CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-612/S025

20-066/S007

ADMINISTRATIVE DOCUMENTS

DEC 18 1998

Division of Over-the-Counter Drug Products
Labeling Review

NDA #: 18-612/SE4-025 and 20-066/SE4-007
SUBMISSION DATE: May 15, 1998
SPONSOR: Smith Kline Beecham Consumer Healthcare, LP
DRUG PRODUCT: Nicorette ® (nicotine polacrilex) 2 mg and 4 mg gum
INDICATIONS: Stop Smoking Aid
ACTIVE INGREDIENT: Nicotine
REVIEWER: Mary S. Robinson, M. S.
REVIEW DATE: November 20, 1998
PM: Sakineh Walther

The attached draft labeling was submitted for review by SmithKline Beecham Consumer Healthcare, LP for Nicorette® (nicotine polacrilex) Mint Flavored 2 mg gum (NDA 18-612/SE4-025) and 4 mg gum (NDA 20-066/SE4-007). [Of note, the original flavor Nicorette 2 mg and 4 mg gum was approved for OTC use in February, 1996.] These submissions are a re-filing of supplements NDA 18-612/SE-023 and NDA 20-066/S-005 for the 2 mg and 4 mg, respectively, submitted March 6, 1996 and are made in response to the October 8, 1996 nonapproval letter. The information in the two supplements (2 mg mint gum (NDA 18-612/SE4-025)and 4 mg mint gum (NDA 20-066/SE4-007) differ only in the content of the chemistry section. Mint flavor Nicorette 4 mg gum contains D& C Yellow No. 10 (the 2 mg strength does not) and the 4 mg product does not contain sodium bicarbonate. This review is based on mock-ups of draft labeling of the 2 and 4 mg mint gum carton, refill carton, individually labeled and perforated blister packs, user's guide, audio tape (starter pack only) and promotional leaflet for the optional Committed Quitters™ behavioral support program. (See Appendix, (AP) 1-28.) Unless otherwise noted, the reviewer's comments and recommendations refer to the labeling for both products.

Reviewer's Comments and Recommendations on the Proposed Nicorette® (nicotine polacrilex) 2 mg and 4 mg Gum Labeling

I. Cartons (2 mg, 4 mg Starter Kit and 2 mg and 4 mg Refill)

A. **Principle Display Panel**. (AP 1 and 2)

1. The current statement of identity is not in conformity with 21 CFR 201.61. The statement of identity needs to be corrected to read: "Nicotine polacrilex gum *[insert number of mg]*, Stop Smoking Aid."
2. The phrase "New Flavor" should be deleted after the first 6 months of OTC marketing.
3. The sponsor needs to define the "FREE COMMITTED QUITTERS PLAN," and state that it is an optional plan, in addition to the "User's Guide and audio tape" provided. [This plan is included with the 108 count chew pieces, only.]
   The sponsor should be asked if this plan will also be provided with the purchase of the original flavor 2 mg and 4 mg nicotine drug products and refill packages.
4. The sentence "Includes stop smoking plan with User's Guide and Audio tape" should be in larger letters.
5. The statement "SMOKERS UNDER 25 CIGARETTES A DAY" on the 2 mg products is

awkward and not clear. The statement should read: "FOR THOSE WHO SMOKE LESS THAN 25 CIGARETTES A DAY." Also, similar to the unflavored 2 mg and 4 mg Nicorette gum labeling, consumers should immediately be told what to do if they smoke 25 or more cigarettes a day. The statement should read: "If you smoke 25 or more cigarettes a day; use 4 mg Nicorette."
Likewise, the statement "SMOKERS OVER 24 CIGARETTES A DAY" should be revised to read: "FOR THOSE WHO SMOKE 25 OR MORE CIGARETTES A DAY." "If you smoke less than 25 cigarettes a day; use 2 mg Nicorette."

The labeling of both the mint flavor and the original flavor should be the same, this may require modification of the original flavored formula. The 2 mg/4 mg original is labeled "FOR SMOKERS OVER 24 CIGARETTES A DAY and "FOR SMOKER UNDER 25 CIGARETTES A DAY." These statements are also not clear for the above reasoning.

6. Note that the American Cancer Society (ACS) icon is a promotional type endorsement and cannot be used in any part of the FDA required labeling. Such statements should not disrupt the required labeling elements, but may appear elsewhere in the labeling, e.g., principal display panel, or side or end panel.

B. **Top Panel, (2/4 mg Starter Kit), and Panel 1, (2/4 mg refill).** (AP 1 and 2)
The statement "* SmithKline Beecham provides an annual grant to the American Cancer Society for stop smoking and cancer-related research and education," is a promotional type endorsement and cannot be used in any part of the FDA required labeling, as stated in I.A.6. above.

C. **Left Panel (2/4 mg Starter Kit) and Panel 3 (2/4 mg refill).** (AP 1, 2, 5 and 6)
Tamper Resistant/Tamper Evident Statement, second sentence, the word "broken" should be replaced with the words "open or torn." to read: "Do not use if individual seals are open or torn" to conform to the labeling of other OTC drug products with similar packaging.

D. **Back Panel**. (AP 3, 4, 5 and 6)

1. The Active Ingredient statement should read: "**Active ingredient** (in each chewing piece) nicotine polacrilex [insert amount] mg." (See prototype label, AP 28 .)
2. The word "**ACTION**" should be replaced by the word "**Purpose**" as recommended in proposed §201.66(c)(2) of the February 27, 1997 Proposed Labeling Requirements for OTC Drug Products. Also, all headings should be in upper and lower case letters to be consistent with the format in the February 27, 1997 Proposed Labeling Requirements for OTC Drug Products. (See prototype label, AP 28.)
3. **Warnings**," bullet 1. The "pregnancy-breast feeding" warning should be moved to before the "Keep out of reach" warning in conformance with the February 27, 1997 Proposed Labeling Requirements for OTC Drug Products § 201.63. For consistency with the labeling of other drug products of this class, the sentence "First try to stop smoking without the nicotine gum" needs to be added. The pregnancy-breast feeding warning should read as follows: "**If pregnant or breast-feeding**, ask a health professional before use. Nicotine can increase your baby's heart rate. First try to stop smoking without the nicotine gum." See prototype label, AP 28.

4. We note that in the User Guide and audio tape, AP 10, column 3 and AP 20, paragraph 1, respectively (See NOTE, below), several statements are made regarding safety concerns when children and pets are exposed to nicotine. Although not a requirement at this time, for consistency with the information provided in the User Guide and audio tape, the sponsor may wish to add the following sentence after the "Keep out of reach" warning: "Pieces of nicotine gum may have enough nicotine to make children and pets sick."

NOTE: **AP 10, column 3** -- (Symptoms of nicotine overdose may include vomiting and diarrhea. Young children are more likely to have additional symptoms, including weakness. Also seizures have been seen in children who swallowed cigarettes.

AP 20, paragraph 1 -- (LEADER: Well if you have kids or pets at home make sure you throw away the used pieces of Nicorette safely. There will still be some nicotine in them -- enough to make children or small animals sick.)

5. The "**Warnings**" need to include specific information on the disposal of the nicotine gum, so that it is out of reach of children and pets.
6. The **READ THE LABEL** icon should not be introduced between FDA required information. However, it may be placed above or below the required information.
7. Directions, bullet 6, (2/4 mg Starter Kit) and Panel 1 (2/4 mg refill). The direction "Do not exceed 24 pieces a day" needs to be clarified because the recommended dosing directions only provide instructions for the administration of 1 piece of gum every 1 to 2 hours when awake during step 1 and even less during step 2 and 3. The sponsor needs to provide specific directions for chewing 24 pieces of gum a day because the User Guide, (AP 10, column 11), states that "An overdose can occur if you chew more than one piece of Nicorette at the same time, or if you chew many pieces one after another." See II.13 below and III.1., below.
8. A new section header titled "**Other information**" should be added to follow "**Directions**" to be consistent with other drug products of this class and the format in the February 27, 1997 Proposed Labeling Requirements for OTC Drug Products. Please refer to the "**Other information**" in prototype label (AP 28.).

   For consistency with the Office of New Drug Chemistry (ONDC) recommendations, the storage statement should read: "Store between 20° C - 25°C (68° F - 77° F). The storage statement should also be moved to "**Other information.**"
9. Expiration Date/Lot Number. The location of the expiration date and lot number needs to be identified in accordance with § 201.17 for the cartons and blister packs (AP 7 and 8).

II. User Guide for the 2 mg and 4 mg Nicorette products (AP 9-12)

1. AP 10, The word "CAUTION" in the heading "**SOME IMPORTANT CAUTIONS**" needs to be replaced with the word "**Warnings**" because the paragraph contains the warnings that are on the back of the cartons.

AP 10, column 2, paragraph 1, the sponsor should include the underlined, italized information in the following paragraph so that the consumer is informed of the need for the warnings. This information is also consistent with the carton labeling and other drug product labeling of this class.

This product is only for those who want to stop smoking. Do not smoke, chew tobacco, use snuff or nicotine patches while using Nicorette; *you may get a nicotine overdose*. *Ask your doctor before using Nicorette* if you have heart disease, *had* a recent heart attack, irregular heartbeats, palpitations; *nicotine can increase your heart rate*. *If you have* high blood pressure not controlled with medication (*nicotine can increase your blood pressure)*, stomach ulcer, or take insulin for diabetes, ask your doctor whether you should use Nicorette.

2. AP 10, column 3, paragraph 1, should begin with the sentence "Nicotine can increase your baby's heart rate. First try to stop smoking without using **Nicorette**," to be consistent with other drug products of this class.
3. AP 10, column 3, paragraph 1, Delete the phrase "As with any drug." The pregnancy-breast-feeding warning should be consistent throughout the labeling (see AP 3, 4, 5 and 6) and in the format in the February 27, 1997 Proposed Labeling Requirements for OTC Drug Products
4. AP 10, column column 3, paragraph 4, the following symptoms need to be included in the first sentence: nausea, dizziness, weakness and rapid heartbeat to be consistent with the labeling warning and other drug product labeling of this class..
5. AP 10, column 4, paragraph 1, the sponsor should be made aware that finalization of the February 27, 1997 Proposed Labeling Requirements for OTC Drug Products may change the Keep out of the reach and the accidental overdose warnings. See prototype label, AP 28.
6. AP 10, column 4, paragraph 2, it is recommended that the following sentences be included at the end of the paragraph: "First, check that you bought the right starting dose. If you smoke 25 or more cigarettes per day; use 4 mg. If you smoke less than 25 cigarettes a day; use 2 mg."
7. AP 10, columns 5 and 6, the headings **"STEP 1, 2, and 3"** need to be followed by the number of weeks for each step: Step 1 (1-6 weeks), Step 2 (7-9 weeks) and Step 3 (10-12 weeks) for clarity.
8. AP 10, column 7, the last sentence states "If you smoke at all, write down what you think caused the slip." Considering the potential for overdose and the close time interval between doses, directions regarding what the consumer is expected to do after the slip need to be inserted here.
9. AP 10, column 11, the sentence: "Don't eat or drink for 15 minutes before using **Nicorette** or while chewing a piece," needs to be included as a step under the heading "How to Use Nicorette Gum" to be consistent with the carton label.
10. AP 11, column 2, number 9, the sponsor needs to provide instruction for the safe disposal of Nicorette gum. The term "throw away" is not clear or meaningful. See I.D.5 and III.2.
11. AP 11, column 3, chart, the directions for use should be the same in all parts of the labeling. The directions statement on the carton back (bullet 6) and in the User Guide

should be made consistent. The direction needs to read: "Do not chew more than 24 pieces a day." Note that this direction needs clarification (See I.D.7, above).

12. AP 11, column 3, paragraph 1, sentence 2, states that "Heavier smokers may need more pieces to reduce their cravings." The User Guide includes both the 2 mg (24 and under cigarettes) and 4 mg (25 and over cigarettes) gum. The phrase "heavier smokers," and the "more pieces" needs to be defined and the sentence clarified. See I.D.7., and III.1.

III. **TAPE SCRIPT (Audio Cassette to Accompany Finished Product) (2/4mg Starter Kit), and Panel 1, (2/4mg refill),** (AP 25)

1. Leader speaking, AP 19, paragraph 8. The sentence "Heavy smokers might need to go all the way up to 24 pieces." needs to be rewritten. See II.12 above.
1. Leader speaking, AP 20, paragraph 1. The following paragraph needs to be revised: "Well, if you have kids or pets at home make sure you throw away the used pieces of Nicorette safely. There will still be some nicotine in them -- enough to make children or small animals sick. The paragraph needs to tell the consumer how to safely dispose of the gum or provide a disposal system so that children and pets will not be harmed. See I.D.4 and 5 above.

IV. **Promotional leaflet for the optional Committed Quitters Program** (AP 26 and 27)

1. See I.A.3, above
2. It is unclear why the leaflet instructs the consumer to "READ ME FIRST."

ADDITIONAL RECOMMENDATIONS:

We suggest that the sponsor consider the label headings and subheading as proposed in the FEDERAL REGISTER of February 27, 1997, (62 FR 9024-9062) In the proposal the labeling information is presented in the following specific order: **Active Ingredient(s), Purpose(s), Uses(s), Warnings, Directions, Other Information, and Inactive Ingredients** (in both upper and lowercase letters). No other information should precede the "**Active Ingredient**" section. We also suggest that the sponsor consider revising the text and format of the labeling to reflect the proposed draft prototype label (AP 28). The sponsor should also be aware that the Proposed Labeling Requirements for OTC Drug Products and the prototype label are subject to change pending finalization of the final rule.

/S/

Mary S. Robinson, M. S.
Regulatory Review Chemist, HFD-560

/S/

Helen Cothran, B.S.
Team Leader, HFD-560

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Ling Chin, M. D., M.P.H.
Medical Officer, HFD-560

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Linda M. Katz, M. D., MPH
Deputy Director, HFD-560
12/18/98

SmithKline Beecham
Consumer Healthcare

Janice McSherry
Senior Counsel

DEBARMENT CERTIFICATION

Pursuant to section 306(a) and (b) of the Federal Food, Drug, and Cosmetics Act [21 USC 335(a) and (b)], and to the best of my information, knowledge and belief, no one involved in the development of this New Drug Application who has been or is currently employed by SmithKline Beecham Consumer Healthcare, has been debarred. Additionally, there are no debarment procedures pending for any current or past employee of SmithKline Beecham Consumer Healthcare. This was determined by comparing the current debarment list, dated November 12, 1997, to the listing of past and present SmithKline Beecham Consumer Healthcare employees.

Further, we certify SmithKline Beecham Consumer Healthcare will not use the services in any capacity of anyone debarred by the United States Food and Drug Administration.

We are not aware of any relevant convictions of SmithKline Beecham Consumer Healthcare personnel for which an individual can be debarred as described in section 306(a) and (b).

Janice McSherry
Janice McSherry, Senior Counsel

April 27, 1998
Date

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Food and Drug Administration
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care and Addiction Drug Products

Memorandum

Date: December 20, 1998

From: Cynthia McCormick, MD, Director /S/
Division of Anesthetics, Critical Care and Addiction Drug Products
ODE III, CDER

Subject: Mint Nicorette Action

To: Debra Bowen, MD
Director, Division of Over the Counter Drug Products
ODE V, CDER

Division File NDA #18-612 S-025
Division File NDA #20-066 S-007

This memorandum documents for the file the Division of Anesthetics Critical Care and Addiction Drug Product's recommendation for approval with concurrence from the Division of Over the Counter Drug Products on the Nicorette 2 mg and 4 mg polacrilex gum for the addition of mint flavoring.

In 1995 SmithKline Beecham undertook to change their Nicorette gum product to add flavoring which would improve its palatability. The FDA agreed that the addition of the specified flavorings would not alter the product's efficacy or safety. However the company was issued a Not Approvable letter dated October 8, 1996. The deficiencies cited included inadequate basis on which to judge the new product's abuse potential, and the absence of essential manufacturing data.

The sponsor was directed to design and perform an abuse liability assessment which would allow the FDA and Sponsor to assess the potential for mint nicotine gum to serve as a gateway product for adolescent smokers. On June 5, 1997 the sponsor met with FDA in an effort to plan what would be needed in order to gain approval of the mint Nicorette program. The sponsor agreed to perform a study, but with the caveat that there is no validated model to assess abuse liability in adolescents and that the main factors that contribute to youth smoking are probably non-

pharmacologic. Nevertheless, an abuse liability study was designed and performed comparing mint and original Nicorette with amphetamine and placebo an effort to assess adolescent appeal. In addition the sponsor agreed to continue monitoring for youth appeal/abuse in phase IV. The FDA clearly specified in the Not Approvable letter that the evaluation of the abuse liability in clinical trials of Mint Nicorette would be a necessary for approval.

I note the reviews by the primary medical officer, abuse liability team leader and biometrics team leader all struggling to interpret the results of the study, which was performed with FDA concurrence. The abuse liability study that was submitted, fraught with methodological problems (outlined by Dr.Permutt) does not contradict that experience. Indeed in the head-to-head comparisons between mint Nicorette and original Nicorette subjects perceptions of the drug effect[1] did not differ significantly between the two groups. The addition of mint flavoring was clearly an important factor in palatability as noted by responses to questions about sweetness and overall liking, where mint Nicorette was ranked higher than unflavored Nicorette.

The lack of a statistical effect difference between any of the products on virtually all endpoints was certainly a function of sample size (underpowered), and as well as very subjective endpoints. The study clearly is not capable of demonstrating the absence of abuse potential of Mint Nicorette. Nevertheless, this weak study taken together with the European experience with flavored Nicorette and the absence of significant evidence of abuse and demonstrated by the postmarketing track record of Nicorette (see Dr.Chin's Review dated December 1998), provides sufficient assurance that there will not be a significant threat of teen smoking arising from the approval of this product.

Conclusion

At the time of the original submission and subsequent resubmission of the mint Nicorette supplement there was little experience and considerable concern with how Nicorette would be viewed by adolescents. Since that time, and particularly since the product has entered the over-the-counter market, the earlier concerns about abuse have been allayed by the paucity of reports that teens are using the unflavored product as a gateway product to teen smoking. This Division, then, supports the approval of Mint Nicorette with a commitment by the sponsor to continue postmarketing surveillance for abuse in phase IV.

[1] Would you chew the gum just to get drug effect? and Do you like the drug effect?

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338.
Expiration Date: April 30, 2000.
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

NDA 20-066

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
SmithKline Beecham Consumer Healthcare, L.P.	**May 15, 1998**
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(973) 889-2509	**(973) 889-2501**
APPLICANT ADDRESS *(Number, Street, City, State, Country, Zip Code or Mail Code, and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, Zip Code, telephone & FAX number) IF APPLICABLE*
1500 Littleton Road **Parsippany, NJ 07054-3884**	**Not Applicable**

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Nicotine polacrilex gum	**Nicorette®**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*: **See attached sheet**

CODE NAME *(If any)*:

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Gum	**4 mg**	**Oral**

(PROPOSED) INDICATION(S) FOR USE:

Stop Smoking Aid (to reduce withdrawal symptoms including nicotine craving associated with quitting smoking)

APPLICATION INFORMATION

APPLICATION TYPE (check one): [X] NEW DRUG APPLICATION (21 CFR 314.50) [ ] ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) [ ] BIOLOGICS LICENSE APPLICATION (21 CFR part 600)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE: [X] 505 (b) (1) [ ] 505 (b) (2) [ ] 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one): [ ] ORIGINAL APPLICATION [ ] AMENDMENT TO A PENDING APPLICATION [ ] RESUBMISSION [ ] PRESUBMISSION [ ] ANNUAL REPORT [ ] ESTABLISHMENT DESCRIPTION SUPPLEMENT [ ] SUPAC SUPPLEMENT [ ] EFFICACY SUPPLEMENT [ ] LABELING SUPPLEMENT [ ] CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT [X] OTHER

REASON FOR SUBMISSION: **Supplement – New Mint Flavor Nicorette® 4 mg Gum**

PROPOSED MARKETING STATUS (check one): [ ] PRESCRIPTION DRUG PRODUCT (Rx) [X] OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: **22**

THIS APPLICATION IS: [X] PAPER [ ] PAPER AND ELECTRONIC [ ] ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached sheet

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

NDA 18-612, NDA 20-066, [redacted]

This application contains the following items: *(Check all that apply)*	
✓	1. Index
✓	2. Labeling (check one) ☑ Draft Labeling ☐ Final Printed Labeling
✓	3. Summary (21 CFR 314.50 (c))
✓	4. Chemistry section
✓	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
✓	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
✓	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
✓	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
✓	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
✓	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
✓	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
✓	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
✓	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
✓	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
✓	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
✓	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
✓	16. Debarment certification (FD&C Act 306 (k) (1))
✓	17. Field copy certification (21 CFR 314.50 (k) (3))
✓	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
David Schifkovitz	**David Schifkovitz** **Associate Director, Regulatory Affairs**	**May 15, 1998**

ADDRESS *(Street, City, State, Zip Code)*	Telephone Number
1500 Littleton Road, Parsippany, NJ, 07054-3884	**(973) 889-2509**

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