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

Cotinine (unadjusted):

Parameter	Test	Reference	T/R Ratio	90% Confidence Interval
Cmax	41.369	47.269	0.875	77.0- 98.1%
AUC	612.404	714.955	0.863	76.5- 96.2%
AUC12	387.313	455.607	0.850	74.0- 96.0%
LCmax	3.654	3.764		
Geometric mean	38.629	43.121	0.896	82.1- 97.7%
LAUC	6.288	6.432		
Geometric mean	538.076	621.416	0.866	76.5- 97.9%
LAUC12	5.862	6.010		
Geometric mean	351.426	407.483	0.862	78.8- 94.4%
Tmax	2.313	2.249		

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

Cotinine (baseline adjusted):

Parameter	Test	Reference	T/R Ratio	90% Confidence Interval
Cmax	15.510	14.750	1.052	91.4-118.9%
AUC	94.404	91.304	1.034	70.8-135.9%
AUC12	88.131	78.631	1.128	82.8-141.4%
LCmax	2.704	2.572		
Geometric mean	14.939	13.092	1.141	96.7-134.6%
LAUC	4.373	4.020		
Geometric mean	79.281	55.701	1.423	102.3-198.1%
LAUC12	4.352	3.969		
Geometric mean	77.634	52.932	1.467	105.8-203.2%
Tmax	2.313	2.249		

NOTE: The baseline adjusted cotinine values are cited here for comparison purpose. See comment #3.

Circa Pharmaceuticals, Inc.
Nicotine Protocol #CIR-011-934

Figure 1

Mean (S.D.) Plasma Nicotine Concentrations Versus Time

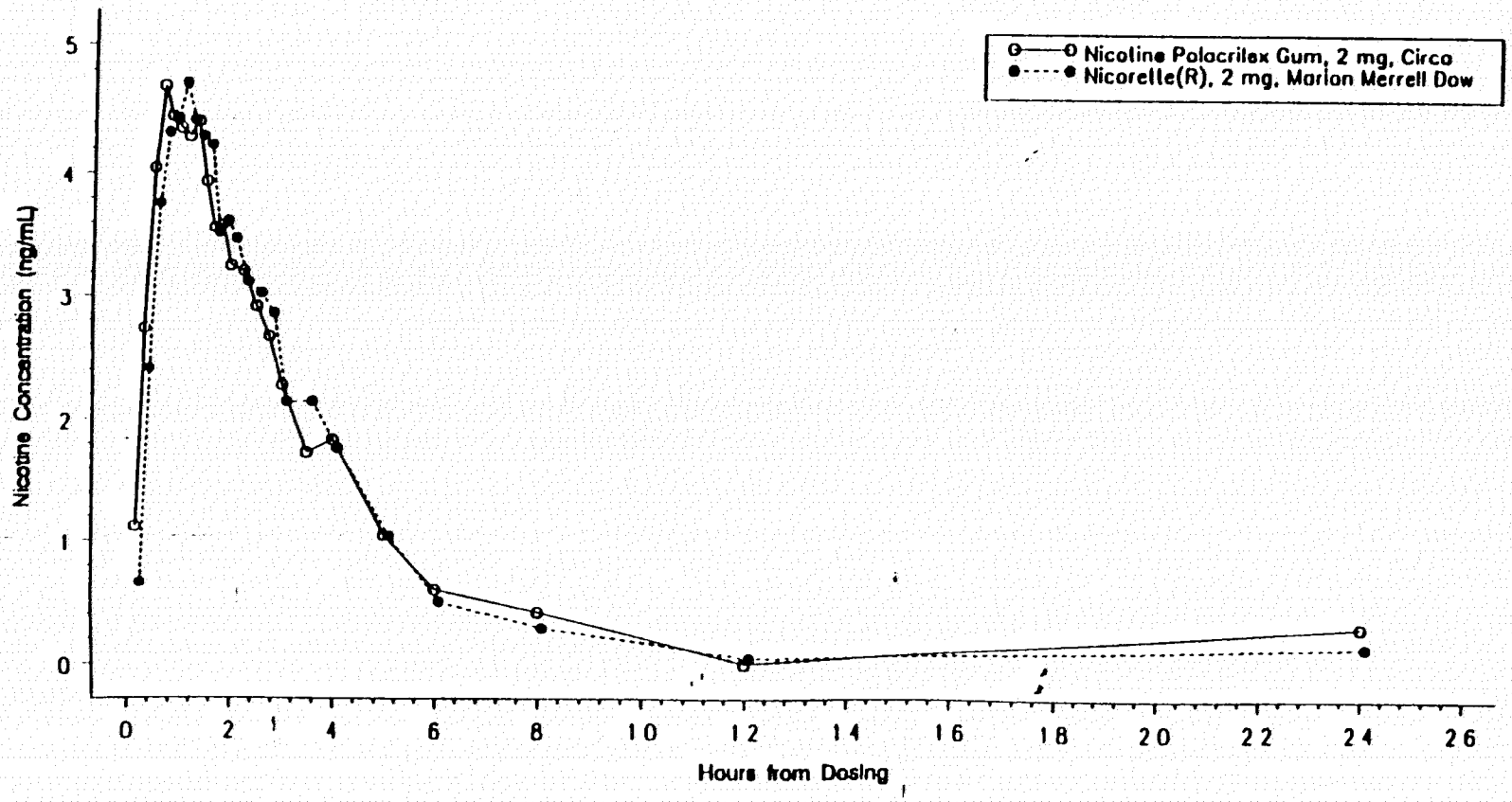
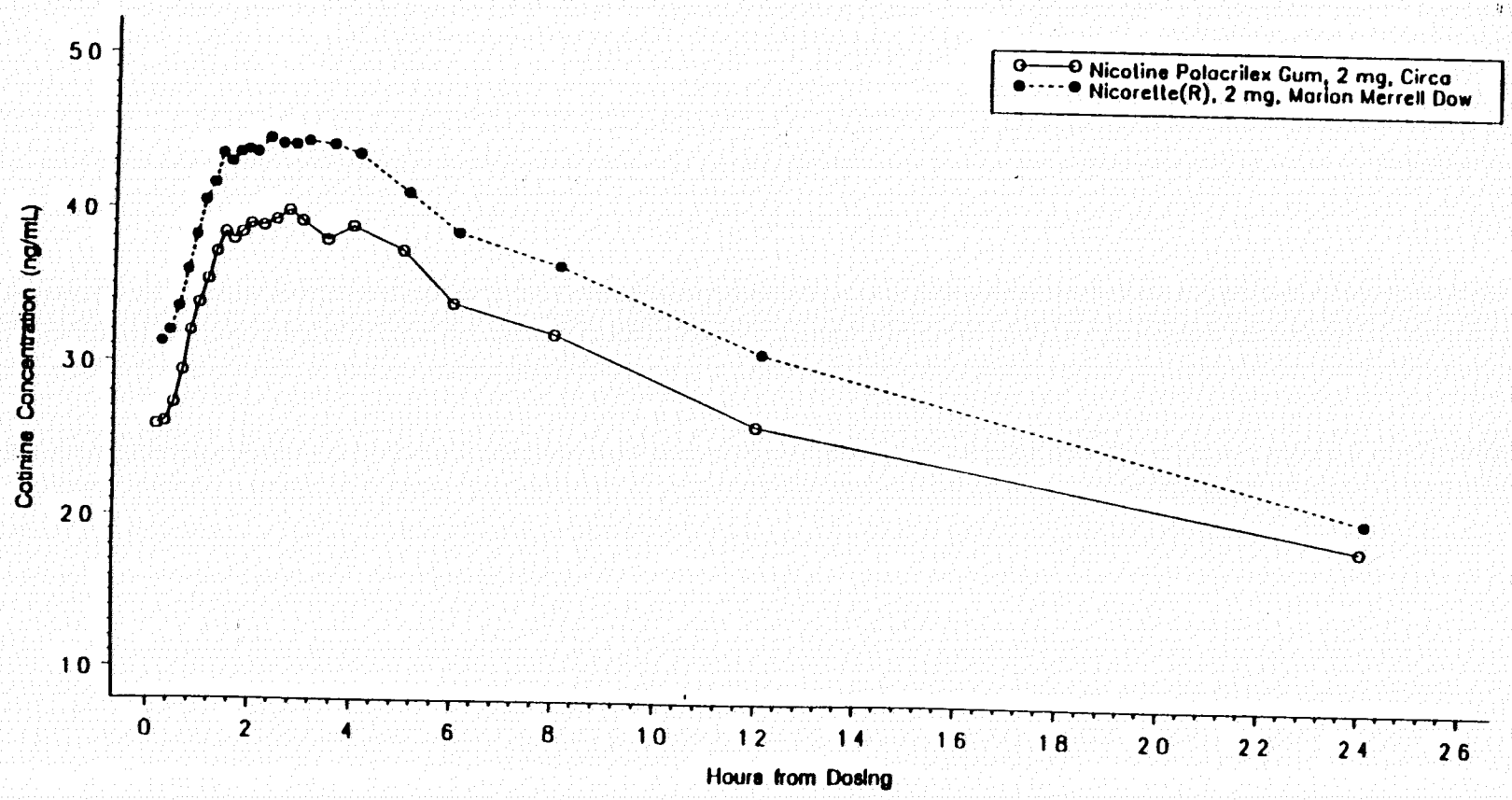


Figure 2

Mean (S.D.) Plasma Cotinine Concentrations Versus Time

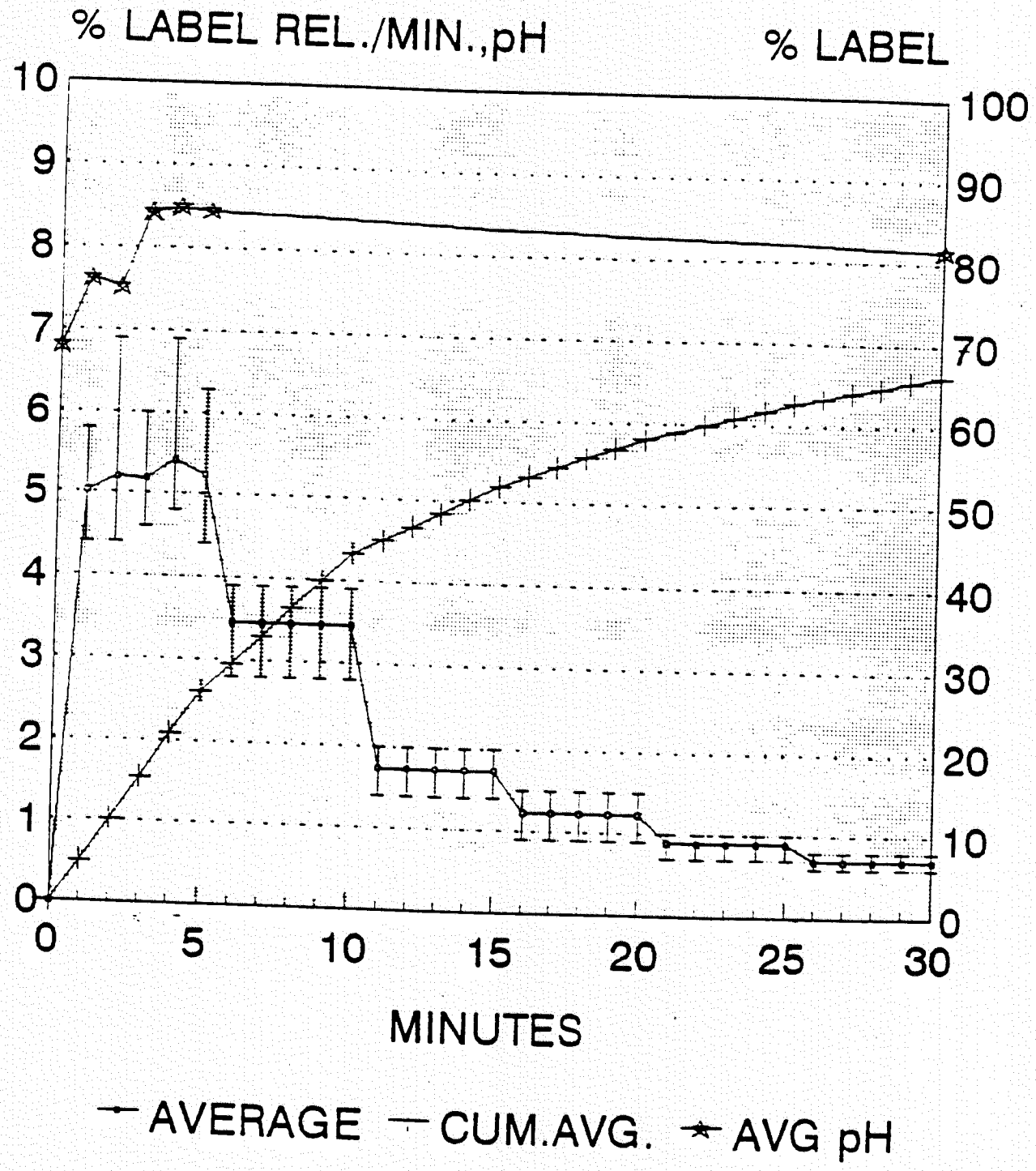


NICOTINE 2 MG GUM LOT RD0930

6 PIECE MAST 4/8/94 TEST

BIOBATCH

Figure 3



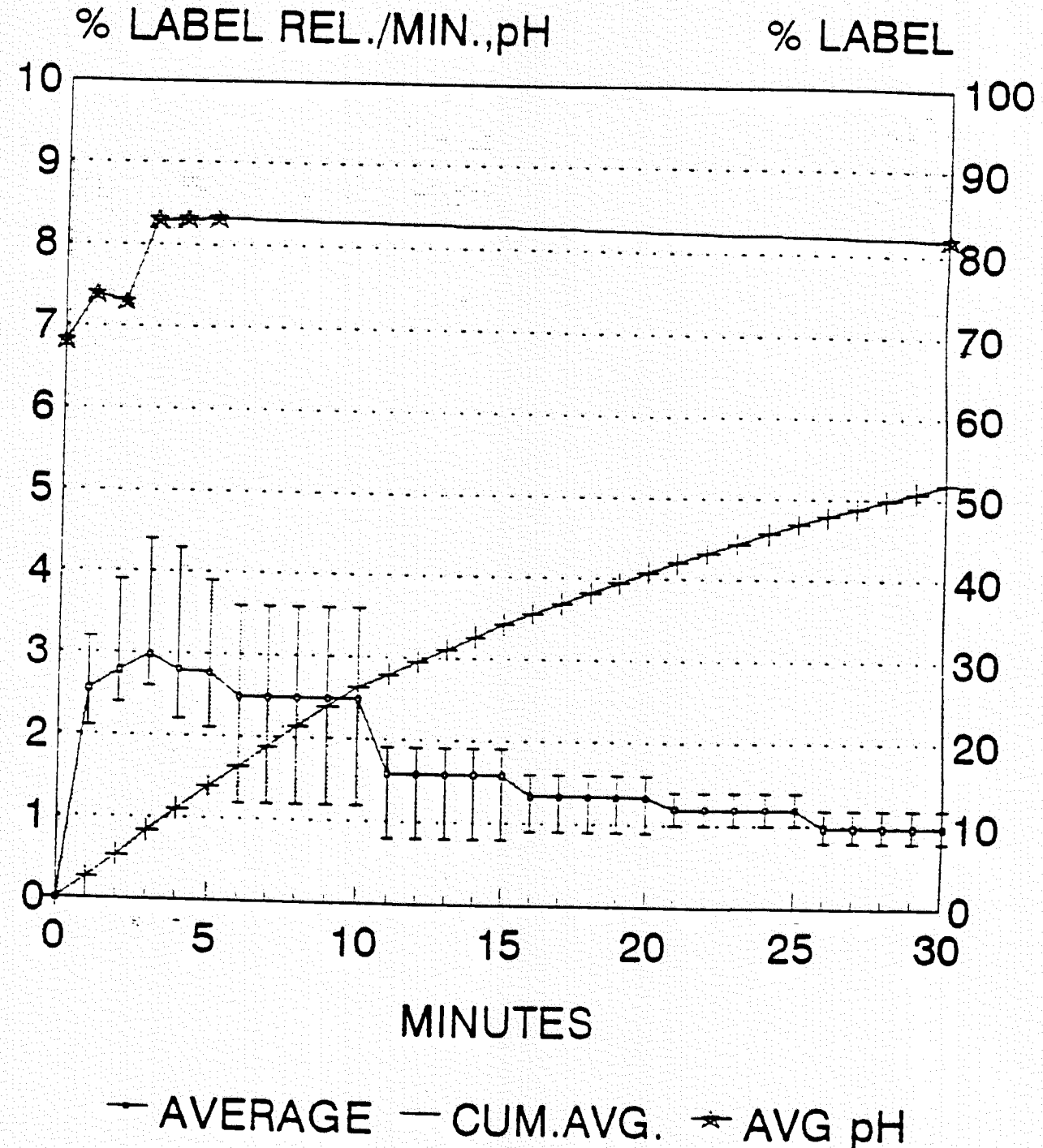
NICORETTE 2MG GUM #170

6 PIECE MASTICATION, 4/11/94 Reference

SUS (pH 6.8) changed to SSS (pH 7.8) @ 3 min.

~~PORT 5 EXCLUDED~~ copy error SJS 5/23/94

Figure 4



BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-507 APPLICANT: Circa

DRUG PRODUCT: Nicotine Polacrilex Gum

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

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.

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

MAY 16 1997

Nicotine Polacrilex Gum	Circa Pharmaceuticals
2 mg/piece Chewing Gum	Copiague, NY
ANDA #74-507	Submission Date:
Reviewer: Moo Park	August 9, 1996
Filename:74507A2.896	

Review of an Amendment

I. Objective

Review of Circa's amendment involving formulation change. 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®, 2 mg/piece (submission date: 6/16/94; review date: 5/10/96).

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 responding to the deficiencies was reviewed by Moo Park. The *in vivo* bioequivalence study conducted by Circa on its Nicotine Polacrilex Gum, 2 mg/piece, lot#RD0930, comparing it to MMD's Nicorette®, 2 mg/piece, Lot#TC137B, was acceptable.

In this amendment, Circa requested a waiver on its new formulation. Circa found chemical stability problem involving nicotine during accelerated stability study of the original formulation and as a result the new formulation was developed.

III. Comments

1. The applicant has changed the amount of nicotine polacrilex

ion, to take into account the change in the of nicotine in the resin when the amount of is decreased from The nicotine loading increases from The new and old formulations are shown in Table 1. The applicant has claimed that this is a minor change since the decrease in glycerol constitutes a change in <1% total and there is no

change in pH buffering capacity. The drug substance is an adduct of nicotine and a cation exchange resin (Amberlite IRP-64).

Table 1. Comparison of Old and New Formulations

Ingredient	Old Formulation mg/piece	New Formulation mg/piece
Nicotine Polacrilex		.16 ıe)
Nicotine Polacrilex (erage	6 e)	
Sorbitol		
Sodium Carbonate		
Sodium Bicarbonate		
Gum base		
Glycerol		
Gum Flavor		
- Partially Hydrogenated Oil		
Talc		ȷ
Purified Water USP		ȷ
Total gum weight		

2. USP23 requires a drug release test ın water. Table 2 shows the results of USP23 release test.

Test method: An accurately weighed quantity of nicotine polacrilex , equivalent to about 4 mg of nicotine, was added into a 50 mL centrifuge tube. The

weighing was made for each time point for each formulation. To each tube, 10 mL of 0.9% sodium chloride solution, warmed to 37°C, was added. All the sample tubes were shaken and each sample tube was taken out at 1, 2, 5, 10 and 15 minutes for assay for released nicotine.

Results: The release profiles of the new nicotine polacrilex .) and old nicotine were almost identical as shown in Table 2. Both old and new nicotine polacrilex resins showed fast nicotine release and met the USP23 specifications of NLT 70% in 10 minutes.

Table 2. Nicotine Release (%) Profiles

Time, min	New Nicotine Polacrilex resin Lot #3892	Old Nicotine Polacrilex resin Lot #3266B
1	69.1	73.7
2	72.6	74.5
5	77.2	76.7
10	77.2	76.2
15	75.2	76.5

3. The firm should perform a chew-out study using the old and new formulations to evaluate nicotine release under use conditions.

4. Waiver will not be granted until the chew-out study data are reviewed.

VI. Deficiency

The firm should submit results of a chew-out study for the old and new formulations performed under use conditions.

V. Recommendation

The amendment submitted for the formulation change of Circa's Nicotine Polacrilex Gum involving the use of nicotine polarilex with instead of nicotine polarilex with used in the original formulation is incomplete. The firm should submit results of a chew-out study for the old and new formulations conducted under use conditions.

The firm should be informed of the recommendation and deficiency.

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

RD INITIALED RMHATRE
FT INITIALED RMHATRE 5/13/97

Conc. _____ Date: 5/16/97
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

DIVISION APPROVAL SUMMARY

ANDA #: 74-507 **DRUG PRODUCT:** Nicotine Polacrilex Gum, 2 mg, USP

FIRM: Circa Pharmaceuticals, Inc.

DOSAGE: Chewing Gum

STRENGTH: 2 mg/piece

cGMP STATEMENT/EIR UPDATE STATUS:
cGMP: GMP Certification is enclosed. (Page 708).
EER: Status pending.

BIO STUDY(ies)/BIOEQUIVALENCE STATUS:
On 1/28/98 the Division of Bioequivalence issued a waiver letter to the firm.

METHODS VALIDATION (Including dosage form description):
N/A. Drug substance and drug product are compendial.

STABILITY(Conditions, Containers, methods):
Bio batch

Evaluation of stability indicating methods:

Stability Assays

Tests	**Method**	**Specification**
Description		
Blister packaging id/Visual Assay		
Chro.Purity*		

Stability studies were done on the bio batch. Packaging configuration (blister packs) is described in the container section. Stability studies are in conformance with FDA Stability Guidelines.

LABELING REVIEW STATUS: Acceptable. See reviewed dated 8/3/98.

STERILIZATION VALIDATION (If Applicable): Not applicable for this product.

BATCH SIZES:

BIO BATCH: Lot RD#1186
NDS source:

STABILITY BATCHES (different from BIO BATCH, manuf. site, process)
Stability batch is the same as the bio-batch

PROPOSED PRODUCTION BATCH
is the proposed production batch size.

The manufacturing process is the same as the one used for the demonstration batch.

COMMENTS: Approvable

CHEMISTRY REVIEWER: **DATE:**

Radhika Rajagopalan August 4, 1998

/98

ANDA 74-507

MAY 28 1997

Circa Pharmaceuticals, Inc.
Attention: Joyce Anne Del Gaudio
33 Ralph Avenue
Post Office Box 30
Copiague, NY 11726-0030

Dear Madam:

Reference is made to the amendment submitted on August 9, 1996, for the formulation change involving the use of nicotine polacrilex gum with instead of nicotine polacrilex gum with and the request for a waiver of *in vivo* bioequivalence requirements.

The Office of Generic Drugs/Division of Bioequivalence has reviewed the waiver request and has found it to be incomplete for the following reasons:

> The results of a chew-out study comparing the old and the new formulations conducted under use conditions to evaluate nicotine release, is required for proper evaluation.

As described under 21 CFR 314.96 an action which will amend this application is required, if you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOAVAILABILITY

CIRCA PHARMACEUTICALS, INC.

33 RALPH AVENUE P.O. BOX 30 COPIAGUE, NY 11726-0030
(516) 842-8383 FAX (516) 842-8630

August 15, 1994

BIOEQUIVALENCE AMENDMENT

Douglas Sporn, Acting Director
Office of Generic Drugs
CDER - FDA
Document Control Room
Metro Park North II
HFD-600, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 74-507; NICOTINE POLACRILEX GUM, 2 mg
Amendment to Pending Application

Dear Mr. Sporn:

Reference is made to a telephone communication on August 9, 1994 between Ms. Joyce DelGaudio of Circa and Mr. Jason Gross of your Division of Bioequivalence. During that conversation, it was requested that we submit a diskette containing data from our bioequivalence study conducted on the above referenced product. Accordingly, we have enclosed a diskette containing the requested information accompanied by a hard copy of the data, as follows:

1. The first file NIC1.XFR contains subject sequence/treatment data including concentration data and values for AUC 0-t, AUC 0-12, CMAX and TMAX.

   Please refer to page 3 of our study report. As indicated in the report, there was a high degree of intrasubject variability in the nicotine values and the terminal eleimination phase of the nicotine and cotinine pharmacokinetic profiles could not be adequately determined in most cases. Therefore, the elimination rate constant, KEL and its dependent parameters, AUC-INF and HALF-LIFE, were not calculated.

   CMIN, CLAST, and TLAST are not required by your guidance entitled "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design". Therefore, these parameters were not determined on this study data.

2. The second data set NIC2.XFR contains the grid of concentration data over time.

3. The third data set NIC3.XFR contains the concentration data by study group.

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provision of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

FIELD COPY CERTIFICATION

Pursuant to 21 CFR 314.96(b), we certify that a true field 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

Please contact us if you have any questions concerning the submitted information.

Sincerely,

Diane Iannello /for

Joyce Anne DelGaudio
Director, Regulatory Affairs

DLS/s

CIRCA

CIRCA PHARMACEUTICALS, INC.

33 RALPH AVENUE P.O. BOX 30 COPIAGUE, NY 11726-0030
(516) 842-8383 FAX (516) 842-8630

June 16, 1994

Douglas Sporn
Acting Director –
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
HFD-600, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RECEIVED
JUN 17 1994
GENERIC DRUGS

RE: NICOTINE POLACRILEX GUM, 2 mg

Dear Dr. Williams:

Pursuant to 21 CFR part 314, subpart C and Section 505(j) of the Federal Food, Drug and Cosmetic Act, we are submitting an Abbreviated New Drug Application for nicotine polacrilex gum, 2 mg.

The concept of developing a gum dosage form that was bioequivalent to Nicorette®, started in mid-1990. It was thought to be a product that was truly unique to the generic drug industry and would offer a development and manufacturing challenge to our new organization. Within Circa Pharmaceuticals, Inc., this is considered to be a product that represents the scientific approach and thoughtful research that will be incorporated into our future development programs.

This submission contains an archival copy (14 volumes in blue jackets) and review copies (4 volumes in red jackets/chemistry, manufacturing and controls technical review section and 11 volumes in orange jackets/pharmacokinetics technical review section). We have also enclosed 2 separately bound copies of the method validation package as this drug is not a USP product. These sections comply with the regulations set forth in 21 CFR §314.94(d)(2).

The pivotal bioequivalence study was conducted in fasting subjects, comparing Circa's Nicotine Polacrilex Gum, 2 mg, Lot # RD0930 to Marion Merrell Dow Nicorette®, Lot #TC137B. A "Chew-Out" Study comparing the release rates of our product to Nicorette® was also conducted. We have also included the results of a multiple dose pilot bioequivalence study comparing an earlier formulation to the Nicorette®. Please note that this latter study was conducted with a different formulation than that proposed in this ANDA. It is included for completeness of the submission and information only. Full reports of these studies are included with this submission.

continued...

There are no requests for biowaivers included in this submission, as it is for only the 2 mg strength of nicotine polacrilex gum.

On March 25, 1993, our name was officially changed from Bolar Pharmaceutical Co., Inc. to **CIRCA PHARMACEUTICALS, INC.**. Research regarding the drug product that is the subject of this application began prior to the name change, therefore, documentation containing the Bolar name may be found periodically throughout this submission.

Following this cover letter, please find the Certification required by the Generic Drug Enforcement Act of 1992, and the Office of Generic Drugs letter dated January 15, 1993. The required patent certification information to show that the drug product provided in this application is the same as the listed drug and a completed Form FDA 356h are also included.

Pursuant to 21 CFR 314.96(b), we certify that a field 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

If you have any questions concerning this ANDA, please contact Joyce Anne DelGaudio at (516) 842-8383.

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provision of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

We look forward to your prompt review of the submitted information.

Sincerely,

Joyce Anne DelGaudio

Joyce Anne DelGaudio
Director, Regulatory Affairs

CIRCA PHARMACEUTICALS, INC.
33 RALPH AVENUE P.O. BOX 30 COPIAGUE, NY 11726-0030
(516) 842-8383 FAX (516) 842-8630

CERTIFICATION

Under 306(k) of the Federal Food, Drug, and Cosmetic Act

1. On April 20, 1993, the Food and Drug Administration ("FDA") notified Circa Pharmaceuticals, Inc., ("Circa"), formerly known as Bolar Pharmaceutical Company, Inc. ("Bolar"), that the FDA is prepared to conduct substantive review of drug applications submitted by Circa. This notification followed a validity assessment inspection by the FDA's New York District office and was based upon a determination that Circa appears to be in compliance with regulatory requirements.

2. Circa is the applicant to the FDA for approval of this abbreviated drug application for nicotine polacrilex gum, 2 mg.

3. In accordance with the requirement of section 306(k) of the Federal Food, Drug, and Cosmetic Act, I certify that, to the best of my knowledge, Circa did not use and will not use in any capacity in connection with this application the services of any person debarred under subsections (a) or (b) of section 306(k).

4. Furthermore, I certify that Circa has been convicted for acts described in subsection (b) of section 306 which occurred within the past five years. On March 22, 1991, in the United States District Court for the District of Maryland, pursuant to a plea agreement between Bolar and the United States Attorney for the District of Maryland, Bolar entered and the Court accepted guilty pleas to twenty counts charged in an Information, which counts alleged violations of:

   18 U.S.C. § 1001 (making false statements to an agency of United States);

   18 U.S.C. § 1503 (obstruction of a grand jury investigation);

   18 U.S.C. § 1505 (obstruction of investigations by Congress and by the Food and Drug Administration); and

   21 U.S.C. §§ 331(a), 333(a), 333(a) (2), and 333(b) (distribution of adulterated and misbranded drugs).

-Continued-

5. Finally, I certify that, to the best of my knowledge, no individual known to have engaged in misconduct or whose conduct was imputed to Bolar, the consequence of which caused Bolar to be charged and to enter pleas of guilty as previously specified, is employed by Circa in any capacity, or had any role in preparing this application.

Melvin Sharoky, M.D.
President & Chief Executive Officer

On this 14th day of June, 1994

CIRCA PHARMACEUTICALS, INC.
33 RALPH AVENUE P.O. BOX 30 COPIAGUE, NY 11726-0030
(516) 842-8383 FAX (516) 842-8630

NAI
Bioavailability
Bio waiver
FDO 10/14/97

September 12, 1997

Rabindra N. Patnaik
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
ATTN: Document Control Room 150
7500 Standish Place
Rockville, MD 20855

Archival Copy

NEW CORRESPONDENCE

BIOAVAILABILITY
NC 1510

Bio OK

RE: Nicotine Polacrilex Gum, 2 mg; ANDA 74-507
RESPONSE TO MAY 28, 1997 LETTER FROM DIVISION OF BIOEQUIVALENCE

Dear Dr. Patnaik:

We refer to a May 28, 1997 letter from the Division of Bioequivalence providing comments on our request for a waiver of *in-vivo* bioequivalence requirements submitted in an amendment dated August 9, 1996, for the above referenced drug product (copy attached). We are hereby amending this application pursuant to 21 CFR 314.96 to respond to the comment. Enclosed is the response.

Should the reviewer find the information contained in this amendment unsatisfactory, we would like to respectfully request a meeting with you and any members of the Division of Bioequivalence that you deem appropriate.

If there are any questions or problems, please do not hesitate to contact me immediately.

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 Ms. Brenda Holman, District Director, Food and Drug Administration (NYK-DO), 850 Third Avenue, Brooklyn, New York, 11232-1593

Sincerely,
CIRCA PHARMACEUTICALS, INC.

Joyce Anne DelGaudio

Joyce Anne DelGaudio
Director, Regulatory Affairs