CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER_____

CORRESPONDENCE

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

Fax transmitted from (516) 842-6638

FAX TRANSMISSION

Date: January 29, 1999

To: Radhika Rajagopalan

From: Joyce A. DelGaudio

Fax #: 301-443-3839

Total number of pages including this cover page: 10

MESSAGE

As per our telephone discussion, please find attached the Telephone Amendment for Nicotine Polacrilex Gum, 4 mg ANDA 74-707.

Thank you.

If you do not receive all pages or have any problems with receiving this transmission, please call (516) 842-8383, extension 241.

CONFIDENTIALITY NOTE

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

January 29, 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, 4 mg; ANDA 74-707
TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to our above mentioned Abbreviated New Drug Application dated July 6, 1995. Reference is also made to a telephone conversation between Radhika Rajagopalan, Chemistry Reviewer, and myself, dated January 28, 1999.

Dr. Rajagopalan contacted Circa in order to request that we include a blister seal integrity test during our stability studies of the drug product that is the subject of this ANDA. She referred to the request made by Dr. Florence Fang, Tertiary Reviewer, Office of Generic Drugs in regard to our nicotine polacrilex gum, 2 mg ANDA,

Dr. Fang had contacted Circa on October 7, 1998 in order to request that we include a blister seal integrity test during our stability studies of this drug product. After careful consideration of this request, Circa contacted Dr. Fang (October 30, 1998) and informed her that the gum product identity, strength, quality and purity will be assured by the current stability specifications, which include potency assay, chromatographic purity and description/appearance. Therefore, we do not feel that the addition of a seal integrity test and specification for which we have no data on which to set a reasonable limit, would yield additional information about this drug product.

However, given the suggestion of Dr. Fang, Circa commited to include a leak test in the post approval stability program for the 2 mg. In this regard, in response to Dr. Rajagopalan's request, we will also commit to include a leak test in the post approval stability program for this product (first three commercial batches and annual batch thereafter). The method of test will be the vacuum/liquid procedure that is commonly used in industry for in-process checks during a blister packaging run. As stated previously, we have no data on which to base a reasonable specification, therefore, at this time, the specification will state "Report Results". When a database has been established, Circa will evaluate the results, and decide what, if any, specification must be set. The ANDA will be supplemented as appropriate at that time.

Dr. Fang had also requested that we report any failures of this leak test to the FDA at the stability timepoint they are discovered, rather than wait until the annual report. While Circa will agree to this request, we would like to reiterate that we are reporting these results, and that there is no specification. Any failure in the leak test will be reviewed in conjunction with our assay, chromatographic purity and description/appearance tests. Should our chemistry analysis be within specification, the relevance of the leak test will be discussed with your office.

Thank you for your prompt review of this information. If there are any questions or problems, please do not hesitate to contact us immediately.

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.

Sincerely,
CIRCA PHARMACEUTICALS, INC.

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

Archival Copy

January 29, 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

NDA ORIG AMENDMENT
N/Ac

RE: Nicotine Polacrilex Gum, 4 mg; ANDA 74-707
TELEPHONE AMENDMENT

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Thank you for your prompt review of this information. If there are any questions or problems, please do not hesitate to contact us immediately.

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Sincerely,
CIRCA PHARMACEUTICALS, INC.

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

Archival Copy

NDA ORIG AMENDMENT

N/Ac

September 2, 1998

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, 4 mg ANDA 74-707**
MAJOR AMENDMENT

Dear Mr. Sporn:

We refer to the April 20, 1998 facsimile letter (copy attached) from the Division of Chemistry II providing CMC comments, and the Division of Labeling and Program Support, providing labeling comments, on the August 14, 1997 amendment to our Abbreviated New Drug Application. The ANDA was originally submitted on July 6, 1995 pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Nicotine Polacrilex Gum, 4 mg.

The following is an item-by-item response to the deficiencies noted in the letter:

Chemistry Deficiencies:

1. *Since the master batch records have gone through significant changes we request you provide a new reprocessing statement.*

Response: A new reprocessing statement is enclosed under Attachment 1.

2. *We notice your response to questions 6.b and 6.c. The gum release sample or the bulk finished product sample subjected to potency testing is not the intent of question 6.b. Since you intend to manufacture at least ig loads per day, blend uniformity of these loads is requested. Content uniformity testing on individual mixing loads needs to be performed to ensure blend uniformity. Please provide a commitment to testing for blend uniformity on individual sub-batches.*

Response: It is Circa's intention to conduct extensive testing on mixer loads on the first validation batches as per an approved validation protocol, in order to prove the homogeneity of the mix. This will be done by sampling a gum mass from the of every an of gum from a particular -batch (not less than samples, which is representative of the entire sub-batch [mixer load]). In order to confirm routine blend uniformity after the mixing process has been validated, we commit to taking a blend sample from any position in the mixer, for each mixer load (individual sub-batch of for analysis.

3. *According to 21 CFR, all manufacturing operations are to be completed within 30 days (compounding to packaging in final form). What time delay do you anticipate between different manufacturing steps including bulk and blister packaging.*

Response: We have enclosed data that supports holding the product in bulk (prior to blister packaging), in either ums or s, for 90 days. As stated in our Master Batch Formula for Rolling and Scoring, at the completion of rolling and scoring, the gum pieces will be transferred to properly prepared). They will then be packaged in ags for shipment to our contract blister packager. This will take place in as short a time span as possible. In support of this process, we placed Nicotine Polacrilex Gum, 4mg, Lot #RD1203 on warehouse stability in drums (double lined with), 12"x16" gs and 15"x21" for 1, 2 and 3 months. The stability summary sheets containing all data for this study are enclosed under Attachment 2.

4. *Please clarify at what stage you will issue a finished product COA. The gum pieces packaged in the double configuration is (as you have indicated yourself) "Bulk Finished Product Release Samples" (Response 6.k.) Complete testing should be carried out after the product is packaged in its commercial form. Page 119 of the amendment indicates that complete testing is performed on the bulk product, but not on the finished packaged product. This is unacceptable. We request that you modify the specifications on page 168 to reflect complete testing and provide a COA for batch RD1203.*

Response: As per your comment, complete testing will be carried out after the product is packaged in its commercial form. In this regard, we have revised the finished product specifications and procedure to include the test for blister packaging identification. The specification and procedure, along with a COA for Lot #RD1203, which includes results for the product after it was packaged in the proposed commercial form, are included under Attachment 3.

5. *Please amend the ANDA with controlled room temperature (25°C/60% RH) stability data gathered after 6 months (5/97).*

Response: The stability summary sheets for Nicotine Polacrilex Gum, Lot #RD1203 are enclosed under Attachment 4. Please note this includes accelerated data (40°C/75% RH) out to 24 weeks and controlled room temperature data (25°C/60% RH) out to 18 months.

Comment:

We request you to provide data as per the letter (dated 4/2/98) issued by the Division of Bioequivalence.

Response: We are currently preparing a response to the letter dated 4/2/98 from the Division of Bioequivalence.

Labeling Deficiencies:

1. *GENERAL COMMENTS*

   a. *We acknowledge your comment to differentiate your two products by the use of contrasting colors.*

   b. *We also acknowledge your submission of a study entitled "Smokers' Attitudes Toward and Preferences in Nicotine Gum". This study is currently under review. We will not comment on this study until its review is completed.*

2. *CONTAINER (Blister Pack)*

   a. *We note your comments concerning the child resistant nature of your container.*

   b. *We encourage the inclusion of "USP" in the established name.*

Response: We have revised our labeling for the blister pack as per FDA comment. We have also revised it as per comments made on the 2 mg product (in that we indicate that there are 4 mg of nicotine in the drug product [e.g., 4 mg (nicotine)].

Four copies of the revised draft, as well as a side-by-side comparison of the revised labeling compared to the previously submitted labeling, are enclosed under Attachment 5.

3. *CARTON (Starter and Refill)*

   a. *We acknowledge your commitments to make the revisions as stated in our letter of March 6, 1997.*

   b. *Front Panel – Add the statement "**IF YOU SMOKE LESS: try Nicotine Polacrilex Gum, 2 mg**" at the bottom immediatey beneath the statement "**FOR SMOKERS OVER 24 CIGARETTES A DAY**" and on the same line as "108 chewing pieces".*

   c. *Bottom Panel – Please submit pictorials as seen on Nicorette's bottom panel.*

   d. *Back Panel – See comment 4 © below.*

Response: We have revised the labeling for our starter and refill cartons as per FDA comment. In response to comment 3(d), please note that our support system contains reference to a toll free telephone number. We have not yet been assigned the toll free number, therefore, at this time, the number reads as 1-800-XXX-XXXX. When this number is assigned, the appropriate reference numbers will appear on the back panel. We have also revised this labeling as per comments made on the 2 mg product (A) in that we indicate that there are 4 mg of nicotine in the drug product [e.g., 4 mg (nicotine)], we have increased the prominence of the established name on the front panel and have included the strength (4 mg) on the right and left flap (starter carton only, as the established name does not appear on the left and right flaps of the refill carton).

Four copies of the revised draft, as well as a side-by-side comparison of the revised labeling compared to the previously submitted labeling, are enclosed under Attachment 6 (starter carton) and Attachment 7 (refill carton).

4. *USER'S GUIDE*

   a. *Will your User's Guide have pictures?*

   b. *Stickers – Please state (below the stickers) where the stickers are to be placed on the calendar, as does the reference listed drug.*

c. *We acknowledge your comments regarding the page numbers and telephone numbers and that you are in the process of developing a support system. Please note that this information should also appear on the back panel of the carton labeling – See comment 3(d) above.*

Response: We have established the final design of our User's Guide, and have incorporated the changes requested in the comments above, including the use of pictures to emphasize the text message. The final design for the User's Guide also includes page numbers and the appropriate page references where applicable. We have also revised this labeling as per comments made on the 2 mg product (AND in that we indicate that there are 4 mg of nicotine in the drug product [e.g., 4 mg (nicotine)].

Four copies of the final design for the User's Guide, as well as a side-by-side comparison of the revised labeling compared to the previously submitted labeling are enclosed under Attachment 8. Please note that the side-by-side comparison has been done with the text version of the User's Guide rather than the final design version, for ease of review.

Additionally, the Support System has now been developed, and four copies of the draft are enclosed under Attachment 9. As stated previously, a final phone number has not been assigned, however, it will be a toll free number. Once the number has been finalized, it will appear on the back panel of the carton label, as well as in the User's Guide. The starter and refill carton have been revised to refer to this number.

5. *AUDIO TAPE*

The text for your proposed audio is not the same as that for the reference listed drug, Nicorette®. Please note that the text of the audiotape for Nicorette® was reviewed and approved by the Medical Review Officer in the appropriate review division. 21 CFR 314.94(a)(8)(iv) requires that your labeling be the same as the labeling approved for the reference listed drug except for the differences cited therein. Please revise your tape text to be in accord with that of Nicorette®.

Response: In response to your comment, our tape text has been revised to be in accord with that of Nicorette®. Four copies of the revised audio tape text, as well as side-by-side comparisons of the proposed labeling to our last submitted labeling, can be found under Attachment 10.

Since we are submitting draft labeling, we note that we will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, we are aware that color and other factors (print size and prominence, etc.) in final printed labeling could be found unacceptable and that further changes may be requested prior to approval.

We note and acknowledge that you reserve the right to request further changes in our labels and/or labeling based upon further changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

Sincerely,
CIRCA PHARMACEUTICALS, INC.

Joyce Anne DelGaudio
Director, Regulatory Affairs

August 14, 1997

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

AMENDMENT

RE: **Nicotine Polacrilex Gum, 4 mg ANDA 74-707**
MAJOR AMENDMENT

Dear Mr. Sporn:

We refer to the January 29, 1997 letter (copy attached) from the Division of Chemistry II providing comments on our Abbreviated New Drug Application dated July 6, 1995, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Nicotine Polacrilex Gum, 4 mg.

As stated in your letter, Circa has made minor changes in the formulation of the drug product to more closely match the flavor and color of the innovator, as well as improve the stability performance. Information regarding these changes was submitted in correspondence to this ANDA dated August 15, 1996 and October 18, 1996. Therefore, in addition to responding to the deficiencies in the above mentioned letter, pursuant to 21 CFR §314.96, we are now submitting the supporting data in this amendment to our ANDA, which provides for the change in the formulation of our drug product to more closely mimic the flavor of the innovator, and provides assurance that our product will remain stable through its proposed expiration dating period of 24 months.

We have manufactured a new batch of nicotine polacrilex gum, 4 mg, Lot #1203, according to the revised formulation contained in this amendment. This lot has been blister packaged in a configuration with PVC as the product contact surface, and placed on stability. The data generated from this new lot of drug product is presented in this amendment, therefore, our response will address only those deficiencies that are pertinent to this modified formulation and the above mentioned packaging configuration.

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

Sincerely,

Joyce Anne DelGaudio

Joyce Anne DelGaudio
Director, Regulatory Affairs

RECEIVED
AUG 15 1997
GENERIC DRUGS

RESPONSE

Details of the flavor and color change, as well as documentation in support of these revisions are included under Attachment 1 as follows:

a) Overview
b) Comparative Composition List (original formulation vs. revised formulation).
c) Documentation for Nicotine Polacrilex Resin, USP (18% nicotine), Lot #4635, the lot of active pharmaceutical ingredient (API) used in Lot #RD1203 (ANDA support batch).
d) Documentation for g Gum Flavor . used in Lot #RD1203.
e) Documentation for Color Lake Blend Lot #3142, used in Lot #RD1203.
f) Revised Master Batch Formula, Mixing Process
g) Revised Master Batch Formula, Rolling and Scoring Process
h) Executed batch records (mixing process) for reformulated nicotine polacrilex gum, 4 mg, Lot #'s RD1201 and RD1202
i) Executed batch record (rolling and scoring process) for reformulated nicotine polacrilex gum, 4 mg, Lot #RD1203
j) In-process QA data (weight and thickness checks) for Lot #RD1203
k) Packaging Records for Lot #RD1203
l) Analytical data for Lot #RD1203
m) Stability data for Lot #RD1203
n) Request for biowaiver with supporting data.

The following

Page(s) 17

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry

Labeling Deficiencies:

1. *GENERAL COMMENTS*

   a. *Please submit draft OTC labeling to this application.*

Response: Draft OTC labeling for this drug product has been submitted under Attachment 14. This attachment contains four copies each of the draft labeling for the Starter Pack Carton, Refill Pack Carton, Patient Instruction Booklet and Audio Tape. We have also enclosed side-by-side comparisons of our labeling to the innovators, Nicorette® labeling.

   b. *We encourage the inclusion of "USP" in the established name for this drug product where it appears on your labels and labeling.*

Response: We have revised our labeling to include the USP designation in the established name where it appears on our labels and labeling.

2. CONTAINER

a. See GENERAL COMMENTS.

b. The innovator is required to market this product in a child-resistant blister. Please provide information regarding the child-resistant nature of your container.

Response: The blister package that Circa will use for the marketed product is a paper backed foil that is sealed to the blister (PVC/PVDC) material. As stated in the instructions on our proposed labeling, to remove the gum the consumer must tear off a single unit. There is a corner on each individual piece that will have a loose edge. The paper backing is pulled off starting at this loose edge. The gum piece is then pushed through the foil. This is identical to the child resistant technology that the innovator is currently using.

3. CARTON

We encourage the use of boxing, contrasting colors, or other means to differentiate the strengths of this product from your proposed 2 mg strength product (ANDA

Response: A commitment is made to differentiate the two strengths with contrasting colors. This will be evident on our final printed labeling.

We note and acknowledge that you reserve the right to request further changes in our labels and/or labeling based upon further changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

Additional Comments and Acknowledgments

1. We have enclosed a copy of the "Consumer Research Preference Study" that was referenced in the August 15, 1996 correspondence. The report can be found under Attachment 15.

2. We acknowledge the fact that the Division of Bioequivalence must conduct a reevaluation of our application based on our request for a waiver from *in-vivo* bioequivalence studies for our reformulated drug product. The comparative analytical data is support of this waiver can be found under Attachment 1.n.

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

Archival Copy

January 29, 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

NDA ORIG AMENDMENT
N/Ac

RE: Nicotine Polacrilex Gum, 4 mg; ANDA 74-707
TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to our above mentioned Abbreviated New Drug Application dated July 6, 1995. Reference is also made to a telephone conversation between Radhika Rajagopalan, Chemistry Reviewer, and myself, dated January 28, 1999.

Dr. Rajagopalan contacted Circa in order to request that we include a blister seal integrity test during our stability studies of the drug product that is the subject of this ANDA. She referred to the request made by Dr. Florence Fang, Tertiary Reviewer, Office of Generic Drugs in regard to our nicotine polacrilex gum, 2 mg ANDA,

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Thank you for your prompt review of this information. If there are any questions or problems, please do not hesitate to contact us immediately.

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.

Sincerely,
CIRCA PHARMACEUTICALS, INC.

Joyce Anne DelGaudio
Director, Regulatory Affairs

ANDA 74-707

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

JUL 29 1997

Dear Madam:

This is in reference to your abbreviated new drug application dated July 6, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nicotine Polacrilex Gum USP, 4 mg.

Reference is also made to the amendments dated November 3, 1995 and March 28, 1996 and to the correspondence dated August 15, 1996 submitted in your behalf by King & Spalding.

We note that it is your intent to reformulate this drug product to more closely match the formulation of the innovator and amend the application to demonstrate the approvability of the reformulation. However, we wish to provide you with the following comments based upon the review of the original formulation. You should address all pertinent comments as part of your forthcoming amendment. As such, the application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

Page(s) 3

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

Chemistry

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. Please submit draft OTC labeling to this application.

b. We encourage the inclusion of "USP" in the established name for this drug product where it appears on your labels and labeling.

2. CONTAINER

a. See GENERAL COMMENTS.

b. The innovator is required to market this product in a child-resistant blister. Please provide information regarding the child-resistant nature of your container.

3. CARTON

We encourage the use of boxing, contrasting colors, or other means to differentiate the strengths of this product from your proposed 2 mg strength product (ANDA

Please revise your labels and labeling, as instructed above, and submit draft labeling reflecting a change to OTC status.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the labeling of the listed drug with all differences annotated and explained.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon further changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

In addition to responding to these deficiencies, please note and acknowledge the following comments in your reponse:

1. Please submit a copy of the "Consumer Research Preference Study" which is referenced in the August 15, 1996 correspondence.

2. Reference is made to the letter dated May 10, 1996 issued from the Division of Bioequivalence stating that the Division had completed its review and has no further questions. As the letter indicated, however, bioequivalency comments may be revised following, amoung other things, other scientific or regulatory issues. The forthcoming comparative analytical data in support of a waiver of new in vivo bioequivalence studies will require a reevaluation of the application by the Division of Bioequivalence.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated when your cover letter is submitted to the Agency. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 1/28/97

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-707

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, 4 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

March 28, 1996

SENT VIA FAX

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

Dear Mr. Anderson:

Reference is made to our telephone conversation with Dr. Moo Park, Reviewer, Division of Bioequivalence, dated March 28, 1996. Dr. Park requested additional data to facilitate his review of the data generated from our nicotine polacrilex gum, 4 mg, abbreviated new drug application 74-707.

In this regard, we are faxing the following documents:

1) Assay and content uniformity data for the test product used in the biostudy, Lot #RD0965, manufactured by Circa.

2) Assay and content uniformity data for the reference product used in the biostudy, Circa control number 17137, Marion Merrell Dow (manufacturer) lot #TF101A. Please note that the report sheet reflects Circa's control number.

3) The batch record for the test batch. Please note that this documentation includes the batch records for Lot numbers RD0966 and RD0967, which reflect the two mixer loads of gum manufactured. The batch record for Lot number RD0965 reflects the rolling and scoring process. This is the lot number used for biostudy purposes, as it is the last process in the manufacture of our gum. ...s are utilized for one rolling and scoring process as this gives us an acceptable yield of more than pieces.

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 74-707

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

MAR 11 1996

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated August 17, 1995, and your amendment dated November 3, 1995.

NAME OF DRUG: Nicotine Polacrilex Gum, 4 mg

DATE OF APPLICATION: July 6, 1995

DATE OF RECEIPT: July 7, 1995

DATE ACCEPTABLE FOR FILING: November 9, 1995

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 594-0305

Sincerely yours,

11/96

/S/

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOAVAILABILITY

KING & SPALDING

1730 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, DC
20006-4706

TELEPHONE: 202/737-0500
FACSIMILE: 202/626-3737

191 PEACHTREE STREET
ATLANTA, GEORGIA 30303-1763
TELEPHONE: 404/572-4600
FACSIMILE: 404/572-5100

120 WEST 45TH STREET
NEW YORK, NY 10036-4003
TELEPHONE: 212/556-2100
FACSIMILE: 212/556-2222

November 3, 1995

Charles Ganley, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, HFD-600, Room 150
7500 Standish Place
Rockville, Maryland 20855-2773

Re: ANDA 74-707/Nicotine Polacrilex Gum, 4 mg./
Amendment to Request ANDA Waiver

Dear Dr. Ganley:

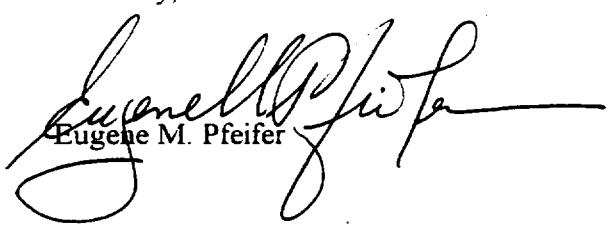
Page(s) 5

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

raw material

Please call me if you have any questions regarding this ANDA amendment and request for a waiver, or if you would like to discuss this matter further.

Sincerely,



Eugene M. Pfeifer

cc: Margaret Jane Porter, Esq.
Roger Williams, M.D.

FIELD COPY CERTIFICATION

Pursuant to 21 C.F.R. § 314.96(b), Circa certifies that a true field copy of this amendment has been sent by overnight courier to:

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

Circa Pharmaceuticals, Inc.
Joyce Anne DelGaudio
Director, Regulatory Affairs

ANDA 74-707

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

AUG 17 1995

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated July 6, 1995, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Nicotine Polacrilex Gum, 4 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> The application is not acceptable for filing under Section 505(j) of the Act because your proposed formulation contains an inactive ingredient that has not been approved for use in a drug product intended for human use by the same route of administration [314.127(a)(8)(ii)]. Since, according to the regulation, there is reasonable basis to conclude that one of the inactive ingredients in your proposed drug product (i.e., raise questions of safety, the Office of Generic Drugs will not file this application.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, while we note that you have provided a list of convictions, you have failed to provide information regarding **affiliated persons** responsible for the development and submission of the application. Please note that contractors responsible for the development of data and other information used to support approval of an application are affiliated persons. Please provide a revised list of convictions with an original signature.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/

Jerry Phillips
Acting 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

July 6, 1995

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

RE: NICOTINE POLACRILEX GUM, 4 mg

Dear Mr. Sporn:

Pursuant to 21 CFR part 314, subpart C and Section 505(j) of the Federal Food, Drug and Cosmetic Act, we are submitting an Abbreviated New Drug Application for nicotine polacrilex gum, 4 mg.

The concept of developing a gum dosage form that was bioequivalent to Nicorette®, started in mid-1990. Soon after developing the 2 mg dosage form that is the subject of ANDA 74- we began development work on a product that would be bioequivalent to Nicorette® DS. Both strengths were thought to be products that were truly unique to the generic drug industry and would offer a development and manufacturing challenge to our new organization.

This submission contains an archival copy (17 volumes in blue jackets) and review copies (5 volumes in red jackets/chemistry, manufacturing and controls technical review section and 12 volumes in orange jackets/pharmacokinetics technical review section). We have also enclosed 2 separately bound copies of the method validation package. These sections comply with the regulations set forth in 21 CFR §314.94(d)(2).

The pivotal bioequivalence study was conducted in fasting subjects, comparing Circa's Nicotine Polacrilex Gum, 4 mg, Lot # RD0965 to Marion Merrell Dow Nicorette® DS, Lot # TF101A. A "Chew-Out" Study comparing the release rates of our product to Nicorette® DS was also conducted. Full reports of these studies are included with this submission.

continued...

There are no requests for biowaivers included in this submission, as it is for only the 4 mg strength of nicotine polacrilex gum.

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

Pursuant to 21 CFR 314.96(b), we are submitting a field copy of the Chemistry, Manufacturing and Controls section of this ANDA. We certify that a true copy of the CMC section of this application has been sent by overnight courier to:

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

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

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

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

Sincerely,

Joyce Anne DelGaudio

Joyce Anne DelGaudio
Director, Regulatory Affairs