ATTACHMENT I

Nicotine Polacrilex Gum
4 mg/piece Chewing Gum
ANDA #74-707
Reviewer: Moo Park
Filename:74707A.897

Circa Pharmaceuticals
Copiague, NY
Submission Date:
August 14, 1997

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 actor of nicotine in the resin when the amount of glycerin is i from %. The nicotine increases from . v. 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 :entrifuge 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

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

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

ATTACHMENT II

Nicotine Polacrilex Gum
2 mg/piece Chewing Gum
ANDA #74-507
Reviewer: Moo Park
Filename:74507A3.997

Circa Pharmaceuticals
Copiague, NY
Submission Date: 9/12/1997

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®, 2 mg, Lot #6B24CE

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

IV. Statistical Analyses of the Results

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

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

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

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

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

V. Recommendation

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

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

Sincerely yours,

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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 ale. 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.

/S/

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

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Concur: /S/ Date: 6/8/98

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

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

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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,

/S/

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