CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 201050

Name: Phenoxybenzamine Hydrochloride Capsules USP, 10 mg

Sponsor: Roxane Laboratories, Inc.

Approval Date: July 16, 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201050

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201050

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 201050

Roxane Laboratories, Inc.
Attention: Randall Wilson, Vice President
Scientific, Medical and Regulatory Affairs
1809 Wilson Road
Columbus, OH 43228

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 7, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Phenoxybenzamine Hydrochloride Capsules USP, 10 mg.

Reference is also made to your amendments dated March 5, and November 18, 2010; February 4, February 8, March 21, April 12, May 24, and September 9, 2011; and May 3 and May 22, 2012.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Phenoxybenzamine Hydrochloride Capsules USP, 10 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug product (RLD), Dibenzyline Capsules, 10 mg, of Wellspring Pharmaceutical Corporation. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST

07/16/2012

Deputy Director, Office of Generic Drugs
for Gregory P. Geba, M.D., M.P.H.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201050

LABELING

Dosage: See accompanying prescribing information.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Dispense in a tight container.

Roxane Laboratories Inc.
Columbus, Ohio 43216

NDC 0054-0349-25 100 Capsules

PHENOXYBENZAMINE HYDROCHLORIDE Capsules USP

10 mg

Each capsule contains 10 mg phenoxybenzamine hydrochloride.

R_x only

Boehringer Ingelheim
Roxane Laboratories

3 00540 34925 7

EXP. LOT

10006461/01

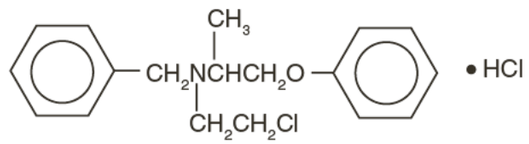
PHENOXYBENZAMINE HYDROCHLORIDE Capsules USP

℞ only

DESCRIPTION

Each Phenoxybenzamine Hydrochloride Capsule USP, with red cap and body, is imprinted with "54 036", and contains 10 mg of phenoxybenzamine hydrochloride USP. Inactive ingredients consist of anhydrous lactose, black monogramming ink, colloidal silicon dioxide, FD&C Red No. 40, gelatin, purified water, sodium lauryl sulfate, sodium stearyl fumarate and titanium dioxide. The black monogramming ink contains 1,4-dioxane, acetaldehyde, ethyl alcohol, ethylene oxide, formaldehyde, isobutyl alcohol, iron oxide, iron oxide black, iron oxide yellow, polyethylene glycol, polyvinyl pyrrolidone, shellac and water.

Phenoxybenzamine is *N*-(2-Chloroethyl)-*N*-(1-methyl-2-phenoxyethyl) benzylamine hydrochloride:



Phenoxybenzamine hydrochloride is a colorless, crystalline powder with a molecular weight of 340.3, which melts between 136° and 141°C. It is soluble in alcohol and chloroform; insoluble in ether and water.

CLINICAL PHARMACOLOGY

Phenoxybenzamine hydrochloride is a long-acting, adrenergic, *alpha*-receptor blocking agent, which can produce and maintain "chemical sympathectomy" by oral administration. It increases blood flow to the skin, mucosa and abdominal viscera, and lowers both supine and erect blood pressures. It has no effect on the parasympathetic system.

Twenty to 30 percent of orally administered phenoxybenzamine appears to be absorbed in the active form.1

The half-life of orally administered phenoxybenzamine hydrochloride is not known; however, the half-life of intravenously administered drug is approximately 24 hours. Demonstrable effects with intravenous administration persist for at least 3 to 4 days, and the effects of daily administration are cumulative for nearly a week.1

INDICATIONS AND USAGE

Phenoxybenzamine Hydrochloride Capsules USP are indicated in the treatment of pheochromocytoma, to control episodes of hypertension and sweating. If tachycardia is excessive, it may be necessary to use a *beta*-blocking agent concomitantly.

CONTRAINDICATIONS

Conditions where a fall in blood pressure may be undesirable; hypersensitivity to the drug or any of its components.

WARNINGS

Phenoxybenzamine-induced *alpha*-adrenergic blockade leaves *beta*-adrenergic receptors unopposed. Compounds that stimulate both types of receptors may, therefore, produce an exaggerated hypotensive response and tachycardia.

PRECAUTIONS

General

Administer with caution in patients with marked cerebral or coronary arteriosclerosis or renal damage. Adrenergic blocking effect may aggravate symptoms of respiratory infections.

Drug Interactions2

Phenoxybenzamine hydrochloride may interact with compounds that stimulate both *alpha*-and *beta*-adrenergic receptors (i.e., epinephrine) to produce an exaggerated hypotensive response and tachycardia. (See **WARNINGS**.)

Phenoxybenzamine blocks hyperthermia production by levarterenol, and blocks hypothermia production by reserpine.

Carcinogenesis and Mutagenesis

Case reports of carcinoma in humans after long-term treatment with phenoxybenzamine have been reported. Hence long-term use of phenoxybenzamine is not recommended.3,4 Carefully weigh the benefits and risks before prescribing this drug.

Phenoxybenzamine hydrochloride showed *in vitro* mutagenic activity in the Ames test and mouse lymphoma assay; it did not show mutagenic activity *in vivo* in the micronucleus test in mice. In rats and mice, repeated intraperitoneal administration of phenoxybenzamine hydrochloride (three times per week for up to 52 weeks) resulted in peritoneal sarcomas. Chronic oral dosing in rats (for up to 2 years) produced malignant tumors of the small intestine and non-glandular stomach, as well as ulcerative and/or erosive gastritis of the glandular stomach. Whereas squamous cell carcinomas of the non-glandular stomach were observed at all tested doses of phenoxybenzamine hydrochloride, there was a no-observed-effect-level of 10 mg/kg for tumors (carcinomas and sarcomas) of the small intestine. This dose is, on a body surface area basis, about twice the maximum recommended human dosage of 20 mg b.i.d.

Pregnancy

Teratogenic Effects- Pregnancy Category C: Adequate reproductive studies in animals have not been performed with phenoxybenzamine hydrochloride. It is also not known whether phenoxybenzamine can cause fetal harm when administered to a pregnant woman. Phenoxybenzamine should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from phenoxybenzamine hydrochloride, 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The following adverse reactions have been observed, but there are insufficient data to support an estimate of their frequency.

Autonomic Nervous System*: Postural hypotension, tachycardia, inhibition of ejaculation, nasal congestion, miosis.

*These so-called "side effects" are actually evidence of adrenergic blockade and vary according to the degree of blockade.

Miscellaneous: Gastrointestinal irritation, drowsiness, fatigue.

OVERDOSAGE

SYMPTOMS - These are largely the result of blocking of the sympathetic nervous system and of the circulating epinephrine. They may include postural hypotension, resulting in dizziness or fainting; tachycardia, particularly postural; vomiting; lethargy; shock.

TREATMENT

When symptoms and signs of overdosage exist, discontinue the drug. Treatment of circulatory failure, if present, is a prime consideration. In cases of mild overdosage, recumbent position with legs elevated usually restores cerebral circulation. In the more severe cases, the usual measures to combat shock should be instituted. Usual pressor agents are not effective. Epinephrine is contraindicated because it stimulates both *alpha*- and *beta*- receptors; since *alpha*- receptors are blocked, the net effect of epinephrine administration is vasodilation and a further drop in blood pressure (epinephrine reversal).

The patient may have to be kept flat for 24 hours or more in the case of overdose, as the effect of the drug is prolonged. Leg bandages and an abdominal binder may shorten the period of disability.

I.V. Infusion of levarterenol bitartrate** may be used to combat severe hypotensive reactions, because it stimulates *alpha*- receptors primarily. Although phenoxybenzamine hydrochloride is an *alpha*-adrenergic blocking agent, a sufficient dose of levarterenol bitartrate will overcome this effect.

The oral LD_{50} for phenoxybenzamine hydrochloride is approximately 2000 mg/kg in rats and approximately 500 mg/kg in guinea pigs.

DOSAGE AND ADMINISTRATION

The dosage should be adjusted to fit the needs of each patient. Small initial doses should be *slowly* increased until the desired effect is obtained or the side effects from blockade become troublesome. *After each increase, the patient should be observed on that level before instituting another increase.* The dosage should be carried to a point where symptomatic relief and/or objective improvement are obtained, but not so high that the side effects from blockade become troublesome.

Initially, 10 mg of phenoxybenzamine hydrochloride twice a day. Dosage should be increased every other day, usually to 20 to 40 mg 2 or 3 times a day, until an optimal dosage is obtained, as judged by blood pressure control.

Long-term use of phenoxybenzamine is not recommended (see **PRECAUTIONS: Carcinogenesis and Mutagenesis**).

HOW SUPPLIED

Phenoxybenzamine Hydrochloride Capsules USP are supplied as opaque red, hard gelatin capsules with "54 036" imprinted in black on the capsule body.

NDC 0054-0349-25 10 mg, opaque red capsule, bottle of 100

Storage

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

REFERENCES

1. Weiner, N.: Drugs That Inhibit Adrenergic Nerves and Block Adrenergic Receptors, in Goodman, L., and Gilman, A., *The Pharmacological Basis of Therapeutics*, ed. 6, New York, Macmillan Publishing Co., 1980, p. 179; p. 182.
2. Martin, E.W.: *Drug Interactions Index 1978/1979*, Philadelphia, J.B. Lippincott Co., 1978, pp. 209-210.
3. Nettesheim O, Hoffken G, Gahr M, Breidert M: Haematemesis and dysphagia in a 20-year-old woman with congenital spine malformation and situs inversus partialis [German]. Zeitschrift fur Gastroenterologie. 2003;41(4):319-24. 165
4. Vaidyanathan S, Mansour P, Soni BM, Hughes PL, Singh G: Chronic lymphocytic leukaemia, synchronous small cell carcinoma and squamous neoplasia of the urinary bladder in a paraplegic man following long-term phenoxybenzamine therapy. Spinal Cord. 2006;44(3):188-91.

** Available as Levophed® Bitartrate (brand of norepinephrine bitartrate) from Abbott Laboratories.

Roxane Laboratories, Inc.
Columbus, Ohio 43216

10006462/01 **Revised May 2012**

Boehringer Ingelheim
Roxane Laboratories

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201050

LABELING REVIEWS

APPROVAL SUMMARY #2
(Supersedes AP summary dated April 22, 2011)
OFFICE OF GENERIC DRUGS
REVIEW OF PROFESSIONAL LABELING

ANDA Number: 201050

Date of Submission: May 22, 2012

Applicant's Name: Roxane Laboratories, Inc.

Established Name: **Phenoxybenzamine Hydrochloride Capsules USP, 10 mg**

Labeling Comments below are considered:

☐ **Minor Deficiency ***

*** Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.**

☒ **No Comments (Labeling Approval Summary or Tentative Approval Summary)**

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated May 22, 2012.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Note RPM - Labeling comments end here

FOR THE RECORD:

REMS required? NO

MedGuides and/or PPIs (505-1(e))	☐ Yes	☐ No
Communication plan (505-1(e))	☐ Yes	☐ No

	Date submitted	Final or Draft	Revision Date	Status
CONTAINER: 100s	April 12, 2011	Final	n/a	Found acceptable on 4/22/11 by previous review team.
PACKAGE INSERT	May 22, 2012	Final	May 2012	Satisfactory

REVISIONS NEEDED POST APPROVAL? NO

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:

FOR THE RECORD (Comments made by previous reviewer James Barlow in AP Summary dated 4.22.2011)

**The labeling was approved dated April 22, 2011. However, the drug substance was revised per CMC review. The previously approved labeling stated "It is soluble in (b) (4) (b) (4), and the newly submitted labeling states "It is soluble in alcohol and chloroform; insoluble in ether and water" to be in line with the description in the CMC review in darrts.

1. **MODELING LABELING** Labeling review based on the labeling of WellSpring Pharmaceutical Corporation's, **Dibenzyline**® (Phenoxybenzamine Hydrochlorothiazide Capsules USP, NDA 008708/S-025, approved, April 3, 2008).

2. INACTIVE INGREDIENTS: The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section appearing in the chemistry review. (See Components and Composition from Chem review)

   What are the components and composition of the final product? What is the function(s) of each excipient?
   The components and composition of the finished drug product Phenoxybenzamine Hydrochloride Capsules, USP 10mg dosage strength is summarized in the following table:
   Phenoxybenzamine HCl Capsules INGREDIENTS:

   Phenoxybenzamine HCl (active)
   Anhydrous Lactose, NF (b) (4)
   Colloidal Silicon Dioxide, NF (b) (4)
   Sodium Lauryl Sulfate, NF (b) (4)
   Sodium Stearyl Fumarate, NF (b) (4)
   * Capsules, Size #3 (b) (4) Opaque/Red (b) (4) Cap Body Imprinted with 54 036

   (b) (4)

   Gelatin
   Purified Water
   (b) (4)
   Titanium Dioxide
   FD & C Red N 40
   Elemental Iron (b) (4)
   * The capsule composition is per the manufacturer's product specification and certificate of analysis. The source of elemental iron is iron oxide contained in the black ink used to print the product identification number onto each capsule

shell/body. The elemental iron present in the capsule is well below the requirement of 5 mg per day per 21 CFR 73.1200.

3. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON:
USP: Preserve in well-closed containers
RLD: Store at 25° C (77° F); excursions permitted to 15° C - 30° C (59° F - 86° F) [see USP Controlled Room Temperature].
ANDA: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container.

4. PACKAGING CONFIGURATIONS
RLD: 100s
ANDA: 100s

5. CONTAINER/CLOSURE
All strength tablets and bottle sizes will utilize HDPE bottles with CRC-closures per the chemistry review –

For packaging and storage of Phenoxybenzamine Hydrochloride Capsules, USP 10mg dosage strength, please see Section 2.3.P.7. The drug product is packaged in a HDPE bottle (100 capsules per bottle) closed with child resistant cap (b) (4) (b) (4)

The packaging system is typical of the container/closure system used to package an immediate release dosage strength

6. FINISHED DOSAGE MANUFACTURING FACILITY The following information, taken from the chemistry review is consistent with statements appearing in the sponsor's labeling. Manufacturing, Packaging, Testing and Stability testing sites for Drug Products:

The drug product Phenoxybenzamine Hydrochloride Capsules 10mg dosage strength is manufactured, packaged and tested for release and stability by:

Name: Boehringer Ingelheim Roxane Inc.

Address: 1809 Wilson Rd. Columbus, OH 43228

7. Code Imprint from HOW SUPPLIED

Phenoxybenzamine Hydrochloride Capsules USP are supplied as opaque red, hard gelatin capsules with "54 036" imprinted in black on the capsule body.

8. Patent Data – NDA/**Exclusivity Data – NDA - 008708**

NONE

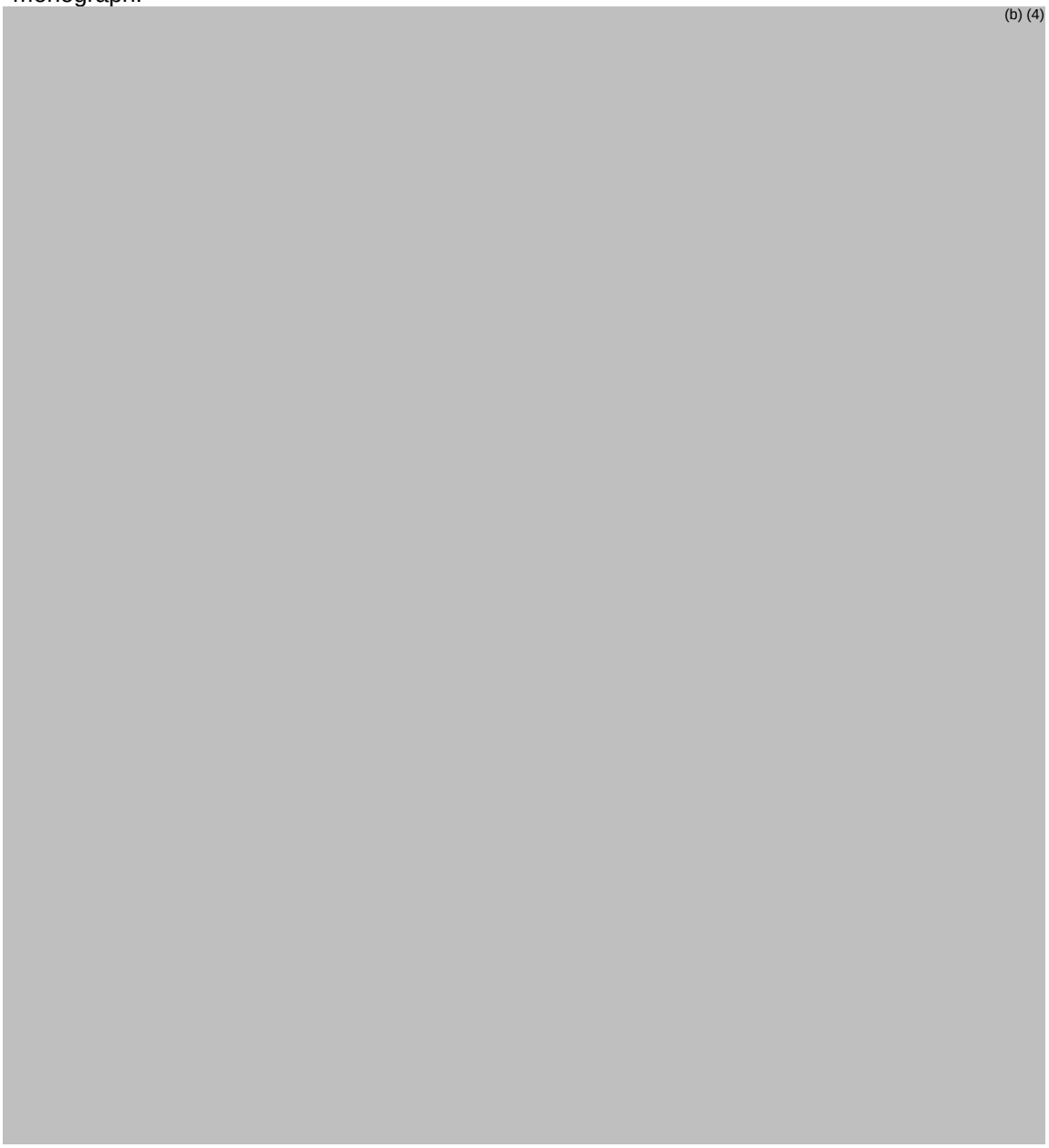
9. Stability Data-

Specifications
The tests and specifications for stability of the finished drug product are as follows:

***** Dissolution: NLT 75% (Q) of the labeled amount is dissolved in 45 minutes (b) (4)

***** The Dissolution testing method and specification is based on the current USP monograph.

(b) (4)



_____

Date of Review: March 4, 2014

Primary Reviewer: Melaine Shin

Team Leader: Lillie Golson

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

/s/

MELAINE M SHIN
03/07/2014

LILLIE D GOLSON
03/11/2014

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 201050

Date of Submission: April 12, 2011

Applicant's Name: Roxane Laboratories, Inc.

Established Name: **Phenoxybenzamine Hydrochloride Capsules USP, 10 mg**

Approval Summary:

REMS required?	☐ Yes	x No		
MedGuides and/or PPIs (505-1(e))	☐ Yes	x No		
Communication plan (505-1(e))	☐ Yes	x No		
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	x No		
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	x No		
Timetable for assessment (505-1(d))	☐ Yes	x No		
ANDA REMS acceptable?	☐ Yes	☐ No	x	N/A

1. **Do you have copies of final printed labels and labeling?** Yes

2. **CONTAINER** – 100s

   Satisfactory in **final print** as of the April 12, 2011 e-submission

3. **PACKAGE INSERT -**

   Satisfactory in **final print** as of the April 12, 2011 e-submission

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Dibenzyline® Tablets
NDA Number: 008708
NDA Drug Name: Phenoxybenzamine Hydrochloride Capsules USP
NDA Firm: WellSpring Pharmaceutical Corporation
Date of Approval of NDA Insert and supplement: NDA 008708/S-025; approved April 3, 2008
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug.

FOR THE RECORD

1. **MODELING LABELING** Labeling review based on the labeling of WellSpring Pharmaceutical Corporation's, **Dibenzyline**® (Phenoxybenzamine Hydrochlorothiazide Capsules USP, NDA 008708/S-025, approved, April 3, 2008).

2. INACTIVE INGREDIENTS: The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section appearing in the chemistry review. (See Components and Composition from Chem review)

   What are the components and composition of the final product? What is the function(s) of each excipient?
   The components and composition of the finished drug product Phenoxybenzamine Hydrochloride Capsules, USP 10mg dosage strength is summarized in the following table:
   Phenoxybenzamine HCl Capsules INGREDIENTS:

   Phenoxybenzamine HCl (active)
   Anhydrous Lactose, NF (b) (4)
   Colloidal Silicon Dioxide, NF (b) (4)
   Sodium Lauryl Sulfate, NF (b) (4)
   Sodium Stearyl Fumarate, NF (b) (4)
   * Capsules, Size #3 (b) (4) Opaque/Red (b) (4) Cap Body Imprinted with 54 036

   (b) (4)

   Gelatin
   Purified Water
   (b) (4)
   Titanium Dioxide
   FD & C Red N 40
   Elemental Iron (b) (4)
   * The capsule composition is per the manufacturer's product specification and certificate of analysis. The source of elemental iron is iron oxide contained in the black ink used to print the product identification number onto each capsule shell/body. The elemental iron present in the capsule is well below the requirement of 5 mg per day per 21 CFR 73.1200.

3. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON:
   USP: Preserve in well-closed containers
   RLD: Store at 25° C (77° F); excursions permitted to 15° C - 30° C (59° F - 86° F) [see USP Controlled Room Temperature].
   ANDA: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container.

4. PACKAGING CONFIGURATIONS
   RLD: 100s
   ANDA: 100s

5. CONTAINER/CLOSURE
   All strength tablets and bottle sizes will utilize HDPE bottles with CRC-closures per the chemistry review –

   For packaging and storage of Phenoxybenzamine Hydrochloride Capsules, USP 10mg dosage strength, please see Section 2.3.P.7. The drug product is packaged in a HDPE bottle (100 capsules per bottle) closed with child resistant cap (b) (4) (b) (4)
   The packaging system is typical of the container/closure system used to package an immediate release dosage strength

6. FINISHED DOSAGE MANUFACTURING FACILITY The following information, taken from the chemistry review is consistent with statements appearing in the sponsor's labeling. Manufacturing, Packaging, Testing and Stability testing sites for Drug Products:

The drug product Phenoxybenzamine Hydrochloride Capsules 10mg dosage strength is manufactured, packaged and tested for release and stability by:

Name: Boehringer Ingelheim Roxane Inc.

Address: 1809 Wilson Rd. Columbus, OH 43228

7. Code Imprint From HOW SUPPLIED

Description:
10mg: Size 3, (b) (4) Opaque/Red (b) (4) capsule with 54 036 printed (b) (4) (b) (4) in black ink on the capsule body, containing a white (b) (4) powder.

8. Bioequivalence – Unacceptable as of 4/11/11

9. Patent Data – NDA/**Exclusivity Data – NDA - 008708**

NONE

10. Stability Data-

Specifications
The tests and specifications for stability of the finished drug product are as follows:

* Dissolution: NLT 75% (Q) of the labeled amount is dissolved in 45 minutes.
Moisture: NMT 0.6%

(b) (4)

Date of Review: 4/13/11 Date of Submission: April 12, 2011

Primary Reviewer: Jim Barlow Date:

Team Leader: Koung Lee Date:

Following this page, 3 Pages of Draft Labeling have been Withheld in Full as (b)(4)

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

/s/

JAMES T BARLOW
04/13/2011

KOUNG U LEE
04/22/2011
For Wm. Peter Rickman

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 201050
Date of Submission: December 7, 2009
Applicant's Name: Roxane Laboratories, Inc.
Established Name: **Phenoxybenzamine Hydrochloride Capsules USP, 10 mg**

Labeling Deficiencies:

1. **CONTAINER** – 100s

   Delete the comma after "Capsules" to read as follows –

   Phenoxybenzamine
   Hydrochloride
   Capsules USP

2. **PACKAGE INSERT -**

   a. See comments above under CONTAINER.

   b. Title: Established Name

   Please relocate the name and address of the firm from the top of the package insert directly above the established name -

   Phenoxybenzamine
   Hydrochloride
   Capsules USP

Revise your labels and labeling as requested above and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

FOR THE RECORD

1. **MODELING LABELING** Labeling review based on the labeling of WellSpring Pharmaceutical Corporation's, **Dibenzyline**® (Phenoxybenzamine Hydrochlorothiazide Capsules USP, NDA 008708/S-025, approved, April 3, 2008).

2. INACTIVE INGREDIENTS: The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section appearing in the chemistry review. (See Components and Composition from Chem review)

   What are the components and composition of the final product? What is the function(s) of each excipient?
   The components and composition of the finished drug product Phenoxybenzamine Hydrochloride Capsules, USP 10mg dosage strength is summarized in the following table:
   Phenoxybenzamine HCl Capsules INGREDIENTS:

   Phenoxybenzamine HCl (active)
   Anhydrous Lactose, NF (b) (4)
   Colloidal Silicon Dioxide, NF (b) (4)
   Sodium Lauryl Sulfate, NF (b) (4)
   Sodium Stearyl Fumarate, NF (b) (4)
   * Capsules, Size #3 (b) (4) Opaque/Red (b) (4) Cap Body Imprinted with 54 036

   (b) (4)

   Gelatin
   Purified Water
   (b) (4)
   Titanium Dioxide
   FD & C Red N 40
   Elemental Iron (b) (4)
   * The capsule composition is per the manufacturer's product specification and certificate of analysis. The source of elemental iron is iron oxide contained in the black ink used to print the product identification number onto each capsule shell/body. The elemental iron present in the capsule is well below the requirement of 5 mg per day per 21 CFR 73.1200.

3. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON:
   USP: Preserve in well-closed containers
   RLD: Store at 25° C (77° F); excursions permitted to 15° C - 30° C (59° F - 86° F) [see USP Controlled Room Temperature].
   ANDA: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container.

4. PACKAGING CONFIGURATIONS
   RLD: 100s
   ANDA: 100s

5. CONTAINER/CLOSURE
   All strength tablets and bottle sizes will utilize HDPE bottles with CRC-closures per the chemistry review –

   For packaging and storage of Phenoxybenzamine Hydrochloride Capsules, USP 10mg dosage strength, please see Section 2.3.P.7. The drug product is packaged in a HDPE bottle (100 capsules per bottle) closed with child resistant cap (b) (4) (b) (4)

The packaging system is typical of the container/closure system used to package an immediate release dosage strength

6. FINISHED DOSAGE MANUFACTURING FACILITY The following information, taken from the chemistry review is consistent with statements appearing in the sponsor's labeling. Manufacturing, Packaging, Testing and Stability testing sites for Drug Products:

The drug product Phenoxybenzamine Hydrochloride Capsules 10mg dosage strength is manufactured, packaged and tested for release and stability by:

Name: Boehringer Ingelheim Roxane Inc.

Address: 1809 Wilson Rd. Columbus, OH 43228

7. Code Imprint From HOW SUPPLIED

Description:
10mg: Size 3, (b) (4) Opaque/Red (b) (4) capsule with 54 036 (b) (4) (b) (4) printed in black ink on the capsule body, containing a white (b) (4) powder.

8. Bioequivalence – Unacceptable as of 4/11/11

9. Patent Data – NDA/**Exclusivity Data – NDA - 008708**

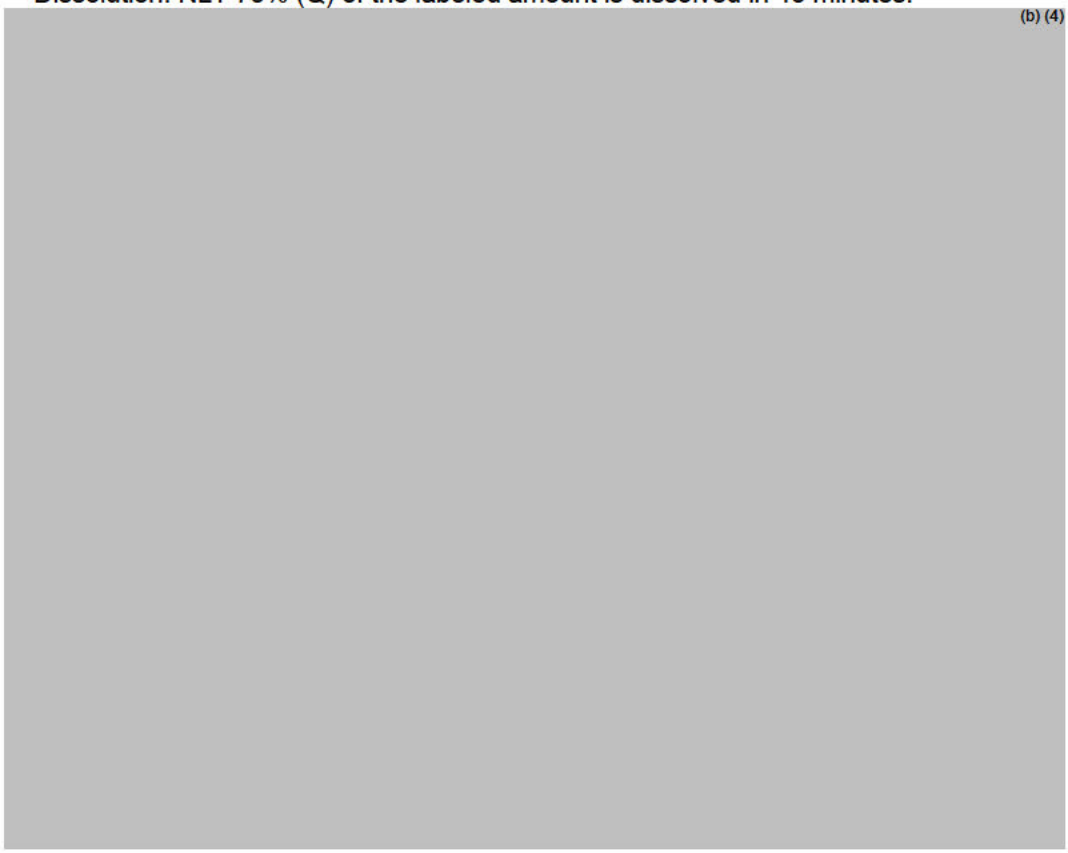
NONE

10. Stability Data-

Specifications
The tests and specifications for stability of the finished drug product are as follows:

* Dissolution: NLT 75% (Q) of the labeled amount is dissolved in 45 minutes.

(b) (4)



(b) (4)

_____

Date of Review: 4/11/11 Date of Submission: December 7, 2009

Primary Reviewer: Jim Barlow Date:

Team Leader: Koung Lee Date:

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

/s/

JAMES T BARLOW
04/11/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201050

CHEMISTRY REVIEWS

ANDA 201-050

Phenoxybenzamine Hydrochloride Capsules, USP
10 mg

Roxane Laboratories Inc.

Rosario D'Costa
Chemistry Division IV

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 201050

2. REVIEW #: 2A

3. REVIEW DATE: 05/04/12

4. REVIEWER: Rosario D'Costa

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Amendment:	September 09, 2011
Gratuitous Amendment:	May 24, 2011
Amendment:	February 04, 2011
Amendment:	March 05, 2010
Original (Application received):	December 07, 2009
Acceptable for Filing:	December 08, 2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment:	May 03, 2012

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Laboratories Inc.

Address: 1809 Wilson Road
Columbus, OH 43228

Chemistry Review Data Sheet

Representative: Elizabeth Ernst

Telephone: 614 272-4785
Facsimile: 614 276-2470

8. DRUG PRODUCT NAME/CODE/TYPE: Phenoxybenzamine HCl Capsules, USP

9. LEGAL BASIS FOR SUBMISSION: FFD & CA

The basis for proposed ANDA, Phenoxybenzamine Hydrochloride Capsules, USP 10mg dosage strength is the approved reference listed drug, Dibenzylene® Capsules 10mg, the subject of NDA #8708 held by Wellspring Pharmaceuticals.

Paragraph II Certification: Roxane hereby certifies that in its opinion and to the best of its knowledge, there are no unexpired patents listed in the orange book for the reference listed drug Dibenzylene® Capsules 10mg dosage strength.

There are no unexpired exclusivities for the reference listed drug Dibenzylene® Capsules 10mg dosage strength.

10. PHARMACOL. CATEGORY: Indicated for the treatment of pheochromocytoma, to control episodes of hypertension and sweating. If tachycardia is excessive, it may be necessary to use a beta-blocking agent concomitantly.

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 10mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __Rx __X_OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X____Not a SPOTS product

Chemistry Review Data Sheet

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

__X__Not a NANO product

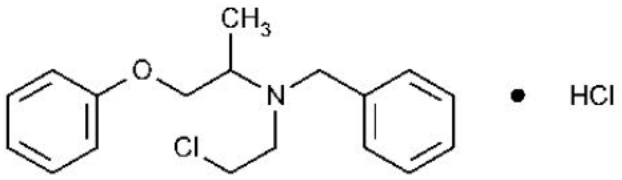
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Generic Name: Phenoxybenzamine Hydrochloride
Chemical Name: Benzenemethanamine, N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)-, hydrochloride OR
N-(2-Chloroethyl)-N-(1-methyl-2-phenoxyethyl) benzylamine hydrochloride

Formula: $C_{18}H_{22}ClNO.\ HCl$

Molecular weight: 340.29
CAS registry number(s): 63-92-3



17. RELATED/SUPPORTING DOCUMENTS: None

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	09/22/11	RD'Costa
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

* Amendment dated may 03, 2012.

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

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

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS: CMC Approvable

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending	01/11/11	
Methods Validation	N/A		
Labeling	Acceptable	04/22/11	J. Barlow

Chemistry Review Data Sheet

Bioequivalence	Acceptable	04/04/12	T. Ramsom
EA	Categorical Exclusion Requested (Acceptable)	10/28/09	
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

Executive Summary

The Chemistry Review for ANDA 201-050

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The chemistry section is adequate in areas of manufacturing and controls and is therefore recommended for "approvable" .

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

N/A

II. Summary of Chemistry Assessments

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

Phenoxybenzamine Hydrochloride is a white (b) (4) powder, insoluble in water and soluble in alcohol, chloroform (b) (4) The drug substance (b) (4) are characterized by standard analytical techniques such as UV, IR, (b) (4)

Phenoxybenzamine Hydrochloride Capsules 10mg dosage strength, is a long acting, adrenergic, alpha-receptor blocking agent indicated in the treatment for pheochromocytoma, to control episodes of hypertension and sweating.

The manufacture of the drug product is based on (b) (4) The drug product is packaged in bottles of 100 capsules.

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

The recommended daily dose is 2 x 10mg capsules and may be increased to 20mg to 40mg 2 to 3 times a day until an optimal dosage is obtained, as judged by blood pressure control.

C. Basis for Approvability or Not-Approval Recommendation

The "approvable" recommendation is based on adequate chemistry and manufacturing controls.

Executive Summary

- Labeling is acceptable.
- Bioequivalence is acceptable.
- EER is pending.

APPEARS THIS WAY ON ORIGINAL

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(b) (4)

[redacted]

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-623/RD'Costa, Ph.D./05/07/12
HFD-623/AMueller, Ph.D. /05/07/12
HFD-617/Mark Goenitzke, PM./05/07/12
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F/T by/:

TYPE OF LETTER: CMC APPROVABLE

C. CC Block
ANDA
ANDA DUP
DIV FILE
Field Copy

APPEARS THIS WAY ON ORIGINAL

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

/s/

ROSARIO D COSTA
05/16/2012

ROBERT L ISER
05/16/2012
Division comments added to review with reviewer and TL concurrence.

CMC/LBL OK al EES on withhold.
Dat 10/25/11…Bio pending DSI

ANDA 201-050

Phenoxybenzamine Hydrochloride Capsules, USP
10 mg

Roxane Laboratories Inc.

Rosario D'Costa
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 201050

2. REVIEW #: 2

3. REVIEW DATE: 02/18/11

4. REVIEWER: Rosario D'Costa

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Amendment:	March 05, 2010
Original (Application received):	December 07, 2009
Acceptable for Filing:	December 08, 2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment:	September 09. 2011
Gratuitous Amendment:	May 24, 2011
Amendment:	February 04, 2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories Inc.
Address:	1809 Wilson Road Columbus, OH 43228
Representative:	Elizabeth Ernst

Chemistry Review Data Sheet

Telephone: 614 272-4785
Facsimile: 614 276-2470

8. DRUG PRODUCT NAME/CODE/TYPE: Phenoxybenzamine HCl Capsules, USP

9. LEGAL BASIS FOR SUBMISSION: FFD & CA

The basis for proposed ANDA, Phenoxybenzamine Hydrochloride Capsules, USP 10mg dosage strength is the approved reference listed drug, Dibenzylene® Capsules 10mg, the subject of NDA #8708 held by Wellspring Pharmaceuticals.

Paragraph II Certification: Roxane hereby certifies that in its opinion and to the best of its knowledge, there are no unexpired patents listed in the orange book for the reference listed drug Dibenzylene® Capsules 10mg dosage strength.

There are no unexpired exclusivities for the reference listed drug Dibenzylene® Capsules 10mg dosage strength.

10. PHARMACOL. CATEGORY: Indicated for the treatment of pheochromocytoma, to control episodes of hypertension and sweating. If tachycardia is excessive, it may be necessary to use a beta-blocking agent concomitantly.

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 10mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __Rx __X_OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X____Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

__X__Not a NANO product

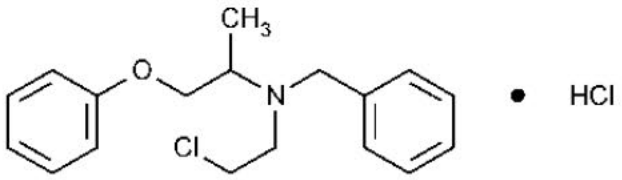
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Generic Name: Phenoxybenzamine Hydrochloride
Chemical Name: Benzenemethanamine, N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)-, hydrochloride OR
N-(2-Chloroethyl)-N-(1-methyl-2-phenoxyethyl) benzylamine hydrochloride

Formula: $C_{18}H_{22}ClNO.\ HCl$

Molecular weight: 340.29
CAS registry number(s): 63-92-3



17. RELATED/SUPPORTING DOCUMENTS: None

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	09/22/11	RD'Costa
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

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

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

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS: CMC Approvable

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	* Withhold	01/11/11	
Methods Validation	N/A		
Labeling	Acceptable	04/22/11	J. Barlow

Chemistry Review Data Sheet

** Bioequivalence	Pending		
EA	Categorical Exclusion Requested (Acceptable)	10/28/09	
Radiopharmaceutical	N/A		

*** The supplier of the drug substance has a withhold status.**

**** Pending a For Cause DSI inspection requested for the current ANDA.**

19. ORDER OF REVIEW

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

Executive Summary

The Chemistry Review for ANDA 201-050

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The chemistry section is adequate in areas of manufacturing and controls and is therefore recommended for "approvable" .

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

N/A

II. Summary of Chemistry Assessments

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

Phenoxybenzamine Hydrochloride is a white (b) (4) powder, insoluble in water and soluble in alcohol, chloroform (b) (4). The drug substance (b) (4) are characterized by standard analytical techniques such as UV, IR, (b) (4)

Phenoxybenzamine Hydrochloride Capsules 10mg dosage strength, is a long acting, adrenergic, alpha-receptor blocking agent indicated in the treatment for pheochromocytoma, to control episodes of hypertension and sweating.

The manufacture of the drug product is based on (b) (4) The drug product is packaged in bottles of 100 capsules.

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

The recommended daily dose is 2 x 10mg capsules and may be increased to 20mg to 40mg 2 to 3 times a day until an optimal dosage is obtained, as judged by blood pressure control.

C. Basis for Approvability or Not-Approval Recommendation

The "approvable" recommendation is based on adequate chemistry and manufacturing controls.

Executive Summary

- Labeling is acceptable.
- Bioequivalence is pending.
- EER is on withhold for ChemPacific the drug substance supplier located in Baltimore and China.

Following this page, 23 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-623/RD'Costa, Ph.D./10/03/11
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F/T by/:

TYPE OF LETTER: CMC APPROVABLE

C. CC Block

ANDA
ANDA DUP
DIV FILE
Field Copy

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/s/

ROSARIO F D COSTA
10/26/2011
CMC is OK. EES is on withhold. BIO is pending DSI inspection.

DAT T DOAN
10/26/2011

ALBERT J MUELLER
10/26/2011

ANDA 201-050

Phenoxybenzamine Hydrochloride Capsules, USP
10 mg

Roxane Laboratories Inc.

Rosario D'Costa
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 201-050

2. REVIEW #: 1

3. REVIEW DATE: 02/12/10

4. REVIEWER: Rosario D'Costa

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment:	March 05, 2010
Original (Application received):	December 07, 2009
Acceptable for Filing:	December 08, 2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories Inc.
Address:	1809 Wilson Road Columbus, OH 43228
Representative:	Elizabeth Ernst
Telephone:	614 272-4785
Facsimile:	614 276-2470

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE: Phenoxybenzamine HCl Capsules, USP

9. LEGAL BASIS FOR SUBMISSION: FFD & CA

The basis for proposed ANDA, Phenoxybenzamine Hydrochloride Capsules, USP 10mg dosage strength is the approved reference listed drug, Dibenzylene® Capsules 10mg, the subject of NDA #8708 held by WellSpring Pharmaceuticals.

Paragraph II Certification: Roxane hereby certifies that in its opinion and to the best of its knowledge, there are no unexpired patents listed in the orange book for the reference listed drug Dibenzylene® Capsules 10mg dosage strength.

There are no unexpired exclusivities for the reference listed drug Dibenzylene® Capsules 10mg dosage strength.

10. PHARMACOL. CATEGORY: Indicated for the treatment of pheochromocytoma, to control episodes of hypertension and sweating. If tachycardia is excessive, it may be necessary to use a beta-blocking agent concomitantly.

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 10mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __Rx __X_OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X____Not a SPOTS product

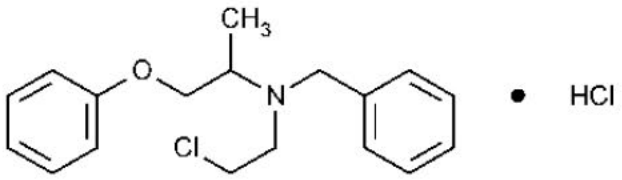
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Generic Name: Phenoxybenzamine Hydrochloride
Chemical Name: Benzenemethanamine, N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)-, hydrochloride OR
N-(2-Chloroethyl)-N-(1-methyl-2-phenoxyethyl) benzylamine hydrochloride

Formula: $C_{18}H_{22}ClNO.\ HCl$

Molecular weight: 340.29
CAS registry number(s): 63-92-3



17. RELATED/SUPPORTING DOCUMENTS: None

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Inadequate	02/28/10	RD'Costa
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

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

Chemistry Review Data Sheet

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

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

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS: Not Approvable

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	Categorical Exclusion Requested (Acceptable)	10/28/09	
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

Executive Summary

The Chemistry Review for ANDA 201-050

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The chemistry section is deficient in areas of manufacturing and controls and is therefore recommended for "not-approvable" .

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

N/A

II. Summary of Chemistry Assessments

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

Phenoxybenzamine Hydrochloride is a white (b) (4) powder, insoluble in water and soluble in alcohol, chloroform (b) (4) The drug substance (b) (4) (b) (4) are characterized by standard analytical techniques such as UV, IR, (b) (4) (b) (4)

Phenoxybenzamine Hydrochloride Capsules 10mg dosage strength, is a long acting, adrenergic, alpha-receptor blocking agent indicated in the treatment for pheochromocytoma, to control episodes of hypertension and sweating.

The manufacture of the drug product is based on (b) (4) The drug product is packaged in bottles of 100 capsules.

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

The recommended daily dose is 2 x 10mg capsules and may be increased to 20mg to 40mg 2 to 3 times a day until an optimal dosage is obtained, as judged by blood pressure control.

C. Basis for Approvability or Not-Approval Recommendation

The "not-approvable" recommendation for chemistry is based on the following issues:

- There are issues in the Drug Master File that need to be addressed.

Executive Summary

- There are issues in the analytical methodology, manufacturing, impurities and stability data.
- Labeling and Bioequivalence are pending.
- EER is pending

Following this page, 21 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-623/RD'Costa, Ph.D./06/11/10
HFD-623/AMueller, Ph.D. /06/11/10
HFD-617/Doan Dat, PM./06/11/10
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F/T by/:

TYPE OF LETTER: NOT APPROVABLE - MINOR

C. CC Block

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ANDA DUP
DIV FILE
Field Copy

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 201-050 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Phenoxybenzamine Hydrochloride Capsules USP, 10mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide current room temperature stability data.

2. The labeling information submitted in the application is being reviewed by Labeling Division and Program Support. Any deficiencies found will be communicated to you under a separate cover.

3. The information submitted to the Division of Bioequivalence is under review. Any deficiencies found will be communicated to you under a separate cover.

4. The firms referenced in your ANDA relative to the manufacturing and testing of the drug substance and the product must be in compliance with the cGMP's at the time of approval.

Sincerely yours,

Paul Schwartz, Ph. D.
Acting Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

B. Endorsement Block
HFD-623/RD'Costa, Ph.D./06/11/10
HFD-623/AMueller, Ph.D. /06/11/10
HFD-617/Doan Dat, PM./06/11/10
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F/T by/:

TYPE OF LETTER: NOT APPROVABLE – MINOR
.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201050	ORIG-1	ROXANE LABORATORIES INC	Phenoxybenzamine Hydrochloride

---

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

/s/

ROSARIO F D COSTA
06/21/2010
ANDA #201050 is not approvable.

ALBERT J MUELLER
06/21/2010

DAT T DOAN
06/22/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201050

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE
ACCEPTABLE OSI INSPECTION REPORT REVIEW

ANDA No.	201050
Drug Product Name	Phenoxybenzamine Hydrochloride Capsules USP
Strength(s)	10 mg
Applicant Name	Roxane Laboratories, Inc.
Original Submission Date(s)	December 7, 2009
Date of Report	July 8, 2009 (clinical site though NDA 022456), NAI April 4, 2012 (analytical site through this ANDA 201050), NAI
Reviewer	Teresa Ramson, Pharm.D.
Clinical Site/Address	CEDRA Clinical Research, LLC 2455 N.E. Loop 410, Suite 150 San Antonio, Texas 78217
Analytical Site/Address	(b) (4)
OUTCOME DECISION	**ADEQUATE**

EXECUTIVE SUMMARY

The Office of Scientific Investigations (OSI) inspection reports of clinical and analytical site was received by the Division of Bioequivalence and found acceptable. The clinical site inspection for CEDRA Clinical Research, LLC at 2455 N.E. Loop 410, Suite 150 San Antonio, Texas 78217, was requested for NDA 022456 and was found to be NAI. The analytical site inspection for (b) (4) was requested for ANDA 201050 and was found to be NAI. Given the acceptable inspection of the sites, the bioequivalence section of the application is now acceptable

COMMENTS:

None

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for in-vivo bioequivalence and in-vitro dissolution testing. The bioequivalence section of the application is acceptable.

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

/s/

TERESA V RAMSON
04/04/2012

AIDA L SANCHEZ
04/04/2012

DIVISION OF BIOEQUIVALENCE REVIEW OF AN AMENDMENT

ANDA No.	201050		
Drug Product Name	Phenoxybenzamine Hydrochloride Capsules USP		
Strength(s)	10 mg		
Applicant Name	Roxane Laboratories, Inc.		
Address	1809 Wilson Road Columbus, Ohio 43228		
Applicant's Point of Contact	Elizabeth Ernst		
Contact's Telephone Number	614-272-4785		
Contact's Fax Number	614-276-2470		
Original Submission Date(s)	December 7, 2009 November 18, 2010 (Telephone Amendment)		
Submission Date(s) of Amendment(s) Under Review	February 8, 2011 March 21, 2011		
Reviewer	Suman Dandamudi		
Study Number (s)	PHEN-C10-PVFS-1		
Study Type (s)	Fasting		
Strength (s)	10 mg		
Clinical Site	CEDRA Clinical Research, LLC		
Clinical Site Address	2455 N.E. Loop 410, Suite 150 San Antonio, Texas 78217		
Analytical Site	(b) (4)		
Analytical Site Address			
OVERALL REVIEW RESULT	**INADEQUATE***		
WAIVER REQUEST RESULT	**N/A**		
DSI REPORT RESULT	**INADEQUATE***		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**DISSOLUTION**	**10 MG**	**ADEQUATE**
1	**FASTING STUDY**	**10 MG**	**INADEQUATE***

***Pending a For Cause DSI inspection requested for the current ANDA**

1 EXECUTIVE SUMMARY

The submission references NDA 008708, Dibenzyline® (Phenoxybenzamine Hydrochloride) Capsules, 10 mg from Wellspring Pharmaceuticals.

Roxane laboratories submitted its responses to the deficiency comments made by the Division of Bioequivalence (DBE) in the letter dated January 5, 2011. In the original application, the firm submitted the results of fasting bioequivalence study comparing its Phenoxybenzamine Hydrochloride Capsules, 10 mg, to the Wellspring Pharmaceutical's, Dibenzyline® (Phenoxybenzamine Hydrochloride) Capsules, 10 mg.

However, the fasting BE study was found **incomplete** due to deficiencies based on the DSI inspection of the analytical site. The analytical site was inspected for ANDA 079218 (for cause) on (b) (4) and the outcome was (b) (4). After the evaluation of the DSI inspection report for ANDA 079218, the DBE determined that the DSI's findings may have an impact on fasting BE study of the current ANDA 201050. The firm was asked to address the DBE concerns related to the DSI's findings.

In this amendment the firm submitted its responses for the objectionable DSI findings. (b) (4) (b) (4) **Based on the firm's responses, the DBE requests a For Cause DSI inspection** (b) (4)

The firm has conducted acceptable comparative dissolution testing on Phenoxybenzamine Capsules using the USP-recommended dissolution method (**DARRTS: WILLIAMS, ZAKIA R 05/26/2010 N/A 05/26/2010 REV-BIOEQ-02(Dissolution Review) Original-1 (Not Applicable) Archive**).

DSI Inspections:

The clinical site was inspected for NDA 022456 (routine) on 7/8/2009 and the outcome was NAI. The analytical site was inspected for NDA 022456 (routine) on (b) (4) and the outcome was (b) (4). The Clinpharm review of the DSI inspection report [**MADA, SRIPAL R 07/08/2009 N/A 07/08/2009 REV-CLINPHARM-01(General Review) Original-1 (Type 3 New Dosage Form and Type 4 New Combination) Archive**] does not have items that would apply to the integrity of the analytical data submitted in this ANDA.

The analytical site was inspected for ANDA 079218 (for cause) on (b) (4) and the outcome was (b) (4) [**DARRTS: KWON, HYOJONG 07/21/2010 N/A 07/21/2010 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 Archive**]. After the evaluation of the DSI inspection report for ANDA 079218, the DBE determined that the DSI's findings may have an impact on fasting BE study of the

current ANDA 201050. The firm was asked to address the DBE concerns related to the DSI's findings **DARRTS for ANDA 201050- DANDAMUDI, SUMAN 12/22/2010 N/A 12/22/2010 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive]**. The firm responded to the DSI-related deficiencies in the current amendment. Based on the firm's responses, the DBE requests a For Cause DSI inspection (b) (4)

During the time of reviewing, the reviewer found that the analytical site is also inspected for ANDA 202144 (Routine) on (b) (4) and the outcome was (b) (4) **[DARRTS: RAHA, ABHIJIT 06/08/2011 N/A 06/08/2011 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Not Applicable)].** This review also contains the evaluation of a Division of Scientific Investigations (DSI) inspection report for A**NDA 202144** and its **impact** on the fasting bioequivalence (BE) study of the current **ANDA 201050.**

A For Cause Division of Scientific Investigations (DSI) inspection is being requested for the analytical site.

The application is **incomplete (inadequate).**

2 TABLE OF CONTENTS

3 BACKGROUND INFORMATION

1. Roxane Laboratories has submitted ANDA 201050 for its product, Phenoxybenzamine Hydrochloride Capsules, 10 mg. The submission references NDA 008708, Dibenzyline® (Phenoxybenzamine Hydrochloride) Capsules, 10 mg from Wellspring Pharmaceuticals.

2. DBE had done a **"dissolution only"** review on this ANDA [**DARRTS: WILLIAMS, ZAKIA R 05/26/2010 N/A 05/26/2010 REV-BIOEQ-02(Dissolution Review) Original-1 (Not Applicable) Archive].** The firm conducted its dissolution testing using the USP- recommended dissolution method. The firm's data met the USP recommended specification of NLT 75% (Q) in 45 minutes at S1 level. The dissolution testing was found to be acceptable.

3. The firm, in its original application, also submitted the fasting bioequivalence study comparing its Phenoxybenzamine Capsules, 10 mg, to the Wellspring Pharmaceutical's, Dibenzyline® (Phenoxybenzamine Hydrochloride) Capsules, 10 mg. The fasting BE study was found **incomplete** due to deficiencies based on the DSI inspection of the analytical site **[DARRTS: DANDAMUDI, SUMAN 12/22/2010 N/A 12/22/2010 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive]**.

4. In the current amendment, the firm submitted its response to the objectionable DSI findings of the analytical site.

4 SUBMISSION SUMMARY

A. Drug Product Information, PK/PD Information, and Relevant DBE History

See the review of the original submission in **DARRTS for ANDA 201050-DANDAMUDI, SUMAN 12/22/2010 N/A 12/22/2010 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive.**

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	2

C. Review of Submission

Following the inspection of the analytical site, (b) (4) (b) (4) by the Division of Scientific Investigations (DSI) for bioequivalence (BE) study from another application, Form FDA- 483 was issued for the site. Subsequently, the analytical site provided its response to Form 483 and this response was included in the final evaluation by the DSI, which recommended that the inspected study be considered unacceptable based on the DSI original findings and the site's response.

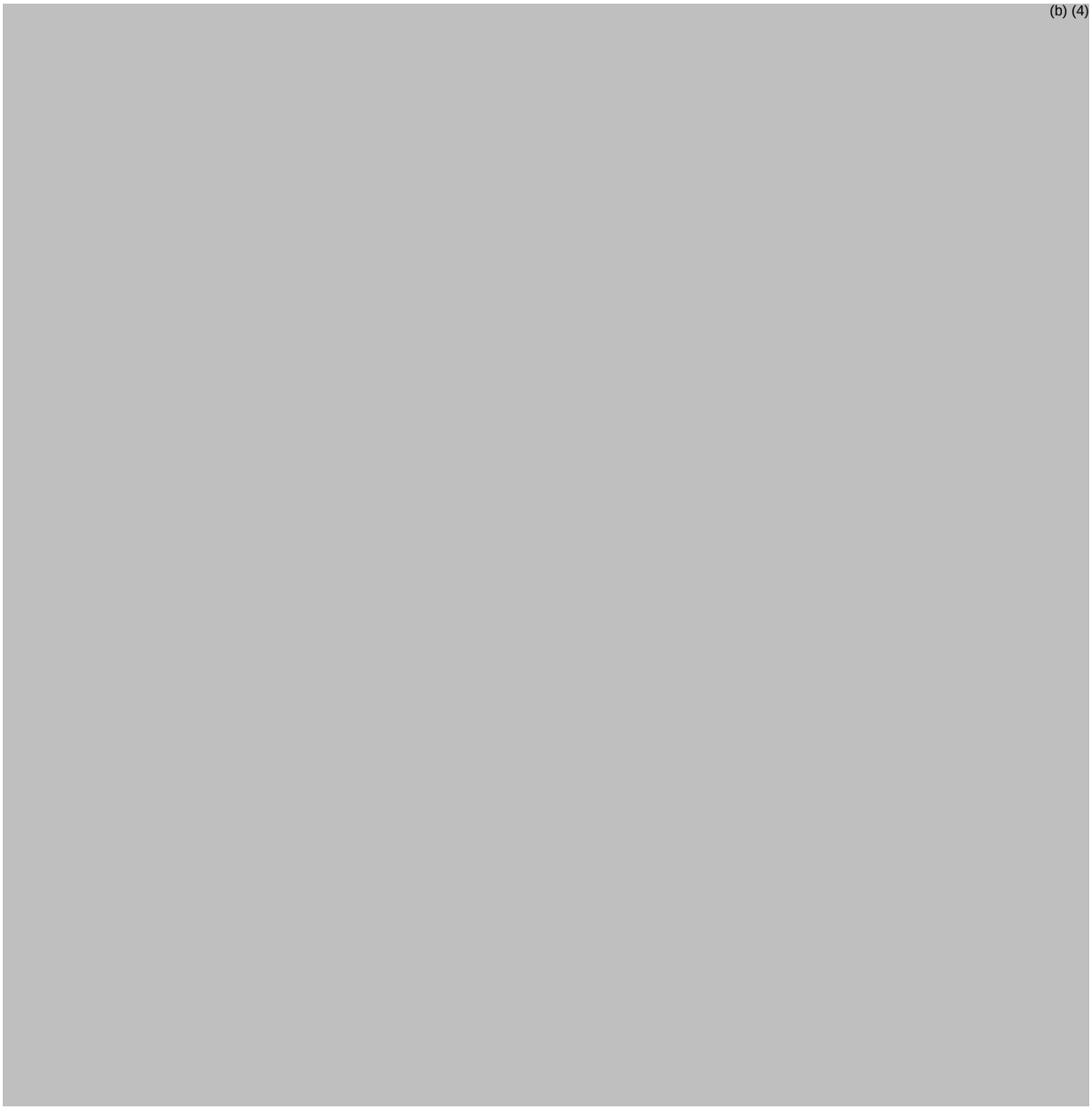
(b) (4)

Following this page, 9 Pages Withheld in Full as (b)(4)

D. DSI Report

DSI Report pertaining to ANDA 202144

DSI conducted an audit of the analytical portion (b) (4) of the BE studies for ANDA 202144 and following the inspection a form 483 was issued to the (b) (4) (b) (4) The analytical site of ANDA 202144 is same as the analytical site of the current application. The outcome of the DSI inspection of the analytical site for ANDA 202144 (Routine) was (b) (4) [**DARRTS: RAHA, ABHIJIT 06/08/2011 N/A 06/08/2011 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Not Applicable) Archive**].



(b) (4)

E. Deficiency Comments

The firm's (b) (4) responses to the DSI-inspection related deficiencies are inadequate. Therefore, the DBE requests that the DSI conduct a For Cause inspection for the BE study of the current ANDA and BE studies of several other ANDAs (e.g., 090482, 200143, (b) (4) The DBE requests that the For Cause inspection focus on the following major concerns:

(b) (4)

F. Recommendations

1. The Division of Bioequivalence finds the **fasting** BE study No. PHEN-C10-PVFS-1 conducted by the Roxane Laboratories, Inc. on its Phenoxybenzamine Hydrochloride Capsules, 10 mg, USP lot # 4000064, comparing it to Wellspring pharmaceutical's Dibenzyline® (Phenoxybenzamine) Capsules, 10 mg, lot 8A3991, **inadequate** pending the results of the requested For Cause inspection mentioned above.

2. The firm's *in vitro* dissolution testing is acceptable. The dissolution testing should be conducted in 500 mL of 0.1 N HCl at 37ºC ± 0.5ºC using USP apparatus I (Basket) at 100 rpm. The test product should meet the following specification:

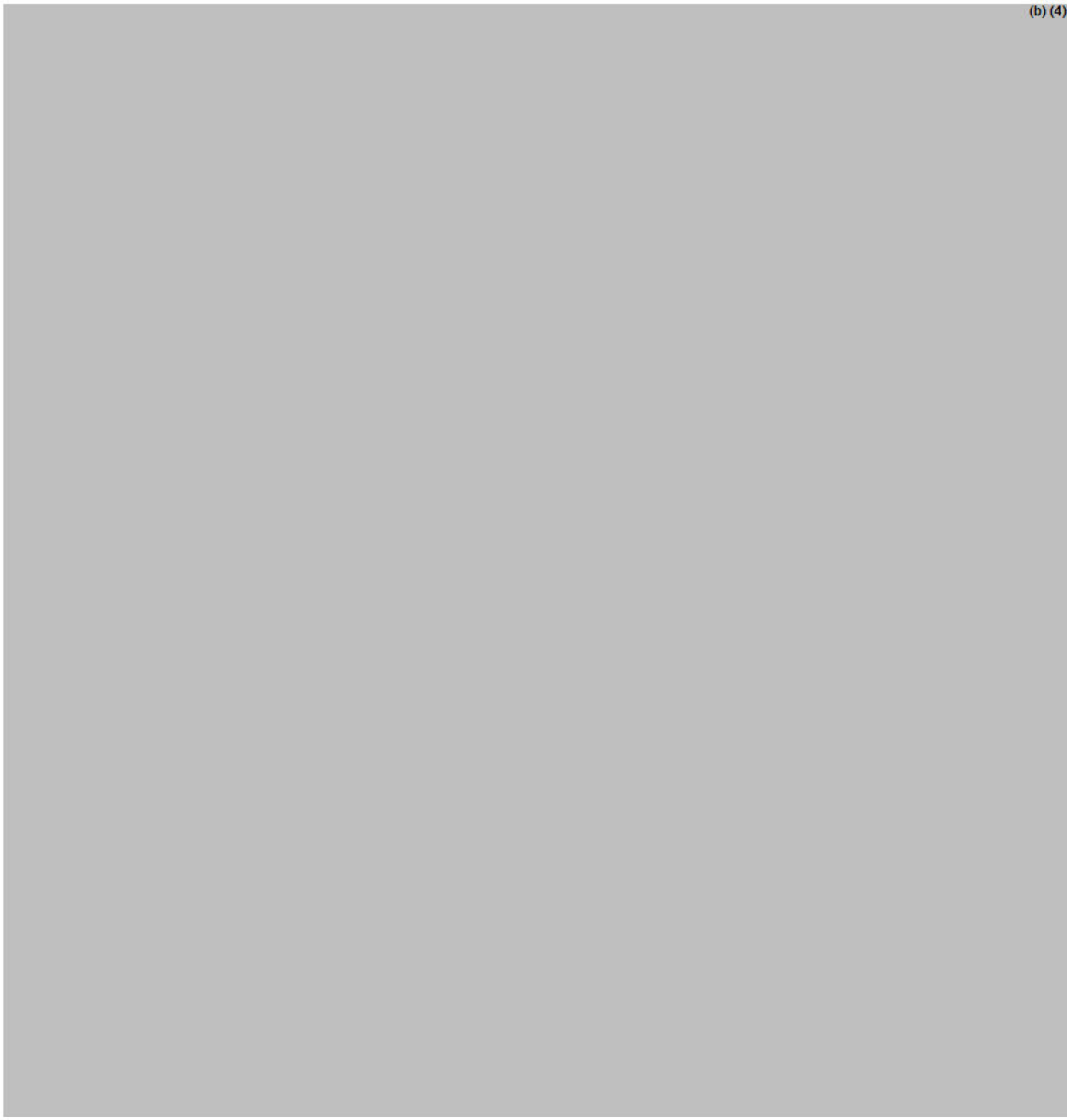
   NLT 75% (Q) of Phenoxybenzamine is dissolved in 45 minutes

G. Comments for Other OGD Disciplines

Discipline	Comment
PMs	Please request a For Cause DSI inspection for the analytical site, as mentioned under the Deficiency Comment section above.

H. Attachments

(b) (4)



Please Don't Send Out the Letter Below Until the For Cause Inspection Requested for the Current ANDA is Completed and Found Acceptable

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 201050

APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Phenoxybenzamine Hydrochloride Capsules USP, 10 mg

The Division of Bioequivalence has completed the review of your submission acknowledged on the cover page and has no further question at this time.

We acknowledge that you will conduct dissolution testing as per the current USP monograph for Phenoxybenzamine Hydrochloride Capsules.

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
Office of Generic Drugs
Center for Drug Evaluation and Research

5 OUTCOME PAGE

ANDA: 201050

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
14626	2/8/2011	Other	Study Amendment	1	1
14626	12/7/2009	Other	DSI Inspection Report	1	1
				Bean Total:	2

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

/s/

SUMAN DANDAMUDI
08/03/2011

SHRINIWAS G NERURKAR
08/04/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
08/04/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	201050		
Drug Product Name	Phenoxybenzamine Hydrochloride Capsules USP		
Strength(s)	10 mg		
Applicant Name	Roxane Laboratories, Inc.		
Address	1809 Wilson Road Columbus, Ohio 43228		
Applicant's Point of Contact	Elizabeth Ernst		
Contact's Telephone Number	614-272-4785		
Contact's Fax Number	614-276-2470		
Original Submission Date(s)	December 7, 2009		
Submission Date(s) of Amendment(s) Under Review	November 18, 2010 (Telephone Amendment)		
Reviewer	Suman Dandamudi		
Study Number (s)	PHEN-C10-PVFS-1		
Study Type (s)	Fasting		
Strength (s)	10 mg		
Clinical Site	CEDRA Clinical Research, LLC		
Clinical Site Address	2455 N.E. Loop 410, Suite 150 San Antonio, Texas 78217		
Analytical Site	(b) (4)		
Analytical Site Address			
OVERALL REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	**N/A**		
DSI REPORT RESULT	**INADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**DISSOLUTION**	**10 MG**	**ADEQUATE**
1	**FASTING STUDY**	**10 MG**	**INADEQUATE**

1 EXECUTIVE SUMMARY

This application contains the results of fasting bioequivalence (BE) study comparing the test product, Phenoxybenzamine Hydrochloride Capsules, 10 mg, to the corresponding reference listed product, Dibenzyline® (Phenoxybenzamine Hydrochloride) Capsules, 10 mg. **As per the publicly available guidance, this drug product needs only a fasting BE study (no fed BE study)**. The BE study was designed as a single-dose, four-way

crossover study in healthy male and female subjects. The results are summarized in the tables below:

Phenoxybenzamine 10 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. PHEN-C10-PVFS-1					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/mL)	2.4275189	2.3936192	1.01	94.385	108.972
AUC∞ (hr *ng/mL)	2.480594	2.4745455	1	92.915	108.152
Cmax (ng/mL)	2.3810764	2.300797	1.03	93.936	114.014

The firm has conducted acceptable comparative dissolution testing on Phenoxybenzamine Capsules using the USP-recommended dissolution method (**DARRTS: WILLIAMS, ZAKIA R 05/26/2010 N/A 05/26/2010 REV-BIOEQ-02(Dissolution Review) Original-1 (Not Applicable) Archive**).

The clinical site was inspected for NDA 022456 (routine) on 7/8/2009 and the outcome was NAI. The analytical site was inspected for NDA 022456 (routine) on (b) (4) and the outcome was (b) (4). The Clinpharm review of the DSI inspection report [**MADA, SRIPAL R 07/08/2009 N/A 07/08/2009 REV-CLINPHARM-01(General Review) Original-1 (Type 3 New Dosage Form and Type 4 New Combination) Archive**] does not have items that would apply to the integrity of the analytical data submitted in this ANDA.

The analytical site was also inspected for ANDA 079218 (for cause) on (b) (4) and the outcome was (b) (4). ANDA 079218 is from Watson Laboratories Inc, for Levonorgestrel and Ethinyl Estradiol Tablets. This review also contains the evaluation of a Division of Scientific Investigations (DSI) inspection report for **ANDA 079218** and its **impact** on the fasting bioequivalence (BE) study of the current **ANDA 201050**. The outcome of the DSI inspection for the analytical site was official action indicated (b) (4) [**DARRTS: KWON, HYOJONG 07/21/2010 N/A 07/21/2010 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 Archive**]. The Form 483 form was issued for analytical site and the DSI recommended the DBE not accept for review of the fasting BE study pertaining to **ANDA 079218**. The DBE reviewed the inspection report on **ANDA 079218** and concurred with DSI's evaluation **[DARRTS: DANDAMUDI, SUMAN 10/31/2010 N/A 10/31/2010 REV-BIOEQ-01(General Review) Original-1 Archive]**.

After the evaluation of the DSI inspection report for ANDA 079218, the DBE determined that the DSI's findings may have an impact on fasting BE study of the current ANDA 201050. The firm is asked to address the DBE concerns related to the DSI's findings. The fasting [PHEN-C10-PVFS-1] BE study, conducted by Roxane Laboratories on its Phenoxybenzamine Hydrochloride Capsules, 10 mg, to the corresponding reference listed product, Dibenzyline® (Phenoxybenzamine Hydrochloride) Capsules, 10 mg, is

considered **incomplete** (**inadequate**) at this time pending the firm's satisfactory response to the deficiencies related to the DSI inspection report of the analytical site.

No Division of Scientific Investigations (DSI) inspection is pending or necessary for clinical site.

The application is **Incomplete (Inadequate).**

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[1, 2]

Test Product	Phenoxybenzamine Hydrochloride Capsules USP, 10 mg
Reference Product	Dibenzyline® (Phenoxybenzamine Hydrochloride) Capsules, 10 mg
RLD Manufacturer	Wellspring Pharm
NDA No.	008708
RLD Approval Date	January 26, 1953
Indication	Dibenzyline is indicated in the treatment of pheochromocytoma, to control episodes of hypertension and sweating.

3.2 PK/PD Information[2, 3]

Bioavailability	Oral absorption of phenoxybenzamine is variable; only about 20—30% of the drug is bioavailable. The onset of action is gradual and extends over a period of several hours after administration of fixed daily doses.
Food Effect	The effect of food on the pharmacokinetics of Dibenzyline® has not been evaluated.
Tmax	The Tmax for current ANDA is 0.7 hrs
Metabolism	Phenoxybenzamine is metabolized by dealkylation to N-phenoxyisopropylbenzylamine
Excretion	Both parent and metabolite are excreted in urine and bile
Half-life	The half-life of orally administered phenoxybenzamine hydrochloride is not known; however, the half-life of intravenously administered drug is approximately 24 hours
Drug Specific Issues (if any)	• Phenoxybenzamine is classified as pregnancy category C. Dibenzyline should be given to pregnant women only if clearly needed. • It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from phenoxybenzamine hydrochloride, 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.

[1] Online-Orange Book (2010). http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
[2] Labeling for the RLD Product.
[3] Online-Clinical Pharmacology (2010). http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=585

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	1, fasting

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-way crossover *in vivo*
	Strength:	10 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

Analytes to measure (in plasma/serum/blood):	The analyte Phenoxybenzamine in plasma
Bioequivalence based on:	(90% CI) Phenoxybenzamine
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations:	Based on Guidance for Industry: Individual product Bioequivalence Recommendations; Jul 2008. http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm089465.pdf
Summary of OGD or DBE History	Currently there are no approved generic products of Phenoxybenzamine Hydrochloride Capsules listed in the Orange Book. This is a first generic application.

3.4 The Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed		
Steady-state		
In vitro dissolution	Yes	1
Waiver requests		
BCS Waivers		
Clinical Endpoints		
Failed Studies		
Amendments		

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data	Data
Bioanalytical method validation Report location	Determination of Phenoxybenzamine in Human EDTA Plasma by LC-MS-MS	Determination of Phenoxybenzamine in Human EDTA Plasma by LC-MS-MS
Analyte	Phenoxybenzamine	Phenoxybenzamine
Internal standard (IS)	(b) (4)	(b) (4)
Method description	(b) (4): Solid-phase extraction; (b) (4) LC-MS-MS; (b) (4)	(b) (4): Solid-phase extraction; (b) (4) LC-MS-MS; (b) (4)
Limit of quantitation	0.0250 ng/mL	0.0250 ng/mL
% recovery (and %CV) at each concentration tested	0.0250 ng/mL- 77.22, %CV- 1.19 0.250 ng/mL- 84.12, %CV- 3.22 5.0 ng/mL- 85.34, %CV- 3.02	-
Average recovery of IS (%)	83.21, %CV- 8.14	-
Standard curve concentrations (units/mL)	0.0250 to 5.0 ng/mL	0.0250 to 15.0 ng/mL
QC concentrations (units/mL)	0.0750, 1.00, 4.00 ng/mL	0.0750, 3.00, 12.0 ng/mL
QC Intraday precision range (%)	1.9-10.7	2.0 to 2.8
QC Intraday accuracy range (%)	-2.4 to 14.6	-10.8 to -2.5
QC Interday precision range (%)	3.9 to 6.0	-
QC Interday accuracy range (%)	-0.3 to 2.9	-
Bench-top stability (hrs)	24 hours @ room temperature	24 hours @ room temperature
Stock stability (days)	-	40 days @ 4°C; 19 hours @ room temperature
Processed stability (hrs)	113 hours @ room temperature	166 hours @ room temperature
Freeze-thaw stability (cycles)	5 cycles	9 cycles
Long-term storage stability (days)	102 days @ -20°C and -70°C	47 days @ -20°C; 51 days @ -70°C

Dilution integrity	25.0 ng/mL diluted 10-fold	75.0 ng/mL diluted 10-fold
Selectivity	No interfering peaks found in blank plasma samples	No interfering peaks found in blank plasma samples

SOPs submitted	Yes
Bioanalytical method is acceptable	Acceptable

Comments on the Pre-Study Method Validation:

- The long term storage data of 47 days exceed the storage period for the samples of the fasted (43 days) BE study.
- The firm used K3EDTA as anticoagulant in their fasting BE study. So they conducted pre-study and with-in study validation using plasma containing K3EDTA as the matrix. The calibration standards and quality control samples were prepared with human plasma containing K3EDTA.
- In the telephone amendment dated November 18, 2010, the firm confirmed that K3 EDTA was used in the pre-study method validation. Also the long term storage stability data of 47 days at -20°C and 51 days at -70°C was conducted using plasma containing K3EDTA as the matrix.
- The firm listed the results of "Dilution integrity" of 75 ng/mL in the above summary table but did not provide the data. However dilution integrity data of 25 ng/mL is sufficient to cover the sample dilution conducted for fasted study sample analyses.
- The pre-study validation data are acceptable.

3.6 In Vivo Studies

Table 1. Summary of all *in vivo* Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (%CV)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng*hour/mL)	AUC_{∞} (ng*hour/mL)	$T½$ (hr)	K_{el} (hr-1)	
PHEN-C10-PVFS-1	A Single Dose, 2-Treatment, 4-Period, Replicate Design Bioequivalence Study of Phenoxybenzamine Hydrochloride Capsules, 10 mg Under Fasted Conditions	Open-Label, Randomized, 2-Treatment, 4-Period Replicate Study (Fasted)	**Test product** Oral Phenoxybenzamine Capsules, 10 mg, Roxane Lot No. 4000064 Exp. Date N/A	39 Healthy Male and Female subjects Male- 20 Female- 19 Mean age: 28 Years (Range= 18-45)	Mean= 2.82 %CV= 61.40	Mean= 0.50 Range= 0.33-5.00	Mean= 2.87 %CV= 61.66	Mean= 2.34 %CV= 56.26	Mean= 1.05 %CV= 94.93	Mean= 0.9378 %CV= 47.72	**Module 5.3**
			Ref. Product Oral Dibenzyline® (Phenoxybenzamine Hydrochloride) Capsules, 10 mg, Wellspring Pharm Lot No. 8A3991 Exp. Date:		Mean= 2.80 %CV= 72.69	Mean= 0.50 Range= 0.33-2.50	Mean= 2.84 %CV= 61.84	Mean= 2.49 %CV= 57.20	Mean= 1.04 %CV= 85.16	Mean= 0.4458 %CV= 47.02	

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Phenoxybenzamine 10 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. PHEN-C10-PVFS-1					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/mL)	2.4275189	2.3936192	1.01	94.385	108.972
AUC∞ (hr *ng/mL)	2.480594	2.4745455	1	92.915	108.152
Cmax (ng/mL)	2.3810764	2.300797	1.03	93.936	114.014

Table 3. Reanalysis of Study Samples

Fasted Study, Study No. PHEN-C10-PVFS-1 Additional Information is in the Bioanalytical report provided in section 5.3 of this ANDA								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0.0	0.0	0.0%	0.0%	0.0	0.0	0.0%	0.0%
Extraction Error	7	12	0.37%	0.64%	7	12	0.37%	0.64%
No Peaks Detected	0	1	0.0%	0.05%	0	1	0.0%	0.05%
Poor Chromatography	2	2	0.10%	0.11%	2	2	0.10%	0.11%
Technical error	0	1	0.0%	0.05%	0	1	0.0%	0.05%
Total	9	16	0.470%	0.86%	9	16	0.470%	0.86%

Did use of recalculated plasma concentration data change study outcome?

There is no pK reassy. The firm reassayed the study samples because of the analytical reasons. The SOP's of sample re-analysis were provided and are acceptable.

3.7 Formulation

Location in appendix	Section 4.2, Formulation Data
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	**Acceptable**
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	WILLIAMS, ZAKIA R 05/26/2010 N/A 05/26/2010 REV-BIOEQ-02(Dissolution Review) Original-1 (Not Applicable) Archive
Source of Method (USP, FDA or Firm)	USP
Medium	0.1 N HCl
Volume (mL)	500 mL
USP Apparatus type	I (Basket)
Rotation (rpm)	100 rpm
DBE-recommended specifications	NLT 75% (Q) in 45 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly Dissolving
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	

Reviewer's notes:

DBE had done earlier "Dissolution Only Review" for the test product, 10 mg and found the following:

There is a USP method for this product. The firm conducted its dissolution testing using the USP- recommended dissolution method. The firm's data met the USP recommended specification of NLT 75% (Q) in 45 minutes at S1 level. The dissolution testing was found to be acceptable **[DARRTS: WILLIAMS, ZAKIA R 05/26/2010 N/A 05/26/2010 REV-BIOEQ-02(Dissolution Review) Original-1 (Not Applicable) Archive].**

3.9 Waiver Request(s)

Strengths for which waivers are requested	N/A
Proportional to strength tested *in vivo*?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	N/A
If not then why?	

3.10 DSI Report

DSI Report Pertaining to NDA 022456

DSI conducted an audit of the analytical portion (b) (4) of the BE study for NDA 022456 and following the inspection a form 483 was issued to the (b) (4) (b) (4) The analytical site of NDA 022456 is same as the analytical site of the current application. The outcome of the DSI inspection of the analytical site for NDA 022456 (routine) was (b) (4)

(b) (4)

Following this page, 1 Page Withheld in Full as (b)(4)

[Note: The applicant of the ANDA 079218 is Watson Laboratories and the applicant for the current ANDA 201050 is Roxane Laboratories].

3.11 Deficiency Comments

(b) (4)

The firm is asked to address the concerns related to the DSI inspection report mentioned above. The BE study is therefore considered inadequate at this time pending the firm's adequate response to the concerns.

3.12 Recommendations

1. The Division of Bioequivalence finds the **fasting** BE study No. PHEN-C10-PVFS-1 conducted by the Roxane Laboratories, Inc. on its Phenoxybenzamine Hydrochloride Capsules, 10 mg, lot # 4000064, comparing it to Wellspring pharmaceutical's Dibenzyline® (Phenoxybenzamine) Capsules, 10 mg, lot 8A3991, incomplete due to deficiencies mentioned above.

2. The firm's *in vitro* dissolution testing is acceptable. The dissolution testing should be conducted in 500 mL of 0.1 N HCl at 37°C ± 0.5°C using USP apparatus I (Basket) at 100 rpm. The test product should meet the following specification.

   NLT 75% (Q) of Phenoxybenzamine is dissolved in 45 minutes

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 4 Study Information

Study Number	PHEN-C10-PVFS-1
Study Title	A Single-Dose, Two-Treatment, Four-Period, Replicate Design Bioequivalence Study of Phenoxybenzamine Hydrochloride 10 mg Capsules Under Fasted Conditions
Clinical Site (Name & Address)	CEDRA Clinical Research, LLC 2455 N.E. Loop 410, Suite 150 San Antonio, Texas 78217 210.635.1500
Principal Investigator	Mark T. Leibowitz, MD
Dosing Dates	Period 1: 08/21/2009 Period 2: 08/28/2009 Period 3: 09/04/2009 Period 4: 09/11/2009
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	09/16/2009 through 10/03/2009
Analytical Director	(b) (6), BS
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	43 days

Table 5. Product information

Product	**Test**	**Reference**
Treatment ID	A	B
Product Name	Phenoxybenzamine Hydrochloride Capsules USP	Dibenzyline® Capsules USP
Manufacturer	BIRI	WellSpring Pharmaceuticals
Batch/Lot No.	4000064	8A3991
Manufacture Date	7/15/2009	
Expiration Date	-	January 2011
Strength	10 mg	10 mg

Dosage Form	Capsules	Capsules
Bio-Batch Size	(b) (4) Capsules	
Production Batch Size	(b) (4) Capsules	
Potency (Assay)	98.7%	97.5%
Content Uniformity (mean, %CV)	$AV_{n=30} = 12.9$	N/A
Dose Administered	1 x 10 mg	1 x 10 mg
Route of Administration	Oral	Oral

As per USP <905> Maximum Allowed Acceptance Value L1=15

Comments:

- The potency of the reference product is listed as 97.5% in the above biosummary table. However in the Certificate of Analysis provided by the firm for the reference product, the potency of the reference product is shown as 98.2%.

- The certificate of Analysis of the reference product does not contain content Uniformity test.

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	48 Enrolled and Dosed 39 Completed
No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	BABA: 201, 203, 204, 208, 211, 212, 213, 214, 216, 220, 221, 223, 226, 227, 230, 232, 234, 236, 239, 240, 242, 244, 247, 248 ABAB: 202, 205, 206, 207, 209, 210, 215, 217, 218, 219, 222, 224, 225, 228, 229, 231, 233, 235, 237, 238, 241, 243, 245, 246
Blood Sampling Times	Predose, 10, 20, 30 and 45 minutes and 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 24.0, 36.0 and 48.0 hours post-dose
Blood Volume Collected/Sample	5 mL
Blood Sample Processing/Storage	Blood samples were collected by direct venipuncture using pre-labeled vacutainers containing K3 EDTA as the anticoagulant. After blood collection, tubes were centrifuged at 3000 rpm for 10 minutes at 4° C to separate plasma. The plasma from each vacutainer was divided into duplicate propylene tubes containing 250 µL of 1.0 M HCl. Plasma samples were immediately frozen at -70° C for storage and transferred to analytical lab for analysis.
IRB Approval	Approved on 07/22/2009
Informed Consent	Yes
Length of Fasting	Ten hours prior to dosing and additional 4 hours after dosing
Length of Confinement	Previous day of dosing until after the 48 hour blood collection
Safety Monitoring	Adverse events were collected and reports were tabulated. The vital signs were measured throughout the study.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. PHEN-C10-PVFS-1			
		Treatment Groups	
		Test Product N=39	Reference Product N=39
Age (years)	Mean ± SD	28 ± 8	28 ± 8
	Range	18-45	18-45
Age Groups	< 18	0 (0.0%)	0 (0.0%)
	18 – 40	35 (89.74 %)	35 (89.74 %)
	41 – 64	4 (10.26%)	4 (10.26%)
	65 – 75	0 (0.0%)	0 (0.0%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	Male	20 (51.28 %)	20 (51.28 %)
	Female	19 (48.72%)	19 (48.72%)
Race	Asian	0 (0.0%)	0 (0.0%)
	Black	7 (17.95%)	7 (17.95%)
	Caucasian	31 (79.49%)	31 (79.49%)
	Hispanic	0 (0%)	0 (0%)
	Other	1 (2.56%)	1 (2.56%)
BMI (Kg/m^2)	Mean ± SD	25.4 ± 2.5	25.4 ± 2.5
	Range	21.2- 29.7	21.2- 29.7
Height (cm)	Mean ± SD	169.4 ± 9.9	169.4 ± 9.9
	Range	151.0 - 190.0	151.0 - 190.0
Weight (kg)	Mean ± SD	73.2 ± 12.1	73.2 ± 12.1
	Range	57.4 - 101.4	57.4 - 101.4

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
202	Subject withdrew consent due to personal reasons prior to period 2 check in.	2	N/A
204	Subject was withdrawn for protocol non-compliance: positive urine cotinine at period 2 check in.	2	N/A
208	Subject withdrew consent due to personal reasons prior to period 2 check in.	2	N/A
216	Subject withdrew consent due to personal reasons prior to period 4 check in.	4	N/A
219	Subject was withdrawn by the investigator due to inability to obtain blood draws during period 1.	1	N/A
231	Subject was withdrawn by the investigator due to out of range vital signs during period 3	3	N/A
232	Subject was withdrawn by the investigator due to out of range vital signs during period 3	3	N/A
239	Subject withdrew consent due to personal reasons prior to period 2 check in.	2	N/A
243	Subject was withdrawn by the investigator due to out of range vital signs during period 3	3	N/A

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups Study No. PHEN-C10-PVFS-1	
	Test	Reference
Atypical chest pain	1 (2%)	0 (0%)
Chills	0 (0%)	1 (2%)
Dizziness	2 (5%)	0 (0%)
Dyspepsia	0 (0%)	1 (2%)
Fatigue	1 (2%)	0 (0%)
Headache	3 (7%)	0 (0%)
Headache - intermittent	0 (0%)	1 (2%)
Nausea	3 (7%)	2 (4%)
Pain- left arm	1 (2%)	0 (0%)
Pain- right arm	1 (2%)	0 (0%)
Pallor	1 (2%)	0 (0%)
Paresthesia of fingers, left hand	1 (2%)	0 (0%)
Rhinitis	0 (0%)	1 (2%)
Vasovagal reaction	1 (2%)	0 (0%)

Total	9 (20%)	3 (7%)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Fasting Study No. PHEN-C10-PVFS-1		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Period 1: Subject did not complete the study.	219	-
Period 1 Sample Collection: Samples not collected at the protocol specified timepoints. Samples collected 2 minutes early to 15 minutes late.	205, 207, 209, 215, 217, 218, 222, 233, 238, 241, 243, 245	203, 211, 212, 213, 214, 220, 221, 226, 227, 230, 234, 240, 242, 247, 248
Period 1 Sample Processing: Samples not processed per protocol requirements.	235	230
Period 1 Meal Consumption: Subject did not consume entire meal on Day 1.	225	226
Period 1 Meal Consumption: Subject did not consume entire meal on Day 2.	202, 210	226, 230
Period 2: Subject did not complete the study.	204, 208, 239	202
Period 2 Sample Collection: Samples not collected at the protocol specified timepoints. Samples collected 1 to 9 minutes late or were not collected.	201, 212, 216, 220, 221, 227, 248	205, 206, 207, 209, 210, 214, 215, 217, 218, 222, 224, 225, 228, 231, 232, 233, 238, 243
Period 2: Subject did not dose, but were allowed to continue in the study by the sponsor.	214, 232	210, 222, 225, 228, 231
Period 2 Meal Consumption: Subject did not consume entire meal on Day 8.	230	-
Period 2 Meal Consumption: Subject did not consume entire meal on Day 9.	226	-
Period 3: Subject did not complete the study.	231, 243	232
Period 3 Sample Collection: Samples not collected at the protocol specified timepoints. Samples collected 1 to 10 minutes late.	207, 209, 210, 215, 217, 222, 233, 235, 237, 238, 246	201, 214, 220, 221, 240, 247, 248
Period 3: Subject's predose vital signs were not in range and subject was allowed to dose.	235	-
Period 3 Meal Consumption: Subject did not consume entire meal on Day 15.	-	226
Period 3 Meal Consumption: Subject did not consume entire meal on Day 16.	224	230
Period 4: Subject did not complete the study.	216	
Period 4 Sample Collection: Samples not collected at the protocol specified timepoints. Samples collected 1 to 37 minutes late.	212, 221, 236, 240, 242, 244, 248	207, 209, 215, 217, 222, 224, 229, 233, 235, 241, 246
Period 4: Subject's predose vital signs were not in range and subject was allowed to dose.	-	225
Period 4 Meal Consumption: Subject did not consume entire meal on Day 23.	212	210, 217, 224
Period 4 Vital Signs: Vital signs not performed per	-	205

protocol requirements.		

Comments on Dropouts/Adverse Events/Protocol Deviations:

- All adverse events were mild to moderate in intensity. There is no strong evidence suggesting that the test drug caused substantially more serious adverse events compared to the reference drug

- There were some blood sampling deviations during fasting bioequivalence study. However, these sampling time deviations occurred in less than 10% of the nominal time points, thus are considered to be insignificant by the reviewer. The sample time deviations did not compromise the outcome of the BE study. The firm used actual sampling times for its PK calculation.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. – PHEN-C10-PVFS-1 Phenoxybenzamine									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	0.0250	0.0500	0.200	0.500	2.00	5.00	10.0	13.5	15.0
Inter day Precision (%CV)	2.9	5.9	5.6	3.2	3.9	2.6	3.9	3.7	3.9
Inter day Accuracy (%Actual)	99.2	100.6	102.5	101.8	100.5	101.2	98.8	97.8	98.0
Linearity	0.9925 to 1.0000								
Linearity Range (ng/mL)	0.0250 to 15.0								
Sensitivity/LOQ (ng/mL)	0.0250								

Parameter	**Quality Control Samples**				
Concentration (ng/mL)	0.0750	0.750	1.50	3.00	12.0
Inter day Precision (%CV)	6.5	7.0	7.1	8.2	6.8
Inter day Accuracy (%Actual)	104.7	103.5	103.3	100.3	97.5

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)	(b) (4)	Biological Fluid Assay – Study Sample Analysis

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	There is no PK repeat
Does the reviewer agree with the outcome of the repeat assays?	
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

Acceptable

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters- Reviewer Calculated

Mean plasma concentrations are presented in Table 18 and Figure 1.

Replicate 1

Fasting Bioequivalence Study, Study No. PHEN-C10-PVFS-1									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *ng/ml)	3.00	60.20	0.66	7.67	2.86	68.85	0.47	9.37	1.05
AUC∞ (hr *ng/ml)	3.06	61.75	0.70	7.78	2.89	69.54	0.51	9.44	1.06
Cmax (ng/ml)	2.95	64.54	0.67	9.11	2.68	78.04	0.59	11.60	1.10
Tmax* (hr)	0.74		0.33	5.00	0.72		0.33	2.50	1.02
Kel (hr^{-1})	0.85	33.17	0.23	1.36	0.85	33.50	0.21	1.40	1.01
T1/2 (hr)	0.93	49.00	0.51	3.04	0.97	58.22	0.50	3.34	0.96

Tmax values are presented as median, range.

Replicate 2

Fasting Bioequivalence Study, Study No. PHEN-C10-PVFS-1									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	2.73	63.71	0.76	9.74	2.82	55.24	0.62	8.97	0.97
AUC∞ (hr *ng/ml)	2.59	51.29	0.78	5.60	2.87	55.62	0.66	9.07	0.90
Cmax (ng/ml)	2.71	57.47	0.82	6.80	2.90	69.57	0.51	11.50	0.93
Tmax* (hr)	0.58		0.33	2.00	0.70		0.50	1.75	0.83
Kel (hr^{-1})	0.92	31.58	0.38	1.56	0.91	35.39	0.30	1.83	1.02
T1/2 (hr)	0.84	38.21	0.44	1.82	0.89	46.20	0.38	2.30	0.95

Tmax values are presented as median, range.

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Phenoxybenzamine 10 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. PHEN-C10-PVFS-1				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (ng *hr/mL)	2.43	2.40	101.37	94.45- 108.81
AUC∞ (ng *hr/mL)	2.27	2.27	99.80	92.17- 108.05
Cmax (ng/mL)	2.37	2.32	102.33	93.03- 112.57

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Phenoxybenzamine 10 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. PHEN-C10-PVFS-1					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/mL)	2.4275189	2.3936192	1.01	94.385	108.972
AUC∞ (hr *ng/mL)	2.480594	2.4745455	1	92.915	108.152
Cmax (ng/mL)	2.3810764	2.300797	1.03	93.936	114.014

Table 17. Additional Study Information, Fasting Study No. PHEN-C10-PVFS-1

Root mean square error, AUC0-t	See variances in SAS Output Section
Root mean square error, AUC∞	See variances in SAS Output Section

Root mean square error, Cmax	See variances in SAS Output Section	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	21(firm) 36 (Reviewer)	24 (firm) 34 (Reviewer)
Do you agree or disagree with firm's decision?	No	No
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Comments on Pharmacokinetic and Statistical Analysis:

- The number of subjects who completed the study are:

Replicate	Treatment A	Treatment B
1	40	37
2	39	40

Forty-eight subjects were enrolled and 39 subjects completed all four periods, one subject completed three of the four periods, one subject completed two of the four periods and seven subjects only completed one period. The firm stated that the samples from 41 subjects that completed two or more periods were analyzed. The protocol for the clinical study clearly states that "Samples from all subjects who complete at least 2 periods (one of which must include the reference product) will be analyzed." Since 41 subjects completed at least 2 periods of the study, so the firm analyzed samples from 41 subjects.

- The firm excluded the following subjects for the calculation of Kel and AUCi.

Period	Treatment A	Treatment B
1	207, 210, 228, 235, 245, 246	203, 213, 220, 221, 227
2	203, 211, 213, 216, 220, 226, 227, 240, 247	241, 246
3	225, 233, 246	203, 213, 220, 221, 227
4	213, 220, 221, 226, 227, 247	205, 206, 207, 225, 233, 235, 246

After checking the data, the reviewer excluded only following subjects for the calculation of Kel and AUCi. A review of ln/linear concentration vs time profiles of these subjects indicates the Ke cannot be estimated from the terminal portion of the curve. So the reviewer excluded the following subjects from Kel and AUCi analysis.

Period	Treatment A	Treatment B
1	-	203, 213
2	211, 213	-
3	-	213, 220
4	227	225, 246

- The 90% CI's for the least squares geometric means of Ln AUC0-t, Ln AUC∞ and LnCmax calculated by the reviewer agree with the firm's calculations and meet the criteria for BE.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

Incomplete due to the deficiency stated in the Deficiency Section.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study Replicate 1

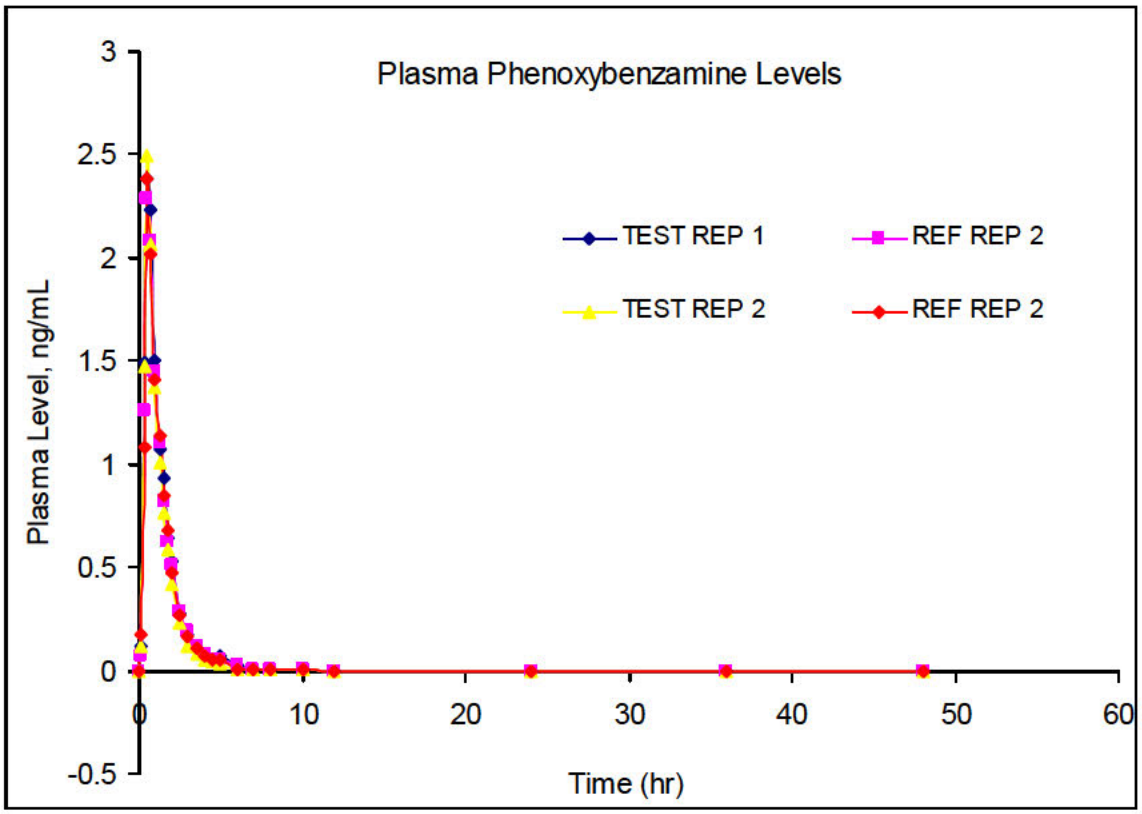
	Treatment A				Treatment B				T/R
Time	Mean	CV%	Min	Max	Mean	CV%	Min	Max	Ratio
C1	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
C2	0.12	155.03	0.00	0.68	0.09	219.48	0.00	0.97	1.35
C3	1.49	106.56	0.04	6.16	1.26	115.45	0.03	6.34	1.19
C4	2.38	82.23	0.29	9.11	2.29	89.42	0.19	11.60	1.04
C5	2.23	66.30	0.57	6.33	2.08	64.49	0.34	6.88	1.07
C6	1.50	71.75	0.37	4.38	1.45	66.52	0.21	5.44	1.04
C7	1.07	77.36	0.28	3.56	1.10	73.09	0.17	4.42	0.98
C8	0.93	88.69	0.18	3.17	0.82	95.30	0.13	4.39	1.14
C9	0.64	88.04	0.04	2.15	0.62	94.55	0.09	3.12	1.05
C10	0.53	95.05	0.09	2.28	0.51	98.65	0.06	2.15	1.04
C11	0.28	94.04	0.05	1.12	0.29	133.53	0.03	2.23	0.95
C12	0.17	105.47	0.00	0.77	0.19	190.04	0.00	2.18	0.89
C13	0.11	158.12	0.00	1.04	0.12	229.57	0.00	1.69	0.95
C14	0.07	171.82	0.00	0.75	0.08	238.66	0.00	1.16	0.91
C15	0.05	197.02	0.00	0.56	0.05	231.11	0.00	0.73	0.98
C16	0.07	393.17	0.00	1.86	0.05	347.73	0.00	1.16	1.37
C17	0.02	235.59	0.00	0.30	0.02	270.61	0.00	0.30	1.10
C18	0.01	193.14	0.00	0.09	0.01	224.88	0.00	0.11	1.00
C19	0.01	183.06	0.00	0.05	0.01	293.55	0.00	0.06	1.55
C20	0.01	193.49	0.00	0.05	0.01	240.77	0.00	0.05	1.20
C21	0.00	454.31	0.00	0.04	0.00	296.55	0.00	0.04	0.48
C22	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
C23	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
C24	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
CMAX	2.95	64.54	0.67	9.11	2.68	78.04	0.59	11.60	1.10

	Treatment A				Treatment B				T/R
Time	Mean	CV%	Min	Max	Mean	CV%	Min	Max	Ratio
TMAX	0.74	99.73	0.33	5.00	0.72	60.47	0.33	2.50	1.02
THALF	0.93	49.00	0.51	3.04	0.97	58.22	0.50	3.34	0.96

Replicate 2:

	Treatment A				Treatment B				T/R
Time	Mean	CV%	Min	Max	Mean	CV%	Min	Max	Ratio
C1	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
C2	0.12	257.04	0.00	1.70	0.17	303.99	0.00	2.86	0.67
C3	1.47	85.19	0.06	6.47	1.08	100.80	0.00	4.95	1.37
C4	2.49	64.26	0.31	6.80	2.38	94.42	0.06	11.50	1.05
C5	2.06	61.18	0.69	6.63	2.02	61.82	0.44	7.22	1.02
C6	1.37	60.81	0.37	4.09	1.41	65.14	0.00	4.15	0.97
C7	1.01	72.38	0.24	3.78	1.14	61.02	0.23	3.13	0.89
C8	0.76	82.26	0.15	3.34	0.85	67.14	0.16	2.26	0.90
C9	0.59	76.60	0.10	2.33	0.68	76.86	0.13	1.97	0.86
C10	0.42	93.38	0.06	1.86	0.47	88.00	0.09	1.88	0.88
C11	0.23	94.09	0.04	0.94	0.27	113.26	0.06	1.76	0.85
C12	0.12	107.26	0.00	0.68	0.16	137.63	0.03	1.30	0.76
C13	0.08	123.98	0.00	0.49	0.11	158.20	0.00	1.00	0.75
C14	0.05	129.44	0.00	0.28	0.07	169.09	0.00	0.69	0.74
C15	0.04	162.92	0.00	0.28	0.05	175.59	0.00	0.54	0.71
C16	0.03	189.60	0.00	0.27	0.05	282.48	0.00	0.83	0.57
C17	0.01	221.28	0.00	0.17	0.01	201.82	0.00	0.15	0.96
C18	0.01	219.13	0.00	0.11	0.01	201.20	0.00	0.07	1.09
C19	0.01	211.61	0.00	0.08	0.01	215.87	0.00	0.06	1.10
C20	0.01	259.20	0.00	0.09	0.01	267.02	0.00	0.13	0.83
C21	0.00	624.50	0.00	0.05	0.00	338.40	0.00	0.08	0.29
C22	0.00	624.50	0.00	0.03	0.00	.	0.00	0.00	.
C23	0.00	624.50	0.00	0.03	0.00	.	0.00	0.00	.
C24	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
CMAX	2.71	57.47	0.82	6.80	2.90	69.57	0.51	11.50	0.93
TMAX	0.58	47.39	0.33	2.00	0.70	42.95	0.50	1.75	0.83
THALF	0.84	38.21	0.44	1.82	0.89	46.20	0.38	2.30	0.95

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.2 Formulation Data

Ingredient	Amount (mg) / Capsule	Amount (%) / Capsule	Functional category
Phenoxybenzamine Hydrochloride USP	10.0	5	Active
Lactose Anhydrous USP			
Colloidal Silicon Dioxide NF			
Sodium Lauryl Sulfate NF			
Sodium Stearyl Fumarate NF			
Capsules, Size #3 (b) (4) Opaque/Red (b) (4) Cap Body Imprinted with 54 036			
Total	**200 mg**	**100.0%**	

(b) (4)

Thus amount of elemental iron ingested based on maximum dose per day is (b) (4) mg/day. This is within FDA limit for elemental iron of 5 mg per day [21 CFR 73.1200(c)].

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

Reviewer's Comments on Formulation:

- The amounts of all inactive ingredients in the tablet are below those used in the approved drug products based on CDER's Inactive Ingredient Guide (IIG) for Approved Drug Products, based on MDD.

- The formulation is acceptable.

4.3 Dissolution Data

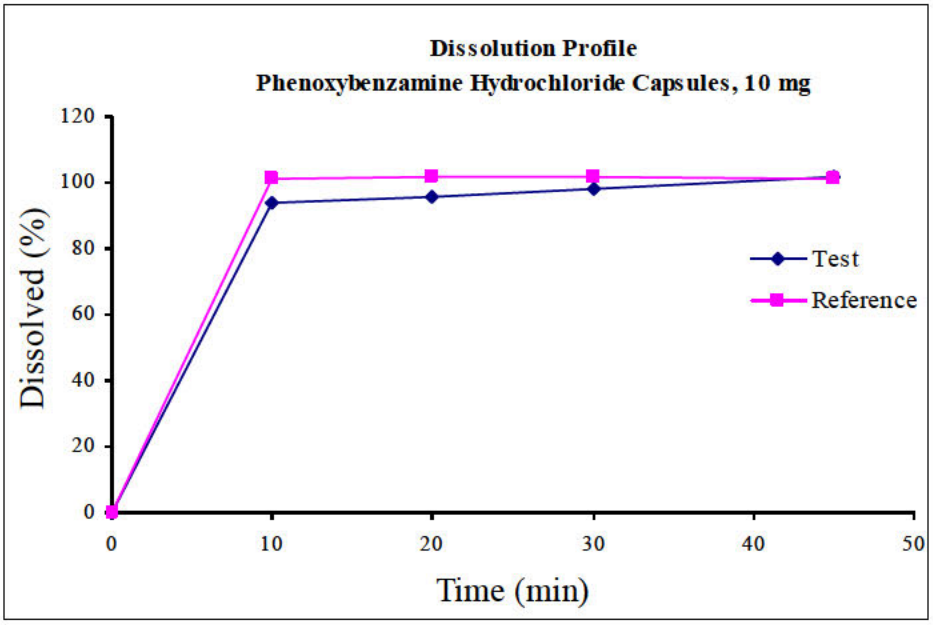
Dissolution Review Path	Current Review

Table 19. Dissolution Data

Dissolution Conditions	**Apparatus:**	I (Basket)
	Speed of Rotation:	100 rpm
	Medium:	0.1 N HCl
	Volume:	500 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	NLT 75% (Q) of the labeled amount dissolves in 45 minutes	
Dissolution Testing Site (Name, Address)	Boehringer Ingelheim Roxane Inc. 1809 Wilson Road Columbus, Ohio 43228	

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) 10	20	30	45	Study Report Location
N/A	7/21/2009	Phenoxybenzamine Hydrochloride Capsules 4000064 Manufacture Date – 7/15/2009	10 mg Capsules	12	Mean	94	96	98	102	Module 5
					Range				(b) (4)	
					%CV	3.6	3.1	3.3	3.2	
N/A	7/21/2009	Dibenzyline® Capsules Lot 8A3991 Expiration Date – January 2011	10 mg Capsules	12	Mean	101	102	102	101	
					Range				(b) (4)	
					%CV	4.0	3.2	2.4	2.0	

Figure 2. Dissolution profiles



4.4 SAS Output

4.4.1 Fasting Study Data

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
1	201	2	1	1	B	0	0.0000	0.2350	0.7840	1.790	1.300	0.826	0.570	0.4110	0.2770	0.1190	0.0549	0.0333	0.0000	0.0000	0.0000
2	201	2	2	1	A	0	0.0290	2.4600	1.8700	1.410	0.843	0.453	0.233	0.1710	0.1140	0.0479	0.0000	0.0000	0.0000	0.0000	0.0000
3	201	2	3	1	B	0	0.0000	1.8600	3.6500	2.520	1.340	0.742	0.448	0.2650	0.1470	0.0683	0.0278	0.0000	0.0000	0.0000	0.0000
4	201	2	4	1	A	0	0.0000	0.2050	0.9020	1.600	0.995	0.557	0.397	0.4460	0.3290	0.1900	0.0920	0.0392	0.0000	0.0000	0.0000
5	202	1	1	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
6	202	1	2	1	B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
7	202	1	3	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
8	202	1	4	1	B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
9	203	2	1	1	B	0	0.6510	6.3400	5.6000	2.940	1.780	1.050	0.700	0.5390	0.3590	0.2260	0.1200	0.0691	0.0501	0.0339	0.0307
10	203	2	2	1	A	0	0.2890	5.9500	7.1800	4.490	2.380	1.520	0.834	0.6660	0.4620	0.2260	0.1300	0.0271	0.0576	0.0403	0.0332
11	203	2	3	1	B	0	0.1170	1.9400	9.2600	5.380	3.140	1.920	1.120	0.6810	0.4680	0.2380	0.1220	0.0828	0.0590	0.0433	0.0339
12	203	2	4	1	A	0	0.1150	2.5000	6.8000	3.450	2.080	1.310	0.941	0.7310	0.5520	0.2590	0.1450	0.0900	0.0610	0.0388	0.0314
13	204	2	1	1	B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
14	204	2	2	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
15	204	2	3	1	B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
16	204	2	4	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
17	205	1	1	1	A	0	0.0000	0.0835	0.6160	1.280	1.230	0.966	0.843	0.7320	0.4800	0.2580	0.1250	0.0639	0.0283	0.0000	0.0000
18	205	1	2	1	B	0	0.0000	0.5420	1.3300	1.850	1.010	0.558	0.273	0.1340	0.0701	0.0473	0.0363	0.0252	0.0000	0.0000	0.0000
19	205	1	3	1	A	0	0.0380	0.2040	1.8000	1.390	0.685	0.403	0.239	0.1450	0.1080	0.0695	0.0374	0.0000	0.0000	0.0000	0.0000
20	205	1	4	1	B	0	0.0000	0.5330	1.1800	1.910	1.800	1.630	1.350	1.3400	1.3600	0.6330	0.3260	0.2150	0.1050	0.0718	0.0893
21	206	1	1	1	A	0	0.0294	0.3350	1.0500	2.750	2.240	1.370	0.862	0.6480	0.4800	0.1020	0.1280	0.0715	0.0485	0.0295	0.0000
22	206	1	2	1	B	0	0.0400	0.3060	1.3500	1.850	1.740	2.180	1.450	1.0600	1.0300	0.4640	0.2270	0.1460	0.0767	0.0486	0.0324
23	206	1	3	1	A	0	0.0392	0.7190	2.4600	2.650	1.890	1.060	0.641	0.5290	0.3740	0.1470	0.0819	0.0525	0.0312	0.0275	0.0000
24	206	1	4	1	B	0	0.0000	0.1810	0.5730	1.570	3.680	2.240	1.460	1.4800	1.2100	0.4790	0.3080	0.1850	0.1000	0.0597	0.0434
25	207	1	1	1	A	0	0.2250	2.8900	5.3000	2.600	1.300	0.701	0.413	0.2830	0.1970	0.0585	0.0472	0.0318	0.0000	0.0000	0.0000

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
26	207	1	2	1	B	0	0.3090	0.9250	1.9200	2.020	1.520	1.100	0.540	0.2500	0.1860	0.0752	0.0406	0.0266	0.0000	0.0000	0.0000
27	207	1	3	1	A	0	0.0577	2.4500	2.4000	2.090	1.640	1.210	1.140	0.5660	0.3300	0.1640	0.0862	0.0432	0.0282	0.0252	0.0000
28	207	1	4	1	B	0	0.0260	4.9500	5.0100	2.340	1.450	0.802	0.343	0.3340	0.2530	0.0993	0.0734	0.0379	0.0363	0.0265	0.0000
29	208	2	1	1	B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
30	208	2	2	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
31	208	2	3	1	B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
32	208	2	4	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
33	209	1	1	1	A	0	0.0000	0.2490	0.7340	0.627	0.452	0.280	0.291	0.2040	0.2060	0.2490	0.0616	0.0280	0.0000	0.0000	0.0000
34	209	1	2	1	B	0	0.0000	0.0852	1.0500	0.987	0.647	0.352	0.259	0.4370	0.2770	0.1410	0.0717	0.0000	0.0311	0.0000	0.0000
35	209	1	3	1	A	0	0.0000	0.3720	0.8170	0.759	0.466	0.342	0.205	0.1580	0.0792	0.0504	0.0298	0.0000	0.0000	0.0000	0.0000
36	209	1	4	1	B	0	0.0000	0.3000	0.9860	0.821	0.487	0.347	0.233	0.1680	0.1160	0.0587	0.0303	0.0000	0.0000	0.0000	0.0000
37	210	1	1	1	A	0	0.1320	6.1600	9.1100	3.960	1.250	0.751	0.586	0.4750	0.2450	0.1190	0.0604	0.0392	0.0374	0.0000	0.0000
38	210	1	2	1	B	0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
39	210	1	3	1	A	0	0.0359	1.0800	1.8600	1.360	1.060	0.789	0.668	1.3900	1.8600	0.7220	0.2950	0.1840	0.1110	0.0597	0.0368
40	210	1	4	1	B	0	0.0000	1.1700	3.7800	2.800	1.250	0.801	0.934	1.5700	0.9740	0.3080	0.1490	0.0930	0.0660	0.0422	0.0258
41	211	2	1	1	B	0	0.2190	2.1000	2.8600	3.700	2.530	2.030	1.540	1.1400	0.8820	0.6080	0.3490	0.1980	0.1220	0.0936	0.0621
42	211	2	2	1	A	0	0.0000	1.2500	3.7500	2.250	1.700	1.640	1.150	1.0100	0.7690	0.3590	0.1650	0.0928	0.0635	0.0421	0.0288
43	211	2	3	1	B	0	0.0451	1.3500	3.0500	2.510	0.000	1.400	1.020	0.7330	0.4980	0.2510	0.1400	0.0800	0.0497	0.0333	0.0251
44	211	2	4	1	A	0	0.1460	2.8200	3.7200	2.880	2.500	1.750	1.310	1.0600	0.7950	0.4470	0.2040	0.1100	0.0658	0.0512	0.0489
45	212	2	1	1	B	0	0.0441	0.7720	1.0300	0.676	0.421	0.239	0.142	0.0933	0.0583	0.0282	0.0000	0.0000	0.0000	0.0000	0.0000
46	212	2	2	1	A	0	0.1820	1.3500	1.1500	0.701	0.436	0.328	0.179	0.1360	0.0946	0.0489	0.0277	0.0000	0.0000	0.0000	0.0000
47	212	2	3	1	B	0	0.0000	0.0659	0.7250	1.280	0.658	0.491	0.303	0.2170	0.1530	0.0741	0.0330	0.0000	0.0000	0.0000	0.0000
48	212	2	4	1	A	0	0.0309	1.9900	1.7100	0.909	0.428	0.260	0.150	0.1040	0.0621	0.0375	0.0270	0.0000	0.0000	0.0000	0.0000
49	213	2	1	1	B	0	0.0372	0.7650	1.5800	1.470	1.040	0.631	0.377	0.2640	0.1830	0.0967	0.0489	0.0347	0.0279	0.0301	0.0261
50	213	2	2	1	A	0	0.0000	0.1840	0.9490	1.080	0.686	0.462	0.343	0.1900	0.1930	0.0970	0.0557	0.0392	0.0312	0.0265	0.0000
51	213	2	3	1	B	0	0.0000	0.1330	0.8350	1.920	1.120	0.674	0.403	0.2930	0.1700	0.1110	0.0719	0.0492	0.0393	0.0326	0.0328
52	213	2	4	1	A	0	0.0000	0.7060	1.8900	1.990	1.240	0.857	0.527	0.4030	0.2920	0.1680	0.0866	0.0586	0.0433	0.0395	0.0327
53	214	2	1	1	B	0	0.0506	0.7470	1.7900	1.620	0.963	0.689	0.449	0.2950	0.2410	0.0790	0.0305	0.0000	0.0000	0.0000	0.0000
54	214	2	2	1	A	0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
55	214	2	3	1	B	0	0.0000	0.1540	1.0100	1.680	1.230	1.080	1.090	0.7610	0.4970	0.1800	0.0623	0.0397	0.0000	0.0000	0.0000
56	214	2	4	1	A	0	0.0000	0.1530	0.7900	1.650	1.130	0.860	0.654	0.7330	0.4850	0.2000	0.0779	0.0403	0.0000	0.0000	0.0000
57	215	1	1	1	A	0	0.6750	1.8000	1.1300	0.819	0.547	0.391	0.247	0.1840	0.1400	0.0698	0.0480	0.0363	0.0284	0.0000	0.0000
58	215	1	2	1	B	0	.	1.9300	1.4100	0.743	0.538	0.317	0.232	0.1780	0.1490	0.1500	0.0664	0.0326	0.0279	0.0000	0.0000
59	215	1	3	1	A	0	0.6790	2.3000	2.3900	1.250	0.692	0.474	0.275	0.2020	0.1320	0.0764	0.0456	0.0290	0.0000	0.0000	0.0000
60	215	1	4	1	B	0	2.8600	2.7800	2.9500	1.070	0.875	0.945	0.662	0.3550	0.1910	0.1150	0.0705	0.0482	0.0385	0.0313	0.0260
61	216	2	1	1	B	0	0.0000	0.1190	0.1900	0.472	0.744	1.190	1.150	1.0600	2.1500	2.2300	2.1800	1.6900	1.1600	0.7250	1.1600
62	216	2	2	1	A	0	0.0000	0.0522	0.2930	0.565	0.441	0.515	0.573	0.5660	0.4680	0.6570	0.7020	1.0400	0.7480	0.5560	1.8600
63	216	2	3	1	B	0	0.0000	0.0716	0.2530	0.442	0.738	1.340	1.210	1.9700	1.8800	1.7600	1.3000	0.9950	0.6890	0.5410	0.8260
64	216	2	4	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
65	217	1	1	1	A	0	0.0296	0.5670	1.4300	1.960	1.980	1.530	1.730	1.2100	0.7820	0.3530	0.2000	0.0967	0.0602	0.0389	0.0327
66	217	1	2	1	B	0	0.0000	0.3120	1.2900	2.160	1.640	1.390	1.000	1.0900	0.7440	0.3360	0.1830	0.1080	0.0740	0.0484	0.0319
67	217	1	3	1	A	0	0.0000	0.9110	2.8600	2.620	1.670	1.260	1.050	0.9460	0.5600	0.2310	0.0980	0.0598	0.0505	0.0335	0.0275
68	217	1	4	1	B	0	0.0000	1.3700	3.5100	2.920	1.710	1.160	0.742	0.5180	0.2830	0.1390	0.0817	0.0551	0.0411	0.0345	0.0000
69	218	1	1	1	A	0	0.1890	4.4400	3.0800	1.690	0.669	0.378	0.252	0.1940	0.1240	0.0580	0.0448	0.0000	0.0000	0.0000	0.0000
70	218	1	2	1	B	0	0.0510	2.1000	2.0700	1.540	1.830	1.740	0.716	0.4600	0.2770	0.1210	0.0574	0.0343	0.0261	0.0000	0.0000
71	218	1	3	1	A	0	0.0534	1.7000	3.0800	1.580	0.818	0.568	0.306	0.2790	0.1660	0.0912	0.0426	0.0292	0.0251	0.0000	0.0000
72	218	1	4	1	B	0	0.0716	1.3400	2.3800	1.820	1.070	0.638	0.360	0.2950	0.1860	0.0937	0.0464	0.0331	0.0000	0.0000	0.0000
73	219	1	1	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
74	219	1	2	1	B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
75	219	1	3	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
76	219	1	4	1	B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
77	220	2	1	1	B	0	0.0000	0.5760	1.7800	3.560	2.300	1.550	1.290	0.9880	0.7400	0.4480	0.3410	0.1920	0.1460	0.1170	0.1090
78	220	2	2	1	A	0	0.0000	0.0414	0.9170	2.300	2.530	1.740	1.190	0.9260	0.6840	0.5230	0.3630	0.2700	0.1960	0.1690	0.1530
79	220	2	3	1	B	0	0.0000	0.3320	1.4000	1.700	1.400	1.070	0.829	0.6060	0.4480	0.2590	0.1750	0.1440	0.1290	0.1420	0.1270
80	220	2	4	1	A	0	0.0000	0.0559	0.3110	0.891	0.960	0.832	0.717	0.6160	0.5880	0.5820	0.4090	0.3350	0.2590	0.2820	0.2650
81	221	2	1	1	B	0	0.2870	2.4400	2.8000	2.900	1.750	0.957	0.534	0.3510	0.2470	0.1090	0.0757	0.0508	0.0338	0.0452	0.0341
82	221	2	2	1	A	0	0.6390	3.9200	3.8600	1.820	1.080	0.531	0.383	0.2570	0.1820	0.0950	0.0633	0.0395	0.0354	0.0320	0.0266
83	221	2	3	1	B	0	0.9720	2.9800	2.9700	1.600	0.826	0.574	0.402	0.2350	0.1430	0.0779	0.0529	0.0391	0.0328	0.0350	0.0359

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
84	221	2	4	1	A	0	1.7000	2.6800	3.0700	3.310	1.780	1.070	0.538	0.3620	0.2280	0.1190	0.0717	0.0484	0.0410	0.0344	0.0364
85	222	1	1	1	A	0	0.0589	1.6000	2.3900	1.790	0.880	0.485	0.290	0.1610	0.1050	0.0547	0.0302	0.0000	0.0000	0.0000	0.0000
86	222	1	2	1	B	0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
87	222	1	3	1	A	0	0.0331	1.3600	2.4000	1.740	0.980	0.690	0.764	0.4940	0.2540	0.1020	0.0525	0.0293	0.0000	0.0000	0.0000
88	222	1	4	1	B	0	0.0000	0.5610	1.3800	2.660	1.850	1.510	1.200	0.8460	0.3550	0.1450	0.0704	0.0452	0.0312	0.0255	0.0000
89	223	2	1	1	B	0	0.0258	2.7600	4.3300	1.920	0.819	0.478	0.264	0.2440	0.1100	0.0560	0.0357	0.0268	0.0000	0.0000	0.0000
90	223	2	2	1	A	0	0.3900	4.4600	3.6000	1.650	0.894	0.551	0.337	0.2110	0.1890	0.0820	0.0518	0.0323	0.0000	0.0000	0.0000
91	223	2	3	1	B	0	0.0000	0.8490	3.0200	1.640	0.828	0.522	0.317	0.2130	0.1430	0.0747	0.0324	0.0283	0.0000	0.0000	0.0000
92	223	2	4	1	A	0	0.0000	1.8000	1.3400	0.754	0.506	0.365	0.221	0.1550	0.1040	0.0597	0.0313	0.0000	0.0000	0.0000	0.0000
93	224	1	1	1	A	0	0.0348	3.7300	5.2700	6.130	4.210	3.270	2.210	1.6500	1.1400	0.5700	0.3330	0.2020	0.1210	0.0928	0.0607
94	224	1	2	1	B	0	0.0000	0.6790	4.9700	3.390	2.130	1.460	0.899	0.4980	0.4560	0.2400	0.1410	0.0774	0.0556	0.0433	0.0298
95	224	1	3	1	A	0	0.4380	6.4700	6.2800	3.570	2.070	1.350	0.845	0.5910	0.4110	0.2370	0.1150	0.0694	0.0531	0.0356	0.0327
96	224	1	4	1	B	0	0.1020	2.5300	2.9500	2.240	1.400	0.914	0.515	0.3910	0.2690	0.1320	0.0745	0.0493	0.0358	0.0354	0.0271
97	225	1	1	1	A	0	0.1140	1.4400	2.3600	2.760	1.960	0.300	0.842	0.6360	0.3800	0.1480	0.0764	0.0547	0.0393	0.0430	0.0427
98	225	1	2	1	B	0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
99	225	1	3	1	A	0	0.2210	1.8000	2.3200	3.680	2.270	1.350	0.768	0.5150	0.2930	0.1340	0.0830	0.0664	0.0539	0.0630	0.0576
100	225	1	4	1	B	0	0.0000	0.4280	1.3400	1.290	1.150	0.927	0.673	0.4190	0.2610	0.1410	0.0693	0.0591	0.0524	0.0983	0.0671
101	226	2	1	1	B	0	0.0000	0.2010	0.7030	1.010	0.731	0.534	0.458	1.2100	1.2400	0.6210	0.2260	0.1010	0.0507	0.0368	0.0000
102	226	2	2	1	A	0	0.0955	1.2700	4.4900	3.990	2.220	1.340	0.931	0.2930	0.4580	0.2220	0.1360	0.0753	0.0460	0.0252	0.0251
103	226	2	3	1	B	0	0.0000	0.0000	0.0634	2.460	3.140	3.090	2.260	1.4900	0.8850	0.4610	0.2590	0.1390	0.0876	0.0544	0.0454
104	226	2	4	1	A	0	0.0000	1.6500	4.7200	3.750	2.740	2.210	1.790	1.2600	1.0200	0.5640	0.1570	0.1640	0.0992	0.0703	0.0424
105	227	2	1	1	B	0	0.0000	1.6700	4.8000	6.880	5.440	4.420	4.390	3.1200	2.0400	0.8240	0.5000	0.2370	0.1350	0.1060	0.0816
106	227	2	2	1	A	0	0.0266	0.8510	5.9500	6.330	4.380	3.560	2.880	0.6420	1.6100	0.8790	0.4090	0.2370	0.1450	0.0902	0.0674
107	227	2	3	1	B	0	0.4520	3.4100	11.5000	7.220	4.150	3.130	2.000	1.5700	0.9770	0.5230	0.3100	0.1970	0.1270	0.0870	0.0740
108	227	2	4	1	A	0	0.0261	3.7500	6.5200	6.630	4.090	3.780	3.340	2.3300	1.5200	0.7000	0.4040	0.2400	0.1480	0.1030	0.0815
109	228	1	1	1	A	0	0.0412	0.8510	1.2800	0.733	0.519	0.386	0.284	0.2180	0.1370	0.0720	0.0542	0.0414	0.0259	0.0356	0.0312
110	228	1	2	1	B	0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
111	228	1	3	1	A	0	0.0000	0.7750	1.2500	1.240	0.941	0.647	0.456	0.3290	0.2350	0.1070	0.0631	0.0363	0.0272	0.0000	0.0000
112	228	1	4	1	B	0	0.0000	0.9960	1.5200	1.140	0.821	0.615	0.381	0.2960	0.1730	0.1010	0.0519	0.0355	0.0000	0.0000	0.0000

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
113	229	1	1	1	A	0	0.0516	1.0400	2.0600	1.670	1.160	0.785	0.513	0.2610	0.1760	0.0741	0.0385	0.0260	0.0000	0.0000	0.0000
114	229	1	2	1	B	0	0.0000	0.2500	1.1900	1.780	1.410	1.240	0.936	0.1240	0.3440	0.1300	0.0571	0.0000	0.0000	0.0000	0.0000
115	229	1	3	1	A	0	0.0598	2.3300	3.1100	2.220	1.380	0.973	0.631	0.3940	0.2470	0.0907	0.0518	0.0311	0.0000	0.0000	0.0000
116	229	1	4	1	B	0	0.0000	0.5390	2.1300	2.770	1.800	1.100	0.780	0.4580	0.3380	0.1580	0.0779	0.0449	0.0281	0.0000	0.0000
117	230	2	1	1	B	0	0.0000	0.3640	2.2700	2.220	1.060	0.693	0.378	0.2270	0.1480	0.0709	0.0493	0.0299	0.0000	0.0000	0.0000
118	230	2	2	1	A	0	0.4610	1.5000	1.8700	3.050	1.520	1.230	0.760	0.0444	0.4620	0.1930	0.1080	0.0544	0.0398	0.0267	0.0000
119	230	2	3	1	B	0	0.0000	0.1860	2.0700	2.970	2.380	1.800	1.350	0.9220	0.6850	0.4010	0.2280	0.1130	0.0639	0.0473	0.0301
120	230	2	4	1	A	0	0.0000	0.4660	1.3800	1.310	1.020	0.623	0.386	0.2610	0.1470	0.0614	0.0297	0.0000	0.0000	0.0000	0.0000
121	231	1	1	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
122	231	1	2	1	B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
123	231	1	3	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
124	231	1	4	1	B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
125	232	2	1	1	B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
126	232	2	2	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
127	232	2	3	1	B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
128	232	2	4	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
129	233	1	1	1	A	0	0.0000	0.6150	2.1000	3.670	2.470	1.830	1.270	1.6100	2.2800	1.1200	0.7670	0.5130	0.2490	0.3310	0.2660
130	233	1	2	1	B	0	0.0284	1.0600	1.8800	1.740	1.200	0.781	0.567	0.3880	0.3470	0.1950	0.1150	0.0663	0.0489	0.0444	0.0381
131	233	1	3	1	A	0	0.0271	0.7460	1.6200	1.530	1.080	0.738	0.695	0.7930	0.2390	0.2060	0.1150	0.0703	0.0406	0.0301	0.0339
132	233	1	4	1	B	0	0.0000	0.1870	0.7370	1.060	0.656	0.506	0.309	0.2520	0.2420	0.2850	0.1410	0.0705	0.0479	0.0477	0.0319
133	234	2	1	1	B	0	0.0000	0.2620	1.8100	2.540	2.980	2.390	2.640	1.8100	1.2100	0.5770	0.3470	0.2070	0.1750	0.0905	0.0589
134	234	2	2	1	A	0	0.0000	0.5420	1.8500	4.050	3.210	1.510	1.710	1.0900	0.7720	0.4850	0.2860	0.1850	0.1410	0.0888	0.0664
135	234	2	3	1	B	0	1.6000	0.1230	0.3270	0.963	0.885	1.860	2.260	1.9100	1.2400	0.6470	0.4730	0.3160	0.1740	0.1290	0.0889
136	234	2	4	1	A	0	0.0000	1.0700	2.7600	3.550	2.850	2.900	2.390	1.3700	0.8230	0.4390	0.3410	0.1990	0.1350	0.1000	0.0640
137	235	1	1	1	A	0	0.0292	1.3500	2.2500	1.990	0.949	0.595	0.711	0.5770	0.5710	0.4120	0.3070	0.1660	0.1080	0.0553	0.0363
138	235	1	2	1	B	0	0.0447	2.5400	3.0300	1.790	1.240	0.802	0.574	0.4010	0.3050	0.1310	0.0700	0.0508	0.0385	0.0323	0.0285
139	235	1	3	1	A	0	0.1340	1.8200	2.0600	1.290	0.956	0.537	0.403	0.3080	0.1680	0.1010	0.0558	0.0385	0.0300	0.0259	0.0000
140	235	1	4	1	B	0	0.0292	1.8500	4.3200	2.320	1.320	0.830	0.685	0.5130	0.3760	0.1850	0.0978	0.0743	0.0545	0.0376	0.0267
141	236	2	1	1	B	0	0.0000	1.0100	1.7900	1.160	0.730	0.696	0.602	0.4470	0.3050	0.1230	0.0685	0.0386	0.0000	0.0000	0.0000

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
142	236	2	2	1	A	0	0.0000	0.5710	1.1800	1.670	1.150	0.735	0.586	0.4300	0.3600	0.1540	0.0970	0.0501	0.0270	0.0000	0.0000
143	236	2	3	1	B	0	0.0000	0.6630	3.5400	1.700	1.070	0.704	0.576	0.4420	0.2860	0.1540	0.0829	0.0539	0.0357	0.0268	0.0000
144	236	2	4	1	A	0	0.0000	0.4190	1.5000	0.698	0.639	0.684	0.645	0.5340	0.4050	0.2060	0.1150	0.0647	0.0351	0.0000	0.0000
145	237	1	1	1	A	0	0.0000	0.1490	0.4760	0.673	0.428	0.372	0.222	0.1520	0.1060	0.0507	0.0339	0.0000	0.0000	0.0000	0.0000
146	237	1	2	1	B	0	0.0000	0.4410	0.5940	0.335	0.207	0.169	0.134	0.0942	0.0676	0.0480	0.0000	0.0000	0.0000	0.0000	0.0000
147	237	1	3	1	A	0	0.0000	0.6660	1.0800	0.690	0.365	0.237	0.160	0.1100	0.0645	0.0383	0.0000	0.0000	0.0000	0.0000	0.0000
148	237	1	4	1	B	0	0.0000	0.1230	0.2310	0.489	0.513	0.425	0.267	0.1880	0.1250	0.0564	0.0290	0.0000	0.0000	0.0000	0.0000
149	238	1	1	1	A	0	0.2790	1.7500	2.3200	1.640	1.010	0.631	0.308	0.2390	0.1320	0.0593	0.0348	0.0259	0.0000	0.0000	0.0000
150	238	1	2	1	B	0	0.0572	1.3200	2.8300	2.120	1.130	0.668	0.355	0.2230	0.1500	0.0760	0.0560	0.0353	0.0303	0.0000	0.0000
151	238	1	3	1	A	0	0.0339	0.9240	2.2100	2.160	1.870	1.260	0.765	0.4650	0.2510	0.1220	0.0660	0.0445	0.0333	0.0270	0.0000
152	238	1	4	1	B	0	0.1500	1.1800	1.9500	1.950	1.370	0.944	0.498	0.3080	0.1800	0.0729	0.0429	0.0341	0.0295	0.0255	0.0000
153	239	2	1	1	B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
154	239	2	2	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
155	239	2	3	1	B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
156	239	2	4	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
157	240	2	1	1	B	0	0.0297	0.3160	1.5200	3.050	1.990	1.400	1.000	0.8100	0.6130	0.3740	0.2000	0.0850	0.0539	0.0343	0.0000
158	240	2	2	1	A	0	0.1650	1.8100	3.3600	3.760	3.320	2.300	3.170	2.1500	1.5600	0.7100	0.3920	0.2250	0.1470	0.0953	0.0666
159	240	2	3	1	B	0	0.1280	1.0300	2.0100	1.980	1.290	1.490	1.400	1.0000	0.4360	0.2050	0.1010	0.0558	0.0394	0.0327	0.0284
160	240	2	4	1	A	0	0.4420	0.3740	2.4100	2.330	1.770	1.640	1.080	0.6430	0.3090	0.1530	0.0788	0.0555	0.0385	0.0265	0.0000
161	241	1	1	1	A	0	0.6210	1.2300	1.8500	1.340	0.972	1.100	1.550	0.9610	0.4520	0.1670	0.0881	0.0467	0.0314	0.0000	0.0000
162	241	1	2	1	B	0	0.3180	3.5100	3.3900	2.740	1.600	1.120	0.936	0.7430	0.4530	0.2160	0.0993	0.0609	0.0468	0.0342	0.0345
163	241	1	3	1	A	0	0.0000	0.9830	2.6700	1.830	0.955	0.780	0.592	0.4510	0.2400	0.1170	0.0709	0.0421	0.0304	0.0000	0.0000
164	241	1	4	1	B	0	0.0000	0.8090	3.2900	2.600	1.470	0.974	0.507	0.3130	0.1960	0.1220	0.0756	0.0425	0.0306	0.0000	0.0000
165	242	2	1	1	B	0	0.0000	0.2320	0.5110	0.603	0.619	0.597	0.477	0.2970	0.2410	0.1110	0.0713	0.0362	0.0309	0.0000	0.0000
166	242	2	2	1	A	0	0.0000	0.4810	0.8100	0.589	0.370	0.280	0.216	0.1820	0.1450	0.0821	0.0534	0.0349	0.0000	0.0000	0.0000
167	242	2	3	1	B	0	0.0000	0.6310	1.0700	0.581	0.322	0.231	0.156	0.1290	0.0878	0.0562	0.0323	0.0000	0.0000	0.0000	0.0000
168	242	2	4	1	A	0	0.0000	0.8920	1.3300	0.835	0.562	0.378	0.258	0.1780	0.1330	0.0882	0.0601	0.0401	0.0317	0.0000	0.0000
169	243	1	1	1	A	0	0.0000	0.1480	0.4820	0.832	0.578	1.220	2.220	2.0400	1.4400	0.5460	0.2280	0.1020	0.0488	0.0404	0.0285
170	243	1	2	1	B	0	0.0000	0.0297	1.9100	1.970	0.889	0.594	0.349	0.2320	0.1360	0.0617	0.0307	0.0000	0.0000	0.0000	0.0000

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
171	243	1	3	1	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
172	243	1	4	1	B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
173	244	2	1	1	B	0	0.0000	0.1220	0.3120	0.346	0.646	0.610	0.615	0.3860	0.3110	0.1670	0.0938	0.0564	0.0453	0.0283	0.0000
174	244	2	2	1	A	0	0.0000	0.2210	0.7940	1.120	0.771	0.665	0.390	0.2430	0.1760	0.0926	0.0720	0.0381	0.0286	0.0000	0.0000
175	244	2	3	1	B	0	0.2100	1.9200	2.2700	1.400	0.733	0.545	0.370	0.2980	0.1730	0.0850	0.0486	0.0285	0.0000	0.0000	0.0000
176	244	2	4	1	A	0	0.0251	1.3200	2.0800	1.190	0.494	0.328	0.232	0.1450	0.1330	0.0760	0.0432	0.0333	0.0256	0.0000	0.0000
177	245	1	1	1	A	0	0.0000	0.5720	1.7900	0.832	0.365	0.327	0.290	0.2800	0.2160	0.1240	0.0385	0.0361	0.0276	0.0000	0.0000
178	245	1	2	1	B	0	0.1000	1.4200	1.1800	0.786	0.542	0.381	0.309	0.2450	0.2250	0.1240	0.0907	0.0625	0.0379	0.0000	0.0000
179	245	1	3	1	A	0	0.0000	0.9900	1.2900	1.060	0.563	0.449	0.385	0.2490	0.1660	0.1170	0.0706	0.0365	0.0000	0.0000	0.0000
180	245	1	4	1	B	0	0.0327	1.7800	2.1000	1.140	0.559	0.517	0.341	0.2830	0.2360	0.1460	0.0936	0.0613	0.0449	0.0275	0.0000
181	246	1	1	1	A	0	0.0000	0.2550	1.4800	3.980	3.480	2.270	1.410	1.0400	0.6300	0.3730	0.1890	0.1340	0.0809	0.0482	0.0444
182	246	1	2	1	B	0	0.0000	1.6300	3.8200	3.990	2.430	1.620	0.894	0.5910	0.5030	0.2430	0.1610	0.1100	0.0738	0.0542	0.0518
183	246	1	3	1	A	0	0.0578	1.8800	3.2300	2.430	1.710	1.320	0.950	0.7530	0.5560	0.3180	0.1690	0.0984	0.0679	0.0467	0.0435
184	246	1	4	1	B	0	0.0256	1.2700	2.2100	2.480	2.310	1.810	1.380	1.0500	0.9380	0.7100	0.3270	0.2000	0.1320	0.0907	0.0656
185	247	2	1	1	B	0	0.0875	5.7100	11.6000	4.850	2.660	2.170	1.290	1.1500	0.6950	0.3590	0.2140	0.1520	0.1120	0.1250	0.0900
186	247	2	2	1	A	0	0.0824	0.9500	1.8800	3.300	2.260	2.780	3.150	1.8700	1.2300	0.5190	0.2760	0.1780	0.1140	0.0739	0.0569
187	247	2	3	1	B	0	0.0362	0.2160	1.0700	2.990	2.670	2.290	1.910	1.3900	0.9140	0.3730	0.1530	0.0855	0.0523	0.0377	0.0317
188	247	2	4	1	A	0	0.1150	3.6200	5.9300	4.530	2.620	1.990	1.450	1.0300	0.6860	0.3340	0.1860	0.0991	0.0732	0.0530	0.0449
189	248	2	1	1	B	0	0.0000	0.6540	1.6300	1.590	1.300	1.120	0.904	0.8240	1.0300	0.7700	0.4910	0.4070	0.2500	0.1770	0.1190
190	248	2	2	1	A	0	0.0000	0.5260	0.8770	1.350	1.120	0.897	0.747	0.9560	0.7950	0.6250	0.3860	0.2640	0.1610	0.0920	0.0623
191	248	2	3	1	B	0	0.0709	0.2880	0.4840	0.657	0.747	0.943	0.943	0.7530	0.4990	0.5090	0.6380	0.3720	0.1960	0.0993	0.0628
192	248	2	4	1	A	0	0.0000	0.3890	0.9430	1.080	0.806	0.730	0.793	0.8870	1.0200	0.9390	0.6770	0.4900	0.2760	0.2130	0.1450

Obs	c17	c18	c19	c20	c21	c22	c23	c24	ke_first	ke_last
1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	8	11
3	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
4	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
5	.	.	.	.	.	.	.	.	.	.
6	.	.	.	.	.	.	.	.	.	.
7	.	.	.	.	.	.	.	.	.	.
8	.	.	.	.	.	.	.	.	.	.
9	0.0000	0.0272	0.0000	0.0000	0.0000	0.0000	0.0000	0	.	.
10	0.0261	0.0288	0.0279	0.0000	0.0000	0.0000	0.0000	0	13	19
11	.	0.0313	0.0310	0.0268	0.0000	0.0000	0.0000	0	14	20
12	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	12	16
13	.	.	.	.	.	.	.	.	.	.
14	.	.	.	.	.	.	.	.	.	.
15	.	.	.	.	.	.	.	.	.	.
16	.	.	.	.	.	.	.	.	.	.
17	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	14
18	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
19	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
20	0.0299	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	17
21	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15
22	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
23	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15
24	0.0279	0.0000	0.0270	0.0000	0.0000	0.0000	0.0000	0	12	17
25	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
26	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
27	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15
28	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15
29	.	.	.	.	.	.	.	.	.	.
30	.	.	.	.	.	.	.	.	.	.
31	.	.	.	.	.	.	.	.	.	.
32	.	.	.	.	.	.	.	.	.	.
33	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
34	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
35	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
36	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
37	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	10	14
38	.	.	.	.	.	.	.	.	.	.
39	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
40	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16

Obs	c17	c18	c19	c20	c21	c22	c23	c24	ke_first	ke_last
41	0.0401	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	13	17
42	0.0000	0.0000	0.0000	0.0257	0.0000	0.0000	0.0000	0	.	.
43	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
44	0.0302	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	13	17
45	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	8	11
46	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
47	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
48	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
49	0.0327	0.0000	0.0000	0.0262	0.0000	0.0000	0.0000	0	.	.
50	0.0336	0.0394	0.0312	0.0344	0.0000	0.0000	0.0000	0	.	.
51	0.0298	0.0457	0.0310	0.0334	0.0000	0.0000	0.0000	0	.	.
52	0.0285	0.0333	0.0290	0.0279	0.0000	0.0000	0.0000	0	14	20
53	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
54	.	.	.	.	.	.	.	.	.	.
55	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
56	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
57	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	10	14
58	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	14
59	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
60	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
61	0.3030	0.1100	0.0637	0.0539	0.0314	0.0000	0.0000	0	14	21
62	0.2970	0.0856	0.0407	0.0420	0.0251	0.0000	0.0000	0	14	21
63	0.1490	0.0689	0.0477	0.0476	0.0251	0.0000	0.0000	0	14	21
64	.	.	.	.	.	.	.	.	.	.
65	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
66	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
67	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
68	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15
69	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
70	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	10	14
71	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	10	14
72	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
73	.	.	.	.	.	.	.	.	.	.
74	.	.	.	.	.	.	.	.	.	.
75	.	.	.	.	.	.	.	.	.	.
76	.	.	.	.	.	.	.	.	.	.
77	0.0627	0.0481	0.0485	0.0536	0.0256	0.0000	0.0000	0	14	21
78	0.0813	0.0550	0.0516	0.0400	0.0000	0.0000	0.0000	0	14	20
79	0.0837	0.0565	0.0629	0.1290	0.0784	0.0000	0.0000	0	.	.
80	0.1670	0.1070	0.0683	0.0908	0.0000	0.0000	0.0000	0	14	20

Obs	c17	c18	c19	c20	c21	c22	c23	c24	ke_first	ke_last
81	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
82	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
83	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
84	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
85	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
86	.	.	.	.	.	.	.	.	.	.
87	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
88	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15
89	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
90	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
91	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
92	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
93	0.0439	0.0350	0.0345	0.0265	0.0000	0.0000	0.0000	0	15	20
94	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
95	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
96	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
97	0.0337	0.0000	0.0253	0.0000	0.0000	0.0000	0.0000	0	12	17
98	.	.	.	.	.	.	.	.	.	.
99	0.0418	0.0280	0.0325	0.0000	0.0000	0.0000	0.0000	0	14	19
100	0.0288	0.0324	0.0449	0.0408	0.0000	0.0000	0.0000	0	.	.
101	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15
102	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
103	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
104	0.0251	0.0307	0.0325	0.0263	0.0000	0.0000	0.0000	0	14	20
105	0.0520	0.0499	0.0501	0.0398	0.0406	0.0000	0.0000	0	14	21
106	0.0433	0.0476	0.0519	0.0480	0.0407	0.0000	0.0000	0	14	21
107	0.0563	0.0573	0.0626	0.0556	0.0468	0.0000	0.0000	0	14	21
108	0.0637	0.0710	0.0835	0.0719	0.0512	0.0294	0.0273	0	.	.
109	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
110	.	.	.	.	.	.	.	.	.	.
111	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	10	14
112	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
113	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
114	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
115	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
116	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	14
117	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
118	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15
119	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
120	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12

Obs	c17	c18	c19	c20	c21	c22	c23	c24	ke_first	ke_last
121	.	.	.	.	.	.	.	.	.	.
122	.	.	.	.	.	.	.	.	.	.
123	.	.	.	.	.	.	.	.	.	.
124	.	.	.	.	.	.	.	.	.	.
125	.	.	.	.	.	.	.	.	.	.
126	.	.	.	.	.	.	.	.	.	.
127	.	.	.	.	.	.	.	.	.	.
128	.	.	.	.	.	.	.	.	.	.
129	0.0851	0.0425	0.0319	0.0363	0.0000	0.0000	0.0000	0	14	20
130	0.0270	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	13	17
131	0.0251	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	13	17
132	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	12	16
133	0.0454	0.0292	0.0000	0.0000	0.0000	0.0000	0.0000	0	14	18
134	0.0396	0.0262	0.0000	0.0000	0.0000	0.0000	0.0000	0	14	18
135	0.0487	0.0359	0.0000	0.0000	0.0000	0.0000	0.0000	0	14	18
136	0.0422	0.0377	0.0322	0.0000	0.0000	0.0000	0.0000	0	14	19
137	0.0292	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	14	17
138	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	12	16
139	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15
140	0.0279	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	14	17
141	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
142	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	10	14
143	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15
144	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	10	14
145	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
146	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	8	11
147	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	8	11
148	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
149	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
150	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	10	14
151	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15
152	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15
153	.	.	.	.	.	.	.	.	.	.
154	.	.	.	.	.	.	.	.	.	.
155	.	.	.	.	.	.	.	.	.	.
156	.	.	.	.	.	.	.	.	.	.
157	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15
158	0.0349	0.0000	0.0282	0.0000	0.0000	0.0000	0.0000	0	13	17
159	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	12	16
160	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15

Obs	c17	c18	c19	c20	c21	c22	c23	c24	ke_first	ke_last
161	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	14
162	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	12	16
163	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	14
164	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	14
165	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	10	14
166	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
167	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
168	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	10	14
169	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	16
170	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	12
171	.	.	.	.	.	.	.	.	.	.
172	.	.	.	.	.	.	.	.	.	.
173	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15
174	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	10	14
175	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
176	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	10	14
177	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	10	14
178	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	10	14
179	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	9	13
180	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	11	15
181	0.0316	0.0303	0.0000	0.0264	0.0000	0.0000	0.0000	0	14	18
182	0.0358	0.0288	0.0000	0.0277	0.0000	0.0000	0.0000	0	14	18
183	0.0280	0.0290	0.0254	0.0275	0.0000	0.0000	0.0000	0	16	20
184	0.0417	0.0300	0.0291	0.0321	0.0296	0.0000	0.0000	0	.	.
185	0.0594	0.0599	0.0487	0.0372	0.0279	0.0000	0.0000	0	16	21
186	0.0415	0.0313	0.0299	0.0306	0.0000	0.0000	0.0000	0	16	20
187	0.0000	0.0253	0.0000	0.0000	0.0000	0.0000	0.0000	0	12	16
188	0.0318	0.0286	0.0254	0.0264	0.0000	0.0000	0.0000	0	16	20
189	0.0554	0.0357	0.0000	0.0000	0.0000	0.0000	0.0000	0	14	18
190	0.0302	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	14	17
191	0.0288	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0	13	17
192	0.0643	0.0424	0.0332	0.0255	0.0000	0.0000	0.0000	0	16	20

FASTED REVIEWER-CALCULATED PHARMACOKINETIC DATASET

Obs	SUBJ	TRT	SEQ	PER	GROUP	auct	auci	CMAX	TMAX	THALF	kel
1	201	A	2	2	1	1.63654	1.68610	2.460	0.333	0.71712	0.96657
2	201	A	2	4	1	1.49512	1.54112	1.600	0.750	0.81338	0.85218
3	201	B	2	1	1	1.62599	1.65805	1.790	0.750	0.66732	1.03870
4	201	B	2	3	1	2.49569	2.51084	3.650	0.500	0.37775	1.83492
5	202	A	1	1	1	.	.	.	.	.	.

Obs	SUBJ	TRT	SEQ	PER	GROUP	auct	auci	CMAX	TMAX	THALF	kel
6	202	A	1	3	1	.	.	.	.	.	.
7	202	B	1	2	1	.	.	.	.	.	.
8	202	B	1	4	1	.	.	.	.	.	.
9	203	A	2	2	1	5.51582	5.55373	7.180	0.500	0.94170	0.73606
10	203	A	2	4	1	4.49295	4.52712	6.800	0.500	0.75432	0.91890
11	203	B	2	1	1	4.50465	.	6.340	0.333	.	.
12	203	B	2	3	1	5.94413	5.99239	9.260	0.500	1.24838	0.55524
13	204	A	2	2	1	.	.	.	.	.	.
14	204	A	2	4	1	.	.	.	.	.	.
15	204	B	2	1	1	.	.	.	.	.	.
16	204	B	2	3	1	.	.	.	.	.	.
17	205	A	1	1	1	1.81561	1.85371	1.280	0.750	0.93321	0.74276
18	205	A	1	3	1	1.21569	1.26688	1.800	0.500	0.94860	0.73070
19	205	B	1	2	1	1.39819	1.41623	1.850	0.750	0.49633	1.39654
20	205	B	1	4	1	3.60960	3.65108	1.910	0.750	0.96163	0.72080
21	206	A	1	1	1	2.60947	2.65248	2.750	0.750	1.01047	0.68597
22	206	A	1	3	1	2.63508	2.66728	2.650	0.750	0.81184	0.85380
23	206	B	1	2	1	3.28458	3.33843	2.180	1.250	1.15185	0.60177
24	206	B	1	4	1	3.85066	3.89358	3.680	1.000	1.10186	0.62907
25	207	A	1	1	1	3.08262	3.10629	5.300	0.500	0.51588	1.34361
26	207	A	1	3	1	2.87028	2.89607	2.450	0.333	0.70934	0.97717
27	207	B	1	2	1	2.09758	2.11939	2.020	0.750	0.56836	1.21955
28	207	B	1	4	1	3.41529	3.44244	5.010	0.500	0.71014	0.97606
29	208	A	2	2	1	.	.	.	.	.	.
30	208	A	2	4	1	.	.	.	.	.	.
31	208	B	2	1	1	.	.	.	.	.	.
32	208	B	2	3	1	.	.	.	.	.	.
33	209	A	1	1	1	0.89755	0.93215	0.734	0.500	0.85668	0.80911
34	209	A	1	3	1	0.77713	0.80110	0.817	0.500	0.55755	1.24321
35	209	B	1	2	1	1.12161	1.16439	1.050	0.500	0.95338	0.72704
36	209	B	1	4	1	0.84996	0.87553	0.986	0.500	0.58513	1.18461
37	210	A	1	1	1	4.91308	4.94363	9.110	0.500	0.56622	1.22417
38	210	A	1	3	1	3.28291	3.35018	1.860	2.000	1.26716	0.54701
39	210	B	1	2	1	.	.	.	.	.	.
40	210	B	1	4	1	3.52249	3.54774	3.780	0.500	0.67851	1.02157
41	211	A	2	2	1	3.62438	.	3.750	0.500	.	.
42	211	A	2	4	1	4.43336	4.47067	3.720	0.500	0.85633	0.80944
43	211	B	2	1	1	4.80010	4.85592	3.700	0.750	0.96489	0.71837
44	211	B	2	3	1	2.75398	2.78537	3.050	0.500	0.86660	0.79984
45	212	A	2	2	1	1.00670	1.02988	1.350	0.333	0.57992	1.19524

Obs	SUBJ	TRT	SEQ	PER	GROUP	auct	auci	CMAX	TMAX	THALF	kel
46	212	A	2	4	1	1.20455	1.22825	1.990	0.333	0.60848	1.13915
47	212	B	2	1	1	0.77237	0.79931	1.030	0.500	0.66217	1.04677
48	212	B	2	3	1	1.00206	1.03968	1.280	0.750	0.79024	0.87713
49	213	A	2	2	1	1.27013	.	1.080	0.750	.	.
50	213	A	2	4	1	2.23109	2.28742	1.990	0.750	1.39948	0.49529
51	213	B	2	1	1	1.67475	.	1.580	0.500	.	.
52	213	B	2	3	1	1.69449	.	1.920	0.750	.	.
53	214	A	2	2	1	.	.	.	.	.	.
54	214	A	2	4	1	1.77784	1.82644	1.650	0.750	0.83597	0.82916
55	214	B	2	1	1	1.64752	1.68253	1.790	0.500	0.79571	0.87110
56	214	B	2	3	1	2.01393	2.05720	1.680	0.750	0.75563	0.91731
57	215	A	1	1	1	1.33134	1.35761	1.800	0.333	0.64112	1.08115
58	215	A	1	3	1	1.83532	1.85737	2.390	0.500	0.52696	1.31536
59	215	B	1	2	1	1.46584	1.49096	1.930	0.333	0.62423	1.11040
60	215	B	1	4	1	2.76076	2.78493	2.950	0.500	0.64446	1.07554
61	216	A	2	2	1	4.70953	4.81947	1.860	5.000	3.03600	0.22831
62	216	A	2	4	1	.	.	.	.	.	.
63	216	B	2	1	1	7.52993	7.64706	2.230	2.500	2.58561	0.26808
64	216	B	2	3	1	5.86642	5.94982	1.970	1.750	2.30300	0.30098
65	217	A	1	1	1	3.17581	3.22452	1.980	1.000	1.03233	0.67144
66	217	A	1	3	1	3.08777	3.11370	2.860	0.500	0.65359	1.06053
67	217	B	1	2	1	2.80259	2.84068	2.160	0.750	0.82761	0.83753
68	217	B	1	4	1	2.99564	3.02492	3.510	0.500	0.58827	1.17828
69	218	A	1	1	1	2.29536	2.32827	4.440	0.333	0.50918	1.36130
70	218	A	1	3	1	1.97190	1.99648	3.080	0.500	0.67887	1.02103
71	218	B	1	2	1	2.57799	2.60378	2.100	0.333	0.68504	1.01184
72	218	B	1	4	1	1.92509	1.95783	2.380	0.500	0.68566	1.01091
73	219	A	1	1	1	.	.	.	.	.	.
74	219	A	1	3	1	.	.	.	.	.	.
75	219	B	1	2	1	.	.	.	.	.	.
76	219	B	1	4	1	.	.	.	.	.	.
77	220	A	2	2	1	3.75504	.	.	.	.	.
78	220	A	2	4	1	2.89815	3.13681	2.530	1.000	1.82186	0.38046
79	220	B	2	1	1	4.18663	4.30984	0.960	1.000	3.33597	0.20778
80	220	B	2	3	1	3.00713	3.19695	3.560	0.750	1.67826	0.41301
81	221	A	2	2	1	2.78913	.	1.700	0.750	.	.
82	221	A	2	4	1	3.38622	3.42138	3.920	0.333	0.66966	1.03507
83	221	B	2	1	1	2.91925	2.95097	3.310	0.750	0.64479	1.07500
84	221	B	2	3	1	2.36795	2.40571	2.900	0.750	0.72898	0.95084
85	222	A	1	1	1	1.75030	1.78051	2.980	0.333	0.69344	0.99958

Obs	SUBJ	TRT	SEQ	PER	GROUP	auct	auci	CMAX	TMAX	THALF	kel
86	222	A	1	3	1	2.07918	2.10419	2.390	0.500	0.59167	1.17151
87	222	B	1	2	1	.	.	.	.	.	.
88	222	B	1	4	1	2.68304	2.70527	2.660	0.750	0.60423	1.14716
89	223	A	2	2	1	2.61473	2.63900	4.460	0.333	0.52087	1.33075
90	223	A	2	4	1	1.15602	1.17657	1.800	0.333	0.45511	1.52303
91	223	B	2	1	1	2.39169	2.41539	4.330	0.500	0.61287	1.13099
92	223	B	2	3	1	1.76528	1.78484	3.020	0.500	0.47911	1.44673
93	224	A	1	1	1	7.38271	7.42998	6.130	0.750	1.23651	0.56057
94	224	A	1	3	1	4.98341	5.01413	6.470	0.333	0.65103	1.06469
95	224	B	1	2	1	3.70065	3.72948	4.970	0.500	0.67055	1.03371
96	224	B	1	4	1	2.68945	2.71920	2.950	0.500	0.76073	0.91116
97	225	A	1	1	1	2.77688	2.81818	2.760	0.750	1.13152	0.61258
98	225	A	1	3	1	3.40524	3.45911	3.680	0.750	1.14889	0.60332
99	225	B	1	2	1	.	.	.	.	.	.
100	225	B	1	4	1	1.99300	.	1.340	0.500	.	.
101	226	A	2	2	1	3.78730	3.81439	4.490	0.500	0.74830	0.92630
102	226	A	2	4	1	5.26875	5.31048	4.720	0.500	1.10001	0.63013
103	226	B	2	1	1	2.13934	2.19587	1.240	2.000	1.06464	0.65106
104	226	B	2	3	1	3.96694	4.02343	3.140	1.000	0.86234	0.80380
105	227	A	2	2	1	7.67455	7.77521	6.330	0.750	1.71442	0.40430
106	227	A	2	4	1	9.73802	.	6.630	0.750	.	.
107	227	B	2	1	1	9.36581	9.44359	6.880	0.750	1.32808	0.52192
108	227	B	2	3	1	8.96765	9.06940	11.500	0.500	1.50703	0.45994
109	228	A	1	1	1	1.12416	1.17046	1.280	0.500	1.02866	0.67383
110	228	A	1	3	1	1.49104	1.51514	1.250	0.500	0.61422	1.12851
111	228	B	1	2	1	.	.	.	.	.	.
112	228	B	1	4	1	1.44620	1.47494	1.520	0.500	0.56116	1.23520
113	229	A	1	1	1	1.83731	1.86266	2.060	0.500	0.67579	1.02568
114	229	A	1	3	1	2.61749	2.64624	3.110	0.500	0.64087	1.08157
115	229	B	1	2	1	1.87052	1.92626	1.780	0.750	0.67676	1.02422
116	229	B	1	4	1	2.53502	2.55843	2.770	0.750	0.57727	1.20074
117	230	A	2	2	1	2.74503	2.77161	3.050	0.750	0.69007	1.00446
118	230	A	2	4	1	1.35857	1.38011	1.380	0.500	0.50280	1.37858
119	230	B	2	1	1	1.80148	1.82442	2.270	0.500	0.53182	1.30335
120	230	B	2	3	1	3.50906	3.54316	2.970	0.750	0.78528	0.88268
121	231	A	1	1	1	.	.	.	.	.	.
122	231	A	1	3	1	.	.	.	.	.	.
123	231	B	1	2	1	.	.	.	.	.	.
124	231	B	1	4	1	.	.	.	.	.	.
125	232	A	2	2	1	.	.	.	.	.	.

Obs	SUBJ	TRT	SEQ	PER	GROUP	auct	auci	CMAX	TMAX	THALF	kel
126	232	A	2	4	1	.	.	.	.	.	.
127	232	B	2	1	1	.	.	.	.	.	.
128	232	B	2	3	1	.	.	.	.	.	.
129	233	A	1	1	1	6.00900	6.07919	3.670	0.750	1.34039	0.51712
130	233	A	1	3	1	2.03409	2.07260	1.620	0.500	1.06339	0.65183
131	233	B	1	2	1	2.14920	2.19143	1.880	0.500	1.08427	0.63927
132	233	B	1	4	1	1.27533	1.32412	1.060	0.750	1.06017	0.65381
133	234	A	2	2	1	4.35337	4.38921	4.050	0.750	0.94812	0.73107
134	234	A	2	4	1	5.07824	5.12481	3.550	0.750	1.00257	0.69137
135	234	B	2	1	1	4.76718	4.80874	2.980	1.000	0.98645	0.70267
136	234	B	2	3	1	3.79238	3.86491	2.260	1.500	1.40023	0.49502
137	235	A	1	1	1	2.68436	2.73424	2.250	0.500	1.18403	0.58541
138	235	A	1	3	1	1.81048	1.83755	2.060	0.500	0.72466	0.95652
139	235	B	1	2	1	2.54666	2.58015	3.030	0.500	0.81456	0.85094
140	235	B	1	4	1	3.03018	3.06804	4.320	0.500	0.94060	0.73692
141	236	A	2	2	1	1.77615	1.80180	1.670	0.750	0.65839	1.05280
142	236	A	2	4	1	1.53601	1.57671	1.500	0.500	0.80360	0.86255
143	236	B	2	1	1	1.66991	1.70289	1.790	0.500	0.59229	1.17029
144	236	B	2	3	1	2.24868	2.27345	3.540	0.500	0.64055	1.08212
145	237	A	1	1	1	0.65938	0.69518	0.673	0.750	0.73192	0.94702
146	237	A	1	3	1	0.76033	0.78490	1.080	0.500	0.44468	1.55875
147	237	B	1	2	1	0.46943	0.51058	0.594	0.500	0.59427	1.16638
148	237	B	1	4	1	0.62147	0.65810	0.513	1.000	0.87552	0.79170
149	238	A	1	1	1	1.88157	1.90155	2.320	0.500	0.53472	1.29628
150	238	A	1	3	1	2.48405	2.51501	2.210	0.500	0.79483	0.87206
151	238	B	1	2	1	2.09083	2.12161	2.830	0.500	0.70409	0.98446
152	238	B	1	4	1	2.05909	2.08426	1.950	0.750	0.68412	1.01319
153	239	A	2	2	1	.	.	.	.	.	.
154	239	A	2	4	1	.	.	.	.	.	.
155	239	B	2	1	1	.	.	.	.	.	.
156	239	B	2	3	1	.	.	.	.	.	.
157	240	A	2	2	1	6.17300	6.21538	3.760	0.750	1.04174	0.66538
158	240	A	2	4	1	2.78950	2.81667	2.410	0.500	0.71073	0.97526
159	240	B	2	1	1	3.03188	3.08688	3.050	0.750	1.11154	0.62359
160	240	B	2	3	1	2.78944	2.82200	2.010	0.500	0.79460	0.87233
161	241	A	1	1	1	2.50292	2.53328	1.850	0.500	0.67036	1.03399
162	241	A	1	3	1	2.08496	2.10998	2.670	0.500	0.57044	1.21511
163	241	B	1	2	1	3.53603	3.57116	3.510	0.333	0.70580	0.98208
164	241	B	1	4	1	2.48786	2.51218	3.290	0.500	0.55083	1.25836
165	242	A	2	2	1	0.78907	0.82534	0.810	0.500	0.72027	0.96235

Obs	SUBJ	TRT	SEQ	PER	GROUP	auct	auci	CMAX	TMAX	THALF	kel
166	242	A	2	4	1	1.13057	1.16100	1.330	0.500	0.66529	1.04188
167	242	B	2	1	1	1.00077	1.03789	0.619	1.000	0.83270	0.83241
168	242	B	2	3	1	0.75201	0.77742	1.070	0.500	0.54527	1.27119
169	243	A	1	1	1	2.87736	2.91724	2.220	1.500	0.96984	0.71470
170	243	A	1	3	1	.	.	.	.	.	.
171	243	B	1	2	1	1.50121	1.53181	1.970	0.750	0.69094	1.00319
172	243	B	1	4	1	.	.	.	.	.	.
173	244	A	2	2	1	1.17410	1.20471	1.120	0.750	0.74194	0.93424
174	244	A	2	4	1	1.38741	1.41730	2.080	0.500	0.80914	0.85664
175	244	B	2	1	1	1.04107	1.08644	0.646	1.000	1.11141	0.62367
176	244	B	2	3	1	1.80324	1.82802	2.270	0.500	0.60268	1.15010
177	245	A	1	1	1	1.17915	1.20557	1.790	0.500	0.66347	1.04474
178	245	A	1	3	1	1.27548	1.30798	1.290	0.500	0.61731	1.12286
179	245	B	1	2	1	1.29731	1.34877	1.420	0.333	0.94111	0.73652
180	245	B	1	4	1	1.71794	1.75558	2.100	0.500	0.94882	0.73053
181	246	A	1	1	1	4.16644	4.21268	3.980	0.750	1.21420	0.57087
182	246	A	1	3	1	3.50057	3.55463	3.230	0.500	1.36254	0.50872
183	246	B	1	2	1	4.08989	4.13590	3.990	0.750	1.15142	0.60199
184	246	B	1	4	1	4.27395	.	2.480	0.750	.	.
185	247	A	2	2	1	5.13650	5.19555	3.300	0.750	1.33758	0.51821
186	247	A	2	4	1	5.55176	5.59710	5.930	0.500	1.19055	0.58221
187	247	B	2	1	1	7.51766	7.58040	11.600	0.500	1.55877	0.44468
188	247	B	2	3	1	3.80751	3.84801	2.990	0.750	1.10956	0.62470
189	248	A	2	2	1	2.66188	2.71060	1.350	0.750	1.11813	0.61992
190	248	A	2	4	1	3.30613	3.36504	1.080	0.750	1.60117	0.43290
191	248	B	2	1	1	3.47950	3.54347	1.630	0.500	1.24221	0.55800
192	248	B	2	3	1	2.32720	2.40452	0.943	1.500	1.86108	0.37244

Note: The reviewer does not agree with the firm's calculation of Kel and AUCi. However the SAS program for four-way replicate design can be done only using the SAS code 'Continu". Since with the continu program, the reviewer-calculated pK parameters cannot be obtained, so the reviewer run the SAS program for 2 way cross over design to obtain the pK parameters. Then the reviewer re-run the SAS program for four-way replicate design by using reviewer calculated pK parameters to calculate the confidence intervals.

4.4.2 Fasting Study Output

Ln AUCt

Covariance Parameter Estimates			
Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.5431
FA(2,1)	subj		0.5135
FA(2,2)	subj		0
Residual	subj	TRT A	0.06772
Residual	subj	TRT B	0.07485

Ln AUC∞

Covariance Parameter Estimates			
Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.5288
FA(2,1)	subj		0.5039
FA(2,2)	subj		0
Residual	subj	TRT A	0.06725
Residual	subj	TRT B	0.07689

Ln Cmax

Covariance Parameter Estimates			
Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.4712
FA(2,1)	subj		0.4882
FA(2,2)	subj		1.36E-17
Residual	subj	TRT A	0.1161
Residual	subj	TRT B	0.1437

LAUCT

Model Information	
Data Set	WORK.REPL
Dependent Variable	lauct
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	TRT
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information		
Class	**Levels**	**Values**
SEQ	2	1 2
subj	48	201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240 241 242 243 244 245 246 247 248
PER	4	1 2 3 4
TRT	2	A B

Dimensions	
Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	48
Max Obs Per Subject	4
Observations Used	155
Observations Not Used	37
Total Observations	192

Iteration History			
Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	291.22585938	
1	3	159.15622323	0.00216968
2	2	159.02333433	0.00037809
3	3	158.99814559	0.00002106
4	1	158.99692534	0.00000000

Convergence criteria met.

Estimated G Matrix					
Row	Effect	TRT	subj	Col1	Col2
1	TRT	A	201	0.2950	0.2789
2	TRT	B	201	0.2789	0.2637

Covariance Parameter Estimates			
Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.5431
FA(2,1)	subj		0.5135
FA(2,2)	subj		0
Residual	subj	TRT A	0.06772
Residual	subj	TRT B	0.07485

Fit Statistics	
-2 Res Log Likelihood	159.0
AIC (smaller is better)	167.0
AICC (smaller is better)	167.3
BIC (smaller is better)	174.5

Null Model Likelihood Ratio Test		
DF	Chi-Square	Pr > ChiSq
3	132.23	<.0001

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
SEQ	1	39.1	1.71	0.1989
PER	3	111	0.42	0.7389
TRT	1	106	0.11	0.7460

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T VS. R	0.01406	0.04330	106	0.32	0.7460	0.1	-0.05779	0.08592

Least Squares Means						
Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > |t|
TRT	A	0.8869	0.08983	39.1	9.87	<.0001
TRT	B	0.8728	0.08617	39.6	10.13	<.0001

Obs	PARAMETER	LCI	UCI
1	LAUCT	94.3848	108.972

LAUCI

Model Information	
Data Set	WORK.REPL
Dependent Variable	lauci
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	TRT
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information		
Class	**Levels**	**Values**
SEQ	2	1 2
subj	48	201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240 241 242 243 244 245 246 247 248
PER	4	1 2 3 4
TRT	2	A B

Dimensions	
Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	48
Max Obs Per Subject	4
Observations Used	146
Observations Not Used	46
Total Observations	192

Iteration History			
Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	268.46469843	
1	3	153.81672280	0.00082787
2	2	153.76722954	0.00013474
3	3	153.75786400	0.00000466
4	1	153.75762343	0.00000000

Convergence criteria met.

Estimated G Matrix					
Row	Effect	TRT	subj	Col1	Col2
1	TRT	A	201	0.2796	0.2665
2	TRT	B	201	0.2665	0.2540

Covariance Parameter Estimates			
Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.5288
FA(2,1)	subj		0.5039
FA(2,2)	subj		0
Residual	subj	TRT A	0.06725
Residual	subj	TRT B	0.07808

Fit Statistics	
-2 Res Log Likelihood	153.8
AIC (smaller is better)	161.8
AICC (smaller is better)	162.1
BIC (smaller is better)	169.2

Null Model Likelihood Ratio Test		
DF	Chi-Square	Pr > ChiSq
3	114.71	<.0001

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
SEQ	1	39.3	1.91	0.1746
PER	3	101	0.34	0.7957
TRT	1	100	0.00	0.9575

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T VS. R	0.002441	0.04574	100	0.05	0.9575	0.1	-0.07349	0.07837

Least Squares Means						
Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > |t|
TRT	A	0.9085	0.08819	39.1	10.30	<.0001
TRT	B	0.9061	0.08574	39.8	10.57	<.0001

Obs	PARAMETER	LCI	UCI
1	LAUCI	92.9146	108.152

LCMAX

Model Information	
Data Set	WORK.REPL
Dependent Variable	lcmax
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	TRT
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information		
Class	**Levels**	**Values**
SEQ	2	1 2
subj	48	201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240 241 242 243 244 245 246 247 248
PER	4	1 2 3 4
TRT	2	A B

Dimensions	
Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	48
Max Obs Per Subject	4
Observations Used	155
Observations Not Used	37
Total Observations	192

Iteration History			
Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	294.30396534	
1	4	220.64665504	0.04593161
2	1	219.31293199	0.00146077
3	1	219.27191215	0.00000326
4	1	219.27182315	0.00000000

Convergence criteria met.

Estimated G Matrix					
Row	Effect	TRT	subj	Col1	Col2
1	TRT	A	201	0.2220	0.2300
2	TRT	B	201	0.2300	0.2384

Covariance Parameter Estimates			
Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.4712
FA(2,1)	subj		0.4882
FA(2,2)	subj		1.36E-17
Residual	subj	TRT A	0.1161
Residual	subj	TRT B	0.1437

Fit Statistics	
-2 Res Log Likelihood	219.3
AIC (smaller is better)	227.3
AICC (smaller is better)	227.5
BIC (smaller is better)	234.8

Null Model Likelihood Ratio Test		
DF	Chi-Square	Pr > ChiSq
3	75.03	<.0001

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
SEQ	1	39.5	0.31	0.5830
PER	3	110	0.20	0.8936
TRT	1	109	0.35	0.5581

Estimates								
Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T VS. R	0.03430	0.05838	109	0.59	0.5581	0.1	-0.06256	0.1311

Least Squares Means						
Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > |t|
TRT	A	0.8676	0.08327	40.1	10.42	<.0001
TRT	B	0.8333	0.08785	40.2	9.49	<.0001

Obs	PARAMETER	LCI	UCI
1	LCMAX	93.9361	114.014

Obs	parameter	_NAME_	A	B	ratio
1	LAUCI	gm	2.48059	2.47455	1.00
2	LAUCT	gm	2.42752	2.39362	1.01
3	LCMAX	gm	2.38108	2.30080	1.03

Obs	PARAMETER	LCI	UCI
1	LAUCT	94.3848	108.972
2	LAUCI	92.9146	108.152
3	LCMAX	93.9361	114.014

Obs	parameter	_NAME_	A	B	ratio	LCI	UCI
1	LAUCI	gm	2.48059	2.47455	1.00	92.9146	108.152
2	LAUCT	gm	2.42752	2.39362	1.01	94.3848	108.972
3	LCMAX	gm	2.38108	2.30080	1.03	93.9361	114.014

SUMMARY OF STATISTICAL ANALYSIS
REPLICATE DESIGN-LN-TRANSFORMED DATA

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCI	2.480594	2.4745455	1	92.915	108.152
LAUCT	2.4275189	2.3936192	1.01	94.385	108.972
LCMAX	2.3810764	2.300797	1.03	93.936	114.014

BIOEQUIVALENCE DEFICIENCIES

ANDA: 201050

APPLICANT: Roxane Laboratories, Inc

DRUG PRODUCT: Phenoxybenzamine Hydrochloride Capsules USP, 10 mg

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet and found the following deficiencies.

Following the inspection of the analytical site, (b) (4) (b) (4) (b) (4), by the Division of Scientific Investigations (DSI) for bioequivalence (BE) study from another application, Form FDA- 483 was issued for the site. Subsequently, the analytical site provided its response to Form 483 and this response was included in the final evaluation by the DSI, which recommended that the inspected study be considered unacceptable based on the DSI original findings and the site's response.

(b) (4)

(b) (4)

Please address the above specific findings by the DSI with respect to their impact on the BE study of the current ANDA, providing any necessary supporting documents in your response.

We acknowledge that you will conduct dissolution testing as per the current USP monograph for Phenoxybenzamine Capsules.

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

4.5 Outcome Page

ANDA: 201050

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
12700	12/7/2009	Bioequivalence Study	Fasting Study	1	1
12700	7/21/2010	Other	DSI Inspection Report	1	1
				Bean Total:	2

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/s/

SUMAN DANDAMUDI
12/22/2010

SHRINIWAS G NERURKAR
12/22/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
12/22/2010

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	0201050
Drug Product Name	Phenoxybenzamine Hydrochloride Capsules, USP
Strength (s)	10 mg
Applicant Name	Roxane Laboratories, Inc.
Address	1809 Wilson Rd, Columbus, OH 43228
Applicant's Point of Contact	Elizabeth Ernst, Director – DRA-MA
Contact's Phone Number	(614) 272-4785
Contact's Fax Number	(614) 276-2470
Submission Date(s)	December 07, 2009
First Generic	Yes
Reviewer	Zakia R. Williams, Ph.D.
Study Number (s)	Fasted
Study Type (s)*	PHEN-C10-PVFS-1
Strength(s)	10 mg
Clinical Site	CEDRA Clinical Research, LLC
Clinical Site Address	2455 N.E. Loop 410, Suite 150 San Antonio, Texas 78217 210.635.1500
Analytical Site	(b) (4)
Analytical Address	
OUTCOME DECISION	ADEQUATE
DSI INSPECTION RESULT	N/A

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	**DISSOLUTION**	**10 mg**	**ADEQUATE**

* The OGD recommends only a fasting study to demonstrate BE of Phenoxybenzamine Hydrochloride Capsules (http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm089465.pdf)

1. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is a USP method for this product. The firm's dissolution testing data on its test product Phenoxybenzamine Hydrochloride Capsules USP, 10 mg using the USP method are acceptable at the S1 level. The DBE acknowledges that the firm will follow the USP method using 500 mL of 0.1 N HCl in USP Apparatus I (Basket) at a speed of 100 rpm. The data will meet the USP specification of NLT 75% (Q) of the labeled amount of Phenoxybenzamine is dissolved in 45 minutes.

The DBE will review the fasted BE study at a later date.

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

Submitted along with the following table, the firm stated "In vitro dissolution data is provided in table format as requested by the Division of Bioequivalence. The dissolution testing was conducted using the method recommended by the FDA Division of Bioequivalence in the correspondence letter dated April 22, 2008." It is noted that the DBE had recommended that the firm conduct dissolution testing using the method specified in the USP (V:\Firmsnz\roxane\ltrs&rev\P08-009).

Dissolution Conditions										
					Apparatus:	USP Apparatus I (Baskets)				
					Speed of Rotation:	100 rpm				
					Medium:	0.1 N HCl				
					Volume:	500 mL				
					Temperature	37.0° +/- 0.5° C				
Firm's Proposed Specifications					**NLT 75% (Q) of the labeled amount dissolves in 45 minutes**					
Dissolution Testing Site (Name, Address)					**Boehringer Ingelheim Roxane Inc. 1809 Wilson Road Columbus, Ohio 43228**					
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 COA Attached to 2.7.1.4**
						10	**20**	**30**	**45**	
Study Report #: NA	7/21/2009	Dibenzyline® (Phenoxybenzamine Hydrochloride) Capsules USP, 10 mg WellSpring Pharmaceuticals Lot No.8A3991 Expiration date 01/2011	10 mg capsules	12	Mean %	101	102	102	101	
					Range %	(b) (4)				
					%CV	3.6	3.1	3.3	3.2	
Study Report #: NA	7/21/2009	Phenoxybenzamine Hydrochloride Capsules USP, 10 mg Roxane Lot No. 4000064 Manufacture Date 7/15/2009	10 mg capsules	12	Mean %	94	96	98	102	
					Range %	(b) (4)				
					%CV	7.5	6.7	6.8	6.6	

2. COMMENTS:

1. The firm conducted acceptable *in vitro* dissolution testing on its test product Phenoxybenzamine Hydrochloride Capsules USP, 10 mg (Lot No. 4000064) comparing it to WellSpring Pharmaceutical's reference listed drug (RLD) product Dibenzyline® (phenoxybenzamine hydrochloride) Capsules, 10 mg (Lot No. 8A3991) using the USP method. The firm's data meet the specification of Not Less Than (NLT) 75% (Q) in 45 minutes at the S1 level. The dissolution testing is **acceptable**.

3. DEFICIENCY COMMENTS:

None

4. RECOMMENDATIONS:

The *in vitro* dissolution testing conducted by Roxane Laboratories on its test product Phenoxybenzamine Hydrochloride Capsules USP, 10 mg (Lot No. 4000064) is acceptable. The DBE acknowledges that the firm will conduct dissolution testing using the following USP method and specification:

Apparatus:	USP Type I (Basket)
Speed of Rotation:	100 rpm
Medium:	0.1 N HCl
Volume:	500 mL
Temperature:	37 ± 0.5° C
NLT 75% (Q) of the labeled amount of Phenoxybenzamine is dissolved in 45 minutes	

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 0201050

APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Phenoxybenzamine Hydrochloride Capsules USP, 10 mg

The Division of Bioequivalence has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the fasted bioequivalence study will be conducted later.

Your dissolution testing using the USP method is acceptable. We acknowledge that you will conduct dissolution testing for the test product using the method and specification as described in the USP monograph for Pheonxybenzamine Hydrochloride Capsules.

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

5. OUTCOME

ANDA: 0201050

Enter Review Productivity and Generate Report

(b) (4)

Completed Assignment for 201050 ID: 11101

Reviewer: Williams, Zakia **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Phenoxybenzamine HCl Capsules, USP 10 mg

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
11101	12/7/2009	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201050	ORIG-1	ROXANE LABORATORIES INC	Phenoxybenzamine Hydrochloride

---

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/s/

ZAKIA R WILLIAMS
05/25/2010

NILUFER M TAMPAL
05/26/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
05/26/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201050

OTHER REVIEWS

M E M O R A N D U M

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

DATE: March 30, 2012

TO: Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence I, OGD

FROM: Jyoti B. Patel, Ph.D.
Division of Bioequivalence and GLP Compliance
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 (OSI)
and
William H. Taylor, Ph.D., DABT
Director (Acting),
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIR Covering ANDA 201-050, phenoxybenzamine hydrochloride capsules USP, 10 mg, sponsored by Roxane Laboratories, Inc.

At the request of the Division of Bioequivalence I, OGD, the Division of Bioequivalence and GLP Compliance conducted an audit of the bioanalytical portion of the following study:

Study Number: PHEN-C10-PVFS-1
Study Title: "A single-dose, two-treatment, four-period, replicate design bioequivalence study of phenoxybenzamine hydrochloride 10 mg capsules under fasted conditions"

The inspection and data audit of the bioanalytical portion were conducted at (b) (4)

The concerns and the deficiencies noted by the review division were investigated during this 'For Cause' inspection. Following the inspection, no Form FDA 483 was issued at the analytical

site; however, there were some discussion items, which address the concerns raised by the review division. Provided below are the discussion items and DBGC's evaluation.

(b) (4)

[redacted]

(b) (4)

Conclusions:

Following the inspection of the bioanalytical portion of Study PHEN-C10-PVFS-1, **DBGC recommends that the study data should be accepted for review.**

Jyoti B. Patel, Ph.D.

Final Classification:
NAI: (b) (4)

CC:
CDER OSI PM TRACK
OSI/DBGC/Taylor/Haidar/Skelly/Dejernett/Patel/CF (HFD-48)
OPS/OGD/DBI/Conner/Ramson/Dandamudi/Nerurkar
HFR-SW1540/Martinez (BIMO)/Ramirez
HFR-SW1515/Bias (BIMO)

HFR-SW150/Turcovski (DIB)
Draft: JBP 3/30/2012
Edit: MFS 3/30/12
OSI: 6252; O:\BE\EIRCOVER\201050.rox.phe.doc
FACTS: **1318241**

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/s/

JYOTI B PATEL
04/02/2012

SAM H HAIDAR
04/03/2012

WILLIAM H TAYLOR
04/04/2012

MEMORANDUM

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

DATE: August 24, 2011

TO: Director, Investigations Branch
Dallas District Office (DAL-DO)
4040 N. Central Expressway, Suite 300
Dallas, TX 75204

FROM: Martin K. Yau, Ph.D.
Acting Team Leader—Bioequivalence Branch
Division of Bioequivalence and Good Laboratory Practice Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2011, **High Priority CDER ANDA, For-Cause Pre-Approval Data Validation Inspection**, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: ANDA 201-050
DRUG: Phenoxybenzamine Hydrochloride Capsules USP, 10 mg
SPONSOR: Roxane Laboratories, Inc.
1809 Wilson Road
Columbus, OH 43228
SPONSOR'S CONTACT: Elizabeth Ernst
Executive Director, Drug Regulatory Affairs and Medical Affairs
TEL: 1-614-272-4785
FAX: 1-614-276-2470
EMAIL ADDRESS: Not available

This memo requests a For-Cause inspection of the analytical portion of the following bioequivalence study. **This inspection should be completed before December 31, 2011.**

Please provide a minimum period of advance notice to the inspectional site. The site should not be informed in advance of the application, drug name, the name of the analytical investigator, the study to be audited or the focus of the inspection. The studies will be identified to the firm at the start of the inspection.

Study PHEN-C10-PVFS-1: "A Single-Dose, Two-Treatment, Four-Period, Replicate Design Bioequivalence Study of Phenoxybenzamine Hydrochloride 10 mg Capsules Under Fasted Conditions"

Analytical Site: (b) (4)

Analytical Investigator: (b) (6) B.S.

(b) (4)

Following identification of the investigator background material will be forwarded directly. **An OSI scientist with specialized knowledge may participate in this inspection to provide scientific and technical expertise.**

Headquarters Contact Person: Abhijit Raha, Ph.D.
(301)-796-3708

cc:

CDER OSI PM TRACK
OSI/DBGC/Salewski/Haidar/Dejernett/Raha/CF
HFD-650/Teresa Ramson (DBE-I)
HFR-SW1540/Joel Martinez (BIMO)
HFR-SW1515/Alanna Bias (BIMO)
HFR-SW150/Susan Turcovski (DIB)
Draft: AR 8/23/2011, 8/24/2011
Edit: MKY 8/24/2011(2)
DSI: 6252; O:\BE\assigns\bio201050.doc
FACTS: 1318241

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/s/

ABHIJIT RAHA
08/24/2011

MARTIN K YAU
08/25/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201050

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ **APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **CGMP**

Division: IV	**Team: 41**	**PM: Dat Doan**

Electronic ANDA: Yes ☒ No ☐

ANDA #:201050
Firm Name:Roxane Laboratories, Inc.
ANDA Name:Phenoxybenzamine Hydrochloride Capsules USP, 10 mg
RLD Name:Dibenzyline® Capsules; NDA 008708; Wellspring Pharmaceutical Corppration

Electronic AP Routing Summary Located:
V:\Chemistry Division IV\Team 41\Electronic AP Summary

AP/TA Letter Located:
V:\Chemistry Division IV\Team 41\Final Version For DARRTS Folder

Project Manager Evaluation: **Date:** **Initials:**

☐ Previously reviewed and tentatively approved --- Date _____
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date 12/8/09	Date of Application 12/7/09	Date Acceptable for Filing _____
Patent Certification (type) II	Date Patent/Excl. expires	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ **DMF#:** _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☐ Acceptable ☐ OAI *EES Date Acceptable:*_____ ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) 10/26/11 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 4/4/12 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 4/22/11 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) _____

Methods Val. Samples Pending: Yes ☐ No ☐**;** Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☐ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☐ (If yes, enter dissolution information in Letter)

Routing:

☐ Labeling Endorsement, Date emailed: _____ REMS Required: Yes ☐ No ☐ REMS Acceptable: Yes ☐ No ☐

☐ Regulatory Support

☐ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

☒ Division

☐ 1st Generic Review

☐ Bob West / Peter Rickman
☐ Keith Webber

☐Filed AP Routing Summary in DARRTs	☐Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 4/6/2012**

Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD =Dibenzyline NDA# 8-708 Date Checked N/A Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☐ No ☐ Was applicant sued w/in 45 days:Yes ☐ No ☐ Has case been settled: Yes ☐ No ☐ Date settled: Is applicant eligible for 180 day	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒	
Type of Letter: ☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:	
Comments:ANDA submitted on 12/8/2009, BOS=Dibenzyline, NDA 08-708, PII cert. ANDA ack for filing on 12/8/2009 (LO dated 12/23/2009). There are no remaining unexpired patents which protect the RLD. This ANDA is eligible for immediate Full Approval.	

2. ***Labeling Endorsement***

Reviewer, :
Date_____
Initials_____

Labeling Team Leader, :
Date 7/16/12
Initials rlw/for

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☐n/a

Comments:

From: Vezza, Adolph E
Sent: Thursday, April 05, 2012 5:06 PM
To: Doan, Dat
Cc: Barlow, James T
Subject: FW: Please endorse 201050/Phenoxybenzamine/Roxane
Importance: High

Hi Dat,

Labeling still current.

Adolph

From: Doan, Dat
Sent: Thursday, April 05, 2012 4:03 PM
To: Barlow, James T; Vezza, Adolph E
Subject: Please endorse 201050/Phenoxybenzamine/Roxane
Importance: High

thanks

Dat Doan, Pharm.D.

3. ***Paragraph IV Evaluation*** **PIV's Only**

David Read — **Date 7/16/12**
OGD Regulatory Counsel — **Initials rlw/for**

Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:N/A. There are no paragraph IV certifications associated with this ANDA.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 5/16/2012**

Chemistry Div. **IV (Iser)** — **InitialsRLI**

Comments:CMC OK, no additional first generic review is neecessary.

5. ***First Generic Evaluation*** **First Generics Only**

Frank Holcombe — **Date 7/16/12**
Assoc. Dir. For Chemistry — **Initials rlw/for**

Comments: (First generic drug review)
N/A. See R. Iser's comment above.

OGD Office Management Evaluation

6. Peter Rickman — **Date 7/16/12**

Director, DLPS — **Initials rlw/for**

Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments: Bioequivalence studies (fasting only per Guidance) found acceptable. DSI inspection of analytical study analysis site, [redacted] (b) (4) (requested on for cause basis) found acceptable. Dosing site has acceptable DSI inspection history. Office-level bio endorsed 12/22/10, 4/4/12.

Final-printed labeling (FPL) found acceptable for approval 4/22/11 as endorsed 4/5/12. Verified via email from J. Barlow to R. West dated 7/16/12.

CMC found acceptable for approval (Chemistry Review #2A) 5/16/12.

AND/OR

7. Robert L. West — **Date 7/16/12**

Deputy Director, OGD — **Initials RLWest**

Para.IV Patent Cert: Yes☐ No☒
Pending Legal Action: Yes☐ No☒
Petition: Yes☐ No☒
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 7/10/12 (Verified 7/16/12). No "OAI" Alerts noted.

There are no patents or exclusivity listed in the current "Orange Book" for this drug product.

This first-generic ANDA is recommended for approval. It is the subject of a Medical Necessity determination.

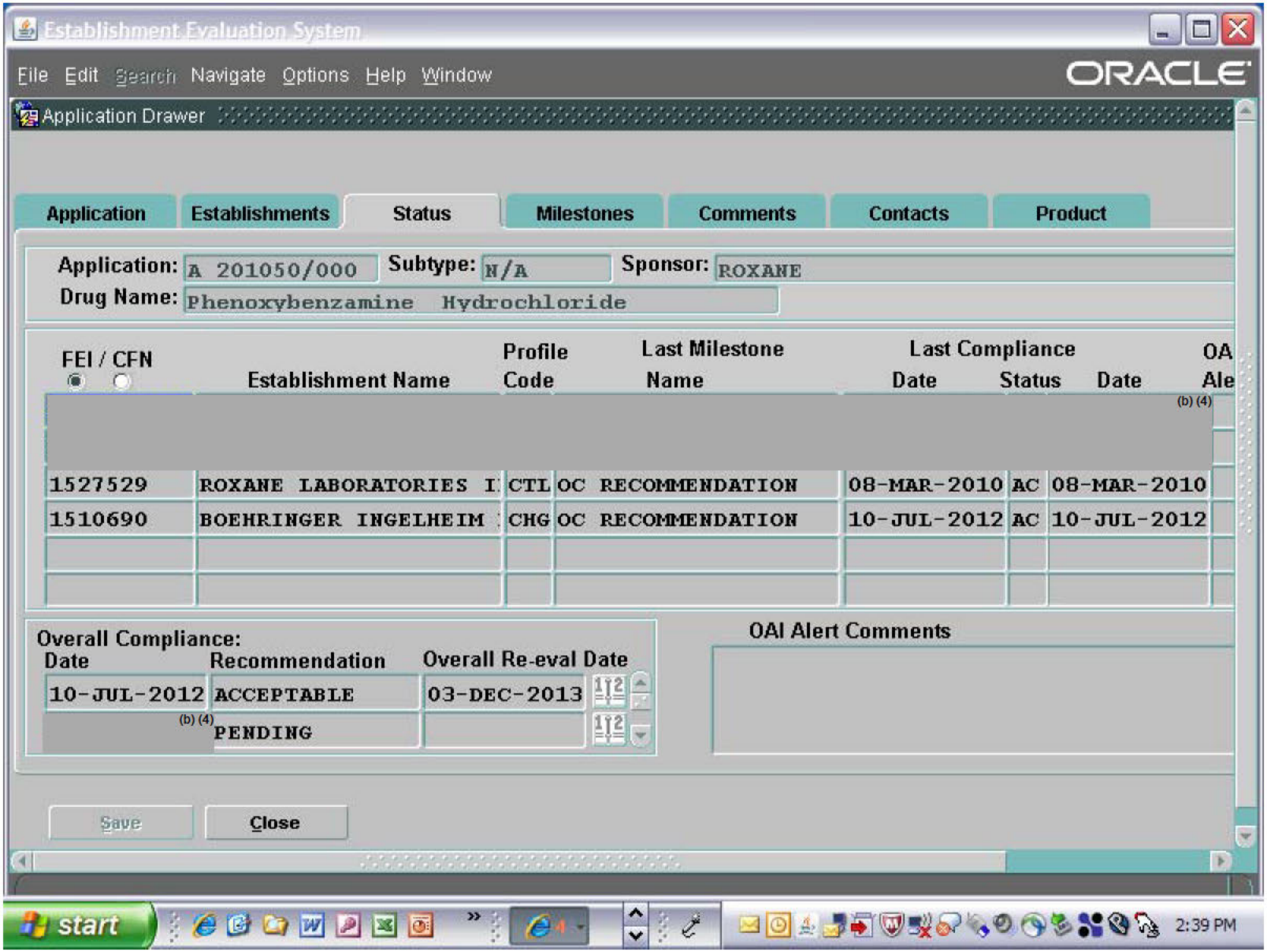
8. ***OGD Director Evaluation***
   Keith Webber
   Deputy Director, OPS
   Comments: RLWest for Gregory P. Geba, M.D., M.P.H. 7/16/12.
   First Generic Approval ☒
   PD or Clinical for BE ☐
   Special Scientific or Reg.Issue ☐
   Press Release Acceptable ☐

   Comments:

9. Project Manager
   Date 7/16/12
   Initials dd

   Check Communication and Routing Summary into DARRTS

EER DATA:



Reference ID: 3159722

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

- 
-  [1]
-  [2]

- FDA Home[3]
- Drug Databases[4]
- Orange Book[5]

-

Patent and Exclusivity Search Results from query on Appl No 008708 Product 001 in the OB_Rx list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

Exclusivity Data

There is no unexpired exclusivity for this product.

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/s/

DAT T DOAN
07/16/2012

MEMORANDUM

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

Date Requested: 8/5/2011

TO: Sam Haidar, Ph.D., R.Ph.
Acting Branch Chief for Bioequivalence and GLP
Division of Scientific Investigations
WO, Bldg 51, Room 5210

FROM: Dale P. Conner, Pharm D
Director, Division of Bioequivalence I, HFD-650

SUBJECT Biopharmaceutics Compliance Program 7348.001

REQUEST FOR INSPECTION:

Electronic Submission: Yes
Bio Study Status: Completed Inadequate
Priority: B
Due Date: 11/3/2011

DIVISION OF BIOEQUIVALENCE REVIEW OF AN AMENDMENT

ANDA No.	201050
Drug Product Name	Phenoxybenzamine Hydrochloride Capsules USP
Strength(s)	10 mg
Applicant Name	Roxane Laboratories, Inc.
Address	1809 Wilson Road Columbus, Ohio 43228
Applicant's Point of Contact	Elizabeth Ernst
Contact's Telephone Number	614-272-4785
Contact's Fax Number	614-276-2470
Original Submission Date(s)	December 7, 2009 November 18, 2010 (Telephone Amendment)
Submission Date(s) of Amendment(s) Under Review	February 8, 2011 March 21, 2011
Reviewer	Suman Dandamudi
Study Number (s)	PHEN-C10-PVFS-1
Study Type (s)	Fasting

Strength (s)	10 mg
Analytical Site	(b) (4)
Analytical Site Address	

Reason for Inspection: For Cause

Comments: Please inspect the Analytical site.

Bio Study Status: Completed, pending DSI.
Project Manager: Ramson, Teresa

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/s/

TERESA V RAMSON
08/05/2011

SUMAN DANDAMUDI
08/05/2011

SHRINIWAS G NERURKAR
08/05/2011

DALE P CONNER
08/08/2011

Please send an email to the labeling reviewer (james.barlows@fda.hhs.gov) to confirm that you received the labeling comments

Labeling Comments

ANDA 201050

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8988)

TO: Roxanne Laboratories Inc. TEL: (614) 272-4785

ATTN: Mukul Agrawal and/or Marrissa Craddock FAX: (614) 276-2470

FROM: James Barlow

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Phenoxybenzamine HCL capsules USP

Pages (including cover and signature page): 3

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 201050
Date of Submission: December 7, 2009
Applicant's Name: Roxane Laboratories, Inc.
Established Name: **Phenoxybenzamine Hydrochloride Capsules USP, 10 mg**

Labeling Deficiencies:

1. **CONTAINER** – 100s

   Delete the comma after "Capsules" to read as follows –

   Phenoxybenzamine
   Hydrochloride
   Capsules USP

2. **PACKAGE INSERT -**

   a. See comments above under CONTAINER.

   b. Title: Established Name

   Please relocate the name and address of the firm from the top of the package insert directly above the established name -

   Phenoxybenzamine
   Hydrochloride
   Capsules USP

Revise your labels and labeling as requested above and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

JAMES T BARLOW
04/11/2011

BIOEQUIVALENCE AMENDMENT

ANDA 201050

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Roxane Laboratories, Inc. TEL: 614-272-4785

ATTN: Elizabeth Ernst FAX: 614-276-2470

FROM: Teresa Ramson FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on December 7, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Phenoxybenzamine Hydrochloride Capsules USP, 10 mg.

Reference is also made to your amendment dated November 18, 2010.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Effective 01-Aug-2010, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

After the effective date, 01-Aug-2010, ANDAs will only be accepted at the new mailing address listed above. DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 201050

APPLICANT: Roxane Laboratories, Inc

DRUG PRODUCT: Phenoxybenzamine Hydrochloride Capsules USP, 10 mg

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet and found the following deficiencies.

Following the inspection of the analytical site, (b) (4) by the Division of Scientific Investigations (DSI) for bioequivalence (BE) study from another application, Form FDA- 483 was issued for the site. Subsequently, the analytical site provided its response to Form 483 and this response was included in the final evaluation by the DSI, which recommended that the inspected study be considered unacceptable based on the DSI original findings and the site's response.

(b) (4)

Please address the above specific findings by the DSI with respect to their impact on the BE study of the current ANDA, providing any necessary supporting documents in your response.

We acknowledge that you will conduct dissolution testing as per the current USP monograph for Phenoxybenzamine Capsules.

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

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/s/

DALE P CONNER
01/04/2011

QUALITY DEFICIENCY - MINOR

ANDA 201050

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Roxane Laboratories, Inc. TEL: (614) 272-4785

ATTN: Elizabeth Ernst FAX: (614) 276-2470

FROM: Dat Doan FDA CONTACT PHONE: (240) 276-8573

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 07, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Phenoxybenzamine Hydrochloride Capsules USP, 10 mg.

Reference is also made to your amendment dated March 5, 2010.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20857

*After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010.** For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/*

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 201050 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Phenoxybenzamine Hydrochloride Capsules USP, 10 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide current room temperature stability data.

2. The labeling information submitted in the application is being reviewed by Labeling Division and Program Support. Any deficiencies found will be communicated to you under a separate cover.

3. The information submitted to the Division of Bioequivalence is under review. Any deficiencies found will be communicated to you under a separate cover.

4. The firms referenced in your ANDA relative to the manufacturing and testing of the drug substance and the product must be in compliance with the cGMP's at the time of approval.

Sincerely yours,

{See appended electronic signature page}

Paul Schwartz, Ph.D.
Acting Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201050	ORIG-1	ROXANE LABORATORIES INC	Phenoxybenzamine Hydrochloride

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/s/

ALBERT J MUELLER
06/22/2010
For Paul Schwartz

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA/SUPPLEMENT #:201050 **APPLICANT: Roxane Laboratories Inc.**
DRUG: Phenoxybenzamine Hydrocloride Capsules USP, 10 mg **DATE OF SUBMISSION: 12/07/2009**

The Office of Generic Drugs MaPP # 5240.1 lists the following criteria for granting expedited review status to a supplemental abbreviated new drug application. At least one of the criteria must be met.

1. PUBLIC HEALTH NEED. Events that affect the availability of a drug for which there is no alternative

2. EXTRAORDINARY HARDSHIP ON THE APPLICANT.

   a) Catastrophic events such as explosion, fire storms damage.

   b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:

      - Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
      - Relocation of a facility or change in an existing facility because of a catastrophic event (see item 2.a)

3. AGENCY NEED.
   a) Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
   b) Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
   c) Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
   d) Request for approval of a strength that was previously tentatively approved (To be used in those cases where 180-day generic drug exclusivity prevented full approval of all strengths).

RECOMMENDATIONS:

DISCIPLINE	STATUS	SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant☒ Deny☐	
Chemistry Team Leader (sign as needed)	Grant☒ Deny☐	
Micro Team Leader (sign as needed)	Grant☒ Deny☐	
Labeling Team Leader (sign as needed)	Grant☒ Deny☐	
Chem. Div./Deputy Director (DO must Endorse)	Grant☒ Deny☐	

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: **SELECT TEAM # 1 Dat Doan**
a) When expedited review is denied, notify the applicant by telephon

DATE December 15, 2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201050	ORIG-1	ROXANE LABORATORIES INC	Phenoxybenzamine Hydrochloride

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/s/

SHANNON L HILL
12/17/2009

MARTIN H Shimer
01/04/2010

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 201050 **FIRM NAME**: ROXANE LABORATORIES INC.

PIV: NO **Electronic or Paper Submission:** CTD FORMAT PAPER

RELATED APPLICATION(S): NA

First Generic Product Received? YES PER MARTY 12/10/09

DRUG NAME: PHENOXYBENZAMINE HYDROCHLORIDE
DOSAGE FORM: CAPSULE USP, 10 MG

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC1 Team 1 ☒***Activity***	***Bio Team 4: Yih-Chain Huang*** ☒***Activity***
ANDA/Quality RPM: Dat Doan ☒ ***FYI***	Bio PM: Alpita Popat ☐ ***FYI***
Quality Team Leader: Mueller, Albert No assignment needed in DARRTS	***Clinical Endpoint Team Assignment: (No)*** ☐***Activity***
Labeling Reviewer: James Barlow ☒***Activity***	***Micro Review (No)*** ☐***Activity***

*****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s). *****

Letter Date: DECEMBER 7, 2009 **Received Date**: DECEMBER 8, 2009

Comments: EC- 1 YES **On Cards:** YES
Therapeutic Code: 1020100 ANTI HYPERTENSIVE AGENTS

Archival copy: CTD FORMAT PAPER **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Shannon Hill **Date December 17, 2009**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date:** ____

1. Edit Application Property Type in DARRTS where applicable for
   a. First Generic Received
      ☒ Yes ☐ No
   b. Market Availability
      ☒ Rx ☐ OTC
   c. Pepfar
      ☐ Yes ☒ No
   d. Product Type
      ☒ Small Molecule Drug (usually for most ANDAs except protein drug products)
   e. USP Drug Product (at time of filing review)
      ☒ Yes ☐ No
2. Edit Submission Patent Records
   ☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☒ Yes
4. Requested EER
   ☒ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

1. Firm has requested an Expedited Review; emailed Bob West on 12/10/09; Granted by Peter Rickman for for Bob West on 12/11/09.
2. Contact firm for DMF #; spoke with Liz Ernst on 12/10/09 @ 1:30 pm; as of today, no DMF # assigned; she will get back with me on Monday 12/14/09; called Liz to follow up on 12/17/09; DMF # (b) (4) (b) (4)

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: DECEMBER 7, 2009	☒
1.2.1	**Form FDA 3674** **(PDF)** YES	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES SEE SECTION 1.3 **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES SEE SECTION 1.3 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES **SEE SECTION 1.3** Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NO	☒

1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) N/A 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☒ PIII ☐ PIV ☐ (Statement of Notification) ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? N/A b. Expiration of Pediatric Exclusivity? N/A 4. Exclusivity Statement: YES **Patent and Exclusivity Search Results from query on Appl No 008708 Product 001 in the OB_Rx list.** **Patent Data** **There are no unexpired patents for this product in the Orange Book Database.** [Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.] **Exclusivity Data** **There is no unexpired exclusivity for this product.**	☒

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES; (b) (4); filed letter date (b) (4) Type II DMF No. N/A b. Type III DMF authorization letter(s) for container closure (b) (4) (b) (4) 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A	☒

(b) (4)

1.12.11	**Basis for Submission** NDA# : 008708 Ref Listed Drug: DIBENZYLINE Firm: WELLSPRING PHARMACEUTICALS ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	**Environmental Impact Analysis Statement YES SEE SECTION 1.12.14**	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): N/A	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? N/A (If yes, send email to Labeling Reviewer indicating such.) **HOW SUPPLIED** Phenoxybenzamine Hydrochloride Capsules, USP are supplied as opaque red, hard gelatin capsules with “54 036” imprinted in black on the capsule body. NDC 0054-0349-25 10 mg, opaque red capsule, bottle of 100	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES; container label provided with side by side comparison	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** YES **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** YES **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** YES **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary YES Table 4. Bioanalytical Method Validation YES Table 6. Formulation Data YES **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution YES **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies YES Table 3. Statistical Summary of the Comparative BA Data YES **2.7.1.4 Appendix** N/A **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study YES **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies YES	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) YES 2. Function or Responsibility YES 3. Type II DMF number for API YES; (b) (4) 4. CFN or FEI numbers YES; (b) (4) (b) (4)	☒
3.2.S.3	**Characterization** refer to DMF	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) YES **3.2.S.4.2 Analytical Procedures** YES **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) 10035437 & 10035438 **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials** YES	☒
3.2.S.6	**Container Closure Systems** refer to DMF	☒
3.2.S.7	**Stability** refer to DMF	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition YES 2. Inactive ingredients and amounts are appropriate per IIG YES	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report YES	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: **YES SEE SECTION 3.2.P.3.1** 3. Function or Responsibility YES 4. CFN or FEI numbers YES; (b) (4) (b) (4) **3.2.P.3.2 Batch Formula** YES **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Reprocessing Statement YES **3.2.P.3.4 Controls of Critical Steps and Intermediates** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation N/A 2. Filter validation (if aseptic fill) N/A **PROPOSED COMMERCIAL BATCH SIZE:** (b) (4) capsules (ANDA (b) (4) capsules)	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified YES **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) YES; COA 2. Suppliers' COA (specifications and test results) YES **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA YES	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** YES **3.2.P.5.2 Analytical Procedures** YES **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers 4000064 **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form YES **3.2.P.5.5 Characterization of Impurities** **3.2.P.5.6 Justification of Specifications**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period (b)(4) MONTHS **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments YES **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch **4000064D**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** refer to DMF **3.2.R.2.S Comparability Protocols** N/A **3.2.R.3.S Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation YES (b) (4) **3.2.R.1.P.2 Information on Components** SEE 3.2.P.4 & 3.2.P.7 **3.2.R.2.P Comparability Protocols** N/A **3.2.R.3.P Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒

5.3.1 (complete study data)

Bioavailability/Bioequivalence ☒

1. Formulation data same?

a. Comparison of all Strengths (check proportionality of multiple strengths) one strength

b. Parenterals, Ophthalmics, Otics and Topicals

per 21 CFR 314.94 (a)(9)(iii)-(v) N/A

2. Lot Numbers of Products used in BE Study(ies): ANDA: 4000064 RLD: 8A3991

3. Study Type: IN-VIVO PK STUDY(IES) (Continue with the appropriate study type box below)

5.3.1.2 Comparative BA/BE Study Reports ☒

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)YES

Table 3 Statistical Summary of the Comparative Bioavailability Data

Phenoxybenzamine Hydrochloride Capsule USP					
Dose (1 x 10 mg)					
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasted Bioequivalence Study					
Parameter	Geometric Mean		Ratio (%) (Test/Reference)	90% C.I.	
	Test	Reference		Lower	Upper
$AUC_{(0-t)}$ (hr*ng/mL)	2.43	2.40	101.37	94.45	108.81
AUC_{inf} (hr*ng/mL)	2.27	2.27	99.80	92.17	108.05
C_{max} (ng/mL)	2.37	2.32	102.33	93.03	112.57

2. Summary Bioequivalence tables:

Table 10. Study Information YES

Table 12. Dropout Information YES

Table 13. Protocol Deviations YES

5.3.1.3

In Vitro-In-Vivo Correlation Study Reports

1. Summary Bioequivalence tables:

Table 11. Product Information YES

Table 16. Composition of Meal Used in Fed Bioequivalence Study YES; N/A

5.3.1.4

Reports of Bioanalytical and Analytical Methods for Human Studies

1. Summary Bioequivalence table:

Table 9. Reanalysis of Study Samples YES

Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses YES

Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples YES

5.3.7

Case Report Forms and Individual Patient Listing YES

5.4 **Literature References** ☒

Possible Study Types:

Study Type

IN-VIVO BE STUDY(IES) with PK ENDPOINTS (i.e., fasting/fed/sprinkle) FASTING ON 10 MG ☒

SEE SECTION 5.3.1.2

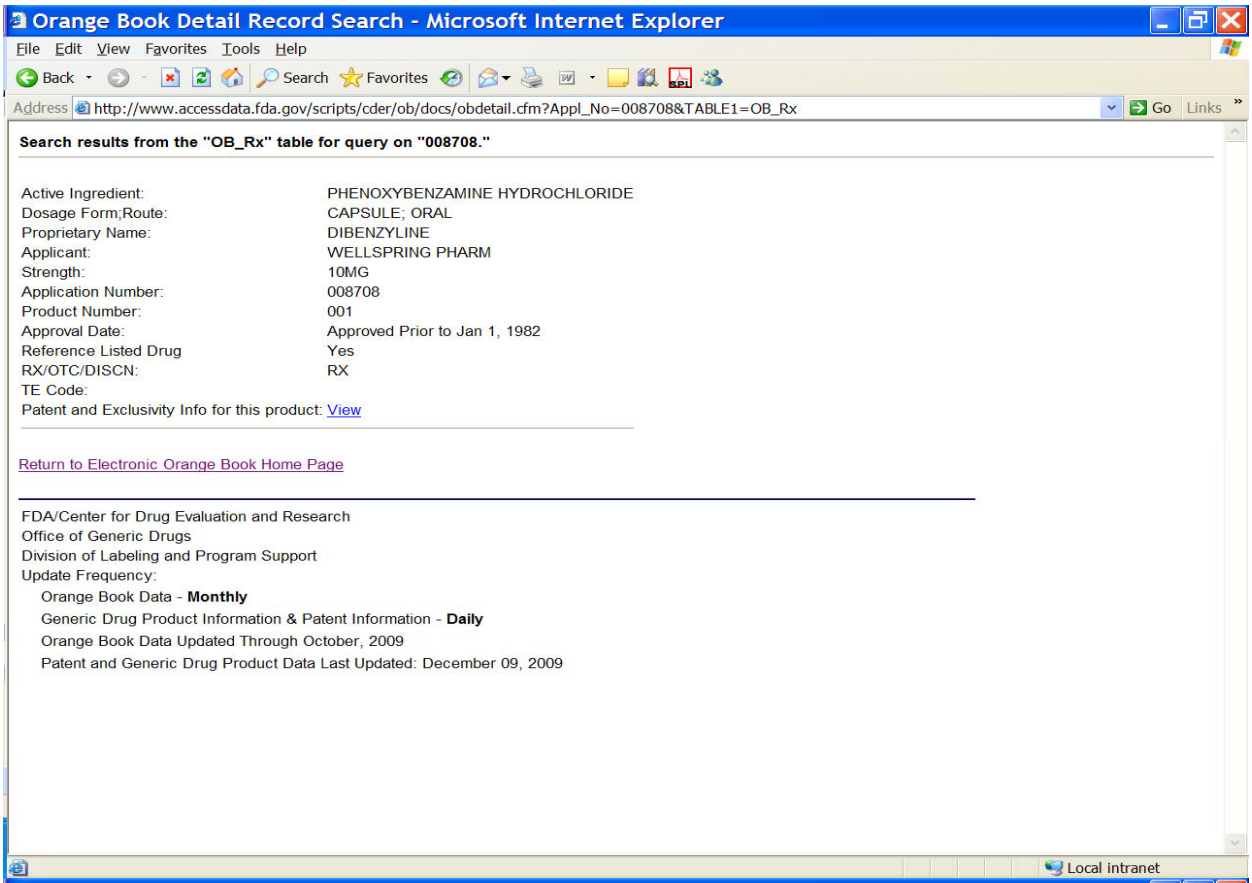
1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) YES

2. EDR Email: Data Files Submitted: YES SENT TO EDR

3. In-Vitro Dissolution: **YES SEE SECTION 2.7 PAGE 48**

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/19/2009


Orange Book Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=008708&TABLE1=OB_Rx
Go Links
Search results from the "OB_Rx" table for query on "008708."
Active Ingredient: PHENOXYBENZAMINE HYDROCHLORIDE
Dosage Form;Route: CAPSULE; ORAL
Proprietary Name: DIBENZYLINE
Applicant: WELLSPRING PHARM
Strength: 10MG
Application Number: 008708
Product Number: 001
Approval Date: Approved Prior to Jan 1, 1982
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through October, 2009
Patent and Generic Drug Product Data Last Updated: December 09, 2009
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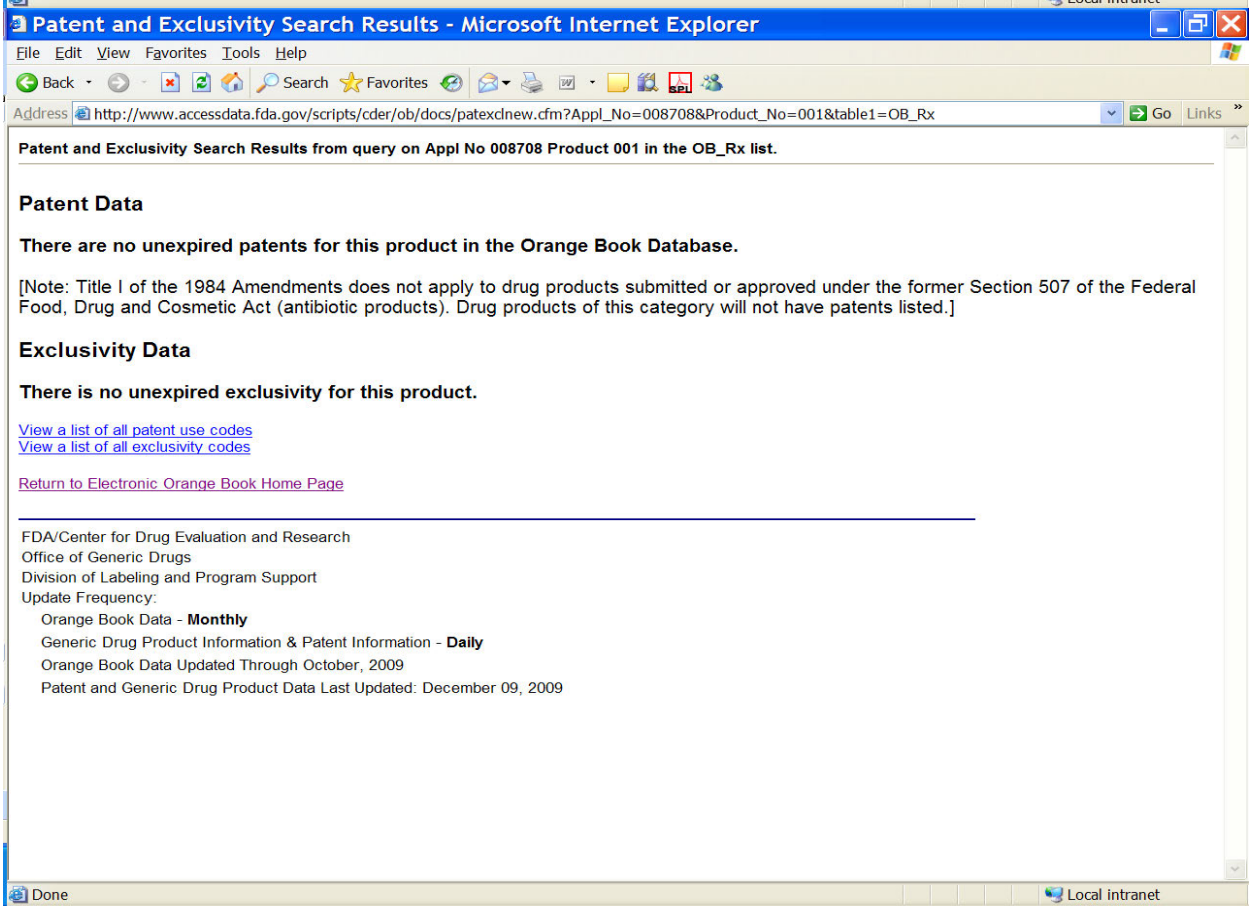
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Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=008708&Product_No=001&table1=OB_Rx
Go Links
Patent and Exclusivity Search Results from query on Appl No 008708 Product 001 in the OB_Rx list.
Patent Data
There are no unexpired patents for this product in the Orange Book Database.
[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]
Exclusivity Data
There is no unexpired exclusivity for this product.
View a list of all patent use codes
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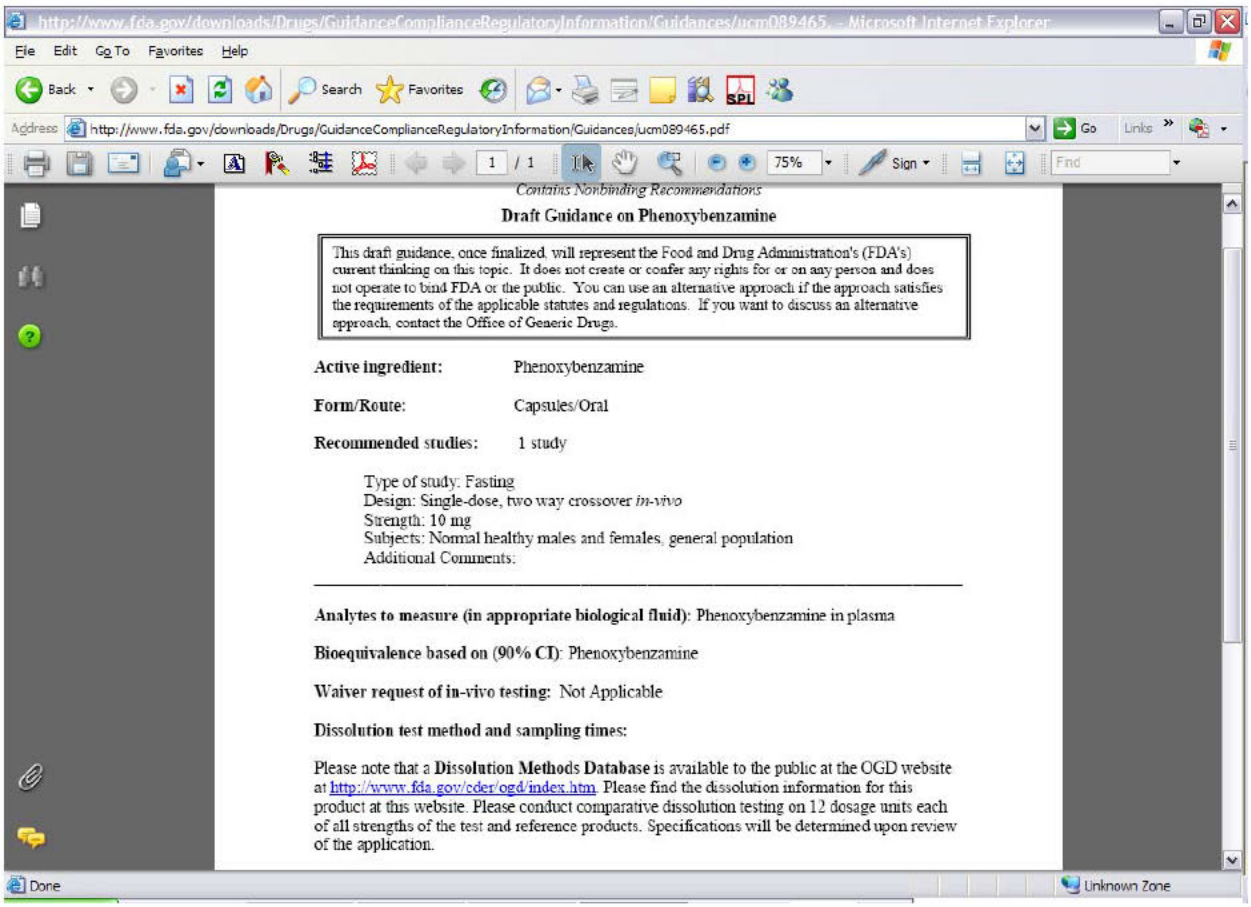

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Address http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm089465.pdf

Contains Nonbinding Recommendations

Draft Guidance on Phenoxybenzamine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Phenoxybenzamine

Form/Route: Capsules/Oral

Recommended studies: 1 study

Type of study: Fasting
Design: Single-dose, two way crossover *in-vivo*
Strength: 10 mg
Subjects: Normal healthy males and females, general population
Additional Comments:

Analytes to measure (in appropriate biological fluid): Phenoxybenzamine in plasma

Bioequivalence based on (90% CI): Phenoxybenzamine

Waiver request of in-vivo testing: Not Applicable

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

Done

Unknown Zone

Table 5. Summary of In Vitro Dissolution Studies – Comparison of Phenoxybenzamine Hydrochloride Capsules USP, 10 mg

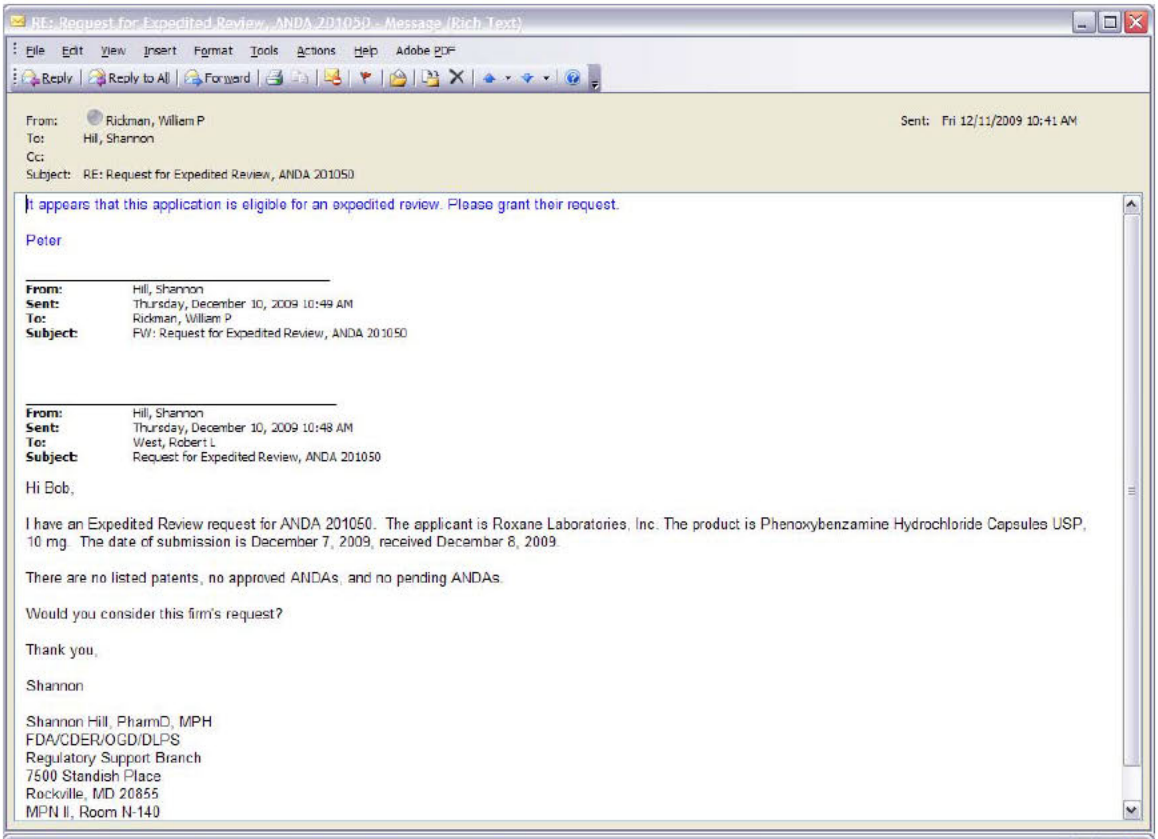
In vitro dissolution data is provided in table format as requested by the Division of Bioequivalence. The dissolution testing was conducted using the method recommended by the FDA Division of Bioequivalence in the correspondence letter dated April 22, 2008.

Dissolution Conditions			**Apparatus:**		USP Apparatus I (Baskets)					
			Speed of Rotation:		100 rpm					
			Medium:		500 mL 0.1 N HCl					
			Volume:		500 mL					
			Temperature		37.0° +/- 0.5° C					
Firm's Proposed Specifications			**NLT 75% (Q) of the labeled amount dissolves in 45 minutes**							
Dissolution Testing Site (Name, Address)			**Boehringer Ingelheim Roxane Inc. 1809 Wilson Road Columbus, Ohio 43228**							
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**
						10	**20**	**30**	**45**	**COA Attached to 2.7.1.4**
Study Report #: NA	7/21/2009	Dibenzyline® (Phenoxybenzamine Hydrochloride) Capsules USP, 10 mg WellSpring Pharmaceuticals Lot No.8A3991 Expiration date 01/2011	10 mg capsules	12	Mean	101	102	102	101	
					Range				(b) (4)	
					%CV	3.6	3.1	3.3	3.2	
Study Report #: NA	7/21/2009	Phenoxybenzamine Hydrochloride Capsules USP, 10 mg Roxane Lot No. 4000064 Manufacture Date 7/15/2009	10 mg capsules	12	Mean	94	96	98	102	
					Range				(b) (4)	
					%CV	7.5	6.7	6.8	6.6	

Table 6. Formulation Data

Ingredient	Amount (mg) / Capsule Strength 10 mg	Amount (%) / Capsule Strength 10 mg
Phenoxybenzamine Hydrochloride, USP	10.0	5
Lactose, NF (Anhydrous)		(b) (4)
Colloidal Silicon Dioxide, NF (b) (4)		
Sodium Lauryl Sulfate, NF		
Sodium Stearyl Fumarate, NF (b) (4)		
Capsules HG#3 (b) (4) Red Opaque 54 036		
Total	**200**	**100.00%**

(b) (4)



RE: Request for Expedited Review, ANDA 201050 - Message (Rich Text)

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Reply | Reply to All | Forward

From: Rickman, William P
Sent: Fri 12/11/2009 10:41 AM
To: Hill, Shannon
Cc:
Subject: RE: Request for Expedited Review, ANDA 201050

It appears that this application is eligible for an expedited review. Please grant their request.

Peter

From: Hill, Shannon
Sent: Thursday, December 10, 2009 10:49 AM
To: Rickman, William P
Subject: FW: Request for Expedited Review, ANDA 201050

From: Hill, Shannon
Sent: Thursday, December 10, 2009 10:48 AM
To: West, Robert L
Subject: Request for Expedited Review, ANDA 201050

Hi Bob,

I have an Expedited Review request for ANDA 201050. The applicant is Roxane Laboratories, Inc. The product is Phenoxybenzamine Hydrochloride Capsules USP, 10 mg. The date of submission is December 7, 2009, received December 8, 2009.

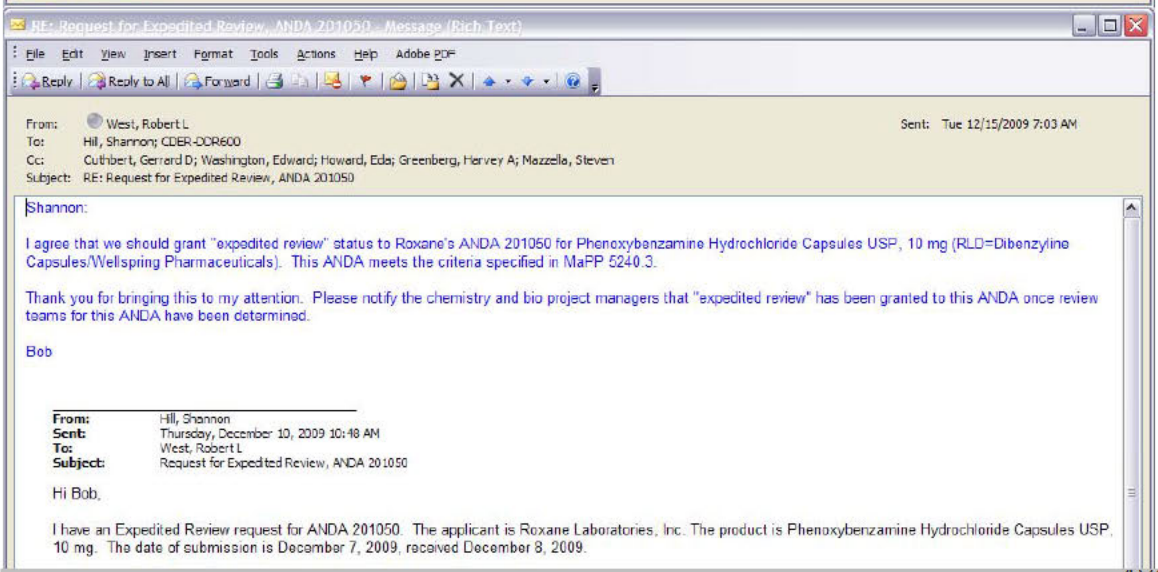
There are no listed patents, no approved ANDAs, and no pending ANDAs.

Would you consider this firm's request?

Thank you,

Shannon

Shannon Hill, PharmD, MPH
FDA/CDER/OGD/DLPS
Regulatory Support Branch
7500 Standish Place
Rockville, MD 20855
MPN II, Room N-140



RE: Request for Expedited Review, ANDA 201050 - Message (Rich Text)

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Reply | Reply to All | Forward

From: West, Robert L
Sent: Tue 12/15/2009 7:03 AM
To: Hill, Shannon; CDER-DDR600
Cc: Cuthbert, Gerrard D; Washington, Edward; Howard, Eda; Greenberg, Harvey A; Mazzella, Steven
Subject: RE: Request for Expedited Review, ANDA 201050

Shannon:

I agree that we should grant "expedited review" status to Roxane's ANDA 201050 for Phenoxybenzamine Hydrochloride Capsules USP, 10 mg (RLD=Dibenzyline Capsules/Wellspring Pharmaceuticals). This ANDA meets the criteria specified in MaPP 5240.3.

Thank you for bringing this to my attention. Please notify the chemistry and bio project managers that "expedited review" has been granted to this ANDA once review teams for this ANDA have been determined.

Bob

From: Hill, Shannon
Sent: Thursday, December 10, 2009 10:48 AM
To: West, Robert L
Subject: Request for Expedited Review, ANDA 201050

Hi Bob,

I have an Expedited Review request for ANDA 201050. The applicant is Roxane Laboratories, Inc. The product is Phenoxybenzamine Hydrochloride Capsules USP, 10 mg. The date of submission is December 7, 2009, received December 8, 2009.

(b) (4)

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA/SUPPLEMENT #:201050 **APPLICANT: Roxane Laboratories Inc.**
DRUG: Phenoxybenzamine Hydrocloride Capsules USP, 10 mg **DATE OF SUBMISSION: 12/07/2009**

The Office of Generic Drugs MaPP # 5240.1 lists the following criteria for granting expedited review status to a supplemental abbreviated new drug application. At least one of the criteria must be met.

1. PUBLIC HEALTH NEED. Events that affect the availability of a drug for which there is no alternative

2. EXTRAORDINARY HARDSHIP ON THE APPLICANT.

   a) Catastrophic events such as explosion, fire storms damage.

   b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:

      - Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
      - Relocation of a facility or change in an existing facility because of a catastrophic event(see item 2.a)

3. AGENCY NEED.
   a) Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
   b) Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
   c) Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
   d) Request for approval of a strength that was previously tentatively approved (To be used in those cases where l8O-day generic drug exclusivity prevented full approval of all strengths).

RECOMMENDATIONS:

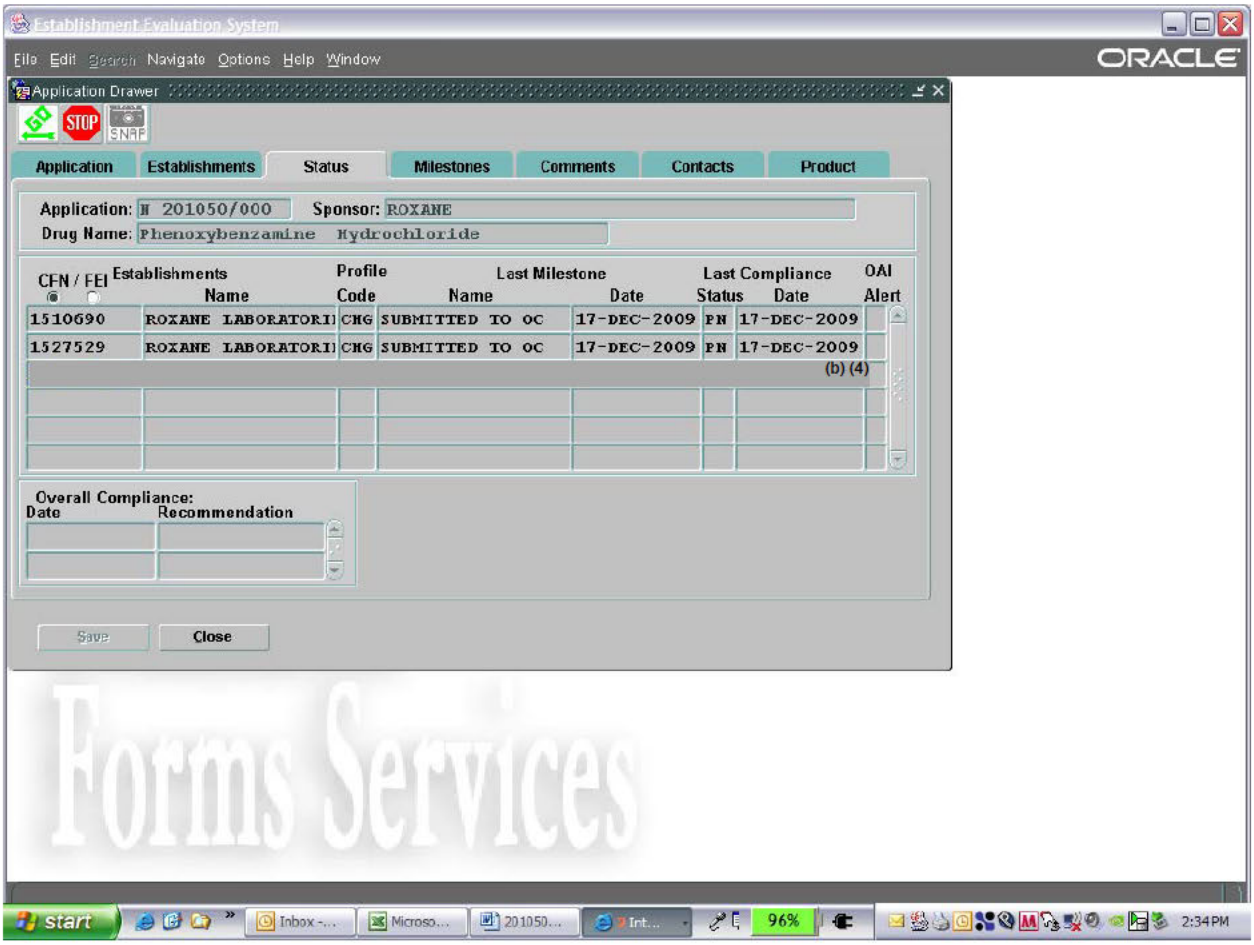
DISCIPLINE	STATUS	SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant☒ Deny☐	
Chemistry Team Leader (sign as needed)	Grant☒ Deny☐	
Micro Team Leader (sign as needed)	Grant☒ Deny☐	
Labeling Team Leader (sign as needed)	Grant☒ Deny☐	
Chem. Div./Deputy Director (DO must Endorse)	Grant☒ Deny☐	

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: **SELECT TEAM # 1 Dat Doan**

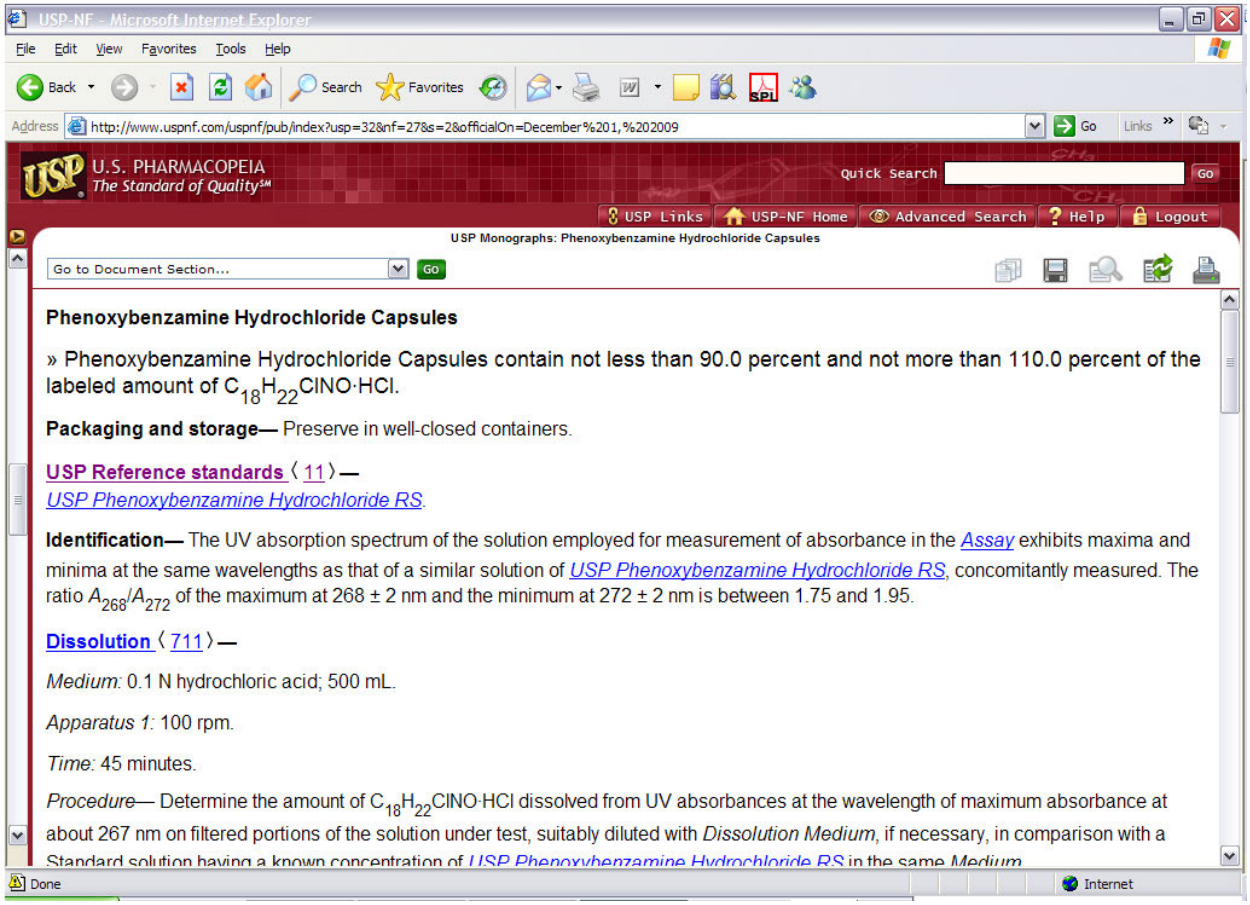
a) When expedited review is denied, notify the applicant by telephone

DATE

ENTER FORM INTO DFS



(b) (4)


USP-NF - Microsoft Internet Explorer
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Address http://www.uspnf.com/uspnf/pub/index?usp=32&nf=27&s=2&officialOn=December%201,%202009
Go Links
U.S. PHARMACOPEIA
The Standard of Quality℠
Quick Search
Go
USP Links
USP-NF Home
Advanced Search
Help
Logout
USP Monographs: Phenoxybenzamine Hydrochloride Capsules
Go to Document Section...
Go
Phenoxybenzamine Hydrochloride Capsules
» Phenoxybenzamine Hydrochloride Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of C18H22ClNO·HCl.
Packaging and storage— Preserve in well-closed containers.
USP Reference standards 〈 11 〉—
USP Phenoxybenzamine Hydrochloride RS.
Identification— The UV absorption spectrum of the solution employed for measurement of absorbance in the Assay exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Phenoxybenzamine Hydrochloride RS, concomitantly measured. The ratio A268/A272 of the maximum at 268 ± 2 nm and the minimum at 272 ± 2 nm is between 1.75 and 1.95.
Dissolution 〈 711 〉—
Medium: 0.1 N hydrochloric acid; 500 mL.
Apparatus 1: 100 rpm.
Time: 45 minutes.
Procedure— Determine the amount of C18H22ClNO·HCl dissolved from UV absorbances at the wavelength of maximum absorbance at about 267 nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Phenoxybenzamine Hydrochloride RS in the same Medium
Done
Internet

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201050	ORIG-1	ROXANE LABORATORIES INC	Phenoxybenzamine Hydrochloride

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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.

/s/

SHANNON L HILL
12/23/2009

MARTIN H Shimer
12/23/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 201050

Roxane Laboratories, Inc.
Attention: Elizabeth Ernst
1809 Wilson Rd.
Columbus, OH 43228

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

In accordance with your request for expedited review under MaPP 5240.3, the Office of Generic Drug has granted expedited review to this ANDA.

Reference is also made to the telephone conversation dated December 10, 2009 and your correspondence dated December 17, 2009.

NAME OF DRUG: Phenoxybenzamine Hydrochloride Capsules USP, 10 mg

DATE OF APPLICATION: December 7, 2009

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 8, 2009

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Dat Doan
Project Manager
240-276-8573

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201050	ORIG-1	ROXANE LABORATORIES INC	Phenoxybenzamine Hydrochloride

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/s/

MARTIN H Shimer
12/23/2009
Signing for Wm Peter Rickman

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 020-1050 **FIRM NAME** **Roxane Laboratories Inc.**

DRUG NAME Phenoxybenzamine Hydrochloride

DOSAGE FORM Capsules

STRENGTH 10 mg

SUBJ: Request for examination of: Bioequivalence Study

Requested by: __Martin Shimmer_____ Date: December 14, 2009
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐ N/A	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

Nilufer M. Tampal_____ Date: 12/14/09

Reviewer

_____ Date: _____
Yih-Chain Huang
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			Volume 1.2, Appendix 16.1.1, Page 74
Assay Methodology	☒	☐			Volume 1.3, page 526
Procedure SOP	☒	☐			Analytical: Volume 1.6
Methods Validation	☒	☐			Volume 1.6, Page 2177
Study Results Ln/Lin	☒	☐			Volume 1.6
Adverse Events	☒	☐			Volume 1.2, Appendix 16.2.7, page 277
IRB Approval	☒	☐			Volume 1.2, Appendix 16.1.3, page 131
Dissolution Data	☒	☐			Volume 1.6, page 2547
Pre-screening of Patients	☒	☐			Part of CRFs (volumes 1.7-1.10)
Chromatograms	☒	☐			Volumes 1.4 and 1.5
Consent Forms	☒	☐			Volume 1.2, Appendix 16.1.3, page 131
Composition	☒	☐			Module 2.3.P.1 QOS and Volume 1.6
Summary of Study	☒	☐			Volume 1.2, page 10
Individual Data & Graphs, Linear & Ln	☒	☐			PK and Statistical Report (Volume 1.6)
PK/PD Data Disk Submitted)	☒	☐			Data sets submitted as .xpt files in DAARTS
Randomization Schedule	☒	☐			Volume 1.2, page 10
Protocol Deviations	☒	☐			Volume 1.2, Appendix 16.2.2, page 251
Clinical Site	☒	☐			Cedra Clinical Research,

					San Antonio, TX
Analytical Site	☒	☐			(b) (4)
Study Investigators	☒	☐			Clinical: Mark T. Leibowitz, M.D. Analytical: (b) (6), BS
Medical Records	☒	☐			Part of CRFs (volumes 1.7-1.10)
Clinical Raw Data	☒	☐			Part of CRFs (volumes 1.7-1.10)
Test Article Inventory	☒	☐			Volume 1.2, Appendix 16.1.6, page 198
BIO Batch Size	☒	☐			(b) (4) capsules (CoA in volume 1.6, page 2549)
Assay of Active Content Drug	☒	☐			Test: 98.7% Ref: 97.5% CoA in volume 1.6
Content Uniformity	☒	☐			CoA in volume 1.6
Date of Manufacture	☒	☐			Test: 7/15/09
Exp. Date of RLD	☒	☐			January 2011
BioStudy Lot Numbers	☒	☐			Test: 4000064D Reference: 8A3991
Statistics	☒	☐			Volume 1.6
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			Yes. The 90% CIs for AUC and Cmax for the fasted study are within the 80-125% BE limits
Waiver requests for other strengths / supporting data	☐	☒			N/A

Additional Comments regarding the ANDA:

The application includes data from a 2-treatment, 4-period replicate design study under fasting conditions. Per the Individual Product Bioequivalence Recommendations for Phenoxybenzamine HCl Capsule @http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm089465.pdf, a fed study is not required to establish BE for this drug product.

Enter Review Productivity and Generate Report

(b) (4)

Reviewer: Tampal, Nilufer **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: First Generic- Phenoxybenzamine HCl Capsules - Roxane Labs

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Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
9943	12/7/2009	Paragraph 4	Paragraph 4 Checklist	1	1
				Bean Total:	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201050	ORIG-1	ROXANE LABORATORIES INC	Phenoxybenzamine Hydrochloride

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/s/

NILUFER M TAMPAL
12/16/2009

YIH CHAIN HUANG
12/16/2009

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

M E M O R A N D U M

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

DATE : December 10, 2009

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 201050 for Phenoxybenzamine Hydrochloride Capsules USP, 10 mg to determine if the application is substantially complete for filing.

Roxane Laboratories Inc. has submitted ANDA 201050 for Phenoxybenzamine Hydrochloride Capsules USP, 10 mg. It is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Roxane Laboratories Inc. on December 7, 2009 for its Phenoxybenzamine Hydrochloride product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201050	ORIG-1	ROXANE LABORATORIES INC	Phenoxybenzamine Hydrochloride

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/s/

EDA E HOWARD
12/10/2009