CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40309

BIOEQUIVALENCY REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-309 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Hydrocodone Bitartrate; Acetaminophen Tablets, 10 mg/500 mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

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

Hydrocodone Bitartrate;
Acetaminophen Tablets
10 mg/500 mg
ANDA #**40-309**
Reviewer: Z.Z. Wahba
wp# 40309w.498

Barr Laboratories, Inc.
Pomona, N.Y.
Submission Date:
April 14, 1998
July 30, 1998

REVIEW OF DISSOLUTION DATA AND WAIVER REQUEST

I. BACKGROUND

1. The firm has submitted comparative in vitro dissolution data for its test drug product, Hydrocodone Bitartrate; Acetaminophen Tablets, 10 mg/500 mg, and the reference listed product, Gramham's Lortab® Tablets, 10 mg/500 mg.

2. The drug product is classified "AA" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".

II. FORMULATION COMPARISON

No	Ingredients	10 mg/500 mg Strength (mg/Tablet)
1	Hydrocodone Bitartrate, USP	[a]10.00
2	Acetaminophen, USP (Powder)	500.00
3	Pregelatinized Starch, NF	
4	Crospovidone, NF	
5	Povidone, USP	
6	Magnesium Stearate, NF	
7	[b]Purified Water, USP	
8	D&C Yellow #10 Aluminum Lake	
9	FD&C Red #40 Lake HT	

10	FD&C Blue #1 Aluminum Lake	[redacted]
	Total Weight	[redacted]

[a] Theoretical quantities based on Hydrocodone Bitartrate, USP, 100% potency. Actual quantity to be calculated according to the Hydrocodone Bitartrate, USP, "as is assay" value. Total corspovidone [redacted] mg to be used in pre-mix as [redacted] and [redacted] mg to be used in final mix as [redacted]

[b] Used but not retained in the finished product.

III. DISSOLUTION

The firm has submitted dissolution data for its drug product, Hydrocodone Bitartrate; Acetaminophen Tablets, 10 mg/500 mg, applying the following conditions:

Method of Dissolution: USP method
Apparatus Type: Apparatus II (Paddle) at 50 rpm
Medium: 900 ml PO_4, pH 5.8 buffer
Temperature: 37°C ± 0.5°C
Number of Tablets: 12
Specification: NLT [redacted] % (Q) in 30 minutes
Reference product: Graham's Lortab® Tablets, 10 mg/500 mg.

Table . In Vitro Dissolution Testing

Drug (Generic Name): Hydrocodone Bitartrate; Acetaminophen
Dose Strengths: 10 mg/500 mg
ANDA No.: 40-309
Firm: Barr Laboratories, Inc.
Submission Date: April 14, 1998
File Name: 40309w.498

I. Conditions for Dissolution Testing:

USP 23 Method Basket: Paddle: X RPM: 50
No. Units Tested: 12 Tablets
Medium: PO_4 Buffer pH 5.8 Volume: 900 mL
Specifications: NLT [redacted] % (Q) is dissolved in 30 minutes

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product: Hydrocodone Bitartrate Lot #7T91901 Strength(mg) 10			Reference Product: Hydrocodone Bitartrate Lot #WL096146A Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
10	98	[redacted]	1.1	101	[redacted]	2.0
20	99		0.8	101		1.7
30	98		1.1	102		2.2
45	98		0.7	103		2.5

Sampling Times (Minutes)	Test Product: Acetaminophen Lot #7T91901 Strength(mg) 500			Reference Prod.:Acetaminophen Lot #WL096146A Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
10	97	[redacted]	1.4	100	[redacted]	2.6
20	97		0.6	100		2.0
30	97		0.8	101		3.1
45	98		1.1	101		2.3

IV. COMMENTS

1. The drug product is classified "AA" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".

2. The dissolution data for the test products are acceptable.

3. The waivers of in vivo bioequivalence study requirements may be granted based on 21 CFR section 320.22(c) of the Bioavailability/Bioequivalence Regulations.

V. RECOMMENDATION

1. The Division of Bioequivalence agrees that the information submitted by Barr Laboratories, Inc. on its drug product, Hydrocodone Bitartrate; Acetaminophen Tablets, 10 mg/500 mg falls under 21 CFR section 320.22(c) of the Bioavailability/ Bioequivalence Regulations. The waivers of in vivo bioequivalence study for the test products are granted.

2. The dissolution testing conducted by Barr Laboratories, Inc. on its drug products, Hydrocodone Bitartrate; Acetaminophen Tablets, 10 mg/500 mg, lot #7T91901, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of PO_4 Buffer pH 5.8, at 37°C using Apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than __% (Q) of both active components of the labeled amount of the drug is dissolved in 30 minutes.

The firm should be informed of the above recommendations.

/S/ 8/5/98

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT 8/5/98
FT INITIALLED BDAVIT /S/ 8/5/98

Concur: /S/ Date: 8/6/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

ANDA #40-309
SPONSOR: Barr Laboratories, Inc.
DRUG: Hydrocodone Bitartrate; Acetaminophen
DOSAGE FORM: Tablets
STRENGTH: 10 mg/500 mg

TYPE OF STUDY: NA

STUDIES:	☐ Acceptable	☐ Not Acceptable
DISSOLUTION:	X Acceptable	☐ Not Acceptable
WAIVER:	X Acceptable	☐ Not Acceptable

PRIMARY REVIEWER: Zakaria Wahba, Ph.D. BRANCH: III
INITIAL: Z.W. DATE: 8/6/98

GROUP LEADER: Barbara Davit, Ph.D. BRANCH: III
INITIAL: BDD DATE: 8/6/98

DIRECTOR: Dale P. Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE
INITIAL: DPC DATE: 8/6/98
