Sorbitol, [redacted]		
Sodium carbonate, [redacted]		
Sodium bicarbonate, USP		
gum base		
Glycerin 96%, USP		
gum flavor, [redacted]		
/ (partially hydrogenated vegetable) oil		
Talc		
TOTAL GUM PIECE WEIGHT	960.00	100.00

Quantity based on 10% active assay and includes an 8% overage.
Used as a processing aid only.

Study design: The study was a single dose, fasting, randomized, two-way crossover study.

Dosing sequence	Subjects
A, B	1,3,6,7,10,12,15,16,17,20,24,26
B, A	2,4,5,9,11,13,14,18,19,21,25,27,28,29

[Note: There were no subjects #8, #22, #23, or #30. Subject #28 dropped after phase 1 and was not replaced. Data from subject #28 were not used. Subjects #1-#15 were assigned to Group 1 and subjects #16-#30 to Group 2. Group 1 received the dose 3 hours before Group 2.]

Clinical site/dates and investigator:

The study was conducted at [redacted] beginning on 2/11/94 and ending on 2/21/94. Phase 1 was dosed on 2/13/94 and Phase 2 was dosed on 2/20/94. [redacted] was the principal investigator.

The study protocol was approved by the [redacted] Institutional Review Board (IRB). All subjects read and signed an IRB approved Informed Consent Form prior to study initiation.

Analytical sites and dates: Assay was performed at [redacted] The sample extraction dates were 2/24/94 through 5/12/94.

Subjects: Twenty-six (26) healthy male volunteers were selected for the study. A total of 25 subjects successfully completed the study. Subject #28 dropped prior to period 2 check-in due to personal reasons. The study group consisted of 24 Caucasians and one Hispanic. The demographics of the subjects were as follows: age, 19-35 years; height, 68-76 inches; weight, 152-206 pounds. Subjects were smokers who smoked no more than 1½ packs of cigarette per day (see protocol amendment).

Drug administration: After a supervised overnight fast, subjects received a single dose of the assigned nicotine polacrilex gum according to a randomization schedule. While seated, subjects

chewed the gum 3 times then switched the location of the gum in the mouth every 4 seconds for a 30 minutes duration (no swallowing of the gum or blowing bubbles). The chewed gums were assayed for nicotine to determine the % of nicotine retained.

Blood samples: Blood samples (10 mL each) were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.17, 1.33, 1.5, 1.67, 1.84, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 12, and 24 hours post-dose. Plasma samples were separated and frozen at -20°C until assayed for nicotine and cotinine concentrations.

Protocol deviations: reported several protocol deviations occurred during the conduct of the study. Two deviations that related to carbon monoxide levels are cited below. None of the protocol deviations are considered to affect the conclusion of the study.

1. On 2/11/94, check-in for Period 1, eight subjects (#2,#3,#6,#12,#14,#18,#24,#25) did not meet the required carbon monoxide (CO) level as stated in the protocol (i.e., to be less than 10 ppm). The CO levels were checked again on 2/12/94 and were less than 10 ppm. The client was notified and approved these subjects to continue in the study. (Reviewer' note: The dosing day for Period 1 was 2/13/94.)
2. On 2/18/94, check-in for Period 2, four subjects did not meet the required CO level as stated in the protocol. The CO levels were checked again on 2/19/94 and were less than 10 ppm. The client was notified and approved these subjects to continue in the study. (Reviewer's note: The dosing day for Period 2 was 2/20/94.)

Analytical Method: The plasma samples were assayed for nicotine and cotinine concentrations using a d.

a. **Analysis of study samples:**

Pgs. 5-6 redacted
in whole
analytical method

Pharmacokinetic data analysis:

1. The pharmacokinetic analysis was conducted on both nicotine and **baseline adjusted** cotinine concentrations.
2. The cotinine concentrations were adjusted for pre-dose values by subtracting off the zero hour value from all subsequent values. Where the baseline value was greater than a subsequent value, the adjusted value was set to zero. The unadjusted data and analysis are presented in Appendix 7.4 of the submission.

3. The following pharmacokinetic parameters were reported: Cmax, Tmax, and AUC.

a. AUC was the area under the plasma concentration versus time curve from time zero to the last quantifiable concentration and was calculated using trapezoidal method. The AUC from zero to 12 hours (AUC12) was also calculated. Samples with concentrations below the limit of quantitation were given a value of zero in the AUC calculation. Missing samples or samples with values that were not reportable were skipped in the calculation of the trapezoidal area.

b. The firm stated that due to the high degree of intrasubject variability in the drug levels, the terminal elimination phase of the nicotine and cotinine pharmacokinetic profiles could not be adequately determined in most cases. Therefore, the elimination rate constant, Kel, AUCinf, and half-life were not calculated.

4. The subjects in the study were divided into two dosing groups. Group 1 (subjects #1-#15) received the dose three hours before Group 2 (subjects #16-#30). An analysis of variance (ANOVA) was run to test for differences between the two groups. This analysis was run using the nicotine pharmacokinetic parameters. The model used for the group analysis was: GROUP SEQ GROUP*SEQ SUBJECT(GROUP*SEQ) PHASE TREAT GROUP*PHASE GROUP*TREAT. The GROUP effect was tested using SUBJECT(GROUP*SEQ) as the error term of the test.

II. **Chew-out study (Protocol #011-P-03)**

Title: A chew-out study to compare the release rate of Circa and Marion Merrel Dow (Nicorette®) nicotine polacrilex gum, 2 mg (multiple dose)

Objective: The objective of the study was to characterize the in-vivo release rate profiles of nicotine from Circa's nicotine gum and the reference listed product, Nicorette®.

Products tested: The test and reference products are identical to those in the single dose bioequivalence study.

Subjects: Subjects were 8 healthy male smokers who had completed the single dose bioequivalence study (protocol no. CIR-011-934). The demographics of the subjects were as follows: age, 19-30 years; height, 68-75 inches; weight, 152-208 pounds.

Clinical site/date and investigator: The study was conducted at [redacted] nning on March 20, 1994 and ending on March 20, 1994. [redacted] the principal investigator.

Procedure: 1. Subjects were admitted at approximately 6 a.m. on the study day and remained in the study unit for approximately 11

hours. 2. All subjects received a light breakfast at 6:30 a.m., 1.5 hours prior to the initial dose of each product. 3. Subjects were not allowed to consume anything by mouth (including food, gum, lozenges, or beverages) 0.5 hours prior to and 0.5 hours after any dose. 4. A lunch was served approximately 4 hours following the first dose. 5. Water was allowed freely during the study, except for 15 minutes prior through 15 minutes post-dose. 6. Alcohol, caffeine, xanthine-containing beverages, and juice or acidic beverages are prohibited during the confinement period of the study.

Drug administration: After an overnight fast, subjects chewed one piece of nicotine gum every hour for four hours according to a randomization schedule. The first piece was chewed for five minutes, the second for 10 minutes, the third for 20 minutes and the fourth for thirty minutes. Subjects used a chew pattern identical to the bioequivalence study protocol (i.e., to chew the gum three times every 4 seconds with an aid of an audible timer). The used gum cuds were collected after the required interval of chewing and were shipped frozen in dry ice and stored at -20°C until analysis for the nicotine content. During Period 1, subjects were dosed at 8:00 a.m., 9:00 a.m., 10:00 a.m. and 11:00 a.m. During Period 2, subjects were dosed at 1:00 p.m., 2:00 p.m., 3:00 p.m., and 4:00 p.m. Subjects were released at 6:00 p.m. on the same day.

Blood samples: No blood samples were drawn for this study.

Safety assessment on oral irritation: Prior to the initial dose and at the completion of each treatment period, the oral cavity (tongue, gums, and buccal mucosa) was inspected for any evidence of irritation.

III. In vitro testing

Currently, other than the routine assay and content uniformity, there is no official in-vitro testing procedure required for this drug product. The firm has used mastication and dissolution methods for their formulation evaluation. In this submission, the firm reported the results of in-vitro drug release testing using mastication and dissolution methods.

Mastication:

7. **Dissolution Procedure:**

a) Surface area and temperature variation are critical parameters that affect the gum.

b) The sample preparation for each dissolution vessel involved taking 5 pieces of gum and cutting each one into nine equal size parts. The resulting 45 smaller pieces were placed into the vessel (NOTE: Dissolution was conducted with 3 vessels only.) The dissolution testing conditions are as follows:

USP Apparatus II (paddle) at 150 rpm
Medium: 500 mL simulated stimulated saliva, pH 7.8 at 45°C.
Sampling times: 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours.
Analytical method:

IV. Results:

a. Pivotal bioequivalence study:

1. The firm enrolled 26 subjects for the study and 25 of them

completed both phases of the study.

2. No serious or unexpected adverse experiences were reported during the study. The complaints included feeling of fuzziness in head, lightheadedness, nausea, and headache. Five incidences were reported after the test product and four after the reference product.

3. Table I summarizes the mean plasma concentration-time data and the derived pharmacokinetic parameters of nicotine. Detectable **pre-dose** nicotine levels were observed in five subjects (#5,6,15,16,20) for the test product and also in five subjects (#11,15,19,20,24) for the reference product (see footnote in Table I). The drug product was chewed for 30 minutes and approximately 50% of subjects had measurable nicotine levels at the first sampling time, 0.17 hour (15 subjects after test product and 10 subjects after the reference product). Almost all of the subjects had measurable nicotine levels at 0.33 hour. The mean Tmax values were 0.93 (range 0.33-2.5) hour and 1.1 (range 0.5-2.5) hour, respectively for the test and reference products. Plasma nicotine levels declined rapidly after the peak time; measurable nicotine levels were observed in approximately 50% and 25% of the subjects at 5 hours and 6 hours postdose, respectively. None had detectable nicotine level at 12 hours after the test product and only one had detectable level at 12 hours after the reference product. Four subjects had measurable nicotine levels 24 hours postdose (3 after test and 1 after reference product). Figure 1 shows the plasma concentration-time profiles.

4. The results of least squares means and 90% confidence intervals for nicotine as reported by the firm are cited in Table II. The reported 90% confidence intervals for LN-AUC and LN-Cmax are within the range of 80-125%. [see comments #1 and #2.]

5. Table III summarizes the **unadjusted** mean plasma concentration-time data and the derived pharmacokinetic parameters of cotinine. The plasma concentration-time profiles are shown in Figure 2. Almost all of the subjects had measurable pre-dose cotinine levels. The firm has also reported individual and mean **"baseline adjusted"** plasma cotinine concentrations, by subtracting each individual's pre-dose cotinine level from the cotinine levels measured after chewing the gum. The 90% confidence intervals of log-transformed AUC and Cmax for both unadjusted and baseline adjusted cotinine were **outside the range of 80-125%** (see Tables IV and V and note the difference in the values between unadjusted and baseline adjusted). [**NOTE:** This reviewer feels that the procedure of baseline adjustment is incorrect and therefore the results of the plasma concentration data are not cited here. The 90%

confidence intervals of baseline adjusted cotinine, however, are cited here for comparison purpose.]

6. The results of the pilot multiple-dose, 3-way crossover study were reported in volumes 10 and 11 of the submission. This study was submitted for information only, since the formulation of nicotine gum in this study was different from that proposed in this ANDA. This pilot study was not reviewed.

b. Chew-out study:

7. There were no adverse experiences reported by any of the subjects during the chew-out study.

8. Results of % nicotine released (mean values, N=8):

Time	Test	Reference
5 minutes (range)	16.9%	18.9%
10 minutes (range)	35.5%	35.6%
20 minutes (range)	57.1%	60.3%
30 minutes (range)	72.8%	74.7%

9. The release profiles of nicotine were similar between the test and reference products.

c. In-vitro testing:

10. Mastication results (N=6): The nicotine release profiles and pH values after mastication are shown in Figures 3 and 4. The mean percentages of nicotine released at 30 minutes were 66.2 and 54.6 % for the test and reference products, respectively.

11. Dissolution results (N=3): expressed as % label released. [Note: The values were not corrected for the lost volume.]

Time (hr)	Test: (RD0930) Mean (range)	%CV	Reference: (TC137B) Mean (range)	%CV
0.5	9.3 ( )		9.1 ( )	
1.0	13.3 ( )		13.5 ( )	
1.5	15.6 ( )		17.9 ( )	
2.0	19.2 ( )		21.2 ( )	
3.0	23.3 ( )		27.4 ( )	
4.0	28.3 ( )		32.7 ( )	

5.0	32.6	36.9	
6.0	37.2	41.9	3.8%

d. On the amount of nicotine delivered after chewing for 30 minutes:

Bioequivalence study (N=25):

	Test	Reference
Initial	104.6%	104.9%
Retained range	32%	30%
Delivered range	72.6%	74.9%
Amount delivered range	1.452 mg	1.498 mg

Chew-out study (N=8):

	Test	Reference
Delivered range	72.8%	74.7%
Amount delivered range	1.456 mg	1.494 mg

NOTE: The range of initial assay was not given.

V. A brief summary for the pivotal bioequivalence study:

The 90% confidence intervals for log-transformed AUC and Cmax for nicotine reported by the firm are within the range of 80-125%. The results on nicotine, however, are considered incomplete. Please see comments below for the reason of this recommendation. The results on cotinine can not be accurately evaluated due to the problems of the pre-dose cotinine plasma levels observed in almost all subjects and the recovery data of the assay. The 90% confidence intervals for both log-transformed AUC and Cmax for cotinine as reported by the firm are outside the range of 80-125%, based on either unadjusted or baseline adjusted cotinine plasma levels.

The firm had been advised in the protocol review to ensure that both pre-dose nicotine and cotinine levels are zero or below the limit of quantitation. Realistically, the pre-dose level of cotinine may be more difficult to control due to its relatively long half life (approximately 19 hours) and the subjects' often exposure to the environmental cigarette smoke (even if one chooses not to smoke). Zero pre-dose nicotine level, however, should be relatively easier to obtain, as evidenced from the zero nicotine levels observed at 5, 6, 8, or 12 hours after the gum treatment in the testing facility. Based on this consideration, the bioequivalence determination for this drug product is based on the measurement of nicotine plasma levels. The data on cotinine are for information only.

VI. Comments

1. **On pre-dose cotinine levels**: Almost all subjects had detectable cotinine levels at 0-hr, except subjects #9 and #11 for the test product and subjects #9 and #15 for the reference product. The 0-hr cotinine levels ranged from 0-106 ng/mL for the test product and 0-122 ng/mL for the reference product. The mean 0-hr plasma cotinine level was 62% of the mean Cmax level for the test product and 70% for the reference product. Because of this observation, it is difficult to evaluate the reliability of the plasma cotinine data.

2. The recovery data (measured by direct comparison of the peak area of extracted standards to unextracted test solution) for nicotine appears to be acceptable considering the range of plasma concentrations of nicotine observed (the highest level observed was approximately 10 ng/mL) following a single dose of 2 mg nicotine gum. The recovery data for cotinine, however, appeared to be too high (127% at 10 ng/mL and 114% at 250 ng/mL. The mean observed Cmax values were 42-47 ng/mL as reported in Table III).

VII. Deficiencies:

1. **On pre-dose nicotine levels**: Five subjects (#5 was in period 2 and #6,#15,#16,#20 were in period 1) for the treatment of test product and five subjects (#11 and #19 were in period 1 and #15,#20,#24 were in period 2) for the treatment of reference product had measurable pre-dose plasma nicotine levels. It should be noted that 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. Therefore, the firm should be advised to 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**: There are several cases that plasma nicotine levels are detectable in the 24-hour samples. The firm had included these concentrations in the calculation of AUC(0-t), despite that "zero" nicotine plasma levels were observed for all these subjects at much earlier time points at 8-hr and 12-hr. 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 firm should be advised to exclude the 24-hr time point from the AUC calculation and resubmit the data for review.

3. In addition, the firm needs to clarify the meaning of AUC and AUC12 as reported in the submission. The majority of the subjects had measurable plasma nicotine levels only up to 5-6 hours after dosing. If the AUC values were AUC from time zero to the last quantifiable concentration as stated in the submission, the firm needs 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. The analytical procedure for nicotine and cotinine appears to be all right. However, there were too many "INC" (incongruous) and "NR" (not reportable) samples in the study samples. Because of this, it is somewhat difficult to evaluate the accuracy/reliability of the study results. NR samples should be limited only to those samples with real analytical problems (such as bad resolution, poor response, broken tubes etc). The firm should be advised to report the statistical analysis based on the first assay results, as long as the assayed values meeting the analytical procedure's acceptance criteria.

5. Although in vitro drug release testing is not required at the present time, the firm should be encouraged to further improve its in vitro testing procedures and have them validated. On the dissolution method, the firm should be advised to 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. The firm reported the mean potency (assay value) of 104.6% and 104.9% for the test (Lot #RD0930) and reference (Lot #TC137B) products, respectively. The firm should be advised to submit the individual assay result and content uniformity data as well.

7. The firm should be advised to supply the information on the size of the biobatch.

VIII. Recommendation

1. The in vivo bioequivalence study conducted under fasting conditions by Circa Pharmaceuticals on its nicotine polacrilex gum, 2 mg, lot #RD0930 comparing it to Marion Merrel Dow's Nicorette®, 2 mg, lot #TC137B, has been found incomplete by the Division of Bioequivalence for reasons cited in deficiencies #1 through #7.

2. The firm should be informed of the recommendation and deficiencies.

Yih-Chain Huang, Ph.D.
Division of Bioequivalence
Review Branch I

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FT INITIALED RMhatre

9/6/95

CONCUR

Keith Chan, Ph.D.
Director
Division of Bioequivalence

Date 9/12/95

YCHuang/05-31-95,07-31-95,08-31-95/74507SD.694

Table I
Mean Plasma Concentrations (ng/mL) And Pharmacokinetic Parameters of Nicotine Following 2 mg Dose Of Nicotine Polacrilex Gum Under Fasting Conditions (N=25)

Time (hr)	Test Product		Reference Product	
	Mean	CV (%)	Mean	CV (%)
0	0.4"	236	0.3"	218
0.17	1.1	100	0.7	136
0.33	2.7	57	2.4	41
0.50	4.0	38	3.8	37
0.67	4.7	30	4.3	28
0.83	4.5	26	4.4	36
1.00	4.4	33	4.7	37
1.17	4.3	31	4.4	31
1.33	4.4	37	4.3	45
1.50	3.9	34	4.2	43
1.67	3.6	36	3.5	42
1.83	3.6	37	3.6	42
2.00	3.3	38	3.5	33
2.25	3.2	37	3.1	35
2.50	2.9	55	3.0	46
2.75	2.7	59	2.9	29
3.00	2.3	61	2.1	56
3.50	1.7	73	2.1	52
4.00	1.8	83	1.8	60
5.00	1.0	128	1.0	105
6.00	0.6	183	0.5	193
8.00	0.4	206	0.3	237
12.00	0		0	500
24.00	0.2#	316	0.1#	490
AUC hr-ng/mL	15.62	54	15.35	55
AUC12	14.49	53	14.43	45
Cmax (ng/mL)	5.90	28	5.47	33
Tmax (hr)	0.93	51	1.10	45
LAUC	2.628	19	2.616	18

LAUC12	2.558	19	2.584	16
LCmax	1.734	17	1.652	19

*: The following subjects had detectable nicotine levels prior to dosing: For the test-product: #5 (1.2 ng/mL), #6 (1.6 ng/mL), #15 (2.5 ng/mL), #16 (1.5 ng/mL), and #20 (4.4 ng/mL). For the reference product: #11 (1.3 ng/mL), #15 (1.1 ng/mL), #19 (2.4 ng/mL), #20 (1.6 ng/mL), and #24 (1.0 ng/mL).

#: The following subjects had measurable nicotine levels at 24-hr: after test product: #5 (2.6 ng/mL), #15 (2.0 ng/mL), #29 (2.0 ng/mL) and after reference product: #17 (3.3 ng/mL). It should be noted that these levels were often higher than the preceding samples at 12-hr and 8-hr.

Note: AUC=AUC(0-t), time zero to the last quantifiable concentration. AUC12 is area under the curve from time zero to 12 hours.

Table II
Least Squares Means and 90% Confidence Intervals
(2 mg nicotine gum chewed for 30 minutes, fasting study, N=25)

Nicotine:

Parameter	Test	Reference	T/R Ratio	90% Confidence Interval
Cmax	5.909	5.462	1.082	97.3-119.1%
AUC	15.647	15.371	1.018	87.0-116.6%
AUC12	14.504	14.408	1.007	91.9-109.5%
LCmax	1.737	1.651		
Geometric mean	5.680	5.212	1.090	98.0-121.1%
LAUC	2.631	2.617		
Geometric mean	13.888	13.695	1.014	88.9-115.5%
LAUC12	2.561	2.584		
Geometric mean	12.949	13.250	0.977	88.7-107.7%
Tmax	0.926	1.111		

Note: The study has been found incomplete. Please see comments.

Table III
Mean Plasma Concentrations (ng/mL) And Pharmacokinetic Parameters of Cotinine Following 2 mg Dose Of Nicotine Polacrilex Gum Under Fasting Conditions (N=25)

Unadjusted cotinine

Time (hr)	Test Product		Reference Product	
	Mean	CV (%)	Mean	CV (%)
0	26	78	33	84
0.17	26	76	31	84
0.33	26	80	32	87
0.50	27	73	34	78
0.67	29	70	36	69
0.83	32	66	38	64
1.00	34	61	40	63
1.17	35	56	42	61
1.33	37	55	44	60
1.50	38	51	43	57
1.67	38	50	44	59
1.83	38	48	44	58
2.00	39	51	44	58
2.25	39	49	45	55
2.50	39	47	44	55
2.75	40	50	44	51
3.00	39	47	44	52
3.50	38	39	44	54
4.00	39	46	44	55
5.00	37	55	41	59
6.00	34	50	38	60
8.00	32	47	36	61
12.00	26	49	31	62
24.00	19	77	20	84
AUC hr-ng/mL	620	58	718	62
AUC12	389	52	457	60
Cmax (ng/mL)	42	47	47	53
Tmax (hr)	2.32	39	2.26	33

LAUC	6.289	8.7	6.435	8.4
LAUC12	5.865	7.5	6.012	7.4
LCmax	3.656	9.7	3.766	10.7

Note: Almost all subjects had detectable cotinine levels at 0-hr, except subjects #9 and #11 for the test product and subjects #9 and #15 for the reference product. The 0-hr cotinine levels ranged from 0-106 ng/mL and 0-122 ng/mL, respectively after test and reference products.

NOTE: After test product, subject #9 and #11 did not have detectable cotinine levels until 0.67 hour and 0.83 hour, respectively. All other subjects had detectable cotinine level at 0.17 hour. These observations, however, were complicated by the fact that all of them had detectable levels at 0-hr. After reference product, subjects #9 and #15 did not have detectable cotinine levels until 0.5-hr. All other subjects had detectable levels at 0.67-hr.

NOTE: Almost all of the subjects had measurable cotinine levels at 12-hr (N=23) and 24-hr (N=22) after the test product. All subjects had measurable cotinine levels at 12-hr (N=25) and 24-hr (N=22).

Note: AUC=AUC(0-t), time zero to the last quantifiable concentration. AUC12 is area under the curve from time zero to 12 hours.