

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**40230**

**BIOEQUIVALENCY REVIEW(S)**

JUN 20 1997

Dicyclomine Hydrochloride, USP  
20 mg Tablets  
ANDA #40-230  
Reviewer: A.P.Patel  
Filename: x:\wpfile\biofinal\40230sd.d96

Lannett Co. Inc.  
Philadelphia, PA  
Submission Date:  
Dec. 19, 1996  
Apr. 22, 1997  
May 1, 1997

## Review of a BE Study and Dissolution Data

### I. Objectives:

Review of Lannett's in-vivo BE study comparing its Dicyclomine Hydrochloride Tablets, 20 mg strength, to Marion Merrell Dow's Bentyl<sup>®</sup> Tablets, 20 mg strength, under fasting conditions.

### II. Background:

Dicyclomine HCl is an anticholinergic (antimuscarinic) and antispasmodic agent which relieves smooth muscle spasm of the gastrointestinal tract. Dicyclomine hydrochloride occurs as a fine, white, crystalline, practically odorless powder with a bitter taste. It is soluble in water, freely soluble in alcohol and chloroform, and very slightly soluble in ether.

It is indicated for the treatment of functional bowel/irritable- bowel syndrome. The effective oral adult dose is 160 mg/day (in 4 divided doses). Due to associated side effects at this dose, treatment is usually initiated at 80 mg/day (in 4 divided doses).

Dicyclomine HCl is rapidly absorbed after oral administration in man and peak plasma concentrations are observed within 60 to 90 minutes of dosing. Dicyclomine HCl exhibits biphasic elimination. The principal route of elimination is via the urine (approximately 80% of the dose), while excretion in the feces accounts for approximately 10% of the dose.

The mean half-life of plasma elimination in one study was determined to be 1.8 hours. However, in subsequent studies, a secondary phase of elimination with longer half-life was shown.

Dicyclomine hydrochloride is available in capsules (10 mg), tablets (20 mg), syrup (10 mg/5 mL), and IM injections.

### III. Study Details:

1. Protocol #950946
2. Applicant: Lannett Co. Inc.
3. Study sites:  
Clinical study:  
Analytical:
4. Investigators:  
Principal investigator:  
Analytical Project Manager:
5. Clinical study sample collection dates: 06/Jun/96 - 03/Jul/96  
Assay dates: July 17, 1996 - August 1, 1996; Duration of sample storage: 56 days
6. Study design:  
Open-label, randomized, comparative, 2-way crossover bioequivalence study.
7. Subject: This study involved healthy male volunteers, 18-45 years of age, weighing at least 60 kg, who are within 15% of their ideal weights (Table of Desirable Weights of Adults",

Metropolitan Life Insurance Company, 1983).

Screening: Medical histories and demographic data, including name, sex, age, race, body weight (kg), height (cm), body build and smoking habits were recorded. Each subject received a complete physical examination, 12-lead EKG and the laboratory tests of hematologic, hepatic and renal functions. Only medically healthy subjects with clinically normal laboratory profiles and EKGs were enrolled in the study.

**Exclusions:**

History or presence of significant: cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric disease.

**More specifically, history or presence of significant:**

- obstructive uropathy;
- obstructive disease of the gastrointestinal tract;
- ulcerative colitis;
- reflux esophagitis;
- glaucoma (personal or family history);
- myasthenia gravis;
- hypersensitivity or idiosyncratic reaction to dicyclomine HCl or any other anticholinergic/antispasmodic agent;
- autonomic neuropathy;
- any form of thyroid disease;
- hypertension;
- any form of cardiac disease or conduction abnormalities;
- hiatal hernia;
- prostatic hypertrophy and/or any form of prostate disease;
- alcoholism or drug abuse within the last year.

Subjects who have been on an abnormal diet (for whatever reason) during the four weeks preceding the study.

Subjects who, through completion of this study, would have donated in excess of 500 mL of blood in 14 days, 750 mL in 3 months, 1000 mL in 6 months, 1500 mL in 9 months or 2000 mL in one year.

Subjects who have participated in another clinical trial within 28 days of study start.

**Prohibitions:** No subject may take medication (including over-the-counter products) for the 7 days preceding the study. This prohibition will not include daily vitamin supplements taken in non-therapeutic doses. The consumption of alcohol- or xanthine-containing beverages and foods will be prohibited for 24 hours before dosing and throughout the period of sample collection. If drug therapy other than that specified in the protocol is required during the time of sample collection, or during the washout period between drug administrations, a decision to continue or discontinue the subject will be made, based on the time the medication was administered and its pharmacology and pharmacokinetics.

**8. Product information:**

- (a) Test product #1: Dicyclomine Hydrochloride Tablets, 20 mg strength, Manufactured by Lannett.
- (b) Reference product: Bentyl<sup>®</sup> Tablets, 20 mg strength, manufactured by Marion Merrell Dow.

9. Dosing: Single oral 20 mg dose with 240 mL water.
10. Food and fluid intake: Subjects fasted overnight before dosing and for 4 hours thereafter. Water was not permitted for 2 hours before and 4 hours after dosing, but was allowed at all other times. Standard meals were provided at 4 and approximately 9 hours after drug administration. During housing, meal plans were identical for both periods. Although not specified in the protocol, subjects were given a snack approximately 13.5 hours after dosing in both periods.
11. Housing: From 12-hours before dosing until after the 24 hour blood draw in each period.
12. Washout period: Seven days between doses.
13. Blood samples: Due to the sensitivity of dicyclomine to light, blood samples were collected and processed under conditions which minimized their ultraviolet (UV) light exposure. Blood samples were collected in Vacutainers containing EDTA before dosing (2 x 10 mL) and at the following times after dosing 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours (1 x 10 mL). Blood samples were cooled in an ice bath and centrifuged under refrigeration as soon as possible. All plasma samples were stored in suitably labeled tubes at -12°C or lower, pending assay.
14. Urine samples: N/A.
15. Subject monitoring: Sitting blood pressure and heart rate determinations were made for each subject before dosing and at approximately 1, 2, 3 and 4 hours following drug administration. Where the time of vital signs monitoring coincides with a blood draw, vital signs were taken approximately 10 minutes before the scheduled blood draw.
16. IRB and informed consent: IRB approval and informed consents were obtained before the initiation of the study.
17. Pharmacokinetic and statistical analysis: SAS-GLM procedures were used on  $AUC_t$ ,  $AUC_{inf}$ ,  $C_{max}$ ,  $T_{max}$ ,  $K_{el}$ ,  $t_{1/2}$  and plasma levels at each sampling points. The 90% confidence intervals (CI) were calculated for  $AUC_t$ ,  $AUC_{inf}$  and  $C_{max}$ .

#### IV. Validation of Assay Method for Plasma Samples

Dicyclomine in human plasma was determined by \_\_\_\_\_ method.

Internal standard: orphenadrine citrate

Concentration range: \_\_\_\_\_ ng/mL

Detection mode: selected ions monitoring

##### A. Pre-study validation

1. Specificity: No significant interference from endogenous components or other sources was observed at the retention times of dicyclomine and internal standard.
2. Sensitivity: The lower limit of quantitation was set at \_\_\_\_\_ ng/mL for dicyclomine.
3. Linearity: Linear response over the concentration range of \_\_\_\_\_ ng/mL for dicyclomine was observed. The correlation coefficients were better than 0.998. Tables 1 shows the back-calculated concentration data for the standard curve samples.

Table 1. Back-calculated Data for Standard Curve Samples  
Dicyclomine in Human Plasma

Input, ng/mL	N	Found, ng/mL	%Nom	%CV
1	14	0.988	98.8	14.2
2.01	14	1.947	96.8	7.4
5.02	12	4.923	98.1	9.1
10.04	14	10.471	104.3	6.5
35.13	14	36.755	104.6	5.7
50.19	13	50.116	99.9	5.4
75.28	14	71.642	95.2	6.1
90.34	14	93.044	103.0	3.9
100.37	13	99.408	99.0	5.6

4. Precision and accuracy: Table 2 shows the between-run precision and accuracy data for the assay of QC samples. Table 3 shows the within-run precision and accuracy data for the assay of QC samples. The precision and accuracy data are acceptable.

Table 2. Between-Batch Precision and Accuracy of QC Sample Assays  
Dicyclomine in Human Plasma

Input, ng/mL	N	Mean, ng/mL	%Input	%CV
3.0 (2.4 - 3.6)	28	3.010	100.3	9.5
39.97 (33.97 - 45.97)	26	41.531	103.9	8.7
79.94 (67.95 - 91.93)	26	82.953	103.8	5.5

Table 3. Within-run Precision and Accuracy of QC Sample Assays  
Dicyclomine in Human Plasma

Input, ng/mL	N	Found, ng/mL	%Input	%CV
1.0	10	0.953	95.3	11.6
3.01	12	2.958	98.3	7.4
40.15	12	43.589	108.6	5.3
80.30	12	84.817	105.6	4.6

5. Recovery: Tables 4 and 5 show the absolute recovery data for dicyclomine and internal standard (orphenadrine), respectively.

Table 4. Absolute Recovery of Dicyclomine in Plasma

Input, ng/mL	N	%Recovery	%CV
80.30	18	87.09	4.7
40.15	24	95.28	7.3
3.01	18	88.57	6.1

Table 5. Absolute Recovery of Orphenadrine in Plasma

Input, mcg/mL	N	%Recovery	%CV
2.5	10	59.98	10.0

6. Stability: Table 6 summarizes the stability data for dicyclomine in plasma. The stability data are acceptable.

Table 6. Stability of Dicyclomine in Plasma

Sample, ng/mL	N	Storage Condition	Storage Time	%Initial	%CV
3.01	10	-22 °C	149 days	94.6	4.3
60.28	10	-22 °C	149 days	96.8	3.6
3.01	10	22 °C	9.5 hrs	98.6	9.6
60.28	9	22 °C	9.5 hrs	97.3	9.9
3.01	10	3 cycles freeze-thaw	-	98.3	12.7
60.28	9	3 cycles freeze-thaw	-	101.6	13.4
3.01	10	wet extract at 22 °C	16 hrs	103.6	4.0
80.30	10	wet extract at 22 °C	16 hrs	99.5	3.1
1.0	1	autoinjector 22 °C	3.8 hrs	108.2	-
3.01	1	autoinjector 22 °C	3.8 hrs	101.56	-
40.15	1	autoinjector 22 °C	3.8 hrs	103.01	-
80.30	1	autoinjector 22 °C	3.8 hrs	102.27	-
100.46 mcg/mL stock solution for standard	10	-22 °C	87 days	95.2	4.4
100.46 mcg/mL stock solution for standard	20	-22 °C	87 days	99.9	2.9
10.11 mcg/mL stock solution for internal standard	10	-22 °C	63 days	94.6	2.5

B. Within-study validation

1. Standard curve samples for the current study

The precision and accuracy data for the standard curve samples in Table 7 are acceptable.

**Table 7. Back-calculated Data for Standard Curve Samples  
Dicyclomine in Human Plasma**

Input, ng/mL	N	Found, ng/mL	%Input	%CV
1	5	1.021	102.1	7.1
2.01	5	2.031	101.0	2.0
5.02	5	4.970	99.0	3.8
10.04	3	9.90	98.6	3.5
35.13	5	34.149	97.2	2.3
50.19	5	50.257	100.1	3.9
75.28	5	75.812	100.7	2.4
90.34	5	92.269	102.1	3.6
100.37	5	98.916	98.6	6.0

2. Precision and accuracy of quality control samples

The precision and accuracy data for the QC samples in Table 8 are acceptable.

**Table 8. Precision and Accuracy of QC Sample Assays  
Dicyclomine in Human Plasma**

Input, ng/mL	N	Found, ng/mL	%Nom	%CV
1.00	15	1.082	108.2	5.9
3.01	15	3.057	101.6	3.0
40.15	15	41.359	103.0	2.4
80.30	15	82.123	102.3	1.6

V. In Vivo Results with Statistical Analysis

Of the 24 healthy male volunteers plus 4 alternates who enrolled in the study, subject No. 10 elected to withdraw from the study for reasons unrelated to the study. Subject #21 vomited 20 minutes after the first dose. He completed the crossover study and his data were not analyzed. Thus, a total of 22 subjects plus 2 alternates (subject#s 26 and 27) completed the crossover.

Medical events: Subject No. 21 vomited soon after first dose, he completed the study and his samples were not analyzed. There were no serious medical events.

1. **Mean plasma levels**

The mean plasma dicyclomine level-time profile for the test and reference products were similar as shown in Table 9 and Figs. 1 and 2. The mean peak dicyclomine concentration was 47.98 ng/mL at 1.7 hours for the test product and 50.47 ng/mL at 1.5 hours for the reference product. The test/reference ratios over the entire sampling period of 24 hours were within 0.51-1.38.

Table 9. MEAN PLASMA DICYCLOMINE LEVELS FOR TEST AND REFERENCE PRODUCTS

TIME h	TEST		REFERENCE		RATIO T/R
	Mean	CV%	Mean	CV%	
0.00	0.00	-	0.00	-	-
0.33	2.20	192.61	4.29	192.68	0.51
0.67	20.07	84.48	27.07	74.49	0.74
1.00	34.97	58.28	41.90	43.19	0.83
1.50	44.17	37.46	45.12	29.58	0.98
2.00	39.81	36.67	38.82	32.75	1.03
3.00	28.61	37.66	28.49	36.42	1.00
4.00	19.66	36.35	19.91	42.82	0.99
6.00	10.75	66.38	8.78	50.33	1.23
8.00	6.22	71.32	5.44	65.20	1.14
10.00	4.41	92.88	3.19	46.70	1.38
12.00	2.85	77.63	2.35	52.09	1.21
16.00	1.56	90.07	1.55	71.89	1.01
24.00	1.03	98.32	0.90	98.35	1.15

2. Pharmacokinetic parameters

The pharmacokinetic parameters for the test and reference products were comparable as shown in Table 10. The test/reference ratios for AUC<sub>T</sub>, AUC<sub>I</sub> and C<sub>MAX</sub> were within 0.91-1.14. The 90% confidence intervals for log-transformed AUC<sub>T</sub>, AUC<sub>I</sub> and C<sub>MAX</sub> were within the acceptable range of 80-125% as shown in Table 11.

Table 10. TEST MEAN/REFERENCE MEAN RATIOS

Parameter	TEST		REFERENCE		RATIO T/R
	Mean	CV%	Mean	CV%	
AUC <sub>T</sub>	195.96	36.66	191.05	36.16	1.03
AUC <sub>I</sub>	207.88	39.44	202.67	39.97	1.03
C <sub>max</sub>	47.98	34.83	50.47	32.04	0.95
T <sub>max</sub>	1.70	62.06	1.49	40.74	1.14
K <sub>el</sub>	0.16	62.97	0.15	64.87	1.01
Half-life	6.09	51.94	6.66	64.11	0.91

Units: AUC=ng.h/ml, C<sub>max</sub>=ng/ml, T<sub>max</sub>=h, K<sub>el</sub>=h<sup>-1</sup>, Half-life= h<sup>-1</sup>

Table 11. Geometric Means and 90% Confidence Intervals (Log-transformed Data)

Parameter	N	TEST	REFERENCE	RATIO T/R	90% Confidence Intervals	
		Mean	N Mean		Lower	Upper
*LAUCT	24	181.31	24 177.55	1.02		
*LAUCINF	22	190.45	20 185.67	1.04		
*LCMAX	24	45.01	24 47.91	0.94		
*LAUCT	24	5.20	24 5.18	1.04		
*LAUCINF	22	5.28	20 5.23	1.01		
*LCMAX	24	3.81	24 3.87	0.98		

Units: AUC=ng.h/ml, C<sub>max</sub>=ng/ml

\* antilog of geometric mean; \* Geometric LS Mean

**3. AUC<sub>t</sub>/AUC<sub>inf</sub> ratios for individual subjects**

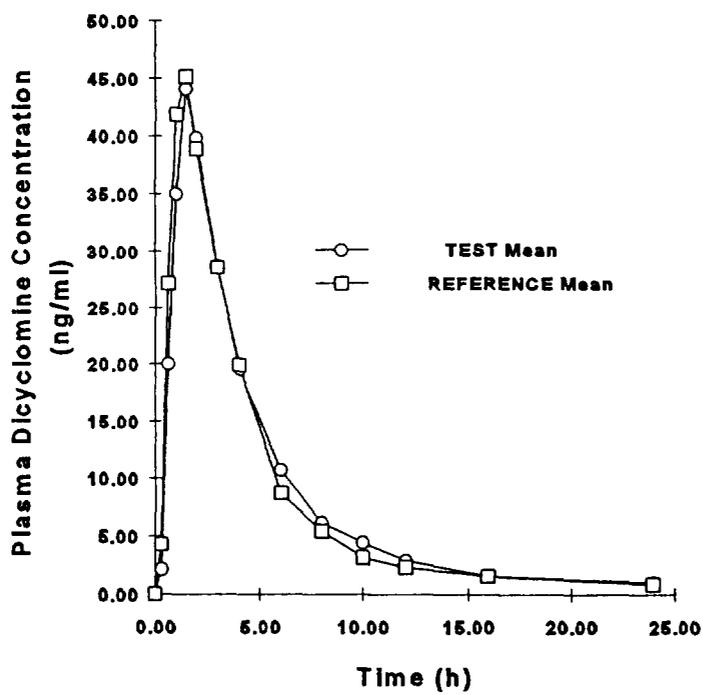
Table 12 shows the AUC<sub>t</sub>/AUC<sub>inf</sub> ratios for individual subjects. Mean AUC<sub>t</sub>/AUC<sub>inf</sub> ratio mean (CV%) for Test=0.93 (2.91) and for Reference=0.93 (3.82).

**Table 12. AUC<sub>t</sub>/AUC<sub>inf</sub> Ratios for Individual Subjects**

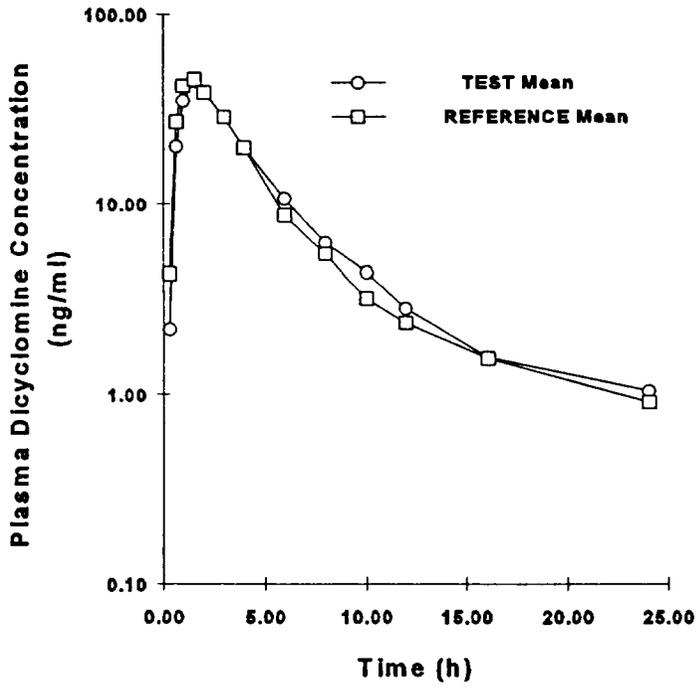
Subjects	AUC <sub>t</sub> / AUC <sub>inf</sub> Ratios	
	Test	Reference
1		
2		
3		
4		
5		
6		
7		
8		
9		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
22		
23		
24		
26		
27		
<b>Mean</b>	<b>0.93</b>	<b>0.93</b>
<b>CV%</b>	<b>2.91</b>	<b>3.82</b>
<b>N</b>	<b>22.00</b>	<b>20.00</b>

\* AUC<sub>inf</sub> not calculable

**Figure 1.**  
**Mean Plasma Dicyclomine Concentration**



**Figure 2.**  
**Mean Plasma Dicyclomine Concentration**



**VI. Product Information**

1. **Formulation** : Formulation of the test product is shown in Table 13.

**Table 13. Test formulation**

Ingredient	Amount/Tablet, mg
√Dicyclomine HCl USP	20
/Lactose Anhydrous NF	
√FD&C Blue No.1 Aluminum Lake	
√Dicalcium Phosphate Dihydrate unmilled, USP	
√Magnesium Stearate, NF	
√Stearic Acid, NF	
√Colloidal Silicon Dioxide, NF	
/Dipac (Compressible Sugar), NF	
√Acacia (Gum Arabic), USP	
√Starch 1500 (Pregelatinized),NF	
<b>Total</b>	

2. **Assay and content uniformity**

The batch size of the test product was                      tablets. The assay and content uniformity of the test and reference products are acceptable as shown in Table 14.

**Table 14. Assay and Content Uniformity Data**

Product	Lot Number	Assay, %	Content Uniformity, % (%CV)
Test	61282001A	97.8	99.2 (2.5)
Reference	4786EL	99.4	99.6 (1.4)

The theoretical yield of lot#61282001 submission and bio-batch lot, is                      tablets.  
The actual final yield was                      tablets or                      %.

**VII. Dissolution**

The comparative dissolution data (Table 15) for the test and reference products met the **USP 23 dissolution specifications:**

Medium: 0.01 N hydrochloric acid; 500 mL

Apparatus 2: 50 rpm

Time: 45 min

Tolerances: NLT    % (Q) in 45 min

Measured Absorbance at 405 nm

Table 15. <i>In Vitro</i> Dissolution Testing Data						
I. General Information						
Drug Product(Generic Name)		Dicyclomine Hydrochloride Tablets				
Strength		20 mg				
ANDA Number		40-230				
Applicant		Lannett				
Reference Drug Product		Marion Merrell Dow's Bentyl <sup>R</sup> Tablets, 20 mg				
Time	Test Product			Reference Product		
	Lot No:61282001A; Exp. 3/98 Strength:20 mg No of Units:12 tablets Units 1-6			Lot No:4786EL; Exp. 7/00 Strength:20 mg No of Units:12 tablets Units 1-6		
Min	Mean	Range	%CV	Mean	Range	%CV
15	72		20.5	65		25.3
30	100		2.04	93		9.4
45	102		2.78	98		3.0
Units 7-12				Units 7-12		
Min	Mean	Range	%CV	Mean	Range	%CV
15	65		17.01	65		18.9
30	101		2.03	95		8.7
45	102		1.39	100		3.6

#### VIII. Comments

1. Open-label, randomized, comparative, 2-way crossover BE study under fasting conditions: Of the 24 plus 4 alternate healthy male volunteers who enrolled in the study, Subject No. 10 elected to withdraw from the study for reasons unrelated to the study. Subject # 21 vomited soon after the first dose. He completed the study and his samples were not analyzed. Two alternates subject #s 26 and 27 replaced subject#s 10 and 21. Thus, a total of 24 subjects completed the crossover.
2. Medical events: No serious medical events reported.
3. The mean plasma dicyclomine for the test and reference products were similar. The mean peak dicyclomine concentration was 47.98 ng/mL at 1.7 hours for the test product and 50.47 ng/mL at 1.5 hours for the reference product. The test/reference ratios over the entire sampling period of 24 hours were within 0.51-1.38.
4. The pharmacokinetic parameters for the test and reference products were comparable. The test/reference ratios for  $AUC_t$ ,  $AUC_{inf}$  and  $C_{max}$  were within 0.91-1.14. The 90% confidence intervals for log-transformed  $AUC_t$ ,  $AUC_{inf}$  and  $C_{max}$  were within the acceptable range of %.
5. Assay method validation data for the Pre-study and within-study are acceptable.
6. The batch size of the test product was                      tablets. The assay and content uniformity of the test and reference products are acceptable.

