

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 74-707

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 74-707

SPONSOR: Circa Pharmaceutical, Inc.

DRUG & DOSAGE FORM: Nicotine Polacrilex Gum, USP

STRENGTH: 4 mg

TYPE OF STUDY: SEE REVIEW

STUDY SUMMARY:
Acceptable (See Review)

PRIMARY REVIEWER: Chandra, S. Chaurasia, Ph.D.
INITIAL: CS

BRANCH: I
DATE: 2/24/99

TEAM LEADER: Yih Chain Huang, Ph.D.
INITIAL: YCH

BRANCH: I
DATE: 2/22/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: DC

DATE: 2/23/99

DIRECTOR, OFFICE OF GENERIC DRUGS:
INITIAL: _____

DATE: _____

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:74-707

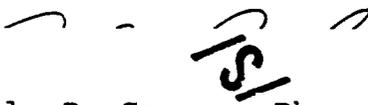
APPLICANT: Circa Pharmaceuticals, Inc.

DRUG PRODUCT: Nicotine Polacrilex gum, 4 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet 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 regulatory 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

Nicotine Polacrilex Gum, USP
4 mg/piece Chewing Gum
ANDA # 74-707
Reviewer: Chandra S. Chaurasia

Circa Pharmaceutical, Inc
Copiague, NY
Submission Date:
November 20, 1998

Review of an Amendment Requesting for a Biowaiver

I. Objective:

Review of Circa's amendment dated 11/20/98. The firm has submitted results of a chew-out study requested by the Agency.

II. Background

A summary background of the issues related to Circa's nicotine polacrilex gum 4 mg that is subject of this ANDA amendment is given below:

1. **Bio study.** On 07/06/95 and 03/28/96 Circa submitted an *in vivo* bioequivalence study (subjects=30) on its Nicotine Polacrilex Gum, 4 mg/piece, Lot #RD0965 (identified as the Original Product in the submission), comparing it to Marion Merrell Dow's Nicorette DS[®], 4mg/piece, Lot #TF101A. The study (also identified as Bio Study 1 in this report) was found acceptable by the Agency (review date: 5/2/96, reviewer: Dr. Moo Park).
2. **Chew-out study.** Along with the above application, Circa also submitted an *in vivo* multiple dose crossover chew-out study (identified as Chew-out Study 1 in this report) in 8 subjects on its Nicotine Polacrilex Gum, 4 mg/piece, Lot #RD0965, comparing it to MMD's Nicorette DS[®], 4mg/piece, Lot #TF101A. The release pattern (summarized in the table below) of nicotine was found comparable for the test and reference products

Table 1. Nicotine 4 mg Chew-out: Mean percentage nicotine release, n=8

Min.	Circa (TEST) Lot#RD0965	MMD (REF) Lot#TF101A
5	24.8	26.1
10	51.1	49.0
20	76.4	72.5
30	84.5	80.9

3. During an accelerated stability testing, Circa found a problem with its original formulation (Lot #RD0965), and developed a new formulation (Lot #RD1203) manufactured in Oct. 1996. On August 14, 1997 the firm submitted an amendment requesting a waiver on its new formulation. The amendment was reviewed March 27, 1998 by Dr. M. Park. Background information related to this new formulation (Lot #RD1203) following its review by the Agency is briefly described below:

- 3.1. The amount of nicotine polacrilex resin in the new formulation was changed to _____ mg/piece compared to that of _____ mg in the original formulation to take into account of the _____ of nicotine in the resin when the amount of glycerin is decreased from _____ to _____. It is also to be noted that there is a increase in sorbitol concentration in the new formulation over the original formulation (for a detail comparison of the compositions, please see Attachment I, Dr. Park's review: table 1, page 2).
- 3.2. Circa conducted a drug release test in water to compare the release profile of the new nicotine polacrilex glycerinated resin (_____ glycerin) and old nicotine polacrilex glycerinated resin (_____ glycerin) following USP method. Both old and new nicotine polacrilex resins showed fast nicotine release and met the USP specifications of NLT 70% in 10 minutes (For details please see Attachment I, table 2, page 3).
- 3.3. In the new formulation (i.e., Lot #RD1203), Circa used a different flavoring agent. Because of Agency's concern as to whether a better tasting nicotine gum might increase the potential for abuse of the new formulation, on Aug 14, 1997 the sponsor submitted a survey report conducted in adult smokers. The survey was conducted using a two-way cross over design comparing the new product with the RLD. The Agency reviewed the survey on April 15, 1998 (reviewer Dr. Moo Park), and found the taste and flavor of Circa's test product to be equivalent to those of reference product.
- 3.4. On April 2, 1998 the Agency issued a deficiency letter and recommended the firm to perform a chew-out study using the original formulation (Lot #RD0965) and new

formulations (Lot #RD1203) to evaluate nicotine release under use conditions.

The amendment of 11/20/98 is Circa's response to this deficiency.

In its response, the firm has reported its inability to conduct a chew-out study as suggested, primarily due to the fact that the batch of the Original Test (Lot #0965) formulation was made in 1994, and has expired. Instead, the firm conducted a chew-out study comparing the new formulation (Lot #RD1203) against the reference listed drug Nicorette®DS.

III. Chew-Out Study Details:

Protocol No. 66-104: A Two-Way Crossover Multiple-Dose, Randomized Study to Characterize and Compare the Release Rate Profile of nicotine from Circa Polacrilex Gum, 4 mg and Nicorette Gum DS, 4 mg

A. Study Information

Clinical Site:

Principal Investigator: .)

Clinical Dates: Beginning: 11/23/97; Ending: 11/23/97

Subjects: Entered - 14 normal healthy subjects (all males, smokers 1-2 packets/day, 19-49 yrs old)
Completed - 14

Analytical Site: Circa Pharmaceuticals Inc., Copiague, NY

Analytical Dates: not provided, presumably completed 12/9/97
(please see Analytical Supervisor's sign-off, Vol. 3.1, page 090)

Storage Period: not more than 20 days at -20 °C

Study Design: Multiple-dose, two-way crossover

Washout Period: 2-3 hours

Products tested:

Test Product: Nicotine Polacrilex Gum, 4 mg
Circa Pharmaceuticals, Inc., Lot #RD1203
Manufacturing Date 10/96; Expiration Date
(To Be Evaluated).

Reference Product: Nicorette® DS (nicotine polacrilex) gum, 4 mg
Marion Merrell Dow, Inc. Lot #YH 703A
Expiration Date 02/00

Randomization: A = reference , B = test

A,B: 1,4,5,8,10,11,14

B,A: 2,3,6,7,9,12,13

Inclusion/Exclusion Criteria:

Listed in Vol. 3.1 page 76. Subjects who participated in the study were all male smokers in the age range of 19-55 years.

Restrictions/Confinement:

Listed in Vol. 3.1, page 76. The subjects were not to take any alcoholic beverages 24 hours prior to or during each study period. The subjects were not to smoke 1 hour prior to the first dose of each study period and during each study period. Smoking was allowed following the last dose of Period 1, and during washout interval until 1 hour prior to the first dose of Period 2. Subjects were confined from 6:00 AM in the morning on the day of dosing, and until 12 hr after dosing.

Drug Administration:

Each subject in each period received four 4 mg oral doses (separated by at least an hour) of test or reference product as follows:

Dose Regimen	Time of Administration	Chewing Duration
First dose 1x4 mg gum	0 hr	30 minutes
Second dose 1x4 mg gum	1.5 hr	20 minutes
Third dose 1x4 mg gum	2.83 hr	10 minutes
Fourth dose 1x4 mg gum	4 hr	5 minutes

Subjects followed a controlled mastication pattern consisting of chews every seconds. The subjects chewed the gum times on of the mouth, and then moved the gum to the f the mouth. The rhythm of chewing was provided by an er.

Approximately one hour prior to the first dose, the subjects completed a 5 minute practice session using a placebo gum piece (vol. 3.1, page 079).

Gum Samples:

At the end of each chewing interval, the chewed gum from each subject was collected and stored in a separate, appropriately labeled glass container in a freezer at -20 °C. The samples from the first 12 subjects were sent to Circa for assay for remaining nicotine in the gum cud.

Study Results

Fourteen subjects completed the study.

Dropouts: none

Adverse events: No serious or unexpected adverse experiences occurred during the conduct of this study.

Nicotine Release Profile:

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 2. In each case the reference product released a higher percentage of nicotine (Table 2 and Figure 1-3). The mean differences in the percentage-label-claimed release rate range from 7.2% (for 5-minute time-point) to 11.6% (for 20-minute time-point). On the average, 9.5% greater *in vivo* release of nicotine was observed from the reference formulation as compared to that of the test formulation. This difference was found to be statistically significant.

While the Test/Reference ratios at 10-, 20- and 30-minute time-points were 0.79, 0.83, and 0.88, respectively, that for 5-minute time-point was 0.70.

Table 2. Percentage Nicotine Release in Chew-out Test Arithmetic Means, n=12 (data as reported by the firm)*

Chewing time, min	Ref mean (\pm)	Test mean (\pm)	T/R ^a	Difference in % Release (Test vs. Ref)
5	24.2 (4.8)	17.04 (3.2)	0.70	-7.2%
10	44.09 (5.0)	34.82 (6.2)	0.79	-9.3
20	68.56 (7.3)	56.93 (8.4)	0.83	-11.6
30	79.73 (7.0)	70.28 (10.1)	0.88	-9.5

*Samples from the first 12 subjects only were sent to the analytical lab

^a Ratio of means of percentage-nicotine release in the test vs reference product

In its effort to draw a similarity vis-à-vis dissolution profile, the sponsor used f_2 test to compare the *in vivo* release profile of Test and Reference nicotine products. For details on this comparison please see Circa's report in Vol. 3.1, Appendix IV, page 131. The f_2 values for the new product (Lot #RD 1203) across the whole profile of 30 minutes were slightly greater than 50. For comparison it may be noted that these f_2 values for Circa's original product (Lot #0965) were greater than 75.

Due to the marginal f_2 values, though greater than 50 in chew-out Study 2 and statistically significant differences observed between test and reference formulations in nicotine release *in vivo* (as per sponsor's statement), Circa has provided a simulated bioequivalence report to determine whether these differences in chew-out Study 2 relate to differences in bioequivalence of the two products. Details of the methods used and results of bioequivalence simulations are presented in Appendix VI, Vol. 1.3, page 177). Briefly, the simulation was based on the following step by step approach:

- 1). The data from chew-out study 1 and 2 were used to determine the release rate constants of nicotine from the test and reference gum products.
- 2). The release rate constants from the chew-out study 1 were used to fit the nicotine plasma concentration observed in a previously conducted bioequivalence study (Biostudy 1) to obtain

the appropriate pharmacokinetic parameters, since both study used the same test formulation.

3). Plasma nicotine concentration data were simulated using the mean of the obtained pharmacokinetic parameters and the release rate constants from the chew-out study 2.

4). The bioavailability of the new test product formulation was compared to the Nicorette[®] DS 4 mg gum.

Results of this simulations study (as provided by the firm) is summarized below:

- The mean nicotine release rate constant (Kr) for the original Circa Nicotine Polacrilex 4 mg gum formulation (Lot #RD0965, chew-out Study 1, $Kr = 4.11 \text{ hr}^{-1}$) was not significantly different ($p = 0.3548$) from that of the Nicorette[®] DS 4 mg gum ($Kr = 3.85 \text{ hr}^{-1}$).
- The mean nicotine release rate constant for the new formulation (Lot #RD1203) of Circa Nicotine Polacrilex 4 mg gum ($Kr = 2.56 \text{ hr}^{-1}$) was significantly different ($p = 0.0001$) from that of the Nicorette[®] DS 4 mg gum ($Kr = 3.36 \text{ hr}^{-1}$, chew-out Study 2).
- Under the conditions of simulation, the new formulation of Circa nicotine polacrilex 4 mg gum meets the bioequivalence criteria when compared with the Nicorette[®] DS 4 mg gum. For example, the 90% confidence intervals for each of the parameters $\text{Ln}C_{\text{max}}$, LnAUC_{0-t} , and LnAUC_{0-1} for nicotine were within the acceptable bioequivalence limit of 80-125%.

Comments:

1. The mean *in vivo* nicotine release at all time points is 7-11% higher for the reference in comparison to that of the test drug, with an average 9.5% higher release for the reference than for the test product. The ratios of mean of percentage nicotine release in the test vs. reference product (T/R) for 20- and 30-minute time points are 0.83 and 0.88, respectively. The T/R ratios for 5-, and 10-minute time points are 0.73 and 0.79, respectively. However, the clinical significance of the nicotine release pattern at the first 5-10 minute during chew-out study is not known. Therefore, the chew-out study is acceptable.

It is to be noted that in an exactly similar situation with its new Nicotine Polacrilex gum 2 mg/piece formulation, the firm was asked to conduct a chew-out study to compare the original 2 mg formulation with the new 2 mg formulation. As in the present case, the original 2 mg formulation exhibited stability problem, and the new formulation has polacrilex matrix with glycerin compared to the in the original 2 mg formulation. Furthermore, due to the expiration of the original 2 mg Nicotine Polacrilex, the firm conducted a chew-out study comparing its new formulation of 2 mg strength with MMD's 2 mg, and found an average 6.4% higher release of nicotine from the test compared to that from the RLD at 10-, 20- and 30-minute time-points, where as that at the 5-minute time-point was almost the same in either case. The T/R ratios were in the range of 0.92 to 1.02 - well within the 0.8-1.25 range (for details see Attachment II, Dr. Park's review on 2 mg strength).

2. The in vitro release profile Circa's new nicotine polacrilex resin is similar to that of its old polacrilex formulation, and meets the USP specifications of NLT 70% in ten minutes.
3. The firm undertook a simulation bioequivalence trial and showed a bioequivalence between the test and reference product. It is to be noted that presently the Agency does not have a policy to grant bioequivalence based upon simulation studies.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:74-707

APPLICANT: Circa Pharmaceuticals, Inc.

DRUG PRODUCT: Nicotine Polacrilex gum, 4 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet 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 regulatory 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,



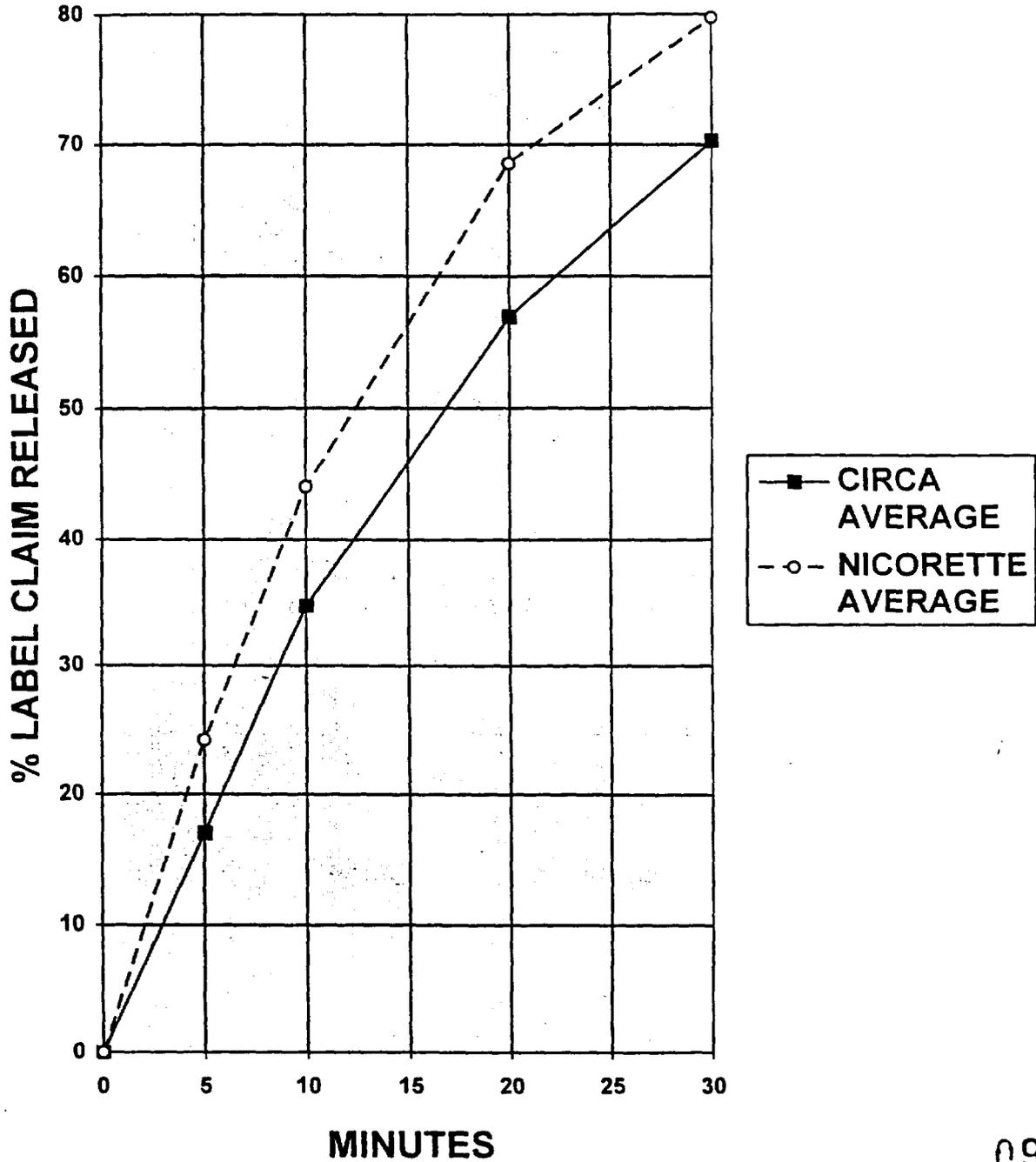
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Table 3. Composition of Old and New Formulations

Ingredient	Old Formulation mg/piece	New Formulation mg/piece
Nicotine Polacrilex Glycerinated glycerol) overage		g
Nicotine Polacrilex Glycerinated glycerol)+ overage	mg	
Sorbitol		
Sodium Carbonate		
Gum base		
Gum Flavor 3945		
Butylated Hydroxytoluene		
FD&C Green Color Blend		
Color Lake Blend		
Total gum weight	960.00	960.00

Fig. 1 (by sponsor)

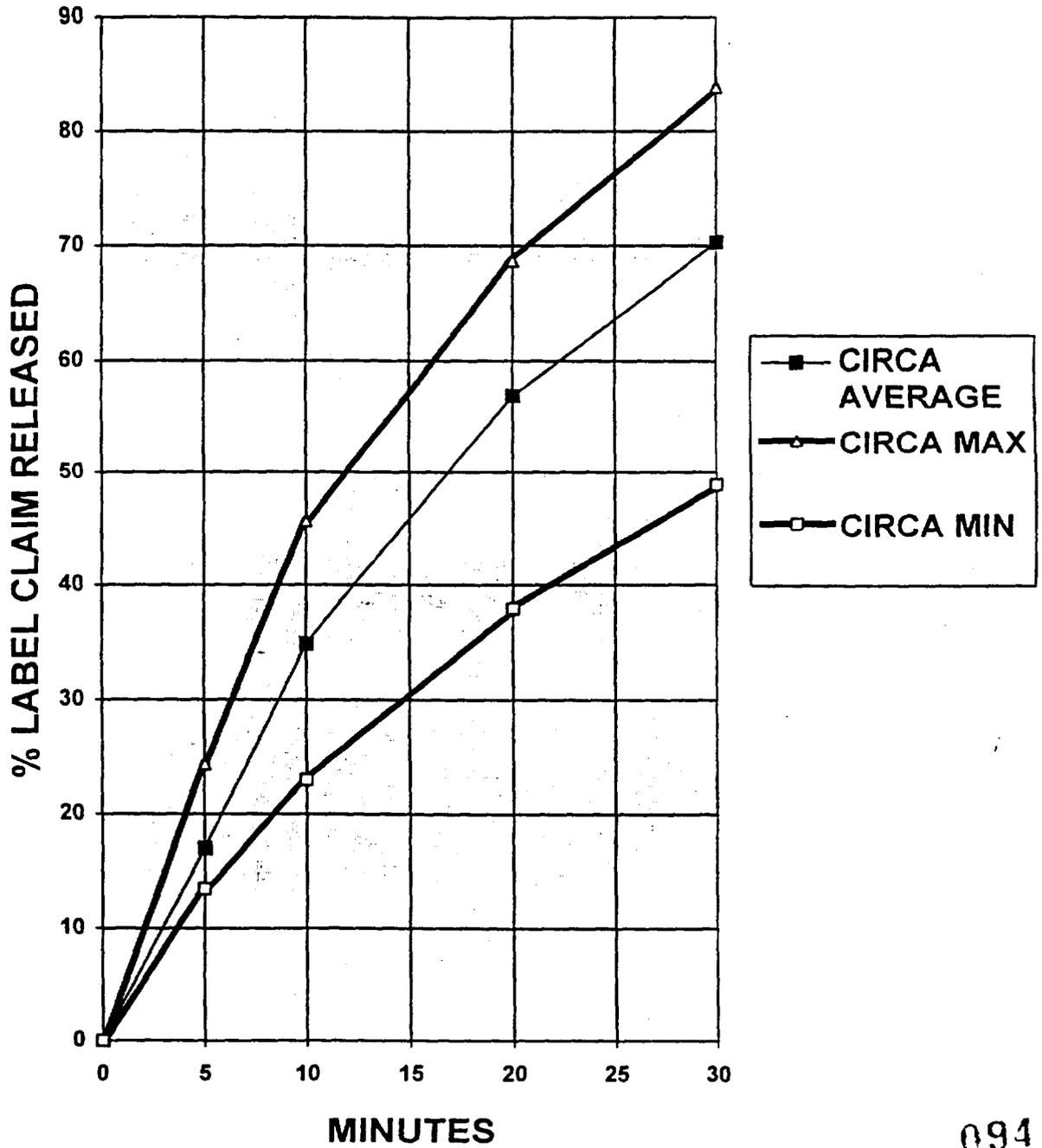
NICOTINE 4 MG GUM
PROTOCOL 66-104
AVERAGE OF ALL SUBJECTS
CIRCA vs. NICORETTE



093

Fig. 2 (by sponsor)

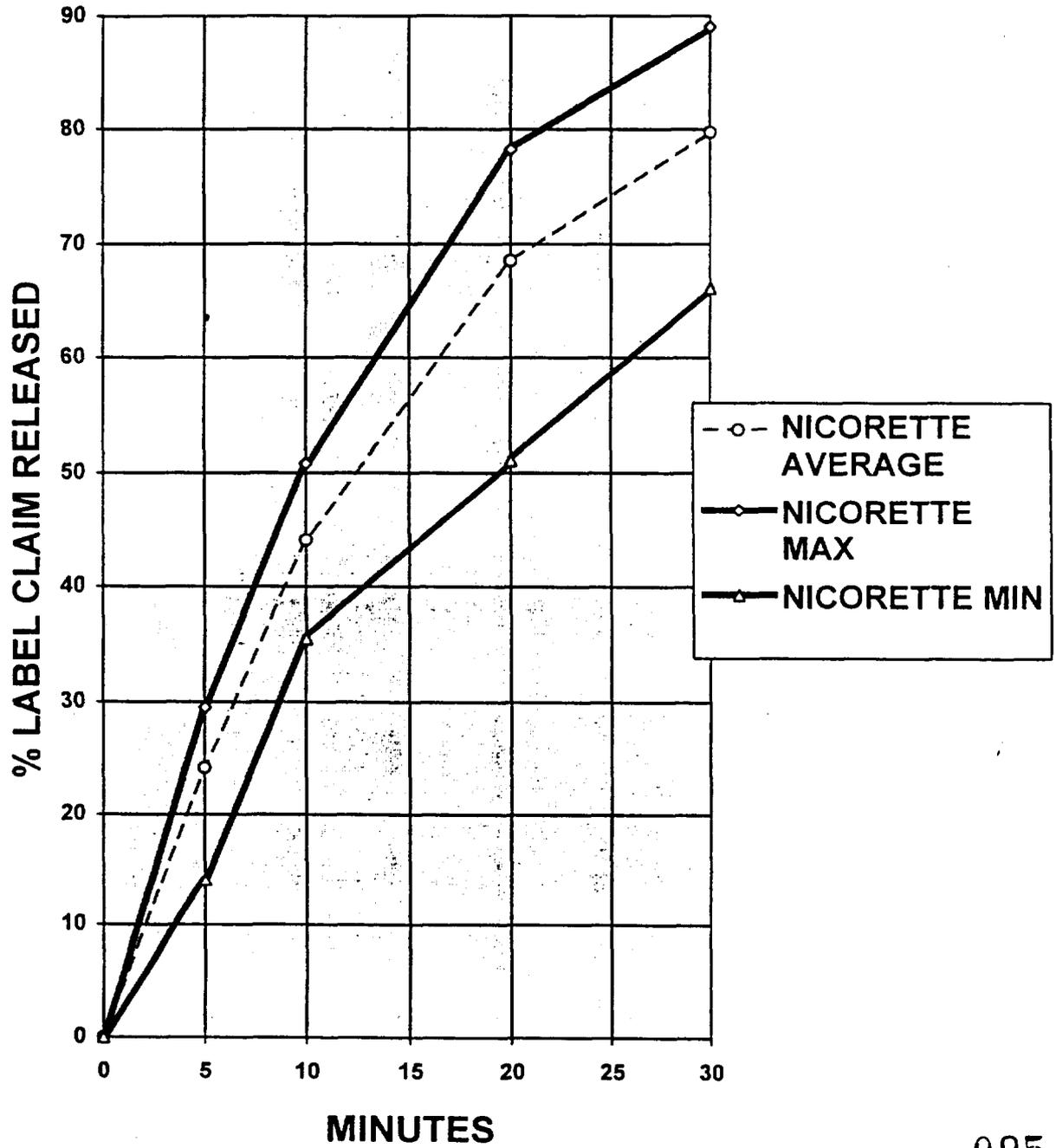
NICOTINE 4 MG GUM
PROTOCOL 66-104
CIRCA AVERAGE
(MAX - MIN)



094

Fig. 3 (by sponsor)

NICOTINE 4 MG GUM
PROTOCOL 66-104
NICORETTE AVERAGE
(MAX - MIN)



095

ATTACHMENT I

1

Nicotine Polacrilex Gum Circa Pharmaceuticals
4 mg/piece Chewing Gum Copiague, NY
ANDA #74-707 Submission Date:
Reviewer: Moo Park August 14, 1997
Filename:74707A.897

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, 4 mg/piece, to Marion Merrell Dow's Nicorette^R DS, 4 mg/piece (submission date: 7/6/95; review date: 5/2/96).

II. Background

The *in vivo* bioequivalence study conducted by Circa on its Nicotine Polacrilex Gum, 4 mg/piece, lot#RD0965, comparing it to MMD's Nicorette^R DS, 4 mg/piece, Lot#TF101A, had been found acceptable (submission date: 7/6/95; review date: 5/2/96).

In this amendment, Circa requested a waiver on its new formulation. Circa found . 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 resin from iece in the old formulation to mg/piece in the new formulation, to take into account the change in the factor of nicotine in the resin when the amount of glycerin is d from %. The nicotine increases from . The new and old formulations are shown in Table 1. The applicant has

claimed that this is a minor change since the 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

Table 1. Comparison of Old and New Formulations

Ingredient	Old Formulation mg/piece	New Formulation mg/piece
Nicotine Polacrilex Glycerinated glycerol)+	-	=4.4 mg nicotine)
Nicotine Polacrilex Glycerinate glycerol)+	(=4.4 mg nicotine)	-
Sorbitol	126.48	148.01
Sodium Carbonate	28.8	28.8
Gum base	729.6	729.6
	28.99	-
Gum Flavor 3945	-	28.8
Butylated Hydroxytoluene	0.21	0.21
FD&C Color Blend	1.92	-
Color Lake Blend	-	0.14
Total gum weight	960	960.00

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

Test method: An accurately weighed quantity of nicotine polacrilex glycerinated resin, equivalent to about 4 mg of

nicotine, was added into a centrifuge tube. The weighing was made for each time point for each formulation. To each tube, of solution, warmed to . 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 glycerinated resin (glycerol) and old nicotine polacrilex glycerinated resin (glycerol) 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.

IV. 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, 4 mg/piece, involving the use of nicotine polarilex with glycerol instead of nicotine polarilex with glycerol 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 MMAKARY
FT INITIALED MMAKARY _____

Concur: _____ Date: _____
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

File history: 1st Draft (3/27/98); Final (3/27/98)

ATTACHMENT II

1

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 stability problem 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 g/piece in the old formulation to mg/piece in the new formulation, to take into account the change in the g factor of nicotine in the resin when the amount of glycerin was decreased from . The nicotine loading increased from : w/w. Circa had claimed that this was a minor change since the : in glycerol 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 glycerinated resin glycerol) and old nicotine

polacrilex glycerinated resin (glycerol) 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	;
Investigators	.
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 ^R , 2 mg, Lot #6B24CE

Dosing	<p>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.</p> <p>Subjects followed a controlled mastication pattern consisting of 3 chews every 4 seconds using an audible timer.</p>
Food and fluid	<p>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.</p>
Housing	n/a
Washout	n/a
Gum cud samples	<p>Gum cud samples were collected and frozen at -20 °C, and kept frozen. The frozen samples were sent to Circa for assay for remaining nicotine in the gum cud.</p>
Statistical analysis	<p>PROC GLM was used to compare the release profiles of the test and reference products in the chew-out test.</p>

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[®], 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 glycerol instead of nicotine polacrilex with glycerol 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.

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.

Sincerely yours,

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:74707

APPLICANT: Circa

DRUG PRODUCT: Nicotine Polacrilex Gum, 4 mg/piece

The Division of Bioequivalence has completed its review of your survey on taste and flavor 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.

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

Nicotine Polacrilex Gum

Circa Pharmaceuticals

4 mg/piece Chewing Gum

Copiague, NY

ANDA #74-707

Submission Date: 8/14/97

Reviewer: Moo Park

Filename:74707ADD.897

Review of a Survey

I. Objective

Review of survey data which measured the product preference between Circa's Nicotine Polacrilex Gum, 4 mg/piece, and Marion Merrell Dow's Nicorette^R DS, 4 mg/piece.

II. Comments

1. Concern exists as to whether a better tasting OTC nicotine gum might increase the potential for abuse of this product resulting in its use for recreational rather than therapeutic purposes. The firm selected 52 adult smokers to measure the preference between the test and reference products. Two-way crossover design was used in the survey. The study was conducted by Communications in July, 1996. A subject was allowed to chew a gum for approximately 20 times and interviewed to find about the taste, flavor, and other opinions. The scoring of the results was done using a 5-point scale. After a brief wash-out period with saltine cracker and water, the subject was asked to chew the other product. The same interview was given.
2. The subjects rated the gum chewed in Period 1 worse than the gum chewed in Period 2. This indicates that there was a period effect for both the test and reference products. The magnitude of the period effect was approximately 1 and the cause is not known.

3. The data collected for Period 1 are summarized Table 1. The data were essentially analyzed in parallel design. According to the data, it appears that the test and reference products are similar in taste and flavor. The subjects who would not chew the test or reference product if not trying to stop smoking were 84.6% for both test and reference products.

Table 1. Quantitative Evaluation of Nicotine Gums
Average Ratings

	Test Product n=26	Ref Product n=26	Test/Ref Ratio
Taste	2.77 (0.65)	3.04 (0.77)	0.91
Flavor	2.54 (0.86)	2.85 (0.93)	0.89

4. It is concluded that the taste and flavor of Circa's Nicotine Polacrilex Gum, 4 mg/piece, is equivalent to those of Marion Merrell Dow's Nicorette^R DS, 4 mg/piece.

III. Recommendation

The taste and flavor preference study conducted by Circa comparing its Nicotine Polacrilex Gum, 4 mg/piece, to Marion Merrell Dow's Nicorette^R DS, 4 mg/piece, is acceptable. The study demonstrated that the taste and flavor of Circa's Nicotine Polacrilex Gum, 4 mg/piece, is equivalent to those of Marion Merrell Dow's Nicorette^R DS, 4 mg/piece.

The firm should be informed of the recommendation.


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

RD INITIALED MMAKARY
 FT INITIALED MMAKARY

Michael R. Murray

Concur: _____

TS
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date: 6/8/98

File history: Draft (4/8/98); Final (4/15/98)

APR 2 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA/AADA: 74-707

APPLICANT: Circa

DRUG PRODUCT: Nicotine Polacrilex Gum, 4mg/piece

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

It is recommended that you submit results of a chew-out study for the old and new formulations performed under use conditions.

Sincerely yours,



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

Nicotine Polacrilex Gum	Circa Pharmaceuticals
4 mg/piece Chewing Gum	Copiague, NY
ANDA #74-707	Submission Date:
Reviewer: Moo Park	August 14, 1997
Filename:74707A.897	

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, 4 mg/piece, to Marion Merrell Dow's Nicorette^R DS, 4 mg/piece (submission date: 7/6/95; review date: 5/2/96).

II. Background

The *in vivo* bioequivalence study conducted by Circa on its Nicotine Polacrilex Gum, 4 mg/piece, lot#RD0965, comparing it to MMD's Nicorette^R DS, 4 mg/piece, Lot#TF101A, had been found acceptable (submission date: 7/6/95; review date: 5/2/96).

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 resin from [redacted] /piece in the old formulation to [redacted] mg/piece in the new formulation, to take into account the change in the [redacted] factor of nicotine in the resin when the amount of glycerin is [redacted] from [redacted] 10%. The nicotine loading increases from [redacted]. The new and old formulations are shown in Table 1. The applicant has

claimed that this is a minor change since the n 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

Table 1. Comparison of Old and New Formulations

Ingredient	Old Formulation mg/piece	New Formulation mg/piece
Nicotine Polacrilex Glycerinated glycerol)+ : e	-	(=4 mg nicotine)
Nicotine Polacrilex Glycerinated glycerol)+ : age	(=4 mg nicotine)	
Sorbitol		
Sodium Carbonate		
Gum base		
Gum Flavor 3945		
Butylated Hydroxytoluene		
FD&C : Color Blend		
Color Lake Blend		0.1
Total gum weight	960	960.00

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

Test method: An accurately weighed quantity of nicotine polacrilex glycerinated resin, equivalent to about 4 mg of

nicotine, was added into a centrifuge tube. The weighing was made for each time point for each formulation. To each tube, of armed to 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 glycerinated resin (glycerol) and old nicotine polacrilex glycerinated resin (glycerol) 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.

IV. 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, 4 mg/piece, involving the use of nicotine polarilex with glycerol instead of nicotine polarilex with glycerol 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.

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

RD INITIALED MMAKARY
 FT INITIALED MMAKARY

IS/

Concur: IS/
 Dale P. Conner, Pharm.D.
 Director
 Division of Bioequivalence

Date: 3/30/98

File history: 1st Draft (3/27/98); Final (3/27/98)

BIOEQUIVALENCY DEFICIENCIES

ANDA/AADA: 74-707

APPLICANT: Circa

DRUG PRODUCT: Nicotine Polacrilex Gum, 4mg/piece

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

It is recommended that you submit results of a chew-out study for the old and new formulations performed under use conditions.

Sincerely yours,



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

MAY 2 1996

1

Nicotine Polacrilex Gum

4 mg/piece Chewing Gum

ANDA #74-707

Reviewer: Moo Park

Filename:74707S.795

Circa Pharmaceuticals

Copiague, NY

Submission Date:

July 6, 1995

March 28, 1996

Review of an In Vivo Bioequivalence Study

I. Objectives

Review of Circa's in vivo bioequivalence study under fasting conditions comparing its Nicotine Polacrilex Gum, 4 mg/piece, to Marion Merrell Dow's Nicorette^R DS, 4 mg/piece.

II. Background

Nicotine is an agonist at nicotinic receptors in the peripheral and central nervous systems. Nicorette, which contains nicotine bound to an ion exchange resin, is indicated as an adjunct to smoking cessation programs. The nicotine present in Nicorette is released from the resin only during chewing. Patients are advised to chew the gum slowly over a period of 30 minutes. The principal site of absorption in subjects who chew nicotine gum is the oral 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. Plasma nicotine and cotinine concentrations of approximately 12 ng/mL and 100 ng/mL respectively, can be expected in subjects who chew 1 piece of gum per hour while abstaining from smoking. 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 Merrell Dow.

III. Study Details

1. Protocol #022-R-03

2. Applicant: Circa Pharmaceuticals, Copiague, NY
3. Study sites:
 - Clinical study:
 - Analytical:
4. Investigators:
 - Principal investigator:
 - Analytical investigator:
5. Clinical study dates: 10/23/94-10/31/94
 Assay dates: 11/2/94-11/15/94
6. Study design: Open-label, randomized, two-way crossover design.
7. Subject: The subjects will be healthy males, 19-55 years of age, who are smokers with a habit of smoking 1 to 1 $\frac{1}{2}$ packs of cigarettes a day, weighing at least 60 kg and who are within 15% of their ideal weight. Thirty (30) healthy male volunteers will be enrolled and dosed, with 24 subjects to complete the study. Dropouts will be replaced prior to analysis with alternate subjects.
8. Product information:
 - (a) Test product #1: Circa's Nicotine Polacrilex Gum, 4mg
 Lot #RD 0965
 - (b) Reference product: MMD's Nicorette^R DS, 4 mg
 Lot #TF101A
 Expiration date: December, 1995
9. Dosing: Before dosing for each period, subjects will undergo a training session with placebo gum provided by Circa Pharmaceuticals, Inc. After a supervised overnight fast, subjects will receive one dose of the assigned chewing gum according to a randomization scheme. While seated, subjects will chew the gum over a period of 30 minutes. The gum will be chewed times every seconds. Rhythm of chewing will be provided by a generation. Subjects will be told to chew the gum times on of the mouth then move the gum to the the mouth. Every seconds the

will sound, prompting the subject to chew always on the side from the previous chew. This process will be repeated for a period of thirty continuous minutes. The subjects will be instructed to at a command given every seconds. Subject compliance will be closely monitored.

10. Food and fluid intake: Subjects will be required to fast overnight 9 hours before dosing and for 4 hours thereafter. Water will not be permitted for 2 hours before and 4 hours after dosing. A standard meal will be provided at 4 hours after dosing and at appropriate times thereafter. During confinement, meal plans will be identical for both periods. The consumption of alcohol or xanthine containing beverages and foods will be prohibited during the study.
11. Housing: From 36 hours before dosing until after the 24 hour blood draw.
12. Washout period: Seven days.
13. Blood samples: Blood samples (mL each) will be collected at 36 hours prior to dosing, time 0 (prior to dosing) and at the following times after dosing: 10, 20, 30, 40, 50 minutes and 1, 1.17, 1.33, 1.5, 1.67, 1.83, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 12, 16 and 24 hours. Plasma samples will be stored at -20°C or lower, pending assay for nicotine and cotinine levels.
14. IRB and informed consent: Yes
15. Pharmacokinetic and statistical analysis: S A S - G L M procedures were used on AUC_t , AUC_{inf} , C_{max} , T_{max} , K_{el} , $t_{1/2}$ and blood levels at each sampling points. The 90% confidence intervals (CI) were calculated for AUC_t , AUC_{inf} and C_{max} .

Page (s) 2

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

raw data

V. In Vivo Results with Statistical Analysis

Thirty (30) subjects participated in the study and completed the crossover study successfully. Nineteen adverse reactions (7 for test and 12 for reference) from 10 subjects were reported. All were not serious.

The plasma cotinine levels and the PK parameters for cotinine are not presented here because cotinine is not used in the evaluation of bioequivalence.

1. Mean plasma levels

The mean plasma nicotine levels for the test and reference products were comparable as shown in Table 4 and Figure p-1.

Table 4. MEAN PLASMA NICOTINE LEVELS FOR TEST AND REFERENCE PRODUCTS
 MEAN1=TEST MEAN2=REFERENCE RMEAN12=TEST/REF RATIO

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.167	1.52	1.13	1.31	1.01	1.16
0.333	5.91	2.34	5.66	1.78	1.04
0.5	7.73	2.44	7.64	2.56	1.01
0.666	8.83	2.37	8.46	2.78	1.04
0.833	9.44	2.16	9.28	3.04	1.02
1	9.69	3.19	9.20	3.25	1.05
1.167	9.31	3.29	9.21	3.11	1.01
1.333	9.05	3.31	8.31	3.04	1.09
1.5	8.45	3.35	8.10	3.07	1.04
1.666	7.75	3.12	7.83	3.15	0.99
1.833	7.54	3.45	7.44	3.45	1.01
2	6.91	3.25	6.80	3.15	1.02
2.25	6.60	3.49	6.23	2.83	1.06
2.5	5.86	2.92	5.83	2.63	1.01
2.75	5.57	3.09	5.38	2.79	1.03
3	5.10	3.04	5.05	2.79	1.01
3.5	4.36	2.66	4.29	2.46	1.02
4	3.74	2.60	3.69	2.09	1.01
5	2.63	2.39	2.50	1.95	1.05
6	1.61	1.90	1.58	1.76	1.02
8	0.79	1.70	0.65	1.50	1.22
12	0.23	0.98	0.22	0.81	1.05
16	0.12	0.67	0.09	0.49	1.37
24	0.04	0.22	0.04	0.21	1.06

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

2. Pharmacokinetic parameters

The pharmacokinetic parameters, CMAX, AUCT and AUCI, are comparable for the test and reference products as shown in Table 5. The test/reference ratio ranges 1.04-1.06 for the non-transformed parameters and 1.02-1.04 for the log-transformed parameters.

The 90% confidence intervals for the log-transformed CMAX, AUCT and AUCI are all within 80-125% as shown in Table 6.

There was no significant effect observed for period, sequence and treatment.

Table 5. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)
MEAN1=TEST MEAN2=REFERENCE RMEAN12=TEST/REF RATIO

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	40.96	30.35	38.73	26.53	1.06
AUCT	36.13	29.14	34.58	25.49	1.04
CMAX	10.96	3.90	10.53	3.16	1.04
KE	0.34	0.07	0.35	0.07	0.99
LAUCI*	36.08	0.45	34.77	0.41	1.04
LAUCT*	31.25	0.48	30.61	0.43	1.02
LCMAX*	10.45	0.30	10.15	0.27	1.03
THALF	2.15	0.75	2.12	0.73	1.01
TMAX	1.01	0.25	1.00	0.39	1.01

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

Table 6. LSMEANS AND 90% CONFIDENCE INTERVALS

PARAMETER	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCI	40.96	38.73	101.59	109.95
AUCT	36.13	34.58	100.21	108.75
CMAX	10.96	10.53	94.51	113.64
LAUCI	36.08	34.77	100.25	107.39
LAUCT	31.25	30.61	98.54	105.73
LCMAX	10.45	10.15	94.97	111.61

3. Residual nicotine in the gums used in the bioequivalence study

Each subjects chewed the gum for 30 minutes. Residual nicotine was measured from the gums collected after 30 minutes' chewing. The results are shown in Table 7. The amount of nicotine release was

comparable for the test and reference products.

Table 7. Residual Nicotine in the gum after 30-minute Chewing

Product	Subject	Residual nicotine Mean, %	%CV
Test	30	22.4	24.3
Reference	30	22.0	24.6

VI. Product Information

1. Formulation

Table 8. Test Formulation

Ingredients	Amount, mg/piece
Gum Base	
?	
Butylated Hydroxytoluene	
Nicotine Polacrilex Glycerinated	ge
Sorbitol,	
Sodium Carbonate,	
Sorbitol,	
FD&C Color Blend	
	12
Total	960

2. Assay and content uniformity

Assay and content uniformity data are comparable for the test and reference products.

Table 9. Assay and Content Uniformity

Product	Assay, %	Content uniformity, % (%CV)
Test product, Circa RD0965	110.1	110.1 (1.8)
Ref product, MMD TF101A	107.3	106.8 (1.8)

3. Chew-out study: Estimation of nicotine release

Eight subjects participated in the chew-out study, which is a multiple dose crossover design. Each subject chewed a new piece of gum for 5, 10, 20 and 30 minutes. Residual nicotine from the gum was determined and % nicotine released is shown in Table 10. The release pattern of nicotine is comparable for the test and reference products.

Table 10. % Nicotine Released:Chew-Out Study

Time, min	Nicotine released,% Test Product	Nicotine released,% Reference product
5	24.8	26.1
10	51.1	49
20	76.4	72.5
30	84.5	80.9

VII. Comments

1. Thirty (30) subjects participated in the study and completed the crossover study successfully. The applicant assayed nicotine and cotinine in the plasma samples from all 30 subjects. Only nicotine levels and its PK parameters were used in the bioequivalence evaluation. Cotinine data were submitted only for reference. Therefore, cotinine data were not used in the review.
2. Nicotine levels in plasma: The mean plasma nicotine levels for the test and reference products were comparable. The mean

peak nicotine levels were 9-10 ng/mL at approximately 1 hour.

3. The pharmacokinetic parameters, CMAX, AUCT and AUCI, are comparable for the test and reference products. The test/reference ratio ranges 1.04-1.06 for the non-transformed parameters and 1.02-1.04 for the log-transformed parameters. The 90% confidence intervals for the log-transformed CMAX, AUCT and AUCI are all within 80-125%. There was no significant effect observed for period, sequence and treatment.
4. Assay validation: Pre-study and within study validations are acceptable.
5. No clinically significant adverse reaction was reported.
6. Formulation, assay and content uniformity data are acceptable. Batch size of the test product was _____ pieces.
7. Chew-out study showed that 30 minutes' chewing released 85% nicotine for the test product and 81% nicotine for the reference product.

VIII. Deficiency

None.

IX. Recommendations

1. The *in vivo* bioequivalence study conducted by Circa on its Nicotine Polacrilex Gum, 4 mg/piece, lot#RD0965, comparing it to MMD's Nicorette^R DS, 4 mg/piece, Lot#TF101A, has been found acceptable. The study demonstrates that Circa's Nicotine Polacrilex Gum, 4 mg/piece, is bioequivalent to the reference product, MMD's Nicorette^R DS, 4 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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Concur:

11.A
S

~~Keith Chan, Ph.D.~~
Director
Division of Bioequivalence

Date:

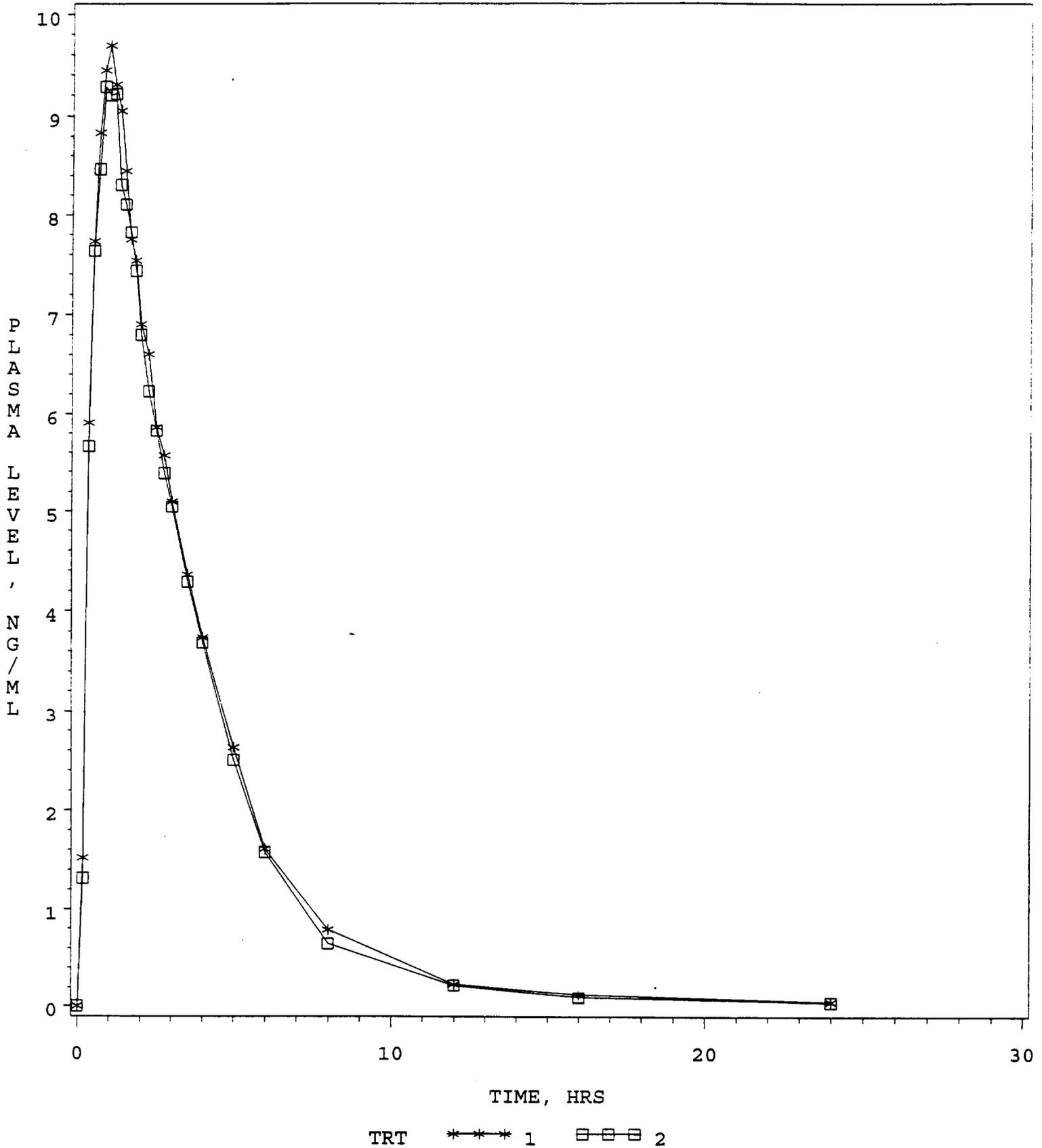
5/2/96

cc: ANDA # 74-707, HFD-630 (OGD), HFD-604 (Hare), HFD-658 (Mhatre, Park), HFD-22 (Hooton), HFC-130/JAllen, Drug File

File history: Draft (4/2/96); Final (4/30/96)

FIG P-1. PLASMA NICOTINE LEVELS

NICOTINE POLACRILEX, 4 MG, ANDA #74-707
UNDER FASTING CONDITIONS
DOSE=1 X 4 MG



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