CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 74-507

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

RAR

RECORD OF TELEPHONE CONVERSATION

I placed a call to Joyce DelGaudio of Circa this afternoon. The call followed a interoffice meeting earlier this morning regarding a controlled correspondence for Nicorette. The issues involve firstly, which of the post-approval commitments required of the innovator will be encouraged for the generics and also,

i or this product. I let Ms. DelGaudio know that we would be encouraging some the initiatives in place for the NDA product that promote the its safe use. I gave her examples of the types of initiatives in place for the innovator. I at e

I let her know that we would keep her updated.

teleconference when further requests from our Office were known.

DATE
1/22/99

ANDA NUMBER
74-507

IND NUMBER

TELECON

INITIATED BY X **APPLICANT/ SPONSOR** — **FDA**

MADE X **BY TELE.** — **IN PERSON**

PRODUCT NAME
Nicotine Polacrilex Gum 2 mg

FIRM NAME
Circa

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Joyce DelGaudio

TELEPHONE NUMBER

516-842-8383

SIGNATURE
Charlie Hoppes

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

Archival Copy

NEW CORRESP
N/FA

November 5, 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, 2 mg; ANDA 74-507
TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to our above mentioned Abbreviated New Drug Application dated June 16, 1994. Reference is also made to telephone conversations between Dr. Florence Fang, Tertiary Reviewer, Office of Generic Drugs, and myself, dated October 7 and October 30, 1998.

Dr. Fang contacted Circa on October 7, 1998 in order to request that we include a during our stability studies of this drug product. After careful consideration of this request, Circa contacted Dr. Fang. During this conversation, Circa informed Dr. Fang that the gum product identity, strength, quality and purity will be assured by the current stability specifications, which include . Therefore, we do not feel that the addition of a 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 will commit to include a st in the post approval stability program for this product (first three commercial batches and annual batch thereafter). The method of test will be the at is commonly used in industry for in-process checks during a 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.

-Continued-

Dr. Fang also requested that we report any failures of this 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 l be reviewed in conjunction with our
Should our chemistry analysis be within specification, the relevance of the 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.

Sincerely,
CIRCA PHARMACEUTICALS, INC.

Joyce Anne DelGaudio
Director, Regulatory Affairs

CIRCA PHARMACEUTICALS, INC.
33 RALPH AVENUE P.O. BOX 30 COPIAGUE, NY 11726-0030
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October 5, 1998

Archival Copy

NEW CORRESP
NC

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
RESPONSE TO TELEPHONE INFORMATION

Dear Mr. Sporn:

Reference is made to 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.

In a telephone conversation with Kassandra Sherrod, Project Manager, Office of Generic Drugs, dated October 5, 1998, we were informed that there is a

They were submitted in the original ANDA as one of the labs that had been used to conduct microbiological testing. Circa's laboratory has not used In this regard, according to the regulations set forth under 21 CFR §314.96 we would like to formally withdraw any reference to ries from the above mentioned ANDA.

Thank you for your attention to this matter. 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

1998

Joyce Anne DelGaudio
Director, Regulatory Affairs

CIRCA PHARMACEUTICALS, INC.
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July 29, 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

NIFA

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

Dear Mr. Sporn:

We refer to the May 18, 1998 facsimile letter from the Division of Labeling and Program Support, providing comments on the May 5, 1998 amendment to 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.

Our May 5, 1998 facsimile amendment contained a response to both CMC and labeling deficiencies. The amendment addressed all of the CMC issues, and resulted in the labeling deficiency letter which prompted this response. Further, in March of 1998, we were informed that there were no further bioequivalency issues for this ANDA. In this regard, as it is our understanding that labeling is the last section that requires acceptance prior to ANDA approval, we respectfully request an expedited review of this amendment.

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

Labeling Deficiencies:

1. *GENERAL COMMENTS*

   a. *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 appear on the back panel of the carton labeling as well as the User's Guide.*

Response: We have enclosed four copies of the draft of our Support System under Attachment 1. 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. Please note that the starter and refill carton have been revised to refer to this number.

b. *Please indicate on the blister pack, carton labeling and User's Guide that there are 2 mg of nicotine in the drug product [e.g., 2 mg (nicotine)].*

Response: We have revised our labeling of the User's Guide, blister pack and carton as per FDA comment.

2. *CONTAINER (Blister Pack)*

See GENERAL COMMENT (1)(b) above.

Response: We have revised our labeling for the blister pack as per FDA comment.

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 2.

3. *CARTON (Starter and Refill)*

a. *See GENERAL COMMENTS above.*

Response: We have revised our labeling for the starter and refill cartons to refer to the phone number, as per FDA comment. As stated in our response to GENERAL COMMENT a., we have not assigned the toll free number. Therefore, at this time, the number reads as a 1-800-XXX-XXXX. We have also added "(nicotine)" after the established name of the product, as per FDA comment.

b. *Please increase the prominence of the established name on the front panel.*

Response: We have revised our labeling for the starter and refill cartons as per FDA comment.

Please note that the target roller thickness for the ≠ have not been revised as they were already . The revised Master Batch Formulas for the Mixing Process and the Rolling and Scoring Process can be found under Attachment 3.

4. *Please specify the amount of gum in steps 6 and 29. Please submit a revised batch record.*

Response: The Master Batch Formula for the mixing process submitted in our amendment dated August 9, 1996 specifies that the amount of gum base used in Step 6 is placed on stainless steel pans, approximately Step specifies that the amount of finished gum per pan is approximately e weights of each pan from step are recorded on a weight print sheet, as they are used to calculate the accountable yield. Revised Master Batch Formulas are submitted under Attachment 3.

5. *The master manufacturing record is incomplete as it does not include blank rolling/scoring records and packaging records. We realize that these were submitted with he previous amendment, but we request a complete copy to enable us to compare it with the executed batch record.*

Response: We have included a revised Master Batch Formula for the both the mixing and rolling and scoring operation under Attachment 3. The revisions were made in response to comments for this ANDA, as well as that of ANDA 74-707 for Nicotine Polacrilex Gum, 4 mg. This was done to assure consistency in the manufacturing processes of our gum drug products. The revisions that have been incorporated into these records are outlined in a cover sheet in Attachment 3.

6. *The executed batch record is not satisfactory:*

   a. *It does not include a packaging batch record for lot# RD1169.*

Response: We have enclosed the completed packaging forms filled out by personnel during the packaging of batch RD1169. A Master Packaging record was not in place at the time this batch was packaged, however, the forms are descriptive of the entire blister operation. The executed forms can be found under Attachment 4.

Additionally, in response to a comment that appeared as a deficiency for our 4 mg drug product (ANDA 74-707), Circa has generated Master Packaging Records for both strengths of the drug product. In this regard, we have included Circa's Master Packaging Records for this strength of the drug product, as well as the blank packaging forms that are utilized our contract packager, under Attachment 5.

There are three separate Master Packaging Records, one for the actual blistering operation that consists of 12 pieces per card, one for the placement of 9 cards into a carton (Starter Pack), and one for placing 4 cards into a carton (refill pack).

.b. It does not include in-process data for the rolling/scoring process.

c. It does not include data in support of QA approval of the rolling/scoring process (page 3 of 7).

Please submit.

Response: The in-process data generated during the rolling and scoring process of Lot RD1169 is included under Attachment 6. This data includes gum thickness sheets, weight print sheets, machine and product information sheets, and a Scoring Line Parameter Sheet. It also includes that data generated as part of the QA start up approval of the rolling/scoring process.

7. The loss in potency and increase in degradation of the product appears to be due to oxidation of nicotine and not due to heat or light. This was demonstrated by the stress studies where nicotine and nicotine polacrilex showed good stability under acid, base, heat and light conditions but degraded extensively under oxidative conditions. The product is a gum that is placed in a blister pack and hence the degradation may depend on the amount of oxygen present in the formulation and in the immediate package. Additionally, oxygen may seep in over the shelf life. The extent of oxidative degradation is thus time dependent and may be dependent on formation of free radicals. For all these reasons, the accelerated stability data may not be sufficient to demonstrate product stability. We request full-term stability data in support of 2 year expiration date.

Response: Circa agrees that the loss in potency and the increase in degradation of the product may be due to oxidation of nicotine. However, the data submitted in our amendment dated August 9, 1996 clearly demonstrated that the change in the raw material had eliminated the initial drop in assay, as well as improved the impurity levels noted. In this amendment, we provided data showing that there was a distinct improvement of the rate of degradation, as visualized by a flattening of the slope in our linear degradation model.

At this time, we have amassed additional stability data for Lot #RD1169, presented in the tables below. Tables 1 and 2 provides a comparison of the stability from our original bioequivalence batch (RD0930) and our modified formula batch (RD1169).

Table 1

Nicotine Polacrilex 2 mg gum
Stability Comparison: Lot #RD0930 and Lot #RD1169

40°C/75% RH				
	ASSAY (%)		TOTAL IMPURITIES (%)	
Time Point	Lot # RD0930	Lot # RD1169	Lot # RD0930	Lot # RD 1169
Initial	104.6	105.2	NP*	ND**
4 weeks	97.6	103.4	NP*	
8 weeks	96.4	100.6	NP*	
12 weeks	94.2	102.8	NP*	
24 weeks	--	96.9	--	

*Not Performed **None Detected

Table 2

Nicotine Polacrilex 2 mg gum
Stability Comparison: Lot #RD0930 and Lot #RD1169

25°C/60% RH				
	ASSAY (%)		TOTAL IMPURITIES (%)	
Time Point	Lot # RD0930	Lot # RD1169	Lot # RD0930	Lot # RD 1169
Initial	104.6	105.2	NP*	ND**
3 month	96.6	102.7		
6 month	97.3	102.2		
9 month	94.5	102.7		
12 month	94.8	100.7		

*Not Performed **None Detected †Determine uperseded meth

Table 3 provides the updated stability for Lot #RD1169 for all three ICH stabili conditions. The stability summary sheets for Lot RD1169 can be found under Attachment 7.

Table 3

Nicotine Polacrilex 2 mg gum
Lot #RD1169

40°C/75% RH			30°C/60% RH		25°C/60% RH		
Time Point	Assay (%)	Total Impurities	Assay (%)	Total Impurities (%)	Time Point	Assay (%)	Total Impurities (%)
Initial	105.2		105.2		Initial	105.2	
4 weeks	103.4		102.5		1 month	104.0	
8 weeks	100.6		103.2		2 months	104.6	
12 weeks	102.8		104.0		3 months	102.7	
24 weeks	96.9		101.4		4.5months	104.1	
--	--		--		6 months	102.2	
--	--		--		9 months	102.7	
--	--		--		12 months	100.7	
--	--	--	--		15 months	99.2	

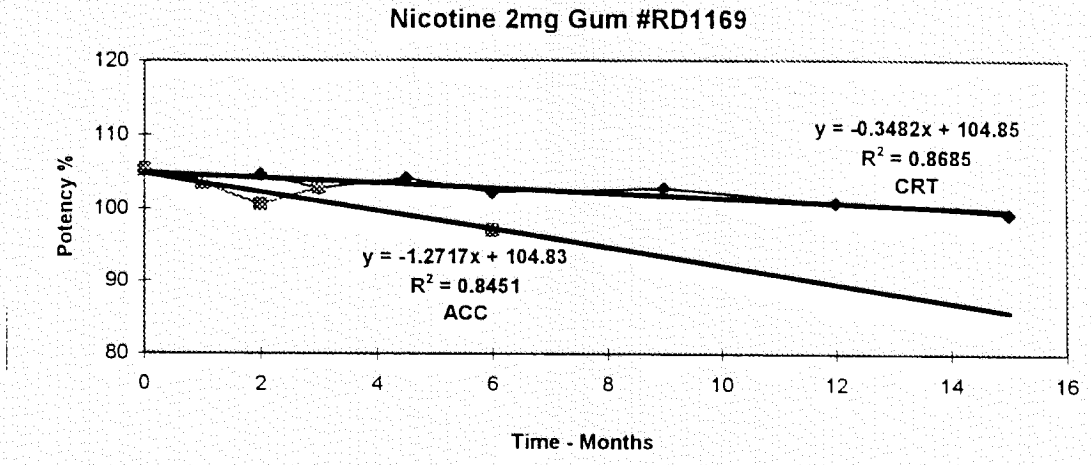
*None Detected

As is evidenced by the data, the formulation change, combined with the change in packaging to orient the PVC as the product contact surface, have dramatically improved our stability profile, both for assay and impurity levels. We have plotted the linear regression of both the accelerated and controlled room temperature stability data, the graphs of which are presented below.

Figure 1

Nicotine Polacrilex 2mg gum
Lot #RD1169

Linear Regression Analysis; Accelerated Conditions (40°C / 75% RH)
and
Linear Regression Analysis; Room Temperature (25°C / 60% RH)



Specification : f label claim

The slope of the best fit line with the additional data points generated to date, show a rate of degradation under real time stability conditions that has improved since our August amendment (y= -0.69x vs. y= -.0036x) and provides increased assurance that our product will meet its proposed expiration dating. Therefore, while we make a commitment to submit full-term stability data when available, we request approval of the tentative 24 month expiration dating based on the data contained in this amendment.

In addition to our deficiency responses, we have revised our finished product and stability specifications and procedures in order that they address the concerns raised in a deficiency letter for our 4 mg drug product. We have also initiated a Post Packaging Specification and procedure. These documents, along with a cover sheet outlining their changes (where applicable) from the previous submission, can be found under Attachment 8.

Labeling Deficiencies:

1. *General Comments*

   a. *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.

   b. *Please note that the listed drug has received approval for an audiotape as a labeling piece for the starter packaging configuration. In your next submission, please provide a transcript for an audiotape based on that of the listed drug.*

Response: A transcript for an audio tape is included in this submission, under Attachment 9. Please note that the tape contains all of the elements of labeling required by 21 CFR Section 201. The pertinent sections are specified in our side-by-side labeling comparison.

2. *CONTAINER*

   a. *See first GENERAL COMMENT.*

   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) 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 (Starter and Refill)*

   a. *We encourage the use of boxing, contrasting colors, or other means to differentiate the strengths of this product from your proposed 4 mg strength product (ANDA 74-707).*

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

b. Front Panel

Ensure that the established name is the most prominent text.

Response: On the final printed labeling, we commit to ensure that the established name is the most prominent text.

c. Back Panel

i) Use boxing and contrasting colors to increase the prominence of the headings under WARNINGS.

Response: A commitment is made to use boxing and contrasting colors to increase the prominence of the headings under WARNINGS.

ii) Use a boxed format for the heading, "READ THE LABEL" on the refill carton.

Response: On the final printed labeling, a commitment is made to use a boxed format for the specified heading.

iii) Use a table format for the 12 week schedule appearing on the starter carton.

Response: On the final printed labeling, a table format will be used for the 12 week schedule appearing on the starter carton.

d. Left panel (refill)

Use a table format for the 12 week schedule.

Response: On the final printed labeling, a table format will be used for the 12 week schedule appearing in the refill carton.

e. *Top Panel (Starter)*

Will the information:

NICOTINE POLACRILEX GUM USP
Active Ingredient: nicotine 2 mg
108 pieces

be on a flap on the top panel folded to appear on the back panel? If not, please include this information on the back panel.

Response: Our actual box design has not been finalized at this time. However, the information specified above will be either on a top panel that is folded to appear on the back panel, or will be included on the back panel.

4. *USER'S GUIDE*

a. *Front Cover (Outside)*

i. • *Nicotine Polacrilex Gum Usage...*

ii. *...USE NICOTINE POLACRILEX GUM TO ...*

Response: We have revised our draft labeling in response to your comments.

b. *We acknowledge that you have removed reference to the page numbers and telephone numbers where appropriate. Please refer your readers to your own page number or section of text rather than merely deleting this page number. Also, in order for this smoking cessation program to work, it is best to provide a support system. The telephone numbers provided by the listed drug are part of such a support system. What are your plans to include a system for telephone support.?*

Response: When the final printed labeling has been designed, we will refer the reader to the appropriate page number in our text. At this time, we are in the process of developing our support system, which will include telephone number that the will appear in the User's Guide.

c. *WHERE TO GET HELP*

Add the following text as the last sentence of the first paragraph:

Toll free numbers are printed on the wallet card on the back cover of this User's Guide.

Response: In response to your comment, we have revised our labeling accordingly.

d. *LET'S GET STARTED (second paragraph)*

Do you intend to put stickers on the next page of your guide?

Response: At this time, it is our intention to put stickers in our guide. The final printed labeling will reflect this.

e. *STICKERS*

When you finalize this section, please include information to the user on where t place the sticker on the calendar, e.g., at the beginning of week #1.

Response: Our final printed labeling will include information regarding the placement of the stickers.

f. *Verify that the first sentence regarding the cost of your product is accurate.*

Response: At this time, our product has not been priced. Our final printed labeling for the drug product will reflect an accurate statement in this section of the User Guide.

Revised draft labels and labeling can be found under Attachment 9.

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,

Joyce Anne DelGaudio

Joyce Anne DelGaudio
Director, Regulatory Affairs

CIRCA PHARMACEUTICALS, INC.
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February 5, 1997

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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

NEW CORRESP

RE: NICOTINE POLACRILEX GUM, 2 MG; ANDA 74-507
RESPONSE TO TELEPHONE REQUEST

Dear Mr. Sporn:

Reference is made to 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. Reference is also made to our August 16, 1996 "NEW CORRESPONDENCE" amendment, in which we submitted six (6) proposed tradenames for our marketed product.

In a telephone conversation with Dr. White, Labeling Reviewer, Office of Generic Drugs, dated January 28, 1997, we were informed that the Nomenclature Committee, in an effort to streamline the review process, has requested that we narrow our original list of six (6) tradenames to our top two (2) choices. In this regard, we offer the following for consideration:

a)
b)

Thank you for your attention. Should you require any additional information, please do not hesitate to contact us.

Pursuant to 21 CFR 314.96(b), we certify that a field copy of this new correspondence has been sent by overnight courier to Mr. Alonzo Cruz, District Director, Food and Drug Administration (NYK-DO), 850 Third Avenue, Brooklyn, New York 11232-1593

Sincerely,
CIRCA PHARMACEUTICALS, INC.

Joyce Anne DelGaudio
Director, Regulatory Affairs

RECEIVED
FEB 06 1997
GENERIC DRUGS