CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 74-507

BIOEQUIVALENCE REVIEW(S)

FIELD COPY CERTIFICATION

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment has been sent by overnight courier to:

Mr. Edward T. Warner, District Director
Food and Drug Administration (NYK-DO)
850 Third Avenue
Brooklyn, New York 11232-1593

A Table of Contents has been enclosed to facilitate the review of this amendment. Should any additional information be required, please do not hesitate to contact us.

Sincerely,
CIRCA PHARMACEUTICALS, INC.

Joyce Anne DelGaudio
Director, Regulatory Affairs

Attachments

MAY 2 1996

Nicotine Polacrilex Gum	Circa Pharmaceuticals
2 mg/piece Chewing Gum	Copiague, NY
ANDA #74-507	Submission Date:
Reviewer: Moo Park	December 14, 1995
Filename:74507A.D95	March 27, 1996

Review of an Amendment

I. Objective

Review of Circa's amendment to the *in vivo* bioequivalence study under fasting conditions comparing its Nicotine Polacrilex Gum, 2 mg/piece, to Marion Merrell Dow's Nicorette^{R}, 2 mg/piece.

II. Background

The in vivo bioequivalence study (submission dates: 6/16/94 and 8/15/94)on the 2 mg gum was reviewed as of 9/12/95 by Dr. Y. Huang as incomplete. Seven deficiencies were pointed out in the review. The amendment of 12/14/95 is Circa's responses to the deficiencies. The seven deficiencies are as follows:

1. On pre-dose nicotine levels: Perform additional analysis on nicotine data: (1) by adjusting the baseline nicotine level accordingly, and (2) by excluding subjects who had measurable pre-dose nicotine levels. Results of both recalculations should be submitted for review.

2. On 24-hr plasma nicotine levels: Exclude the 24-hr time point from the AUC calculation and resubmit the data for review.

3. Clarify the meaning of AUC and AUC12 as reported in the submission.

4. Report the statistical analysis based on the first assay results, as long as the assayed values meeting the analytical procedure's acceptance criteria.

5. Provide the rationale for the sampling times selected in the current testing procedure (from 30 minutes up to 6 hours), considering that the gum will be chewed for only 30 minutes.

6. Submit the individual assay result and content uniformity data as well.

7. Size of the biobatch.

III. Review of data submitted in the amendment

- Deficiencies #1, 2 and 4 were answered by Circa by analyzing the nicotine data 3-ways:

    (1) Original submission without baseline adjustment. Twenty-five (25) subjects were used.

    (2) Baseline adjustment with 25 subjects.

    (3) Eight subjects were excluded in the data analysis due to the measurable baseline.

  The data analysis is summarized in Section IV.

#3. Naming of AUC and AUC12: When the last quantifiable concentration occurs earlier than 12 hours, AUC and AUC12 are identical.

#5. Circa stated that 6-hour dissolution was used to aid its product development effort.

#6. The individual assay result and content uniformity submitted are acceptable.

#7. Size of the biobatch (lot#RD0930):

IV. Pharmacokinetic data analysis

The applicant submitted data analysis based on (1) baseline adjusted data set (n=25) and (2) data set with 8 subjects removed (n=17) who showed non-zero nicotine concentrations at zero time. In both cases, the nicotine level at 24 hour sampling point was ignored (set as zero) as requested by Dr. Y. Huang.

The following results are recalculated by Moo Park and are congruent with the results submitted by the applicant.

The applicant did not calculate AUCI due to the variability of KE, the elimination rate constant.

1. 90% confidence intervals for the data sets with baseline adjustment

Eight subjects (subjects #5, 6, 11, 15, 16, 19, 20, and 24) showed non-zero nicotine levels at 0 time. The applicant adjusted the baseline using the first-order decay of the non-zero

data. The PK parameters and their 90% confidence intervals are acceptable as shown in Tables 1 and 2. However, the baseline adjustment is discouraged for drugs that are non-endogenous in origin.

Table 1. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)
MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=T/R RATIO

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCT	13.94	9.24	13.95	6.47	1.00
CMAX	5.56	1.57	5.30	1.77	1.05
LAUCT	12.14	0.50	12.82	0.41	0.95
LCMAX	5.35	0.29	5.05	0.31	1.06

UNIT: AUC=NG HR/ML CMAX=NG/ML

Table 2. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCT	13.90	13.93	88.56	111.04
CMAX	5.56	5.29	93.86	116.34
LAUCT	12.14	12.82	85.67	104.82
LCMAX	5.35	5.05	95.19	118.08

2. <u>90% confidence intervals for the data sets with 8 subjects removed</u>

The eight subjects (subjects #5, 6, 11, 15, 16, 19, 20, and 24) who showed non-zero nicotine levels at 0 time were eliminated from the data set. The PK parameters and their 90% confidence intervals for the 17 subjects are acceptable as shown in Tables 3 and 4. The T/R ratios for the log-transformed and non-transformed AUCT and CMAX ranged :e 90% confidence intervals for the log-transformed AUCT and CMAX were within 80-125%.

Nicotine levels for the 17 subjects are shown in Fig. P-1.

Table 3. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)
MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=T/R RATIO

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCT	15.13	10.94	14.42	7.51	1.05
CMAX	5.42	1.45	5.49	1.98	0.99
LAUCT*	12.68	0.58	12.96	0.46	0.98
LCMAX*	5.22	0.30	5.20	0.34	1.00

UNIT: AUC=NG HR/ML CMAX=NG/ML

Table 4. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCT	14.90	14.37	90.16	117.19
CMAX	5.46	5.49	86.47	112.64
LAUCT	12.71	13.04	86.97	109.21
LCMAX	5.28	5.22	88.72	115.38

V. Deficiency

None.

VI. Recommendation

1. The *in vivo* bioequivalence study conducted by Circa on its Nicotine Polacrilex Gum, 2 mg/piece, lot#RD0930, comparing it to MMD's Nicorette^{R}, 2 mg/piece, Lot#TC137B, has been found acceptable. The study demonstrates that Circa's Nicotine Polacrilex Gum, 2 mg/piece, is bioequivalent to the reference product, MMD's Nicorette^{R}, 2 mg/piece.

2. The firm has met the *in vivo* bioequivalence study requirements and the application is acceptable.

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

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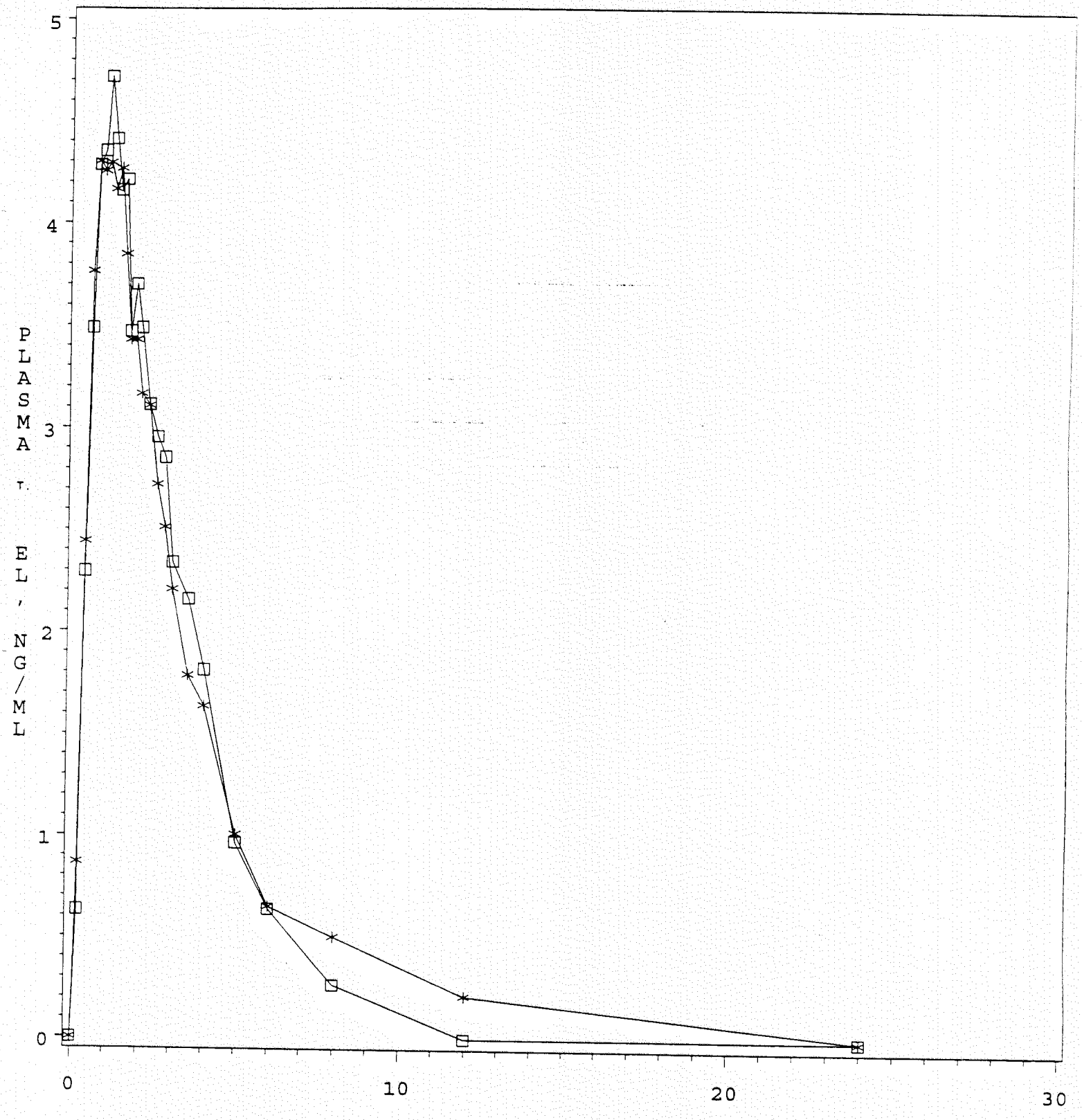
Co[illegible] _____ Date: 2/96

Keith Chan, Ph.D.
Director
Division of Bioequivalence

FIG P-1. PLASMA NICOTINE LEVELS (N=17)

NICOTINE POLACRILEX, 2 MG, ANDA #74-507
UNDER FASTING CONDITIONS
DOSE=1 X 2 MG



1=TEST PRODUCT(CIRCA) 2=REFERENCE PRODUCT(MMD)

Nicotine Polacrilex Gum	Circa Pharmaceuticals
2 mg/piece Chewing Gum	Copiague, NY
ANDA #74-507	Submission Date: 9/12/1997
Reviewer: Moo Park	
Filename:74507A3.997	

Review of an Amendment

I. Objective

Review of Circa's amendment dated 9/12/97. The firm submitted the results of a chew-out study requested by the Agency.

II. Background

Circa had submitted an acceptable *in vivo* bioequivalence study under fasting conditions comparing its Nicotine Polacrilex Gum, 2 mg/piece, to Marion Merrell Dow's Nicorette^{R}, 2 mg/piece (submission date: 6/16/94; review date: 5/10/96). Circa later changed its formulation and requested a waiver on its new formulation in the amendment dated 8/9/96. Circa found out the involving nicotine during accelerated stability study of the original formulation and as a result the new formulation was developed. Circa has changed the amount of nicotine polacrilex resin from in the old formulation to in the new formulation, to take into account the change in the nicotine in the resin when the amount of was decreased from The nicotine loading increased from w/w. Circa had claimed that this was a minor change since the decrease in constituted a change <1% of the total weight and there was no change in pH buffering capacity. The drug substance is an adduct of nicotine and a cation exchange resin (

Circa showed that the release profiles of the new nicotine polacrilex in (and old nicotine

polacrilex glycerinated resin [redacted] were almost identical. Both old and new nicotine polacrilex resins showed fast nicotine release and met the USP23 specifications of NLT 70% in 10 minutes. However, the firm was requested to perform a chew-out study using the old and new formulations to evaluate nicotine release under use conditions. The firm submitted the results of the chew-out study in this amendment.

III. Summary of Chew-out Study

Protocol No.	73-105
Applicant	Circa Pharmaceuticals
Study sites	[redacted]
Investigators	[redacted], M.D
Study dates	6/14/96 and 6/19/96
Study design	A multiple dose, randomized, open-label, two period crossover design.
Subjects	Fourteen subjects were enrolled in the study. A total of 13 subjects completed the two-period study.
Drug products	1. Test product (Circa): Nicotine Polacrilex Gum, 2 mg, Lot #RD 1169 2. Reference product (SmithKline Beecham): Nicorette®, 2 mg, Lot #6B24CE

Dosing	Each subject in each period received four 2 mg doses of test or reference product as follows: First dose: 1 X 2 mg Gum, chewed for 30 minutes. Second dose: 1 X 2 mg Gum, chewed for 20 minutes. Third dose: 1 X 2 mg Gum, chewed for 10 minutes. Fourth dose: 1 X 2 mg Gum, chewed for 5 minutes. Subjects followed a controlled mastication pattern consisting of 3 chews every 4 seconds using an audible timer.
Food and fluid	Subjects reported to the clinic on the morning of dosing and received a light breakfast at -1.5 hours. The subjects then observed a 0.5 hour fast. The subjects received lunch 0.5 hours following the last dose of period 1 and 1.5 hours prior to the first dose of period 2.
Housing	n/a
Washout	n/a
Gum cud samples	Gum cud samples were collected and frozen at -20 °C, and kept frozen. The frozen samples were sent to Circa for [redacted] for remaining nicotine in the gum cud.
Statistical analysis	PROC GLM was used to compare the release profiles of the test and reference products in the chew-out test.

IV. Statistical Analyses of the Results

The firm stated that the test product, lot # RD0930, used in the original chew-out test before the formulation change was expired in 1994. Therefore, the firm made a comparison between the new test lot and the reference product, SmithKline Beecham's Nicorette^{R}, 2 mg, Lot #6B24CE, instead of comparing the old test formulation vs. the new test formulation as described in the deficiency letter.

The mean nicotine releases obtained from the chew-out test at each time point were compared and the test/reference ratios were calculated as shown in Table 1. (Means and lsmeans are identical in this study.)

The Test/Reference ratios at all sampling time points were within 0.8-1.2 range.

Table 1. % Nicotine Release in Chew-Out Test
Arithmetic Means

Chewing Time, min	Number of Subjects	Test mean (sd)	Ref mean (sd)	Test/Ref Ratio
5	13	23.9 (1.75)	23.4 (2.59)	1.02
10	13	41.9 (4.60)	46.5 (5.76)	0.90
20	13	66.3 (5.07)	74.0 (4.62)	0.90
30	13	79.4 (4.78)	86.4 (4.21)	0.92

V. Recommendation

1. The *in vivo* bioequivalence study conducted by Circa on its original formulation, Nicotine Polacrilex Gum, 2 mg/piece, lot#RD0930, comparing it to MMD's Nicorette^{R}, 2 mg/piece, Lot#TC137B, was acceptable. The study demonstrates that Circa's Nicotine Polacrilex Gum, 2 mg/piece, is bioequivalent to the reference product, MMD's Nicorette^{R} DS, 2 mg/piece.

2. The Division of Bioequivalence agrees that the information submitted by Circa demonstrates that its Nicotine Polacrilex Gum, 2 mg strength, manufactured with the revised formulation involving the use of nicotine polacrilex with

falls under 21 CAR 320.22 (d) of the Bioavailability/ Bioequivalence Regulations. The waiver of an *in vivo* bioequivalence study for the new formulation is granted. The test product (new formulation) is deemed bioequivalent to the firm's previously approved formulation.

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

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Concur: e: 1/28/98

Division of Bioequivalence

File history: Draft (1/14/98); Final (1/26/98)

1/1

ANDA 74-507

SEP 27 1995

Circa Pharmaceuticals
Attention: Joyce Anne DelGaudio
33 Ralph Avenue
P.O. BOX 30
Copiague NY 11726-0030

Dear Madam:

Reference is made to the bioequivalence data submitted June 16, 1994 and August 15, 1994, for Nicotine Polacrilex chewing gum, 2 mg.

The Office of Generic Drugs has reviewed the bioequivalence data comparing the test product with the reference listed drug Nicorette®, (Marion Merrell Dow) and has found the study to be incomplete for the following reasons:

1. **Pre-dose nicotine levels**:

   a. Several subjects had measurable pre-dose plasma nicotine levels.

      i. Five subjects for the treatment of test product, subject #5 in period 2 and subjects #6, #15, #16, #20 in period 1.

      ii. Five subjects for the treatment of reference listed drug, subjects #11 and #19 in period 1 and subjects #15, #20, #24 in period 2.

   b. All these subjects had "zero" nicotine plasma levels at 8-hr or 12-hr during the treatment and subject #15 had "zero" nicotine plasma level at 6-hr following the reference product. Based on this observation, one may conclude that these subjects had residual nicotine in the body from previous exposure at the time they received the nicotine gum treatments, which may invalidate the comparison between the test and reference products.

   c. Additional analysis on nicotine data is required: (1) by adjusting the baseline nicotine level accordingly, and (2) by excluding subjects who had measurable pre-dose nicotine levels. Results of both recalculations should be submitted for review.

2. **24-hr plasma nicotine levels**:

a. There are several cases where plasma nicotine levels were detectable in the 24-hour samples, and these concentrations were included in the calculation of AUC(0-t), despite that "zero" nicotine plasma levels were observed for all these subjects at much earlier time points (e.g., 8-hr and 12-hr).

b. Since the 24-hr plasma nicotine levels are not reliable (considering that the subjects were not confined at the testing facility between 12-24 hours after dosing), the 24-hr time point data should be excluded from the AUC calculation. Please recalculate the AUC parameters, and submit it for review.

3. **Clarify AUC and AUC12:**

The majority of the subjects had measurable plasma nicotine levels only up to 5-6 hours after dosing. If the AUC values were calculated from time zero to the last quantifiable concentration as stated in the submission, you need to clarify why identical AUC and AUC12 values were reported in 23 subjects for the test product (except subjects #15 and #29 who had measurable plasma nicotine levels at 24-hr) and in 24 subjects for the reference product (except subject #17 who also had measurable plasma nicotine level at 24-hr), considering that the time for the last quantifiable concentration was less than 12 hours.

4. **Analytical Procedure:**

The analytical procedure for nicotine and cotinine appears to be adequate. However, there were too many "INC" (incongruous) and "NR" (not reportable) samples in the study samples and were reassayed. Because of this, it is somewhat difficult to evaluate the accuracy/reliability of the study results. The NR samples should be limited only to those samples with real analytical problems (such as bad resolution, poor response, broken tubes etc.). The statistical analysis should be reported based on the first assay results, as long as the assayed values meeting the analytical procedure's acceptance criteria.

5. **In vitro drug Release:**

Although *in vitro* drug release testing is not required at the present time, you are encouraged to further improve the *in vitro* testing procedures and have them validated. On the dissolution method, the rationale for the sampling times selected in the current testing procedure (from 30 minutes up to 6 hours) should be provided, considering that the gum will be chewed for only 30 minutes.

6. **Content Uniformity:**

It was reported that the mean potency (assay value) of 104.6% and 104.9% for the test (Lot #RD0930) and reference (Lot #TC137B) products, respectively. The individual assay result and content uniformity data should also be submitted.

7. **Batch Size:**

Please submit information on the size of the bioequivalence batch.

As described under 21 CFR 314.96 an action which will amend this application is required. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

SEP 12 1995

Nicotine Polacrilex
chewing gum, 2 mg
ANDA #74-507
Reviewer: YC Huang
74507SD.694

Circa Pharmaceuticals
Copiague, NY
Submission date:
June 16, 1994
August 15, 1994

Review of a bioequivalence study

Brief information about nicotine gum: Nicotine polacrilex contains nicotine bound to an ion exchange resin in a sugar-free flavored, chewing gum base that provides systemic delivery of nicotine following chewing. When nicotine polacrilex is chewed as directed, nicotine is absorbed through the buccal mucosa. Nicotine is extensively metabolized by the liver and the major metabolites are cotinine and nicotine 1'-N-oxide. About 5% of the dose is excreted in the urine as nicotine and approximately 10% as cotinine in 24 hours. The rate of urinary excretion is increased at lower urinary pH and high urine output. Following inhalation or parenteral administration, the plasma half-life of nicotine ranges from 0.5-2 hours. The plasma half-life of cotinine is approximately 19 hours. Nicotine gum currently is available in two strengths: NICORETTE®, 2 mg and NICORETTE® DS, 4 mg. Both products are marketed by Marion Merrel Dow. (Note: As indicated in PDR, currently both products are marketed by SmithKline Beecham Consumer Healthcare.)

Introduction 1. This submission represents the first generic of this drug product. 2. The submission of 6/16/94 contains the BE study data and drug release data (in 11 volumes). In the submission of 8/15/94 the firm provided the data diskette of the pivotal bioequivalence study, per the Division's request. 3. The firm has also submitted two copies of method validation, because this drug product is not a USP product. [Reviewer's note: This product is now a USP product as of 1/1/95. see USP 23-NF 18, first supplement.]

Contents of this submission
The submission contains the results of the following studies:

1) **Protocol no. CIR-011-934**: Comparative, randomized 2-way crossover bioavailability study of Circa and Marion Merrell Dow (Nicorette®) nicotine polacrilex gum, 2 mg in healthy adult males This study measured the plasma levels of 25 subjects after chewing one dose of the 2 mg gum. The firm also reported the amount of nicotine that remained in the expectorated gum samples. The results are in volumes 2 through 8 of the submission. This is a pivotal bioequivalence study.

2) **Protocol no. 011-P-03**: A chew-out study to compare the release rate of Circa and Marion Merrell Dow (Nicorette®) nicotine polacrilex gum, 2 mg (multiple dose). In the study, the expectorated gum cuds were analyzed for nicotine content and no plasma samples were obtained. An assessment of correlation between the results of the "chew-out study" and the "single-dose bioequivalence study" was also conducted. The release

profiles of nicotine from the gum samples were reported. The results are in volume 9 of the submission.

3) **Protocol no. CIR-011-933A**: Pilot multiple-dose 3-way crossover bioequivalence study of Circa and Marion Merrell Dow 2 mg nicotine chewing gum in healthy adult male. In the study, subjects (N=9) chewed a piece of 2 mg gum every hour for a period of 7 hours. The firm indicated that this study was included for completeness of submission and for information only, since the formulation is different from that proposed in this ANDA. The results are in volumes 10-11 of the submission. [**Reviewer's note**: Since the formulation is different, this reviewer feels that there is no need to conduct a formal review on this pilot study.]

4) **In vitro testing**: The firm has also submitted the results of in vitro testing. The firm indicated that these data were submitted for information only. These in vitro release data were obtained using mastication and dissolution methods. [**Reviewer's note**: Current compendial requirements for this drug product are assay and content uniformity. Drug release is required for nicotine polacrilex but not for nicotine polacrilex gum.]

I. Bioequivalence study (protocol no. CIR-011-934)

[**NOTE**: The study protocol was submitted to the Division for review on 1/3/94. The firm was advised to ensure that the pre-dose levels of both nicotine and cotinine are zero (or below the limit of quantitation)].

Title: Comparative, randomized 2-way crossover bioavailability study of Circa and Marion Merrell Dow (Nicorette®) nicotine polacrilex gum, 2 mg in healthy adult males

Objective: To compare the bioavailability of Circa and Marion Merrel Dow (Nicorette®) nicotine polacrilex gum, 2 mg.

Products tested:

Test (A)	Nicotine Polacrilex Gum, 2 mg, Circa (Lot #RD0930)
Reference (B)	Nicorette®, 2 mg, Marion Merrell Dow (Lot #TC137B)

[The firm reported the assay values of 104.9% for the test product and 104.6% for the reference product. The firm, however, did not submit the raw data from the assay and content uniformity studies.]

Components and composition of the test product:

Component	mg/piece	w/w %
Nicotine polacrilex		