3. *"Each chewing piece contains..." (insert chewing and delete the bold print).*

4. *Usual Dosage: One piece to be chewed slowly in place of a cigarette when there is a craving to smoke. Do not exceed 30 pieces per day. See package insert in this box for additional instructions.*

5. *Delete "#" which appears after "NDC".*

6. *Since the strength (2 mg) of this product is that of nicotine only, please place an asterisk after "2 mg" and before the "Each chewing piece contains" statement. Another option is to say "2 mg of nicotine" following the established name.*

7. *Please assure that there is an adequate space to place the prescription label.*

Response: The recommendations listed above have been incorporated into our carton labeling for the drug product. We have enclosed 12 copies of the final printed mechanical, (Six in the Archival Copy and six in the Review Copy) which will be the template for our cartons, under Attachment 2

INSERT:

1. *TITLE:*

We encourage the inclusion of USP in the established name.

2. *DESCRIPTION*

a. *Paragraph 2, ...more active and is the more prevalent form in tobacco. The free alkaloid is absorbed rapidly through the skin and respiratory tract. The structural formula is:...*

b. *Paragraph 4, sentences 2 and 3 - Each chewing piece, for buccal administration, contains nicotine polacrilex equivalent to 2 mg nicotine as the active ingredient. In addition, each chewing piece contains the following inactive ingredients:...*

-Continued-

c. *We acknowledge your comment concerning talc high stability oil. We note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP general Chapter <1091> for guidance). We believe this is an important public health measure. Please respond accordingly by correctly noting all the inactive ingredients present in this product.*

We note you have used the phrase "and other ingredients". An inactive ingredient need not be listed if deemed a trade secret. If you elect not to mention an inactive ingredient because it is a trade secret, you must provide supporting data concerning the "trade secret".

Response: The recommendations listed above have been incorporated into our package insert labeling. Please note that with regard to Comment *2.c.*, we have revised the inactive ingredient section to include both partially hydrogenated vegetable oil :®) and talc (processing aid).

3. *CLINICAL PHARMACOLOGY*

a. *Pharmacologic Action, line 10 - Delete the comma between "predominate" and "while".*

b. *Pharmacodynamics - Combine paragraphs 1 and 2.*

c. *Pharmacokinetics*

i. *Paragraph l, line 8 - Correct the spelling of the word "cotinine".*

ii. *Paragraph 2, line 4 - Revise as follows:*

...significant consequences.

iii. *Paragraph 3 - Revise the second and third sentences to read as follows:*

About 10% of nicotine is excreted unchanged in the urine. As much as 30% may be excreted in the urine with high urine flow rates and urine acidification to pH 5 or less.

-Continued-

iv. *Paragraph 4*

(1) *Revise the first sentence to read:*

...from nicotine polacrilex gum depends...

(2) *Revise the third sentence to read:*

...from nicotine polacrilex gum occurs...

v. *Paragraph 5, Revise as follows:*

...from a reported bioavailability study in which smokers chewed a single piece of 2 mg nicotine polacrilex gum at a vigorous, prescribed rate. The values in this table thus represent a maximum (higher than expected upon normal use and recommended chewing).

vi. *Table*

(1) *Capitalize the "d" in the word "dose" which appears in the title.*

(2) *Bioavailability (spelling).*

vii. *Delete paragraph 6 (Acidic beverages...).*

viii. *Please revise the title for the table that refers to nicotine concentrations in Plasma as follows:*

Nicotine and Cotinine Concentrations in Plasma While Smoking ad lib (n=14) and Chewing 12 Pieces/Day of Nicotine Polacrilex (n=7) (Mean ± 2 SD)

ix. *Delete figure B and the information beneath the table that is specific for the 4 mg product. In addition it will not be necessary to label figure "A". Revise as follows:*

-Continued-

"Simulated nicotine...dosing of nicotine polacrilex gum, 2 mg, and cigarette smoking...total); 0.85 mg nicotine was absorbed on an average from nicotine polacrilex. An average of thirty-eight cigarettes of these volunteers' own brands were smoked ad lib over the same time period, delivering an average of 1 mg nicotine each.

4. *CLINICAL STUDIES*

a. *Paragraph 1, Revise as follows:*

The efficacy of nicotine polacrilex treatment as an aid to smoking cessation was demonstrated in four placebo-controlled, double-blind trials in otherwise healthy patients. Two of the trials involved the 2 mg dose. Quitting was defined as total abstinence from smoking as measured by patient diary and verified by expired carbon monoxide after an initial two weeks of treatment. The "quit rates" are the proportions of all persons initially enrolled who abstained after Week 2.

b. *Delete the second, third paragraph and the quit rate table.*

c. *Individualization of Dosage*

i. *Paragraph l; final sentence - ...when the first dose is used.*

ii. *Paragraph 5; Line 6 - "...selected with counselling and support over the following month. Those who..."*

iii. *The Fagerstrom Tolerance Questionnaire; item 7; Line 3 - "≤1.1 mg" rather than ">1.0 mg".*

iv. *Paragraph 7; Line 2 - ...(see CLINICAL PHARMACOLOGY; Pharmacodynamics and ADVERSE REACTIONS sections) ...*

v. *Paragraph 8; Lines 1 and 2 - ...comparing nicotine polacrilex and placebo doses suggest that dyspepsia...".*

vi. *Paragraph 9; Line 1 - "...study where, all subjects..."*

5. *INDICATIONS AND USAGE*

Nicotine polacrilex gum is...

-Continued-

6. *CONTRAINDICATIONS*

Nicotine polacrilex gum is...

7. *WARNINGS*

a. *Delete the subsection on Pregnancy Warning.*

b. *Safety Note Concerning Children*

Revise the second sentence to read: Used nicotine polacrilex chewing pieces contain...

8. *PRECAUTIONS*

a. *Oral Pharyngeal Conditions, last line - "...(see Patient Instructions).*

b. *Cardiovascular or Peripheral Vascular Diseases*

Revise paragraph 2 to read:

Tachycardia occurring in association with the use of nicotine polacrilex was reported occasionally. If serious cardiovascular symptoms occur with nicotine polacrilex, it should be discontinued.

c. *Accelerated Hypertension*

Last line - Delete the hyphen between "smoking" and "cessation".

d. *Carcinogenesis, Mutagenesis, Impairment of Fertility:*

The fourth sentence should begin the second paragraph.

e. *Pregnancy*

i. *Pregnancy Category C*

(1) *Line 1 - Delete "(see WARNINGS section)".*

-Continued-

(2) *Line 5 - "...offspring of dams who received toxic doses..."*

(3) *Delete the fourth sentence.*

(4) *Relocate the sixth sentence (Therefore, pregnant...approaches) to appear as the last sentence in paragraph 2.*

(5) *Paragraph 2 - "...only if the likelihood of smoking...of use of nicotine replacement by the patient...".*

f. *Delete the subsection "Human Studies".*

g. *Teratogenicity*

Animal Studies; Revise line 2 to read -
"...abnormalities in mice (see PRECAUTIONS, Pregnancy).

h. *Other Effects*

i. *Animal Studies; Last sentence - "...infusion of 0.1 mg/kg/min nicotine for 20 minutes to pregnant rhesus monkeys (equivalent to smoking about 6 cigarettes every minute for 20 minutes).*

ii. *Add the following text to appear as the last sub-section titles "Human Experience":*

The effect of a single dose of nicotine polacrilex gum or cigarette smoking, on fetal cardiovascular parameters has been studied near term. Cigarettes increased fetal aortic blood flow and heart rate, and decreased uterine blood flow and fetal breathing movements. Nicotine administered as nicotine polacrilex gum had no effect on these parameters.

i. *Pediatric Use*

Revise to read: ...use in pediatric patients...

-Continued-

9. *ADVERSE REACTIONS*

a. *Paragraph 1 "...events in patients who participated in clinical trials of nicotine polacrilex gum is complicated...*

b. *Delete the subsection on Oral Adverse Events, since it is specific for the 4 mg dose.*

c. *Probably Causally Related - delete this subsection. It refers to the 4 mg strength.*

d. *Causal Relationship Unknown*

i. *Delete the second sentence of the first paragraph.*

ii. *Revise the following sub-sections as follows:*

Cardiovascular System - delete Hypertension.

Digestive System - delete all information except for "alteration of liver function tests".

iii. *Delete the following sub-sections which are specific for the 4 mg product.*

Body as a Whole, Mouth/Tooth Disorder, Nervous System, Respiratory System, Urogenital System

In addition, delete the footnotes that are specific for the 4 mg product.

10. *DRUG ABUSE AND DEPENDENCE*

a. *Paragraph 1 - ...frequent use (9 to 12 pieces per day).*

b. *Paragraph 3 - ...therapy after 4 to 8 weeks of usage. Recommended...every 2 to 4 weeks (see DOSAGE AND ADMINISTRATION).*

-Continued-

11. OVERDOSAGE

a. Paragraph 2, last sentence - ...(< 1 mg/kg). Please note spacing.

b. Overdose from Ingestions - Revise the subsection heading

12. DOSAGE AND ADMINISTRATION

a. Create a new paragraph beginning with the third sentence of the first paragraph.

b. ...dependence. Highly dependent smokers (Fagerstrom tolerance Score ≥ 7, or > 25 cigarettes/day) should receive the 4 mg dosage, initially. Other patients should begin treatment with the 2 mg dosage strength. Increasing to the 4 mg dose may be considered for patients who fail to stop smoking with the 2 mg dose, or for those whose nicotine withdrawal symptoms remain so strong as to threaten relapse.

c. Paragraph 4 - Revise to read: Acidic beverages, e.g., coffee, juices, wine, or soft drinks, interfere with the buccal absorption of nicotine. Use of such beverages should therefore be avoided for 15 minutes before and during chewing.

d. Paragraph 5 - "ad libitum" should appear in italics.

e. Gradual Reduction Procedures...

i. Combine items 2 and 3 into one paragraph and revise to read: "...piece for a longer time and reduce the number of pieces used."

ii. Revise the last paragraph to read:

Combining or modifying of the above procedures may be individualized. Nicotine polacrilex gum treatment may be...

iii. Item 4 (last line)

Polacrilex (spelling)

-Continued-

f. Safety and Handling (lower case letters)

Revise to read:

Patients should be instructed in the proper use of nicotine polacrilex gum without undue exposure of health care workers to the chewing pieces. If you do handle nicotine polacrilex chewing pieces, wash with water alone, since soap may increase nicotine absorption. Do not touch your eyes.

13. HOW SUPPLIED

a. Revise "How to Store" to read as "Storage recommendations".

b. "i.e," rather than "ie,".

c. Include the date of the latest revision.

Response: The comments listed above have been incorporated into our package inset labeling.

14. Patient Instructions

The entire patient instructions must be reprinted at the end of the insert, as does the innovator and in accord with 21 CFR 201.57 (f) (2). Please comment.

Response: It is recognized that as per 21 CFR Section 201.57(f)(2), patient instructions must be reprinted at the insert, as does the innovator. Our final printed insert will include the patient instructions as a perforated section, which can be detached. This is similar to the design the innovator utilizes.

In our original submission we separated the draft documents for ease of review. In response to your comment, we have incorporated the patient instructions at the end of the package insert. Four copies of the draft package insert/patient instructions are included under Attachment 3.

PATIENT INSTRUCTION SHEET:

1. IMPORTANT

a. Separate your paragraphs with a line space to improve readability.

-Continued-

b. *Delete "Nicotine Polacrilex Gum" in the second sentence of the third paragraph.*

c. *...pregnant or nursing unless...*

d. *...that you read it carefully...*

2. *INTRODUCTION*

a. *Delete "While using...best for you" that follows the first line of this subsection.*

b. *Paragraph 3, second sentence - After about 3 months,...(Delete "2 to")*

c. *Revise the last paragraph to read:*

There are two doses of Nicotine Polacrilex Gum chewing pieces. Your doctor...

3. *HOW TO USE NICOTINE POLACRILEX CHEWING PIECES*

a. *Item 2 - Delete "or as directed by your physician".*

b. *Item 8 - "...until most of the nicotine..." (insert "most of").*

c. *...NOT MORE THAN 30 PIECES OF 2 MG NICOTINE POLACRILEX GUM A DAY.*

d. *Delete the last paragraph.*

4. *SOME WAYS TO STOP YOUR USE OF NICOTINE POLACRILEX GUM PIECES*

a. *The third through the fifth sentences of the first paragraph should be a separate paragraph.*

b. *Revise the last sentence of the second paragraph to read: ...steps 1 through 8.*

-Continued-

c. *The penultimate bullet should be revised and incorporated into the second bullet as follows:*

...example). You may want to do the opposite and chew each piece for a longer time and reduce the number of pieces used.

5. *PRECAUTIONS*

a. *Delete "mouth or throat inflammation" and "heartburn (esophagitis)".*

b. *What to Watch For (Adverse Effects)*

i. *Paragraph 3 - some of these effects are: Light-headedness...(add a colon).*

ii. *Add the following text as the last paragraph:*

The effect of nicotine polacrilex gum may be reduced by many foods and drinks. Do not eat or drink for at least 15 minutes before or while using nicotine polacrilex gum.

6. *OVERDOSE*

What to Do When Problems Occur - Revise as follows:

IF YOU HAVE ANY OF THE SYMPTOMS LISTED ABOVE, STOP USING NICOTINE POLACRILEX GUM AND CALL YOUR DOCTOR AT ONCE.

7. *PLEASE NOTE (last paragraph)*

The words "...and have been made in such a way to reduce stickiness." Should not appear in italics.

Response: The recommendations listed above have been incorporated into the patient instruction section of our package insert labeling. Four copies of the draft package insert can be found under Attachment 3.

-Continued-

FIELD COPY CERTIFICATION

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

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

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

Sincerely,
CIRCA PHARMACEUTICALS, INC.

Joyce Anne DelGaudio
Director, Regulatory Affairs

JAD:rk

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

NDA ORIG AMENDMENT
AC

Douglas Sporn
Director
Office of Generic Drugs, CDER
FOOD AND DRUG ADMINISTRATION
Doc.Ctrl.Rm., MPN II: HFD-600, Rm. 150
7500 Standish Place
Rockville, MD 20855-2773

August 9, 1996

RECEIVED
AUG 12 1996
GENERIC DRUGS

RE: Nicotine Polacrilex Gum, 2mg; ANDA 74-507
Amendment to Major Amendment Dated April 23, 1996

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Nicotine Polacrilex Gum, 2mg dated June 16, 1994, and our major amendment dated April 23, 1996. Pursuant to 21 CFR 314.96, we are submitting an amendment to this ANDA to provide for a minor change in the formulation of our drug product in order to meet the proposed expiration dating.

Our original application included results of lot # RD 0930 from both accelerated and controlled room temperature stability studies. The results from the 12 weeks accelerated stability study demonstrated the product could be labeled with a tentative two year expiration dating. As part of our ongoing stability commitment, we have been monitoring the drug product in accordance with the submitted stability protocols. Room temperature data from this ongoing evaluation indicates that the drug product does not meet the anticipated stability profile. Based on this information, a comprehensive review of the formulation was undertaken.

Based on this review, a slight modification was made to reduce the amount of an inactive component used in the he raw material. A new lot of drug product was made utilizing this material, packaged and placed on stability. This submission includes updated stability information from the original ANDA, the required documents to support this minor change in the raw material, as well as improved stability data from a new lot which substantiates our 24 month proposed expiration date of the drug product. We commit to the continued stability monitoring of this lot under our stability protocols.

Although there is no established *in-vitro* release criteria for nicotine polacrilex gum, we have provided data on the comparative nicotine release rate profiles of the w material. This information provides satisfactory evidence that the *in-vivo* performance of the drug product will not be affected. Therefore, based on the minor nature of the revision proposed, and the supporting evidence provided, we request a waiver of the *in-vivo* bioequivalence requirements.

Pursuant to 21 CFR 314.96(b), we certify that a true field copy of this amendment has been sent by overnight courier to: Edward T. Warner, District Director, FDA (NYK-DO), 850 Third Avenue, Brooklyn, NY 11232-1593

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

March 10, 1999

ARCHIVAL COPY

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

RE: **Nicotine Polacrilex Gum, 2 mg ANDA 74-507**
Nicotine Polacrilex Gum, 4 mg ANDA 74-707

Dear Mr. Sporn:

Reference is made to the facsimile message received from Mr. Charlie Hoppes, dated March 9, 1999 (copy attached). In this regard, Circa commits to the following:

The marketing of these products will be limited to sites where verification of age is possible, and a process will be in place to restrict sales to adults over 18 years of age.

Additionally, we acknowledge that you will request that we submit an integrated report for your review and evaluation after the first 3 years of surveillance so that you may determine the need for continuation or change of all or parts of our surveillance efforts.

Circa stands ready to address any other issues that you may have in order to advance its tentative approval of our products to their full approval. Please contact me at 516-842-8383 extension 606 should you have a need for any other information or seek clarification on any aspect of these products. We look forward to an early full approval of these products.

Sincerely,
CIRCA PHARMACEUTICALS, INC.

Joyce Anne DelGaudio
Director, Regulatory Affairs

cc: Mr. R. West
Dr. C. McCormick
Dr. R. Williams

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

January 8, 1999

ARCHIVAL COPY

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
Room 204, HFD 637
7500 Standish Place
Rockville, MD 20855

RE: **Nicotine Polacrilex Gum, 2 mg ANDA 74-507**
MINOR AMENDMENT

Dear Mr. Sporn:

We refer to the December 30, 1998 facsimile letter from Roger L. Williams, M.D, Deputy Center Director for Pharmaceutical Science, CDER informing Circa of the Tentative Approval of our Abbreviated New Drug Application, dated June 16, 1994, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Nicotine Polacrilex Gum, 2 mg.

The letter requested that we provide the Agency with an amendment that included final printed labeling, updates to the chemistry, manufacturing and controls section and an updated exclusivity statement. The requested updates are contained in this submission, and are detailed under the List of Attachments.

Pursuant to 21 CFR 314.96(b), we certify that a true field copy of this amendment has been sent by overnight courier to: Ms. Brenda Holman, District Director, FDA (NYK-DO), 850 Third Avenue, Brooklyn, NY 11232-1593.

Thank you for your attention. If there are any questions or problems, please contact me immediately.

Sincerely,
CIRCA PHARMACEUTICALS, INC.

Joyce Anne DelGaudio
Director, Regulatory Affairs

RECEIVED
JAN 11 1999
GENERIC DRUGS

N13

List of Attachments

Attachment 1:

Final Printed Labeling

A) 12 copies of the final printed User's Guide. (6 copies in Archival, 6 copies in Review)

B) 12 copies of the final printed proof for the Starter Carton. (6 copies in Archival, 6 copies in Review)

C) 12 copies of the final printed proof for the Refill Carton. (6 copies in Archival, 6 copies in Review)

D) 12 copies of the final printed proof for the blister backing. (6 copies in Archival, 6 copies in Review) Please note that the text will not be altered, however, the lot number will change to reflect the lot number and expiration date of the product being packaged at a particular time.

E) 2 copies of the final printed audiotape. (1 copy in Archival, 1 copy in Review)

Attachment 2:

Exclusivity Statement.

Attachment 3:

Expiration Date Proposal/Stability Data/Post Approval Stability Protocol

Attachment 4:

The following inactive raw material specifications and procedures are USP23/NF18 and have been updated accordingly. In addition to the compendial updates, format changes and clarifications were made to the overall documents to conform to our current format. All changes would normally be submitted to the ANDA in our Annual Report.

A) Talc

B) Sorbitol NF:

C) Sodium Bicarbonate USP: . 4. In addition to the compendial updates, the test for Identification was added to the tests conducted under our abbreviated testing protocol.

D) Sodium Carbonate Anhydrous NF: n addition to the compendial updates, onding change

Attachment 5:

The following inactive raw materials are non-compendial. The changes made since their last submission are outlined below. Please note that these changes would also normally be submitted to the ANDA in the Annual Report.

A) Stability Oil: The specifications and procedure currently being used is Revision # 3. The changes from Revision #1, the last revision submitted, are a change in the reference for the test for [redacted] lease note that, as approved in the original ANDA, we rely on the manufacturer's data for this test. Previously [redacted] r) used an [redacted] eveals the endpoint after a certain [redacted] el is attained. They now use an [redacted]. The [redacted] eveals the endpoint when certain [redacted] is reached. The use of the [redacted] for the [redacted] n test, rather than make a [redacted] is also now specified.

B) Gum Base: The specifications and procedure currently being used is Revision # 5. The changes from Revision #4, the last revision submitted, are the clarification of the tests that will be conducted during abbreviated testing on resampled raw material.

C [redacted] Gum Flavor [redacted]. The specifications and procedure currently being used is Revision # 2. The changes from Revision #0, the last revision submitted, are that the word [redacted] was added to the specification for odor and the reference was changed to Circa. In addition, under the test for description, the color was clarified to read [redacted] Format changes were also made to the overall specification and procedure to conform to the current format.

The manufacturer of this flavor is now [redacted]. The quantitative composition is the same as that used by [redacted] purchased the business and the formulation from them. We have enclosed the quantitative formulation provided by [redacted], as well as that provided by [redacted] (included in the original application) as support that the formulations are identical.

CIRCA PHARMACEUTICALS, INC.

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

March 3, 1999

ARCHIVAL COPY

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

RE: **Nicotine Polacrilex Gum, 2 mg ANDA 74-507**
Nicotine Polacrilex Gum, 4 mg ANDA 74-707

Dear Mr. Sporn:

Reference is made to a telephone conversation dated March 2, 1999 between Mr. Charlie Hoppes, Ms. Cecelia Parise, Mr. Donald Hare and Mr. Adolph Vezza of the Office of Generic Drugs, and myself. During this conversation, the OGD participants provided comments on our February 25, 1999 submission. They also requested that we provide a compilation of the post marketing plans and commitments made in our letters dated February 5 and February 25, 1999. This submission includes the requested compilation, with the revisions that were requested during the above mentioned teleconference.

Circa stands ready to address any other issues that you may have in order to advance its tentative approval of our products to their full approval. Please contact me at 516-842-8383 extension 606 should you have a need for any other information or seek clarification on any aspect of these products. We look forward to an early full approval of these products.

Sincerely,
CIRCA PHARMACEUTICALS, INC.

Joyce Anne DelGaudio
Director, Regulatory Affairs

cc: Mr. R. West
Dr. C. McCormick
Dr. R. Williams