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

February 25, 1999

NEW CORRESP
ARCHIVAL COPY

N/C

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 February 16, 1999 facsimile letter from Robert L. West, Director, Division of Labeling and Program Support, in regard to the above mentioned ANDAs. This letter provided comments to our proposal related to the marketing of these products. In this regard, we offer the following:

Pg #2 redacted in

whole - Marketing

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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

Rasagoline

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ANDA 74-507 (2 mg)
74-707 (4 mg)

FEB 16 1999

Circa Pharmaceuticals, Inc.
Attention: Joyce DelGaudio
33 Ralph Avenue P.O. Box 30
Copiague, NY 11726-8630

Dear Madam:

This is in reference to your abbreviated new drug applications submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nicotine Polacrilex Gum USP.

Reference is also made to your correspondence dated February 5, 1999.

We have reviewed your proposal related to the marketing of these products and have the following comments:

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product as a target of misuse or abuse over the

that you propose to monitor.

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We ask that you prepare a response to the important issues discussed above, and submit the proposed plans to your applications.

We await your prompt response. If you have further questions or need clarification on any of the items listed above, please contact Mr. Charlie Hoppes, Team Leader - Division II; Labeling Review Branch at (301)827-5846.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CIRCA PHARMACEUTICALS, INC.

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

ARCHIVAL COPY

February 5, 1999

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**
Nicotine Polacrilex Gum, 4 mg ANDA 74-707

Dear Mr. Sporn:

Reference is made to the February 4, 1999 facsimile letter from Robert L. West, Director, Division of Labeling and Program Support, in regard to the above mentioned ANDAs. This letter provides the plan you requested from Circa that would address issues related to the marketing of these products in compliance with the proposed labeling. Specifically, Circa was requested to develop a plan "designed to ensure that retailers and distributors...will only sell ...to persons 18 years of age or older." Therefore, consistent with the innovator's approval letter of February 9, 1996, and promises made by the innovator at an Advisory committee meeting for these products, Circa is submitting the following plan for your review. This plan is intended to mirror those commitments as appropriate for a generic version of these products. Circa is committed to the elements of this plan as conditions of your approval of its ANDAs for these products.

Prior to describing our plan (attached), we would like to point out that the 2 mg application was originally submitted in June, 1994, and the 4 mg ANDA in July, 1995. The 2 mg application was amended in April 1996 and the 4 mg ANDA in August 1997, to provide for the Rx to OTC switch. If one were to look back at the history of the review of these applications, they would find that Circa has been open minded and amenable to working with the Office of Generic Drug, in order to further the approval of the ANDAs. Further, the tentative approval of the 2 mg ANDA dated December 30, 1998 did not mention any of the issues that have suddenly been raised in the February 4, 1999 letter. In this regard, Circa would like to take this opportunity to point out that if these issues had been raised at an earlier date, we could have worked closely with the OGD and any other FDA office, as necessary, to develop a plan that would have satisfied all parties far in advance of today. We therefore respectfully request an expedited review of the information enclosed in this response, in order that we can obtain approval coincident with, or within a reasonable time after, the expiration of innovator exclusivity.

Circa believes that its effort to address public health concerns over use of this product by minors is, in the aggregate, the most comprehensive drug abuse/misuse risk management program ever undertaken to support the marketing of a product under 505(j) of the Federal Food, Drug and Cosmetic Act. While Circa is committed to ensuring that its products are appropriately marketed to meet this concern, Circa also notes parenthetically that by agreeing to these plans, Circa does not implicitly concede that the Agency has the legal authority to impose conditions beyond those related directly to the product itself, including its labeling, as a condition of approval of that product under Section 505(j) of the Federal Food, Drug and Cosmetics Act.

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

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ANDA 74-507 (2 mg) ✓
74-707 (4 mg)

FEB 4 1999

Circa Pharmaceuticals, Inc.
Attention: Joyce DelGaudio
33 Ralph Avenue P.O. Box 30
Copiague, NY 11726-8630

Dear Madam:

This is in reference to your abbreviated new drug applications submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nicotine Polacrilex Gum USP.

The reference listed drug manufacturer of Nicorette®, SmithKline Beecham Consumer Healthcare LP, provides initiatives to safeguard against the potential abuse or misuse of their product. Initiatives are also in place to safeguard against inappropriate sales to minors in compliance with the labeled sales restrictions. It is important that you have a similar program in place to ensure that adequate precautions will be taken to provide for the safe marketing of your products.

Circa should develop a marketing and surveillance plan designed to ensure that retailers and distributors of your products will only sell them to persons 18 years of age or older. The plan should include at a minimum:

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We acknowledge that you have the following elements already in place.

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We ask that you outline any plans you have in addressing the important issues discussed above, and submit the proposed plans to your applications.

We await your prompt response. If you have further questions or need clarification on any of the elements listed above, please contact Mr. Charlie Hoppes, Team Leader - Division II; Labeling Review Branch at (301)827-5846.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

Nicotine Polacrilex Gum	Circa Pharmaceuticals
2 mg/piece Chewing Gum	Copiague, NY
ANDA #74-507	Submission Date: 9/12/97
Reviewer: Moo Park	

REF PRODUCT	Marion Merrell Dow's Nicorette[R], 2 mg/piece.
BE STUDY DESIGN	Randomized 2-way crossover bioavailability study in healthy male subjects.
STUDY RESULTS	The 90% confidence intervals for the log-transformed AUCT and CMAX were within the acceptable range of 80-125%. (Original study was reviewed by Dr. Y. Huang and amendments were reviewed by Moo Park.)
WAIVER	Waiver granted for the formulation change based on the chew-out test for the test and reference products and *in vitro* nicotine release profiles for the old and new polacrilex

INITIAL: _____ DATE: 1/27/98
REVIEWER: Moo Park, Ph.D.
BRANCH: III

INITIAL: M DATE: 1/27/98
TEAM LEADER: Moheb Makary, Ph.D.
BRANCH: III

INITIAL: _____ DATE: 1/28/98
DIRECTOR: Dale P. Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE

INITIAL: _____ DATE: _____
DIRECTOR
OFFICE OF GENERIC DRUGS

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

March 27, 1996

Mark Anderson
Consumer Safety Officer
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
HFD-650, Room 279
7500 Standish Place
Rockville, MD 20855-2773

Noted: This pertains to ANDA 74-507 and should be processed as an AB
M. Anderson 3/29/96

Dear Mr. Anderson:

Reference is made to our telephone conversation with Dr. Moo Park, Reviewer, Division of Bioequivalence, dated March 26, 1996. Dr. Park informed us that the disk that accompanied our amendment dated December 14, 1995 for our nicotine polacrilex gum, 2 mg abbreviated new drug application, contained data that was inconsistent with the hard data that was submitted.

In this regard, we have enclosed a corrected diskette containing datasets for study number CIR-011-934. The SAS Transport file 16245.XFR contains the following datasets:

NICAADJ = adjusted nicotine concentrations (adjusted for carryover levels)
NICAAPK = pharmacokinetic parameters based on the above concentrations
NICFDA = concentrations including only initial assay values, no reassays
NICFDAPK = pharmacokinetic parameters based on the above concentrations

According to the Contract Research Organization , the treatment sequence (SEQ) is now correct and the pharmacokinetic data are included.

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

Sincerely,
CIRCA PHARMACEUTICALS, INC.

Joyce Anne DelGaudio

Joyce Anne DelGaudio
Director, Regulatory Affairs

ANDA 74-507

MAY 10 1996

Circa Pharmaceuticals, Inc.
Attention: Joyce Anne DelGaudio
33 Ralph Avenue
P.O. BOX 30
Copiague NY 11726-0030

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Nicotine Polacrilex Gum, 2 mg.

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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

August 1, 1995

AMENDMENT
N/A

Douglas Sporn
Acting 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**
NEW CORRESPONDENCE: AMENDMENT IN RESPONSE TO PREAPPROVAL INSPECTION.

Dear Mr. Sporn:

Reference is made to the above mentioned ANDA, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act. Reference is also made to a July 31, 1995 telephone communication with Mr. Tim Ames, Consumer Safety Officer, Office of Generic Drugs (OGD), and myself. The purpose of this call was to inform the OGD that we had received our preapproval inspection for the above mentioned ANDA. Observations made by the investigator during the inspection resulted in the revision of certain documents that had been submitted in the ANDA. Mr. Ames requested that these revised documents be submitted as soon as possible.

The preapproval inspection was conducted at Circa Pharmaceuticals, Inc., from May 9 through May 26, 1995. A Form FDA 483 was issued at the conclusion of this inspection, on May 26, 1995. The observations were responded to in a letter to the New York District Office, Brooklyn, dated June 6, 1995. The following is an item-by-item response to the observations that pertained to our ANDA 74-507 for nicotine polacrilex gum, 2 mg. The location of the Attachment under which the revised documents can be found is also included.

Observation 1:

specifie

GENERIC DRUGS

Pgs. 2-6 redacted
in whole.

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

Attachments

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

March 14, 1995

Douglas Sporn
Acting 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

AMENDMENT
NDA

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

Dear Mr. Sporn:

We refer to the January 18, 1995 letter from the Division of Chemistry II providing comments on 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 following is an item-by-item response:

Pgs. 2-22 redacted in whole.

chemistry

FIELD COPY CERTIFICATION

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

A Table of Contents has been enclosed to facilitate the review of this amendment. We believe that this response adequately addresses each of the cited deficiencies. We have also enclosed three copies of the methods validation package for the Chromatographic Impurities in Nicotine Polacrilex Gum, 2 mg lavor in a separate binder, labeled accordingly. Should any additional information be required, please do not hesitate to contact us.

Sincerely,
CIRCA PHARMACEUTICALS, INC.

Joyce Anne DelGaudio
Director, Regulatory Affairs

Attachments

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

April 23, 1996

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

RE: NICOTINE POLACRILEX GUM, 2 MG; ANDA 74-507
MAJOR AMENDMENT

Dear Mr. Sporn:

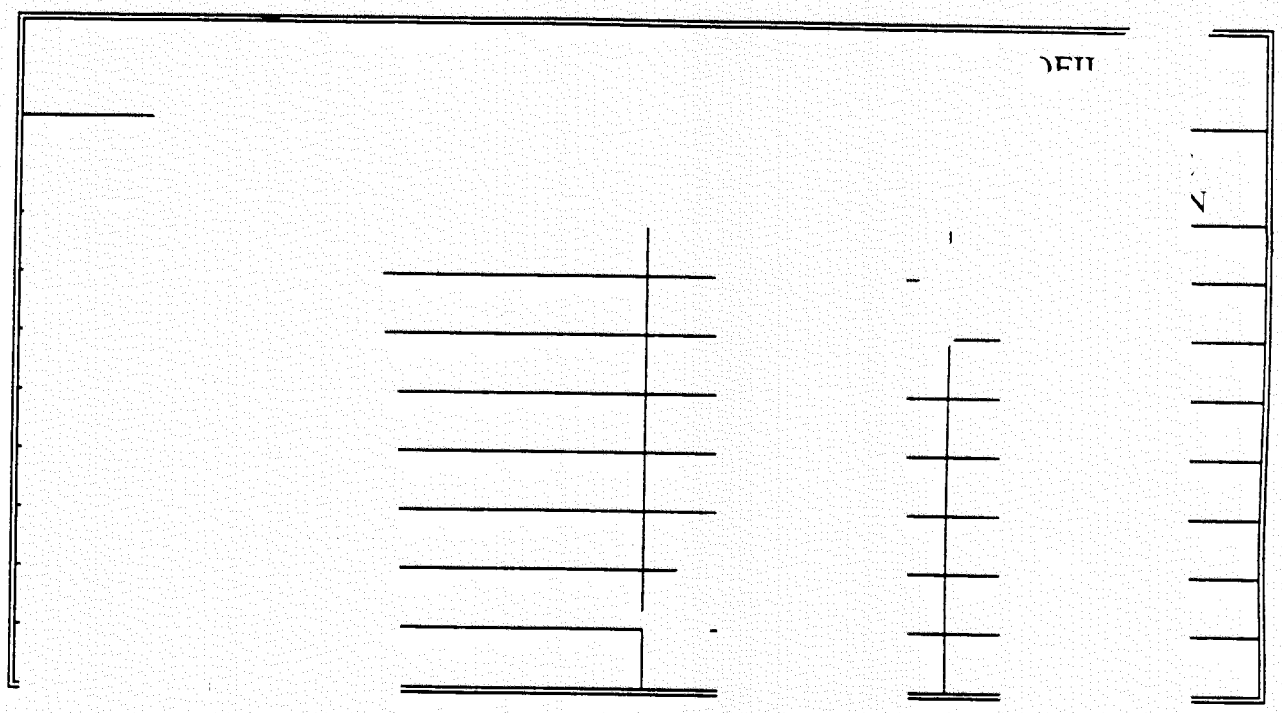
We refer to the December 4, 1995 letter from the Division of Chemistry II providing comments on our Abbreviated New Drug Application dated June 16, 1994, and our amendments dated March 14, and August 1, 1995, submitted pursuant to Section 505(j) of the Food, Drug and Cosmetic Act for Nicotine Polacrilex Gum, 2 mg. We hereby submit this major amendment as a response to the December 4 deficiency letter.

Additionally, on February 9, 1996, the reference listed drug product, Nicorette®, was approved for Over-The-Counter (OTC) marketing status. Therefore, with this amendment, we respectfully request a change in the proposed marketing status of our ANDA 74-507 from a Prescription Drug Product to an Over-The-Counter Product. Our FDA form 356h has been appropriately revised to reflect this change in marketing status.

In further support of this change we have enclosed draft labeling for our drug product, identical to the newly approved labeling for the reference listed drug product. The draft labeling can be found under Attachment 1.

The following is an item-by-item response of the chemistry deficiencies. Please refer to Attachment #1 for the new, OTC, draft labeling. This has been submitted in lieu of a response to the labeling deficiencies noted for our drug product intended for prescription marketing status.

-Continued-



We have enclosed a representative rity under Attachment 7.

Please note that during stability testing, we report a value for both individual and total impurities as compared to nicotine. The stability summary sheets also report the relative retention times of the individual impurity peaks.

In addition to our response, we note and acknowledge that the product is an official article in the compendia and validation of our analytical methods will not be requested.

FIELD COPY CERTIFICATION

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

-Continued-