALENCE REVIEW

| | | | |
|---|---|---|---|
| **ANDA No.** | 091619 | | |
| **Drug Product Name** | Disulfiram Tablets, USP | | |
| **Strength(s)** | 250 and 500 mg | | |
| **Applicant Name** | SigmaPharm Laboratories, LLC | | |
| **Address** | 3375 Progress Drive, Bensalem, PA 19020, USA | | |
| **Applicant's Point of Contact** | Rakesh Grover, Ph.D. | | |
| **Contact's Telephone Number** | (215) 352-6636 | | |
| **Contact's Fax Number** | (215) 352-6634 | | |
| **Original Submission Date(s)** | **July 11, 2009** | | |
| **Submission Date(s) of Amendment(s) Under Review** | **2/3/2010 (Acceptance of Dissolution Specification)** | | |
| **Reviewer** | S. P. Shrivastava, Ph.D. | | |
| | | | |
| **Study Number (s)** | BA08112077/02 | | |
| **Study Type (s)** | Fasting | | |
| **Strength (s)** | 500 mg | | |
| **Clinical Site** | BA Research India Ltd.,<br>1st floor, Silver Arcade,<br>Near Ashwamegh III,<br>Samrajya, Mujmahuda Road,<br>Akota, Vadodara-390020<br>Gujarat, India. | | |
| **Clinical Site Address** | See above | | |
| **Analytical Site** | (b) (4) | | |
| **Analytical Site Address** | | | |
| **Dissolution Testing Site** | Sigma Pharm | | |
| **DSI Inspection Status** | DSI Inspection is not pending or necessary | | |
| **OVERALL REVIEW RESULT** | **ADEQUATE** | | |
| **WAIVER REQUEST RESULT** | **ADEQUATE (250 mg)** | | |
| **DSI REPORT RESULS** (b) (4) | **ANDA** (b) (4) **– Clinical – ADEQUATE**<br>**ANDA –Analytical – ADEQUATE** | | |
| **BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #** | **STUDY/TEST TYPE** | **STRENGTH** | **REVIEW RESULT** |
| | **DISSOLUTION** | 500 mg | **ADEQUATE** |
| | **DISSOLUTION** | 250 mg | **ADEQUATE** |
| | **FASTING TUDY** | 500 mg | **ADEQUATE** |
| | **FED STUDY** | **N/A** | **N/A** |
| | **PERMEABILITY STUDY** | **N/A** | **N/A** |
| | **SOLUBILITY STUDY** | **N/A** | **N/A** |

## 1. EXECUTIVE SUMMARY

This application references Disulfiram Tablets, 250 and 500 mg [Antabuse®, Duramed formerly Odyssey, NDA 088482 (250 mg) and 088483 (500 mg, RLD), Approved 12/8/1983)], and includes one fasting bioequivalence (BE) study.

**The fasting study** is a single-dose, 2-treatment, 2-way crossover study in 69 normal healthy male volunteers given a dose of Disulfiram Tablet 500 mg. The fasting study results (point estimate, 90% CI) for Disulfiram metabolite, S-methyl-diethyl-dithiocarbamate (S-methyl-DDC) are as follows:

**Fasting: S-Methyl-DDC**

| | BA08112077/02 – Fasting (n=69) | | | | |
|---|---|---|---|---|---|
| **PARAMETER** | **Test** | **Reference** | **Ratio, T/R** | **LOWCI12** | **UPPCI12** |
| **LAUCT** | 718.14 | 715.14 | 1.00 | 93.63 | 107.70 |
| **LAUCI** | 753.78 | 754.06 | 1.00 | 93.06 | 107.37 |
| **LCMAX** | 54.10 | 54.70 | 0.99 | 91.02 | 107.48 |

The fasting study is **acceptable.**

Dissolution Review has previously been carried out [DARRTS, ANDA 091619, MITCHELL, DEANAH L 12/17/2009 N/A 12/17/2009 REV-BIOEQ-02(Dissolution Review) Original-1)]. There is no USP method for this product, but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable (at S1 level). The firm's proposed specification of NLT (b) (4)(Q) in 120 minutes was wider. Therefore, FDA-recommended a tighter specification (NLT (b) (4)(Q) in 90 minutes). The firm has acknowledged the FDA-recommended method and specification (see submission, dated 2/3/2010). The 250 mg strength tablets are formulated proportionally similar to 500 mg strength. Waiver of BE for 250 mg strength tablet is granted.

The firm has submitted the CTD summary tables.

BA Research India Ltd. and (b) (4) have recently been inspected (Routine inspection) on (b) (4) and (b) (4) respectively. The inspectors concluded in their routine inspections that protocol/SOP violations in studies for ANDAs (b) (4) and (b) (4) did not impact the outcome of studies. The reviewer concurs with the inspectors. Additionally, according to the inspectors, the labs have updated SOPs and improved upon documentation and the conduct of the study. The reviewer verified the protocol/SOP, CRFs and methods validation, etc. for the current ANDA and did not find any violations in BE studies found by the inspectors in ANDAs (b) (4) and (b) (4) Therefore, the findings of DSI Inspectors in ANDAs (b) (4) and (b) (4) do not impact the current ANDA 091619.

The application is **adequate**.

## 2. TABLE OF CONTENTS

# 3. SUBMISSION SUMMARY

## 3.1. Drug Product Information[1]

| | |
|---|---|
| **Test Product** | Disulfiram Tablets, 250 and 500 mg |
| **Reference Product** | Antabuse® (Disulfiram) Tablets, 250 and 500 mg |
| **RLD Manufacturer** | Duramed formerly Odyssey |
| **NDA No.** | 088482 (250 mg) and 088483 (500 mg, RLD) |
| **RLD Approval Date** | 12/8/1983 |
| **Indication** | Disulfiram is an aid in the management of selected chronic alcohol patients who want to remain in a state of enforced sobriety so that supportive and psychotherapeutic treatment may be applied to best advantage. |

## 3.2. PK/PD Information[2]

| | |
|---|---|
| **Bioavailability** | Disulfiram is absorbed slowly from the gastrointestinal tract |
| **Food Effect** | Not available |
| **Tmax** | Not available |
| Metabolism | Disulfiram blocks the oxidation of alcohol at the acetaldehyde stage. During alcohol metabolism following disulfiram intake, the concentration of acetaldehyde occurring in the blood may be 5 to 10 times higher than that found during metabolism of the same amount of alcohol alone. Disulfiram does not appear to influence the rate of alcohol elimination from the body |
| Excretion | It is eliminated slowly from the body |
| Half-life | Not available |
| **Relevant OGD or DBE History** | **Controls:080753** (b) (4) **090683** (b) (4) \\cdsnas\OGDS6\CONTROLS\2009-docs\09-0683.pdf<br>**ANDAs:** There are number of Approved ANDAs based on single-dose fasting study and dissolution data. 088792 and 088793 (Par), 088482 and 088483 (Odissey), 086889 and 086890 (Watson).<br>**Protocols:** 070539 (b) (4) 08096 (b) (4) 09019 (b) (4)<br><br>Currently the DBE recommends the following[3]: |

[1] http://dailymed nlm nih.gov/dailymed/drugInfo.cfm?id=7504
[2] http://dailymed nlm nih.gov/dailymed/drugInfo.cfm?id=7504
[3] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM194601.pdf, 12/2009.

| | |
|---|---|
| | 2. The firm should conduct a single-dose, two-way, crossover BE study under fasting conditions comparing its test product Disulfiram, immediate release tablets 500 mg to the RLD, Antabuse® (Disulfiram), immediate release tablets, 500 mg manufactured by Odyssey Pharms. FDA's Guidance for Industry: Bioavailability and /Bioequivalence Studies for Orally Administered Drug Products-General Considerations (March, 2003) states that a BE study under fasting conditions should be conducted for all orally administered immediate release products. DBE request a fasting BE study as per the guidance.<br><br>3. The firm may submit a study protocol for review before initiating the bioequivalence study under fasting conditions.<br><br>4. For the BE studies, the DBE agrees with the firm that they should measure plasma concentrations of disulfiram and its active metabolites using a validated analytical method.<br><br>5. Due to instability of the parent compound, disulfiram in blood and its rapid metabolism, bioequivalence should be based on the pharmacokinetic data of its primary metabolite, N, N-diethyldithiocarbamate (DDC), in human plasma and should be subject to the 90% confidence interval approach to establish bioequivalence. If DDC cannot be measured reliably in human plasma, the bioequivalence should be based on the data of secondary metabolite, S-methyl N, N-diethyldithocarbamate (Me-DDC), in human plasma. The metabolite would then be subject to the 90% confidence interval approach. You may conduct feasibility studies for the development of an analytical method to measure the plasma concentrations of DDC prior to proceeding to use the plasma concentration data for Me-DDC to establish bioequivalence between test and reference product.<br><br>6. Disulfiram Tablets, 250 mg are eligible based on (i) acceptable bioequivalence studies on the 500 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.<br><br>Comparative dissolution testing should be conducted on 12 dosage units of all strengths of the test and reference products using the FDA-recommended method:<br><br>Medium: 2% SDS<br>Volume: 900 ml<br>Apparatus: USP Type 2 (Paddle)<br>Speed: 100 rpm<br>Sampling Times: 15, 30, 45, 60, 75, 105, 120 min.<br><br>**Specification (NDA)**: NLT (b) (4) (Q) in 90 minutes<br>(DBE internal dissol. Database) |
| **Agency Guidance** | http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM194601.pdf, 12/2009. |
| **Drug Specific Issues** | None |

## 3.3.OGD Recommendations for Drug Product[4]

| | |
|---|---|
| **Number of studies recommended:** | 1, Fasting |

| | | |
|---|---|---|
| **1.** | **Type of study:** | Fasting |
| | **Design:** | Single-dose, two-treatment, two-period crossover in-vivo |

[4] Product Guidance and Dissolution Database:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM194601.pdf ; http://www.accessdata fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm

| | | |
|---|---|---|
| | **Strength:** | 500 mg |
| | **Subjects:** | Normal healthy males and females, general population |
| | **Additional Comments:** | None |

| | | |
|---|---|---|
| **2.** | **Type of study:** | Fed Study not required (see DBE Protocol Database 09-019, \\cdsnas\ogd99\DIVBE\ProtocolFiles\P09019Review.pdf |
| | **Design:** | N/A |
| | **Strength:** | N/A |
| | **Subjects:** | N/A |
| | **Additional Comments:** | None |

| | |
|---|---|
| **Analytes to measure (in plasma/serum/blood):** | If disulfiram can be reliably measured, analyze the data for the parent compound using the confidence interval approach. The data for the active metabolites can be used as supportive evidence. However, if you can demonstrate that it is not possible to measure disulfiram in plasma accurately and reliably, analyze the primary metabolite DDC using the confidence interval approach. If you demonstrate that DDC in plasma cannot be reliably and accurately measured, analyze the secondary metabolite MeDDC using the confidence interval approach. |
| **Bioequivalence based on:** | See above. (90% CI) on disulfiram or its metabolite DDC or Me-DDC and supportive evidence possibly for the one of the metabolites . |
| **Waiver request of in-vivo testing:** | Yes |
| **Source of most recent recommendations:** | See the footnote 4 above. |

### 3.4.Contents of Submission

| Study Types | Yes/No? | How many? |
|---|---|---|
| **Single-dose fasting** | Yes | 1 |
| **Single-dose fed** | No | |
| **Steady-state** | No | |
| **In vitro dissolution** | Yes | 2 |
| **Waiver requests** | Yes | 1 |
| **BCS Waivers** | No | |
| **Vasoconstrictor Studies** | No | |
| **Clinical Endpoints** | No | |
| **Failed Studies** | No | |
| **Amendments** | Yes (2/3/10) | Acceptance of Dissolution Specification |
| **DSI Inspection Reports** | Yes<br>Clinical - (b) (4)<br>Analytical | 2<br>ANDA (b) (4) - Clinical Lab<br>ANDA analytical Lab |

### 3.5.Pre-Study Bioanalytical Method Validation

**Table 4: Bioanalytical Method Validation**

| Information Requested | Data |
|---|---|
| **Bioanalytical method validation report location** | Disulfiram Validation Report No: (b) (4) VR08110-01 (b) (4) |
| **Analyte** | Secondary Metabolite of Disulfiram (S-Methyl N, N Diethyldithiocarbamate) |
| **Internal standard (IS)** | (b) (4) |
| **Method description** | Type of Extraction: Precipitation<br>Analytical Method: LC/MS/MS |
| **Limit of quantitation** | 1.014 ng/mL |
| **Average recovery of drug (%)** | 94% |
| **Average recovery of IS (%)** | 100% |
| **Standard curve concentrations (units/mL)** | Standard curve range: 1.014 to 253.482ng/mL |
| **QC concentrations (units/mL)** | LQC: 3.042 ng/mL, MQC: 101.393 ng/mL and HQC: 202.786 ng/mL |
| **QC Intraday precision range (%)** | 2-4% |
| **QC Intraday accuracy range (%)** | 98-103% |
| **QC Interday precision range (%)** | 0-2% |
| **QC Interday accuracy range (%)** | 98-103% |
| **Bench-top stability (hrs)** | 6 hours @ room temperature |
| **Stock stability (days)** | 20 days in Freezer (-20°C) |
| **Re-injection Reproducibility (hrs)** | 70 hours @ 4°C, 8 hours on the bench top |
| **Freeze-thaw stability (cycles)** | 3 cycles |
| **Long-term storage stability (days)** | 131 days @ -80°C |
| **Dilution integrity** | Concentration diluted 10-fold |
| **Selectivity** | No interfering peaks noted in blank plasma samples at the retention times of analyte & IS. |

Please include table for each analyte.
Please submit all Method Validation SOPs.

Dilution Integrity: The firm used 2-fold and 10-fold dilution to obtain the final concentration of 405.57 ng/mL. Acceptable

**Comments on the Pre-Study Method Validation:**

1. K3-EDTA anticoagulant was used for method validations, CC and QC standards as well as for collection of the subject samples.

   Methods validation is **acceptable.**

### 3.6.In Vivo Studies

## Table 1. Summary of all in vivo Bioequivalence Studies – Fasting Study

**Table 2: Summary of Bioavailability Studies**

| Study Ref. No. | Study Objective | Study Design | Treatment (Dose, Dosage Form, Route) [Product ID] | Subjects (No. (M/F) Type Age: mean ( range) | Mean Parameters (%CV) | | | | | | Study Report Location |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Cmax (ng/mL) | Tmax (hr) | AUCt (ng*hr/ mL) | AUCi (ng*hr/ mL) | tHalf (hr) | Kel (1/hr) | |
| Study # BA081 12077-02 | To compare the oral bioavailability of Disulfiram tablets 500 mg with that of 'ANTABUSE' tablets 500 mg (Disulfiram tablets 500 mg) in healthy, adult, human subjects under fasting conditions and to monitor safety of subjects. | A double blind, randomized, two period, two treatment, two sequence, crossover, balanced, single dose, fasting study Design. | Disulfiram Tablets, USP 1x500 mg, Oral [Batch No.: BB 0290014] | 75 Enrolled, 70 dosed, 69 completed study (69 males, 0 females) Age: 28.0 (18.0-42.0) years Healthy male subjects. | 59.820 (46.434) | 6.500 (1.500-12.000) | 787.851 (45.901) | 828.581 (46.543) | 9.832 (21.078) | 0.074 (20.847) | m5/53-clin-stud-rep/531-rep-biopharm-stud/5312-compar-ba-be-stud-rep/ba08112077-02/study-report.pdf |
| | | | Antabuse tablets (Disulfiram Tablets, USP) 1x500 mg. Oral, [Batch No.: 7077001SC] | | 62.339 (54.984) | 6.000 (1.000-12.000) | 808.264 (52.234) | 867.737 (61.722) | 9.918 (26.731) | 0.075 (27.696) | |
| | | | | | | | | | | | |

Note: The mean age is calculated based on completed subjects Tmax is presented as Median (Range).

**Table 2. Statistical Summary of the Comparative BA Data for S-Methyl-DDC (Calculated by the Firm, n = 69)**

**Table 3: Statistical Summary of the Comparative Bioavailability Data**

**BA08112077-02**

| Disulfiram Tablets, USP 1x500 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals | | | | |
|---|---|---|---|---|
| **Fast Bioequivalence Study (BA08112077-02)** | | | | |
| **Parameter** | **Test** | **Reference** | **Ratio** | **90%CI** |
| **AUCt** | 718.142 | 715.144 | 100.42% | (93.63%; 107.70%) |
| **AUCi** | 753.780 | 754.061 | 99.96% | (93.06%; 107.37%) |
| **Cmax** | 54.100 | 54.696 | 98.91% | (91.02%; 107.48%) |
| **Fed Bioequivalence Study*** | | | | |
| **Parameter** | **Test** | **Reference** | **Ratio** | **90%CI** |
| **AUCt** | | | | |
| **AUCi** | | | | |
| **Cmax** | | | | |

*Only Fasted study was conducted for this product.

**Table 3. Geometric Means and 90% CI for S-Methyl-DDC (Calculated by the Reviewer, n=69)**

| | LSM1 | LSM2 | RLSM12 | LOWCI12 | UPPCI12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| LAUCT | 718.14 | 715.14 | 1.00 | 93.63 | 107.70 |
| LAUCI | 753.78 | 754.06 | 1.00 | 93.06 | 107.37 |
| LCMAX | 54.10 | 54.70 | 0.99 | 91.02 | 107.48 |

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

**Note:** Actual Sampling times were used in AUC calculations by the firm and the reviewer.

**Table 4. Reanalysis of Study Samples – Fasting Study: S-Methyl-DDC**

**Table 9: Reanalysis of Study Samples**

| Bioequivalence Study No. BA0811277-02 Disulfiram Analytical Report Page No. 27 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Reason why assay was repeated | Number of samples reanalyzed | | | | Number of recalculated values used after reanalysis | | | |
| | Actual number | | % of total assays | | Actual number | | % of total assays | |
| | T | R | T | R | T | R | T | R |
| Pharmacokinetic[1] | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Reason-AI | 0.0 | 1.0 | 0.0 | 0.03 | 0.0 | 1.0 | 0.0 | 0.03 |
| Reason-LIS | 0.0 | 3.0 | 0.0 | 0.10 | 0.0 | 3.0 | 0.0 | 0.10 |
| Total | 0.0 | 4.0 | 0.0 | 0.13 | 0.0 | 4.0 | 0.0 | 0.13 |

1- If no repeats were performed for pharmacokinetic reasons, insert "0.0."

AI: Analytical Interference

LIS: Low Internal Standard

**Did use of recalculated plasma concentration data change study outcome?** There were no PK repeats. However, there were other analytical repeats. The firm accepted repeat values according to the SOP.

**Comments from the Reviewer:** Reanalysis is acceptable.

### 3.7. Formulation

| | |
|---|---|
| **Location in appendix** | See Appendix 4.2<br>Formulation Data |
| **If a tablet, is the RLD scored?** | 250 mg strength is not scored, but the 500 mg strength is scored. |
| **If a tablet, is the test product biobatch scored** | The scoring matches with the reference product (see above). |
| **Is the formulation acceptable?** | **ACCEPTABLE** |
| **If not acceptable, why?** | N/A |

### 3.8. Dissolution Method

| | |
|---|---|
| **Source of Method** | FDA |
| **Medium** | 2% SDS |
| **Volume (mL)** | 900 mL |
| **USP Apparatus type** | I1 (Paddle) |
| **Rotation (rpm)** | 100 rpm |
| **Firm's proposed specifications** | NLT (b) (4) (Q) in 120 minutes (see comment) |
| **FDA-recommended specifications[5]** | NLT (Q) in 90 minutes |
| **F2 metric calculated?** | N/A |
| **If no, reason why F2 not calculated** | N/A |
| **Is method acceptable?** | Yes |
| **If not then why?** | N/A |

[5] Dissolution Database (Externa/Internal), http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm

Dissolution Review has previously been carried out [DARRTS, ANDA 091619, MITCHELL, DEANAH L 12/17/2009 N/A 12/17/2009 REV-BIOEQ-02(Dissolution Review) Original-1)]. There is no USP method for this product, but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable (at S1 level). The firm's proposed specification of NLT (b) (4) (Q) in 120 minutes is not the FDA-recommended specification (NLT (b) (4) (Q) in 90 minutes). The firm has acknowledged the FDA-recommended method and specification (see Amendment dated 2/3/2010).

### 3.9.Waiver Request(s)

| | |
|---|---|
| **Strengths for which waivers are requested** | 250 mg |
| **Is dissolution acceptable?** | Yes |
| **Waivers granted?** | Yes |
| **If not then why?** | N/A |

### 3.10. Review of the DSI Report

Routine DSI Inspections for the clinical Lab [see DARRTS, ANDA (b) (4) CHAN, SAMUEL H 08/06/2009 N/A 08/06/2009 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1], and Analytical Lab [see DARRTS, ANDA (b) (4) DASGUPTA, ARINDAM 05/18/2009 N/A 05/18/2009 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1] were conducted for other products as follows:

(b) (4)

Since DSI Inspection Report Recommendations for clinical and analytical labs are coded as VAI, the reviewer reviewed the DSI Inspection reports (see Appendix, additional Attachments, DSI Inspection of Clinical Lab; DSI Inspection of Analytical Lab).

Following this page, 4 pages withheld in full (b)(4)


**Overall Conclusion of the DSI Inspection Reports:** The deficiencies observed by DSI Inspectors during Clinical and Analytical studies for ANDAs (b) (4) and (b) (4) were not observed in the current ANDA. Therefore, the deficiencies do not impact current ANDA 091619. The BE study is acceptable.

### 3.11. Deficiency Comments

None

### 3.12. Recommendations

1. The Division of Bioequivalence finds the fasting BE study (#BA08112077/02) **acceptable**. SigmaPharm Laboratories, LLC conducted the fasting BE study on its Disulfiram Tablet USP, 500 mg (Lot #BB029-0014) comparing it to DURAMED's (FORMERLY ODYSSEY) Antabuse®, 500 mg (Lot #7077001SC).

2. The dissolution testing conducted by SigmaPharm Laboratories on its Disulfiram Tablets USP, 250 and 500 mg, Lot #s SB-028-0013 and BB029-0014, comparing it to DURAMED's (FORMERLY ODYSSEY) Antabuse®, 250 and 500 mg, Lot #s7067004A and 7077001SC) is acceptable [DARRTS, ANDA 091619, MITCHELL, DEANAH L 12/17/2009 N/A 12/17/2009 REV-BIOEQ-02(Dissolution Review) Original-1)].

3. The dissolution testing should be conducted as follows:

   Medium: 900 mL of 2% SLS in Water at 37 $^{0}$C
   Apparatus: USP 2 (Paddle) at 100 rpm
   Specification: Not less than (b) (4) (Q) of the labeled amount of the drug in the dosage form is dissolved in 90 minutes.

4. The formulation for the 250 mg strength tablet is proportionally similar to the 500 mg strength tablet, which underwent bioequivalence testing. The waiver of *in vivo* bioequivalence study requirements for the 250 mg tablets of the test product is granted.

### 3.13. Comments for Other OGD Disciplines

| Discipline | Comment |
|---|---|
| None | |

# 4. APPENDIX

## 4.1. Individual Study Reviews

### 4.1.1. Single-dose Fasting Bioequivalence Study

#### 4.1.1.1. Study Design

**Table 5 Study Information - Fasting Study**

**BA08112077-02**

| | |
|---|---|
| **Study Number** | BA08112077-02 |
| **Study Title** | A double blind, randomized, two period, two treatment, two sequence, crossover, balanced, single dose, comparative evaluation of relative bioavailability of Disulfiram Tablets 500 mg with that of 'ANTABUSE' tablets 500 mg (Disulfiram Tablets 500 mg) in healthy, adult, human subjects under fasting conditions. |
| **Clinical Site (Name, Address, Phone #)** | BA Research India Ltd.,<br>1st floor, Silver Arcade,<br>Near Ashwamegh III,<br>Samrajya, Mujmahuda Road,<br>Akota, Vadodara-390020,<br>Gujarat, India.<br>Tel# +91 -265 – 2324374 - 76<br>Fax# +91 -265 – 2324378 |
| **Principal Investigator** | Dr. Pruthvi Puwar, MBBS |
| **Dosing Dates** | Period I 06 Feb 09<br>Period II 13 Feb 09 |
| **Analytical Site (Name, Address, Phone #)** | (b) (4) |
| **Analysis Dates** | 09 Mar 2009 thru 26 Mar 2009 |
| **Analytical Director** | (b) (6) Ph.D. |
| **Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)** | 48 days |

Please provide separate table for each Bioequivalence Study

**Table 6. Product information**

**Table 11: Product Information**

**BA08112077-02**

| Product | Test | Reference |
|---|---|---|
| **Treatment ID** | T | R |
| **Product Name** | Disulfiram Tablets | Antabuse Tablets |
| **Manufacturer** | Sigmapharm Laboratories, LLC | Duramed Pharmaceuticals, Inc. |
| **Batch No.** | BB 029 0014 | 7077001SC |
| **Manufacture Date** | 12/2008 | N/A |
| **Expiration Date** | N/A | 05/2010 |
| **Strength** | 500 mg | 500 mg |
| **Dosage Form** | Tablets | Tablets |
| **Bio-batch Size** | (b) (4) | N/A |
| **Production Batch Size** | | N/A |
| **Potency** | 98.5%, 99.0% | 100.0%, 100.2% |
| **Content Uniformity (mean, %CV)** | 98.4%, 0.7% | 100.1%, |
| **Dose Administered** | 500 mg | 500 mg |
| **Route of Administration** | P.O | P.O |

**Table 7. Study Design, Single-Dose Fasting Bioequivalence Study**

| | |
|---|---|
| **Number of Subjects** | 70 Subjects were dosed; 69 completed the study; 69 subject samples were analyzed. |
| **No. of Sequences** | 2 |
| **No. of Periods** | 2 |
| **No. of Treatments** | 2 |
| **No. of Groups** | 1 |
| **Washout Period** | 7 days |
| **Randomization Scheme** | **TR:** 1, 3, 5, 8, 10, 11, 13, 16, 18, 19, 21, 24, 26, 28, 30, 32, 33, 38, 39, 42, 44, 46, 47, 50, 51, 54, 57, 60, 62, 64, 66, 68, 70<br>**RT:** 2, 4, 6, 7, 9, 12, 14, 15, 17, 20, 22, 23, 25, 27, 29, 31, 34, 35, 36, 37, 40, 41, 43, 45, 48, 49, 52, 53, 55, 56, 58, 59, 61, 63, 65, 67, 69 |
| **Blood Sampling Times** | In each period, total 22 venous blood samples (07 mL each) were collected in vacutainers containing K3EDTA at 0.0 (pre-dose), 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 24.0, 36.0 and 48.0 hours post dose. |
| **Blood Volume Collected/Sample** | 7 mL in K3 EDTA. |
| **Blood Sample Processing/Storage** | After collection, blood samples were cooled; immediately centrifuged; plasma samples were separated, and stored at -80 $^{0}$C until analysis. |
| **IRB Approval** | Yes |
| **Informed Consent** | Yes |
| **Length of Fasting** | Subjects fasted overnight for at least 10 hours prior to drug administration and then for a further 4 hours following drug administration. |
| **Length of Confinement** | Subjects were confined to clinical facility from at least 11 hours prior to each drug administration until after the 24-hour blood sample collection. |
| **Safety Monitoring** | Subjects were monitored throughout the study. |
| **Drug Specific Information** | None |

**Comments on Study Design:** The study design is **acceptable**.

**4.1.1.2.Clinical Results**

**Table 8. Demographics Profile of Subjects Completing the Bioequivalence Study**

**Table 7: Demographic Profile of Subjects Completing the Bioequivalence Study**

**BA08112077-02**

| Study No. BA08112077-02 | | | |
|---|---|---|---|
| | | Treatment Groups | |
| | | **Test Product N = 69** | **Reference Product N =69** |
| Age (years) | Mean ± SD | 28 ± 6 | 28 ± 6 |
| | Range | 18 - 42 | 18 - 42 |
| Age Groups | < 18 | - | - |
| | 18 – 45 | 69 (100%) | 69 (100%) |
| | > 45 | - | - |
| Sex | Male | 69 (100%) | 69 (100%) |
| | Female | - | - |
| Race | Asian | 69 (100%) | 69 (100%) |
| | Black | - | - |
| | Caucasian | - | - |
| | Hispanic | - | - |
| | Other | - | - |
| BMI ($Kg/m^2$) | Mean ± SD | 21.73 (±2.00) | 21.73 (±2.00) |
| | Range | 18.52 – 24.83 | 18.52 – 24.83 |
| Tobacco users | Yes | 15 (21.74%) | 15 (21.74%) |
| | No | 54 (78.26%) | 54 (78.26%) |

**Table 9. Dropout Information, Fasting Bioequivalence Study**

**Table 12: Dropout Information**

**BA08112077-02**

| Study No. BA08112077-02 | | | | |
|---|---|---|---|---|
| **Subject No** | **Reason for dropout/replacement** | **Period** | **Replaced?** | **Replaced with** |
| 41 (b) (6) | Subject was discontinued from the study (on 02/05/09 at 2244 hours) on his own accord after check-in. | Period I | Yes | Extra subject E2 (V-BA-09-0382) and allotted same subject no. 41 (b) (6) |
| 48 (b) (6) | Subject was discontinued from the study (on 02/05/09 at 1856 hours) on his own accord after check-in. | Period I | Yes | Extra subject E1 (V-BA-09-0307) and allotted same subject no. 48 (b) (6) |
| 67 (b) (6) | Subject was discontinued from the study (on 02/06/09 at 0800 hours) on his own accord prior to dosing. | Period I | Yes | Extra subject E3 (V-BA-07-0634) and allotted same subject no. 67 (b) (6) |
| 24 (b) (6) | Subject was discontinued from the study (on 02/11/09 at 1455 hours) on medical ground. | Period I | NA | NA |

**Note:** Subject # 24 had a dog bite on right leg.

**Table 10. Incidence of Adverse Events in Individual Studies - Fasted Study**

**Table 8: Incidence of Adverse Events in Individual Studies**

**BA08112077-02**

| Body System / Adverse Event | Reported Incidence by Treatment Groups | |
|---|---|---|
| | Fast Bioequivalence Study Study No. BA08112077-02 | |
| | Test N[1] (%[2]) | Reference N[1] (%[2]) |
| **Musculoskeletal system** | | |
| Dog bite (On Right Leg) | 1(1.43%) | - |
| **Body as a whole** | | |
| Fever of unknown origin | - | 1(1.45%) |
| **Number of subjects dosed with study drug** | 70 | 69 |

[1] The number of subjects that reported adverse event (AE).
[2] % (rate of occurrence) = N divided by number of subjects dosed with respective study drug.

**Table 11. Protocol Deviations, Fasting Bioequivalence Study**

**Table 13: Protocol Deviations**

**BA08112077-02**

| Study No. BA08112077-02 | | |
|---|---|---|
| **Type** | **Subject #s (Test)** | **Subject #s (Ref.)** |
| No sample was collected at 36.0 hours during Period I. | NA | 22 |
| No sample was collected at 48.0 hours during Period I. | NA | 22 |
| +13 minutes sampling deviation at 48.0 hours during period I. | NA | 25 |
| +08 minutes sampling deviation at 48.0 hours during period I. | 32 | NA |
| No sample was collected at 36.0 hours during Period I. | 62 | NA |
| No sample was collected at 48.0 hours during Period I. | 62 | NA |
| +23 minutes sampling deviation at 48.0 hours during period II. | NA | 60 |
| +08 minutes sampling deviation at 48.0 hours during period II. | 67 | NA |
| +07 minutes sampling deviation at 48.0 hours during period II. | 69 | NA |

Please provide a separate table for each Bioequivalence Study

Pharmacokinetic parameters were computed from the plasma concentration data using the actual sample collection times.

**Comments on Dropouts/Adverse Events/Protocol Deviations:** The dropouts were appropriate. Adverse events and protocol deviations were minor and did not compromise the outcome of the study.

#### 4.1.1.3.Bioanalytical Results

**Table 12. Assay Validation – Within the Fasting BE Study – S-Methyl-DDC**

**Table 14: Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses**

| Bioequivalence Study No. BA0811277-02<br>Analyte Name: Secondary Metabolite of Disulfiram (S-Methyl N, N Diethyldithiocarbamate) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Standard Curve Samples** | | | | | | | |
| Concentration (ng/mL) | 1.006 | 2.012 | 4.024 | 10.060 | 25.149 | 50.298 | 125.745 | 251.490 |
| Inter day Precision (%CV) | 1.6 | 3.4 | 2.9 | 3.0 | 2.3 | 2.7 | 2.3 | 2.0 |
| Inter day Accuracy (%Actual) | 100.0 | 99.4 | 100.5 | 101.8 | 99.7 | 99.8 | 98.9 | 99.8 |
| Linearity | Range of r values: 0.9988-0.9999 | | | | | | | |
| Linearity Range (ng /mL) | 1.006 to 251.490 ng/mL | | | | | | | |
| Sensitivity/LOQ (ng /mL) | 1.006 ng/mL | | | | | | | |

| Bioequivalence Study No. BA0811277-02<br>Analyte Name: Secondary Metabolite of Disulfiram (S-Methyl N, N Diethyldithiocarbamate) | | | | |
|---|---|---|---|---|
| **Parameter** | **Quality Control Samples** | | | |
| Concentration (ng/mL) | 3.018 | 30.179 | 100.596 | 201.192 |
| Inter day Precision (%CV) | 4.2 | 3.8 | 3.8 | 3.9 |
| Inter day Accuracy (%Actual) | 99.5 | 98.9 | 98.8 | 101.6 |

**Comments on Study Assay Validation:** K3-EDTA was used as anticoagulant for blood sample collection, for methods validation as well as for QC and CC standards. Method validation is **acceptable**.

| | |
|---|---|
| **Any interfering peaks in chromatograms?** | No |
| **Were 20% of chromatograms included?** | Yes |
| **Were chromatograms serially or randomly selected?** | Serially, Subject, #1-14 |

**Comments on Chromatograms:** Acceptable

**Table 13. SOP's dealing with Bioanalytical Repeats of Study Samples**

**Table 15: SOP's dealing with Bioanalytical Repeats of Study Samples**

| SOP No. | Effective Date of SOP | SOP Title |
|---|---|---|
| (b) (4) LP104 | 12 March 2008 | Criteria for Sample Reanalysis and Reporting |

* Please include the SOP for Bioanalytical Repeats in your submission.

**Table 14. Additional Comments on Repeat Assays**

| | |
|---|---|
| **Were all SOPs followed?** | Yes |
| **Did recalculation of PK parameters change the study outcome?** | There were no PK repeats |
| **Does the reviewer agree with the outcome of the repeat assays?** | Yes |
| **If no, reason for disagreement** | N/A |

| SUBJECT/ PERIOD/HOUR | REASON | ORIGINAL VALUE | REPEAT VALUE | VALUE USED |
|---|---|---|---|---|
| S19/P2/0.0HR | AI | 1.200 | 1.167 | 1.167 |
| S42/P2/10.0HR | LIS | 33.374 | 30.555 | 30.555 |
| S45/P1/1.0HR | LIS | 7.886 | 7.266 | 7.266 |
| S68/P2/7.0HR | LIS | 43.974 | 46.242 | 46.242 |

AI: Analytical Interference

LIS: Low Internal Standard

- **Summary/Conclusions, Study Assays:** There were no PK repeats. The firm has provided the original, repeat and accepted values. The accepted repeat values are according to the SOP.

#### 4.1.1.4.Pharmacokinetic Results

**Comments on Pharmacokinetic and Statistical Analysis: Study #BA08112077/02**

- The reviewer carried out the ANOVA analysis on 69 subjects for S-methyl-DDC using **CONTINU.SAS).** There were no PK repeats. However, there were other analytical repeats. The firm accepted repeat values according to the SOP.

- The summary of PK data and results for S-methyl-DDC are presented in Tables 15-18 and Fig. 1.

- The pharmacokinetic parameters and 90% confidence intervals for S-methyl-DDC in plasma calculated by the reviewer agree with firm's calculations.

- The 90% CIs for LAUCt, LAUCi and LCmax parameters for S-methyl-DDC are within the 80-125%.

**Summary and Conclusions:** The study is **acceptable**.

**Table 15. Arithmetic Means and Ratio: Fasting Study - S-Methyl-DDC (n=69)**

| | MEAN1 | CV1 | MEAN2 | CV2 | RMEAN12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| AUCT | 787.85 | 45.90 | 808.26 | 52.23 | 0.97 |
| AUCI | 828.58 | 46.54 | 867.74 | 61.72 | 0.95 |
| CMAX | 59.82 | 46.43 | 62.34 | 54.98 | 0.96 |
| TMAX | 6.50 | . | 6.00 | . | 1.08 |
| KE | 0.07 | 20.85 | 0.07 | 27.70 | 0.98 |
| THALF | 9.83 | 21.08 | 9.92 | 26.73 | 0.99 |

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
TMAX VALUES ARE PRESENTED AS MEDIAN

**Table 16. Geometric Means and 90% CI - S-Methyl-DDC (n=69)**

| | LSM1 | LSM2 | RLSM12 | LOWCI12 | UPPCI12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| LAUCT | 718.14 | 715.14 | 1.00 | 93.63 | 107.70 |
| LAUCI | 753.78 | 754.06 | 1.00 | 93.06 | 107.37 |
| LCMAX | 54.10 | 54.70 | 0.99 | 91.02 | 107.48 |

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

**Table 17. Additional Study Information, Fasting Study: S-Methyl-DDC**

| | | |
|---|---|---|
| **Root mean square error, AUC0-t** | 0.246613 | |
| **Root mean square error, AUC∞** | 0.251858 | |
| **Root mean square error, Cmax** | 0.292611 | |
| | **Test** | **Reference** |
| **Kel and AUC∞ determined for how many subjects?** | 69 | 69 |
| **AUCt/ AUC∞ Ratio (Range)** | 0.95 (0.87-0.98) | 0.95 (0.56*-98) |
| **Do you agree or disagree with firm's decision?** | Agree | Agree |
| **Indicate the number of subjects with the following:** | | |
| **measurable drug concentrations at 0 hr** | 0 | 1; 167ng/mL conc; Cmax =139.773 ng/mL (Sub #19, Per 2) |
| **first measurable drug concentration as Cmax** | 0 | 0 |
| **Were the subjects dosed as more than one group?** | No | No |

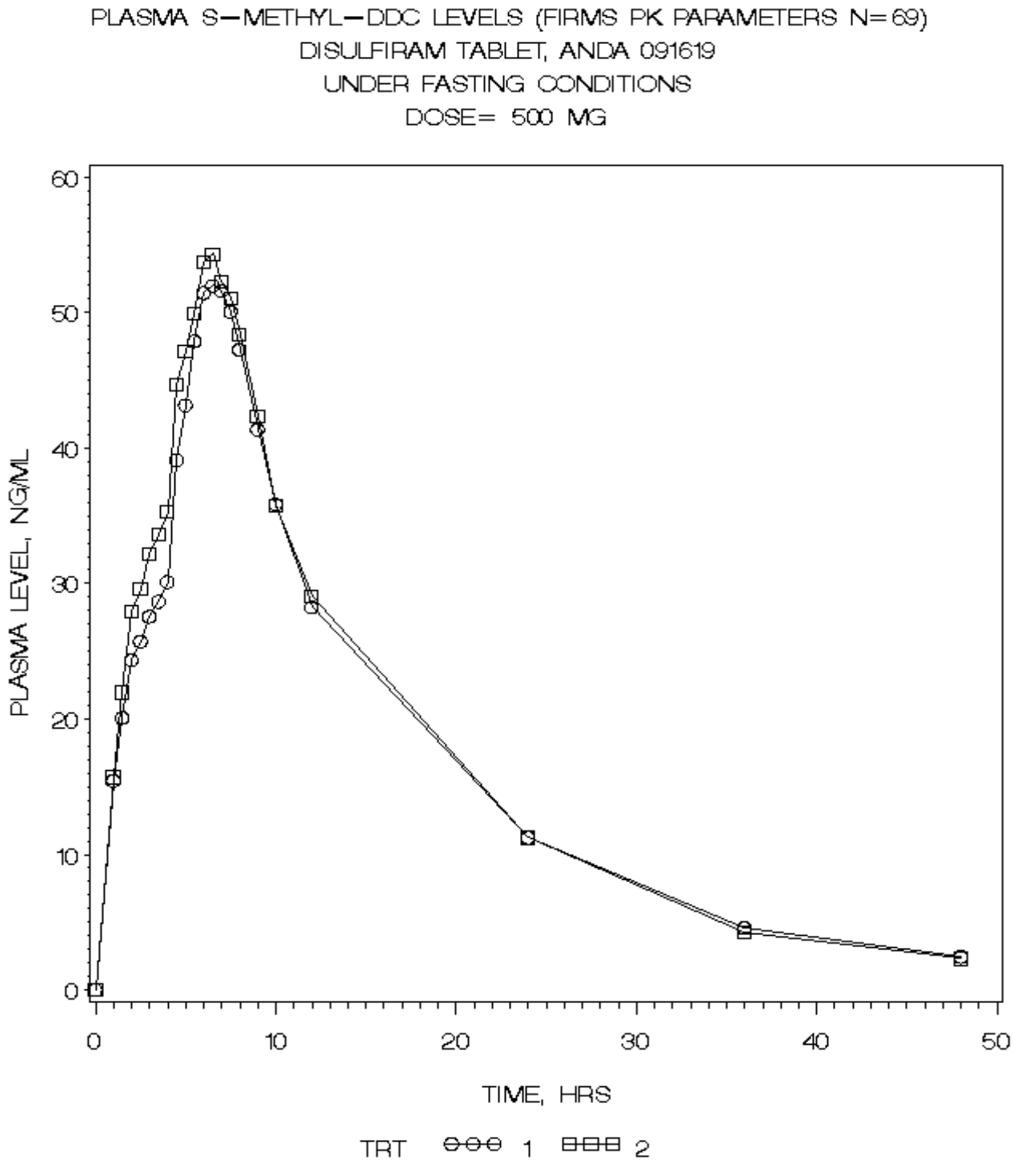
* Only one subject showed low AUCt/AUCi Ratio. Thus, Subject #22 AUCT/AUCI Ratios were: Test = 0.95 and Reference - 0.56. The $T_{1/2}$ values for Test and Reference were 11.1 and 20.18 hrs. respectively. The reason for this difference was not evident.

**Table 18. Mean Plasma Concentration: S-Methyl-DDC (n=69)**

| | MEAN1 | CV1 | MEAN2 | CV2 | RMEAN12 |
|---|---|---|---|---|---|
| TIME HR | | | | | |
| 0 | 0.00 | . | 0.02 | 830.66 | 0.00 |
| 1 | 15.47 | 79.70 | 15.72 | 94.50 | 0.98 |
| 1.5 | 20.09 | 70.17 | 21.99 | 81.01 | 0.91 |
| 2 | 24.36 | 74.25 | 27.91 | 70.78 | 0.87 |
| 2.5 | 25.73 | 73.94 | 29.64 | 66.77 | 0.87 |
| 3 | 27.57 | 77.38 | 32.21 | 74.54 | 0.86 |
| 3.5 | 28.68 | 70.90 | 33.68 | 75.28 | 0.85 |
| 4 | 30.14 | 68.00 | 35.32 | 72.54 | 0.85 |
| 4.5 | 39.12 | 56.89 | 44.70 | 63.07 | 0.88 |
| 5 | 43.18 | 49.84 | 47.17 | 57.62 | 0.92 |
| 5.5 | 47.90 | 48.50 | 49.97 | 60.10 | 0.96 |
| 6 | 51.47 | 51.23 | 53.72 | 60.77 | 0.96 |
| 6.5 | 52.00 | 49.23 | 54.35 | 60.00 | 0.96 |
| 7 | 51.61 | 51.12 | 52.30 | 57.14 | 0.99 |
| 7.5 | 50.08 | 48.03 | 51.10 | 58.88 | 0.98 |
| 8 | 47.28 | 45.51 | 48.37 | 56.07 | 0.98 |
| 9 | 41.38 | 43.26 | 42.37 | 55.60 | 0.98 |
| 10 | 35.86 | 42.97 | 35.74 | 55.22 | 1.00 |
| 12 | 28.25 | 45.42 | 29.04 | 54.65 | 0.97 |
| 24 | 11.26 | 59.02 | 11.27 | 71.48 | 1.00 |
| 36 | 4.57 | 67.11 | 4.27 | 61.00 | 1.07 |
| 48 | 2.45 | 71.40 | 2.34 | 69.08 | 1.05 |

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

**Figure 1. Mean Plasma Concentration – Fasting Study: S-Methyl-DDC (n=69)**



## 4.2.Formulation Data

| Ingredient | Amount Per Tablet (250 mg Strength) | Amount (%) / Tablet |
|---|---|---|
| Disulfiram | 250.0 mg | 57.47 |
| Crospovidone (b) (4) | (b) (4) | |
| Lactose Monohydrate (b) (4) | | |
| Magnesium Stearate | | |
| Microcrystalline Cellulose (b) (4) | | |
| | | |
| Povidone (b) (4) | | |
| Silicon Dioxide (b) (4) | | |
| **Final Tablet Weight** | 435.0 mg | 100 |

(b) (4)

| Ingredient | Amount Per Tablet (500 mg Strength) | Amount (%) / Tablet |
|---|---|---|
| Disulfiram | 500.0 mg | 57.47 |
| Crospovidone (b) (4) | (b) (4) | |
| Lactose Monohydrate (b) (4) | | |
| Magnesium Stearate | | |
| Microcrystalline Cellulose (b) (4) | | |
| | | |
| Povidone (b) (4) | | |
| Silicon Dioxide (b) (4) | | |
| **Final Tablet Weight** | 870.0 mg | 100 |

(b) (4)

**Comments**

- MDD for Disulfiram is 500 mg/day (i.e., 1 x 500 mg). Based on MDD, the daily intake of inactive ingredients and IIG limits are given in the table below.
- The excipients used in the formulation are within the IIG limits.

| Excipient | Test Product Daily Intake, mg | IIG Limit and Reference mg/Unit dose | Daily Intake, mg | NDA/ANDA | Acceptable |
|---|---|---|---|---|---|
| | [redacted] (b) (4) | | | [redacted] (b) (4) | Yes |
| Microcrystalline Cellulose | | | --- | | Yes |
| Lactose Monohydrate | | | --- | | Yes |
| Magnesium Stearate | | | --- | | Yes |
| Crospovidone | | | | | Yes |
| Povidone | | | | | Yes |
| Silicon dioxide | | | | | yes |

| | |
|---|---|
| **Is there an overage of the active pharmaceutical ingredient (API)?** | No. |
| **If the answer is yes, has the appropriate chemistry division been notified?** | N/A |
| **If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?** | N/A |
| **Comments on the drug product formulation:** | None |

### 4.3. Dissolution Data

| | |
|---|---|
| **Dissolution Review Path** | [DARRTS, ANDA 091619, MITCHELL, DEANAH L 12/17/2009 N/A 12/17/2009 REV-BIOEQ-02(Dissolution Review) Original-1)] |

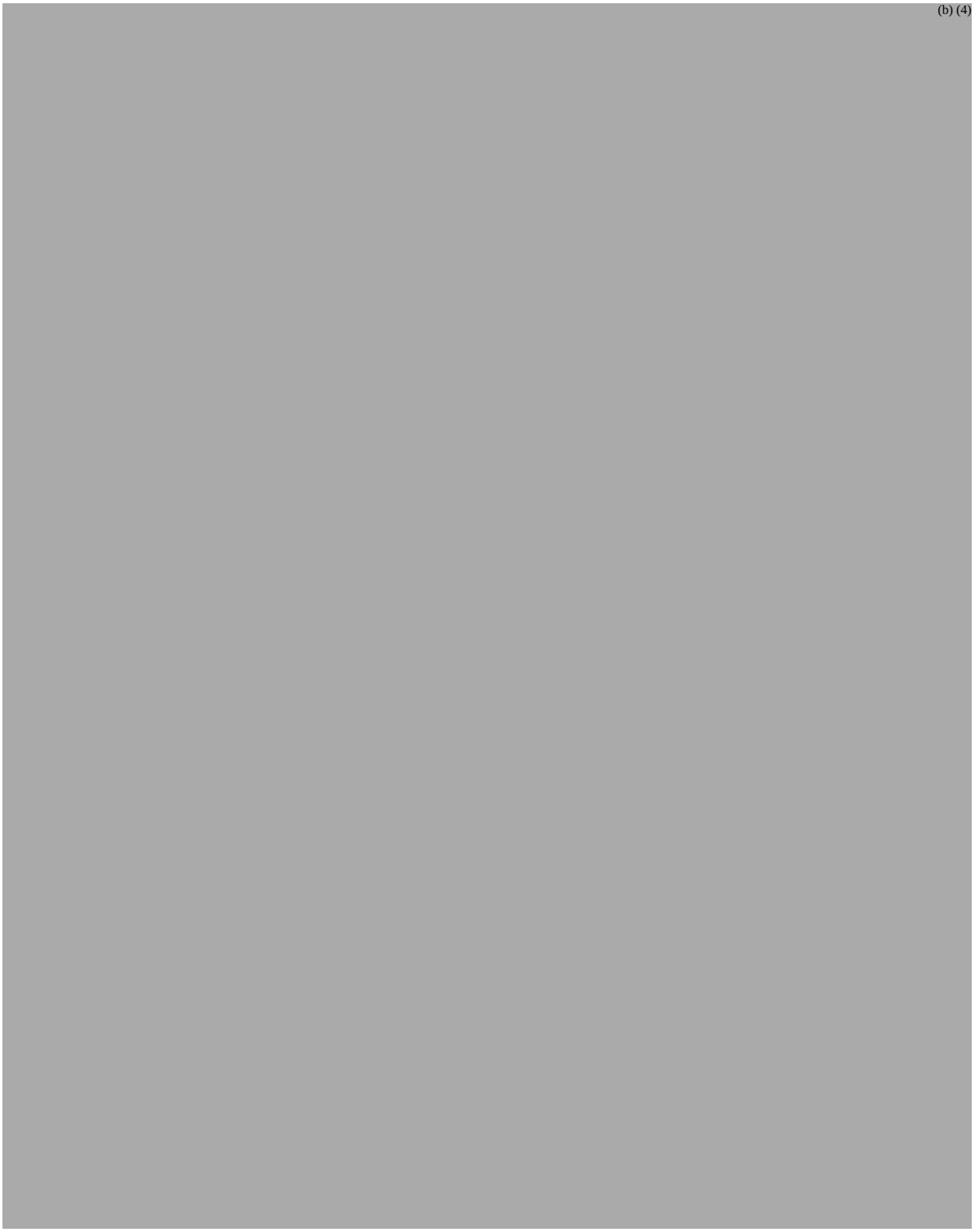
Dissolution Review 0n 250 and 500 mg strength tablets has previously been carried out [DARRTS, ANDA 091619, MITCHELL, DEANAH L 12/17/2009 N/A 12/17/2009 REV-BIOEQ-02(Dissolution Review) Original-1)]. There is no USP method for this product, but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable (at S1 level). The firm's proposed specification of NLT [redacted] (b) (4) (Q) in 120 minutes is not the FDA-recommended specification (NLT [redacted] (b) (4) (Q) in 90 minutes). The firm has acknowledged the FDA-recommended method and specification (see Amendment dated 2/3/2010).

### 4.4.Consult Reviews

None

### 4.5.SAS Output

(b) (4)



Following this page, 41 pages withheld in full (b)(4)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091619

APPLICANT: SigmaPharm Laboratories, LLC

DRUG PRODUCT: Disulfiram Tablets, USP
250 and 500 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge your acceptance of the following dissolution method and specification:

Medium: 900 mL 2% Sodium dodecyl sulfate in water
Apparatus: 2 (Paddle)
Rotation : 100 rpm
Specification: Not less than (b) (4) (Q) in 90 minutes

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

**4.7.Outcome Page**

CC: ANDA: 091619

***5. COMPLETED ASSIGNMENT FOR 091619 ID: 11409***

**Reviewer:** Shrivastava, Surendra **Date Completed:**
**Verifier:** , **Date Verified:**
**Division:** Division of Bioequivalence
**Description:** DISULFIRAM TABLETS

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*Productivity:*

| ***ID*** | ***Letter Date*** | ***Productivity Category*** | ***Sub Category*** | ***Productivity*** | ***Subtotal*** | | |
|---|---|---|---|---|---|---|---|
| 11409 | 7/11/2009 | Bioequivalence Study | Fasting Study | 1 | 1 | Edit | Delete |
| 11409 | 7/11/2009 | Other | Dissolution Waiver | 1 | 1 | Edit | Delete |
| 11409 | 2/3/2010 | Dissolution Data | Dissolution Acknowledgement | 0 | 0 | Edit | Delete |
| 11409 | 5/18/2009 | Other | DSI Inspection Report | 1 | 1 | Edit | Delete |
| 11409 | 8/6/2009 | Other | DSI Inspection Report | 1 | 1 | Edit | Delete |
| | | | | Bean Total: | 4 | | |

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| ANDA-91619 | ORIG-1 | SIGMAPHARM LABORATORIES LLC | DISULFIRAM |

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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/

SURENDRA P SHRIVASTAVA
06/24/2010

YIH CHAIN HUANG
06/24/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
06/24/2010