

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
40308

BIOEQUIVALENCY REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT.

ANDA: 40-308

APPLICANT: Barr Laboratories, Inc.

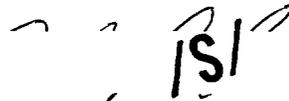
DRUG PRODUCT: Hydrocodone Bitartrate; Acetaminophen Tablets 5 mg/500 mg and 7.5 mg/7500 mg

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,



Dale P. Conner, Pharm. D.

Director

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

Hydrocodone Bitartrate;
 Acetaminophen Tablets
 5 mg/500 mg & 7.5 mg/750 mg
 ANDA #40-308
 Reviewer: Z.Z. Wahba
 wp# 40308w.498

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

REVIEW OF DISSOLUTION DATA AND WAIVER REQUESTS

I. BACKGROUND

1. The firm has submitted comparative in vitro dissolution data for its test drug product, Hydrocodone Bitartrate; Acetaminophen Tablets 5 mg/500 mg & 7.5 mg/750 mg, and the reference listed product, Knoll's Vicodin® Tablets 5 mg/500 mg and Vicodin® ES Tablets 7.5 mg/750 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	5mg/500mg Strength (mg/Tablet)	7.5mg/750mg Strength (mg/Tablet)
1	✓ Hydrocodone Bitartrate, USP	^a 5.00	^b 7.50
2	✓ Acetaminophen, USP (Powder)	500.00	750.00
3	✓ Pregelatinized Starch, NF	✓	✓
4	✓ Crospovidone, NF		
5	✓ Povidone, USP		
6	✓ Magnesium Stearate, NF	↓	↓
7	^c Purified Water, USP	--	--
	✓ D&C Yellow #10 Aluminum Lake	not present	✓ ;

Total Weight		
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- 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 cospovidone [] mg to be used in pre-mix as [] and [] mg to be used in final mix as []
- b 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 cospovidone [] mg to be used in pre-mix as intra-granular disintegrant and [] mg to be used in final mix as extra-granular disintegrant.
- c Used but not retained in the finished product.

III. DISSOLUTION

The firm has submitted dissolution data for its drug product, Hydrocodone Bitartrate; Acetaminophen Tablets, 5 mg/500 mg & 7.5 mg/750 mg, applying the following conditions:

Method of Dissolution: USP method
 Apparatus Type: Apparatus II (Paddle) at 50 rpm
 Medium: 900 ml PO₄, pH 5.8 buffer
 Temperature: 37°C ± 0.5°C
 Number of Tablets: 12
 Specification: NLT [] % (Q) in 30 minutes
 Reference product: Knoll's Vicodin[®] Tablets 5 mg/500 mg and Vicodin[®] ES Tablets 7.5 mg/750 mg.

Table . In Vitro Dissolution Testing
Drug (Generic Name): Hydrocodone Bitartrate; Acetaminophen Dose Strengths: 5 mg/500 mg & 7.5 mg/750 mg ANDA No.: 40-308 Firm: Barr Laboratories, Inc. Submission Date: April 14, 1998 File Name: 40308w.498
I. Conditions for Dissolution Testing:

USP 23 Method Basket: Paddle: X RPM: 50
 No. Units Tested: 12 Tablets
 Medium: PO₄ Buffer pH 5.8 Volume: 900 mL
 Specifications: NLT (Q) is dissolved in 30 minutes

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product: Hydrocodone Bitartrate Lot #7T91501 Strength(mg) 5			Reference Product: Hydrocodone Bitartrate Lot #10760425 Strength(mg) 5		
	Mean %	Range	%CV	Mean %	Range	%CV
10	102	[1.5	89	[9.8
20	103		0.9	101		4.4
30	104		1.1	105		2.3
45	105		1.0	106		1.9

Sampling Times (Minutes)	Test Product: Acetaminophen Lot #7T91501 Strength(mg) 500			Reference Prod.: Acetaminophen Lot #10760425 Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
10	101	[1.4	58	[10.3
20	103		0.6	72		9.8
30	103		0.8	78		7.7
45	104		0.5	84		5.9

Sampling Times (Minutes)	Test Product: Hydrocodone Bitartrate Lot #7T73601 Strength(mg) 7.5			Reference Product: Hydrocodone Bitartrate Lot #10770716 Strength(mg) 7.5		
	Mean %	Range	%CV	Mean %	Range	%CV
10	99	[0.5	95	[4.2
20	99		1.0	96		4.5
30	98		0.9	97		4.0
45	98		0.9	98		4.0

Sampling Times (Minutes)	Test Product: Acetaminophen Lot #7T73601 Strength(mg) 750			Reference Prod.: Acetaminophen Lot #107707716 Strength(mg) 750		
	Mean %	Range	%CV	Mean %	Range	%CV
10	98		0.7	93		3.4
20	99		0.7	98		2.6
30	98		0.7	99		2.8
45	99		0.7	99		2.6

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, 5 mg/500 mg and 7.5 mg/750 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, 5 mg/500 mg and 7.5 mg/750 mg, lot #7T91501, and lot #7T73601, respectively, 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 PO₄ Buffer pH 5.8, at 37°C using Apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

