CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-330

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

EXCLUSIVITY SUMMARY for NDA # 21-330 SUPPL # _____

Trade Name Commit™ Generic Name nicotine polacrilex lozenge 2mg, 4mg

Applicant Name GlaxoSmithKline HFD- 170

Approval Date October 31, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

EXCLUSIVITY SUMMARY for NDA # 21-330 SUPPL # _____

Trade Name Commit™ Generic Name nicotine polacrilex lozenge

Applicant Name GlaxoSmithKline HFD- 170

Approval Date October 31, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X__/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain: _____

_____

APPEARS THIS WAY
ON ORIGINAL

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # S1410043

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # S1410043

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 56295 YES /_X__/ ! NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

APPEARS THIS WAY
ON ORIGINAL

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

Victoria Kao 10-29-02
Signature of Preparer Date

Title: Regulatory Project Manager

_____ _____
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bob Rappaport
10/30/02 01:27:11 PM

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

N21-330

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-330	Efficacy Supplement Type SE-	Supplement Number
Drug: Commit™	Applicant: GlaxoSmithKline	
RPM: Victoria Kao	HFD- 170	Phone # 301-827-7416
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	2S
• Other (e.g., orphan, OTC)	OTC
❖ User Fee Goal Dates	11-01-02
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	NA
• OC clearance for approval	NA
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	ADRA/PM 10-29-02
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE - October 19, 2001
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	NA
• Most recent applicant-proposed labeling	August 30, 2002
• Original applicant-proposed labeling	December 15, 2000
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	ODS Reviews: April 4, 2001; June 17, 2002; October 21, 2002
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	August 30, 2002
• Reviews	ODS Reviews: April 4, 2001; June 17, 2002; October 21, 2002
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	February 26, 2002 submission
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	NA
• Pre-NDA meeting (indicate date)	October 4, 2000, April 11, 2000
• Pre-Approval Safety Conference (indicate date; approvals only)	NA

• Other	NA
Advisory Committee Meeting	NA
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Action Memos: 170: DFS'd OTC: DFS'd
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	September 3, 2002; October 9, 2001
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NA
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Included in Clinical Review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	10-29-02
❖ Demographic Worksheet *(NME approvals only)*	NA
❖ Statistical review(s) *(indicate date for each review)*	August 20, 2001
❖ Biopharmaceutical review(s) *(indicate date for each review)*	September 17, 2002
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	Consult requested February 21, 2001. Email response: March 30, 2001
Clinical Inspection Review Summary (DSI)	
• Clinical studies	NA
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	October 24, 2002; August 28, 2002; August 19, 2001
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	CMC review #1 P. 63
• Review & FONSI *(indicate date of review)*	NA
• Review & Environmental Impact Statement *(indicate date of each review)*	NA
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NA
❖ Facilities inspection (provide EER report)	Date completed: October 18, 2001; July 8, 2002 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	July 8, 2001; October 8, 2001
Nonclinical inspection review summary	NA
Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NA
❖ CAC/ECAC report	NA

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-330 / _____ - _____

Drug Nicotine Polacrilex Lozenge 2 and 4 mg Applicant Glaxo SmithKline

RPM Judit Milstein Phone (301) 827-7440

■505(b)(1)
☐505(b)(2) Reference listed drug _____

☐Fast Track ☐Rolling Review Review priority: ■ S ☐P

Pivotal IND(s) 56,295

Application classifications:
Chem Class 2S
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary : 20-Oct-2001
Secondary 20-Dec-01

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ■ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☐AP ☐ AE ☐ NA

- Labeling & Labels
  FDA revised labeling and reviews.....
  Original proposed labeling (package insert, patient package insert) X
  Other labeling in class (most recent 3) or class labeling.....
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☐ No
  Immediate container and carton labels X
  Nomenclature review X

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ■ is not on the AIP.
  Exception for review (Center Director's memo).....
  OC Clearance for approval.....

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☐ Materials requested in AP letter

- Post-marketing Commitments
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....

- Was Press Office notified of action (for approval action only)?..... ☐ Yes ☐ No
  - Copy of Press Release or Talk Paper.....

- Patent
  - Information [505(b)(1)] X
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... X

- Exclusivity Summary X

- Debarment Statement X

- Financial Disclosure
  - No disclosable information X
  - Disclosable information – indicate where review is located .....

- Correspondence/Memoranda/Faxes X

- Minutes of Meetings .....
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting October 4, 2000 and April 11, 2000 X
  - Date of pre-AP Safety Conference _____

- Advisory Committee Meeting ..... N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....

- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) X

- Clinical review(s) and memoranda X

Continued ⇨

- ♦ Safety Update review(s) X

- ♦ Pediatric Information
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page...Request for deferral..... _____
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable

- ♦ Statistical review(s) and memoranda X

- ♦ Biopharmaceutical review(s) and memoranda..... X

- ♦ Abuse Liability review(s) X
  Recommendation for scheduling ..... _____

- ♦ Microbiology (efficacy) review(s) and memoranda ..... N/A

- ♦ DSI Audits ..... _____
  ☐Clinical studies ☐ bioequivalence studies ..... _____

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- ♦ CMC review(s) and memoranda X

- ♦ Statistics review(s) and memoranda regarding dissolution and/or stability ..... _____

- ♦ DMF review(s) X

- ♦ Environmental Assessment review/FONSI/Categorical exemption X

- ♦ Micro (validation of sterilization) review(s) and memoranda ..... N/A

- ♦ Facilities Inspection (include EES report) X
  Date completed _____ ..... ☐ Acceptable ☐ Not Acceptable

- ♦ Methods Validation ..... ☐ Completed ☐ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- ♦ Pharm/Tox review(s) and memoranda X

Memo from DSI regarding GLP inspection (if any) ..... _____

APPEARS THIS WAY
ON ORIGINAL

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Parinda Jani
10/30/02 02:27:25 PM

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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 June 20, 2000, 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

August 30, 2000

APPEARS THIS WAY
ON ORIGINAL

100 Beecham Drive, PO Box 1467, Pittsburgh, Pa. 15230. Telephone (412) 928-1043. Fax (412) 928-1635
E-mail: janice.mcsherry@sb.com

SmithKline Beecham

20 October 2000

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg. rm. 2-14
12420 Parklawn Dr.
Rockville, MD 20857

Re: Patent Information Respecting SB's Nicotine Polacrilex Lozenge New Drug Application (#21-330) for Reduction of Withdrawal Symptoms, including Nicotine Craving, Associated With Quitting Smoking

Dear Sirs:

In accordance with 21 C.F.R. 314.53 (a)-(d)(4), the undersigned declares that US Patent 5,110,605 covers the formulation, composition and a method of use of nicotine in the form of nicotine polacrilex. This product is currently approved under Section 505 of the Federal Food, Drug and Cosmetic Act.

U.S. Patent No. 5,110,605

a) Expiration Date
The 20 year term expires August 21, 2010

b) Type of Patent
Formulation, and method of use

c) Name of Patent Owner
TheraTech, Inc.
417 Wakara Way
Salt Lake City, Utah, 84108

Please advise the undersigned if further information is required. This letter is being submitted in duplicate.

Very truly yours,

Dara L. Dinner
Associate Patent Counsel
Corporate IP- US

709 Swedeland Road, PO Box 1539, King of Prussia, PA 19460 0939. Telephone (610) 270 4800. Fax (610) 270 5090

Item 13

Patent Information

21 U.S.C. 355 (b) or (c)

1. Active Ingredient:	Nicotine Polacrilex
2. Strength:	2mg and 4mg
3. Trade Name:	To Be Determined
4. Dosage Form, Route of Administration:	Lozenge, Oral
5. Application and Firm Name:	SmithKline Beecham Consumer Healthcare, LP
6. NDA Number Assigned:	21-330
7. Approval Date:	To Be Determined
8. Exclusivity: Date first ANDA could be approved and length of exclusivity period	To be determined pending FDA review and approval
9. Applicable patent numbers and expiration date of each:	

Patent Number	Type of Patent	Patent Owner	Expiration Date
5,110,605	Formulation, Method of Use	TheraTech, Inc.	8/21/10

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

SmithKline Beecham Consumer Healthcare, LP
1500 Littleton Road
Parsippany, NJ 07054-3884

2. TELEPHONE NUMBER (*Include Area Code*)
(973) 889-2509

3. PRODUCT NAME
Nicotine Polacrilex 2mg & 4mg Lozenge

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? **Yes**
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____
(APPLICATION NO. CONTAINING THE DATA)

5. USER FEE I.D. NUMBER
4044

6. LICENSE NUMBER/NDA NUMBER
NDA # 21-330

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IS SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT BEFORE 9/1/92 (*Self Explanatory*)

☐ A 505(B)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (*See item 7, reverse side before checking box.*)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT (*See item 7, reverse side before checking box.*)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXEMPTION UNDER SECTION 736(a)(1)(F) OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT (*See item 7, reverse side before checking box.*)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(*See reverse side if answered YES*)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to either of these addresses.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	**Director, Regulatory Affairs**	**December 8, 2000**

FORM FDA 3397 (5/98)

EF

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : N21-330 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: December 15, 2000 **Action Date:** October 30, 2002

HFD 170 **Trade and generic names/dosage form:** Commit™ (nicotine polacrilex lozenges)

Applicant: GlaxoSmithKline Consumer HealthCare **Therapeutic Class:** 2S/2030700

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): _____

Indication #1: The Over-the-Counter (OTC) marketing of Commit™ step-down regimen for adults 18 years of age and older, to reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking.

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

X No: Please check all that apply: ___Partial Waiver __X_Deferred ___Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo.____	yr.____	Tanner Stage____	
Max____	kg____	mo.____	yr.____	Tanner Stage____	

APPEARS THIS WAY ON ORIGINAL

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed

☐ Other:_____

udies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is omplete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg**____	**mo.**____	**yr.** 10	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.** 17	**Tanner Stage**____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): October 30, 2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

tion D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

udies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see achment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

tion C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

IND 56,295

SmithKline Beecham Consumer Healthcare
1500 Littleton Road
Parsippany, NJ 07054-3884

Attention: Robert Harris
Assistant Director, Regulatory Affairs

Dear Mr.Harris:

Please refer to the pre-NDA meeting between representatives of your firm and FDA on October 4, 2000.

The purpose of the meeting was to discuss SmithKline Beecham Consumer Healthcare's (SBCH) plans for the submission of the NDA for Nicotine Polacrilex Lozenge, 2 mg and 4mg, with a direct-to-OTC switch.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7410.

Sincerely,

Judit Milstein
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Center for Drug Evaluation and Research

Enclosure: Minutes of the meeting

(I)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

6 pages

(I)

must also be updated with the new pregnancy warning.

11. The proposed names Commit Lozenge [redacted] Commit Lozenge [redacted] [redacted]re not acceptable. These proposed names may cause confusion because they make reference to [redacted] as if they are the source of the lozenge.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a re-tabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Although minimal labeling comments have been provided in this letter, complete comments will be provided following resubmission of this application. It is expected that labeling submitted for review will be formatted in accordance with the requirements as set forth in 21 CFR 201.66.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Judit Milstein, Regulatory Project Manager, at (301) 827-7440.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Division of Over-The-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

{See appended electronic signature page}

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Celia Winchell
10/19/01 10:05:10 AM
Signed for Cynthia G. McCormick, M.D., Division Director

Charles Ganley
10/19/01 12:14:38 PM

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

GlaxoSmithKline

Consumer Healthcare
1500 Littleton Road
Parsippany, NJ
07054-3884

Tel. 973 889 2100
Fax. 973 889 2390
www.gsk.com

August 24, 2001

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170)
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

Re: **NDA 21-330 - Nicotine Polacrilex Lozenge 2 mg & 4 mg**
Amendment #8 - Proposed Brand Name

Dear Dr. McCormick,

Reference is made to our New Drug Application submitted to the Agency on December 20, 2000 for nicotine polacrilex 2 mg and 4 mg lozenges. This cover letter contains information on GlaxoSmithKline's (GSK) eighth amendment to the above referenced application. The amendment provides [redacted] for the proposed product. Final selection for GSK [redacted]

[redacted]

The proposed brand names are:

COMMIT LOZENGE [redacted]

COMMIT LOZENGE [redacted]

This amendment is provided in both paper and electronic format. The enclosed 3.5" diskette has been confirmed to be virus free using McAfee VirusScan, version 4.0.2, scan engine 4.1.20, updated 8/8/2001.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions or require additional information, please contact my office by phone at (973) 889-2509 or by FAX at (973) 889-2244.

Sincerely,

David Schifkovitz
Director, Regulatory Affairs

Desk: Daniel Keravich, Division of Over-The-Counter Drug Products
Judit Milstein, Division of Anesthetic, Critical Care and Addiction Drugs

APPEARS THIS WAY
ON ORIGINAL

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: March 31, 2003.
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
GlaxoSmithKline Consumer Healthcare	August 24, 2001
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(973) 889-2509	(973) 889-2244
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): NDA 21-330

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Nicotine Polacrilex	To Be Determined

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(If any)*
Nicotine	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Lozenge	2mg and 4mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

Reduction of Withdrawal Symptoms, Including Nicotine Craving, Associated With Quitting Smoking

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 600)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

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 ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Amendment #8 – Tradename

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION DRUG PRODUCT (Rx) ☒ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED ONE

THIS APPLICATION IS ☐ 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

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

IND 56,295, DMF —— DMF ——

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. Financial Information (21 CFR Part 54)
X	20. OTHER *(Specify)* Proposed Tradename

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 FD&C Act Section 506A, 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** **Director, Regulatory Affairs**	**August 24, 2001**

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

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 356h (4/00)

APPEARS THIS WAY
ON ORIGINAL

Attachments for FDA Form 356h - nicotine polacrilex lozenge 2 mg & 4 mg

Chemical Name:

2 propenoic acid, 2-methyl-polymer with diethenylbenzene, complex with (S)-3-(1-methyl-2-pyrrolidinyl) pyridine

Establishment Information:

Drug Substance Manufacturer (nicotine polacrilex)

Name:	GlaxoSmithKline Pharmaceuticals
Address:	Shewalton Road Irvine Ayrshire, KA11 5AP Scotland, UK
Contact:	Alan Gray Quality Assurance Manager
Telephone No.:	011 44 1294 847136
Registration No.:	FC UK 684
DMF No.:	N/A
Manufacture Steps/Type of testing performed at site:	All aspects of drug substance manufacture, testing and packaging
Ready for Inspection:	Yes

Drug Product Manufacturer:

Name:	GlaxoSmithKline Consumer Healthcare
Address:	Verenes Industrial Park 65 Windham Blvd. Aiken, South Carolina 29805
Contact:	John Coyle Quality Assurance Manager
Telephone No.:	803-641-8664
Registration No.:	1046838/ATL
DMF No.:	N/A
Manufacture Steps/Type of testing performed at site:	All aspects of drug product manufacture, testing and packaging
Ready for Inspection:	Yes

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO (Division/Office): Associate Director, Medication Error Prevention fice of Post Marketing Drug Risk Assessment, HFD-400 .m 15B-03, PKLN Building)	FROM: HFD-170/ Dr. Cynthia McCormick, Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 28, 2001		21,330	Request for Tradename Review	August 24, 2001

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nicotine Polacrilex Lozenge	Urgent	Nicotine Replacement	September 26, 2001

NAME OF FIRM: Glaxo SmithKline

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	■ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISION RICK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Request review of brand names proposed by sponsor. PDUFA due date for this application is October 20, 2001. Planned action on October 5, 2001.

Any questions, please do not hesitate to contact Judit Milstein, Regulatory Project Manger at 301-827-7440. Please, CC review to Aleta Crane (cranea) (7-7421).

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ■ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

E:\N21330 Nicotine Polacrilex Lozenge\consult OPDRA name.doc

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Judit Milstein
8/28/01 10:09:10 AM

APPEARS THIS WAY
ON ORIGINAL

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel:(301) 827-7410

Division Director's Review and Basis for Action

DATE: October 16, 2001

Cynthia G. McCormick, MD, Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

NDA: NDA #21-330 (N000)

DRUG: Nicotine Polacrilex Lozenge, 2-mg and 4-mg

SPONSOR: Glaxo-SmithKline

SUBJECT: Review of Application for Direct to OTC Marketing of Nicotine Polacrilex Lozenge
Approvable Action Memo

Nicotine polacrilex (NPA) lozenge is a form of nicotine replacement therapy (NRT) whereby nicotine is absorbed through the buccal mucosa, as in the nicotine polacrilex gum (Nicorette), developed and marketed by the same Sponsor and already approved for the over the counter (OTC) market. The Sponsor seeks approval for OTC marketing of a new product, Nicotine Lozenge 2-mg and 4-mg.

The development plan for this new product included a large (N=1818) multicenter placebo-controlled trial in a simulated OTC environment, which demonstrated the efficacy of each dose lozenge against placebo as a smoking cessation product. Subjects were assigned to one of two placebo-controlled arms before randomization, depending on their degree of nicotine dependence (assessed by time to first a.m. cigarette). Dr. Blatt's primary review discusses these results in depth. The review team has no questions about the efficacy findings in this study. The results demonstrate a clinically and statistically significant difference in each group between the 2- and 4-mg nicotine lozenges and their

matched placebo lozenges in the proportion of patients achieving abstinence at 6-weeks post-quit[1]. The efficacy was sustained through 3 and 6 months following cessation.

The safety data obtained in clinical trials of this product, coupled with the Agency's finding of safety with similar nicotine exposures to Nicorette, is adequate for the low dose 2-mg lozenge. Dr. Blatt conducted a review of the integrated summary of safety and has found the same spectrum (quantity and severity) of adverse events as seen with Nicorette. The adverse event profiles and exposures to the higher dose nicotine product are acceptable for approval as a prescription drug.

However, there was debate both before and during the NDA review as to whether there would be an adequate safety database for approval in the OTC market, specifically for the 4-mg lozenge. The 4-mg lozenge is capable of delivering more nicotine per dose than the approved 4-mg Nicorette (nicotine polacrilex gum) products. The differences in nicotine release from the lozenge compared with the gum are in the range of 30% more for the lozenge. The sponsor has attempted to resolve this dilemma in the pharmacokinetic arena and with a *post hoc* subgroup analysis of efficacy.

Five studies were conducted to characterize the PK profile of the nicotine lozenge. These consisted of three single dose PK trials comparing NPA lozenge with Nicorette gum 2- and 4-mg, a single dose PK trial comparing the 3-mg NPA lozenge with Nicorette 4 mg, demonstrating bioequivalence, a study comparing various regimens of the NPA lozenge and Nicorette gum, and, finally, studies to compare the PK profile with the lozenge when given as directed, as opposed to taken not as directed (misuse). Finally a PK simulation was performed which compared the PK profile of NPA lozenge given every 60 minutes with the same lozenge given every 90 minutes, the dosing paradigm on which efficacy was established.

In the PK simulation study, the question of whether the nicotine exposure from the NPA lozenge is significantly higher than the highest dose of NRT approved for OTC marketing (Nicorette 4 mg) to necessitate additional safety testing, was addressed. Unfortunately, this simulation has demonstrated that a new regimen, not the one studied and found effective, is capable of providing less exposure to nicotine from 4-mg lozenge than from the 4-mg gum. However, this argument fails to recognize that the Cmax for the 4-mg lozenge is still higher than that seen with Nicorette 4-mg gum, even though the AUC may be comparable with a different dosing regimen. This result merely provides a new hypothesis to test, whether the lozenge, given by a different regimen, attaining previously established "safe" exposure to nicotine but with higher peak levels, would still be safe and effective.

The sponsor has proposed a dosage regimen in the product labeling which, as noted, does not correspond to the dosage regimen studied but which is expected to result in lower exposure than the studied regimen. In support of this change, a *post hoc* analysis of efficacy was performed on all subjects who received 15 or fewer lozenges per day during the first 6 weeks of treatment, tapering from this level downward. The analysis of the

[1] Defined by self-report and verified by exhaled CO.

nonrandomized sample continued to demonstrate efficacy. This approach, with its potential bias, is not acceptable. Additionally as the review team discussed, since the mean daily dose of lozenge was below the maximum allowed, it is possible that patients may not dose to efficacy if instructions were to read "take no more than [redacted] per day."

The Sponsor's dilemma can only be resolved if additional clinical data is generated at the regimen studied in the efficacy trial to establish the safety of the 4-mg product for the broad OTC market. This could be achieved in a large open-label safety study.

There were a number of deficiencies the chemistry, manufacturing, and controls of this product which will need specific resolution before this application can be approved. These are detailed in the Chemistry review and relate to such things as identification, quantification, and qualification of impurities in drug substance, regulatory specifications for acceptance of the drug product, identification, quantification, and qualification of degradation products for those exceeding the ICH limits, implementation of tighter stability specifications, dissolution specifications, and satisfactory completion of all inspections. These will be addressed in the final action letter.

This product cannot be approved for marketing, either OTC or Rx until the chemistry deficiencies are addressed. An Rx approval could be issued at any time for the 2- mg and 4-mg lozenge. This division will defer to OTC on the final decision about the appropriateness of this product for OTC, given the relatively limited exposure of subjects to the 4-mg dose of this lozenge.

The nomenclature review of the proposed names "Commit lozenge [redacted]" "Commit Lozenge [redacted]" were not recommended because of the reference to an existing formulation and because of the potential confusion with the product "Promit", a volume expander. The likelihood of a serious problem resulting from such confusion is unlikely, just as the likelihood of confusing an OTC smoking cessation product with a parenteral volume expander is low. Consultants from OPDRA suggest instead the use of [redacted] This should be conveyed to the sponsor, however, a new consultation should be submitted at the time of the response to the Approvable Letter.

Action: Approvable action.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Cynthia McCormick
10/16/01 06:06:02 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)

Date: October 17, 2001

From: Charles J. Ganley, M.D. _____
Director, Division of Over-the-Counter Drug Products (HFD-560)

Subject: Division Director Memo for Nicotine Polacrilex Lozenge, NDA 21-330

NDA 21-330 proposes to market a nicotine polacrilex lozenge in dosage strengths of 2 mg and 4 mg to relieve the symptoms associated with quitting smoking. This product contains the same active ingredient found in Nicorette Gum. At the time of submission, nicotine polacrilex lozenge had no marketing history. Recently, it was approved in England and France but it is unclear that it has been marketed in these countries. There is a nicotine bitartrate 1 mg lozenge approved in at least 10 countries and a .35 mg lozenge approved in at least one country. The application does not provide an explanation for the higher dosage strength with the nicotine polacrilex lozenge relative to the nicotine bitartrate lozenge.

During the pre-NDA meeting on October 4, 2000, the agency reviewed a limited amount of summary data from the clinical trials. The 4 mg nicotine lozenge provides approximately 30% more nicotine compared to 4 mg Nicorette gum[1]. The single dose pharmacokinetic trials demonstrated an increase in Cmax and AUC with the lozenge relative to the gum. The sponsor demonstrated that a single 4 mg Nicorette gum is bioequivalent to a single 3 mg nicotine lozenge. Aside from the 450 subjects randomized to the 4 mg nicotine lozenge arm in their single efficacy study, the sponsor had no other significant repeat dose exposure. Because of the increased bioavailability of the same dosage strength of the lozenge relative to the gum and the lack of any marketing history with the lozenge, it was felt that the safety of the 4 mg nicotine lozenge should be able to stand on its own. Based on this limited review, the sponsor was informed that additional safety data was needed to support OTC marketing of the 4 mg lozenge if they planned to use the dosage regimen evaluated in their efficacy study.

The sponsor chose the 4 mg lozenge dosage strength for marketing purposes[2] when — lozenge was actually bioequivalent to the 4 mg Nicorette Gum. From a

---

[1] There is residual nicotine remaining in the gum whereas all of the nicotine is released from the lozenge.
[2] They apparently wanted the dosage strengths for the gum and lozenge to be the same.

marketing perspective, they could have just as easily selected a [redacted] lozenge. From a regulatory viewpoint, the greater bioavailability of the lozenge, using the bioequivalence standard, was the threshold that triggered a need for sufficient safety information for the 4 mg lozenge. Rather than obtain additional safety data, the sponsor submitted proposed labeling that provides for less frequent dosing of the lozenge in the hope that the safety of the 4 mg Nicorette Gum would now support the 4 mg lozenge. In doing this, they fail to provide any efficacy data to support the proposed dosing regimen.

The application is approvable pending resolution of the outstanding chemistry issues and issues related to the safety and efficacy of the drug. The efficacy study establishes effectiveness for the dosing regimen studied (one lozenge every 1 – 2 hours during weeks 0 - 6) and not for the proposed dosing regimen (one lozenge every 1 – 2 hours during weeks 0 - 6). If the sponsor insists on pursuing a regimen that was not studied, they will need to provide efficacy data to support the regimen. If the sponsor wishes to pursue the regimen evaluated in their clinical study, they will need to provide additional safety data in approximately 150 – 200 subjects for 12 weeks. This number, when combined with the number exposed in the efficacy study, will provide safety data in 300 to 400 subjects for 12 weeks. The sponsor will need to include a more ethnically diverse population in this safety study because they enrolled a predominately Caucasian population in all but one of their studies. They should also include subjects who have medical conditions that are relative contraindications for use of the product without the intervention of a physician (e.g. heart disease, hypertension, and diabetes).

Pharmacokinetics

The sponsor conducted five pharmacokinetic studies. The majority of subjects enrolled in these studies were Caucasian. Single dose studies (N98001, N96016) established that the 2 mg and 4 mg lozenge are not bioequivalent to the 2 mg and 4 mg nicotine gum marketed by the sponsor. C_{max} and AUC $_{0 \rightarrow \infty}$ were approximately 10% and 25% greater with the lozenge.[3] Study S1410090 suggests that the bioavailability of the lozenge decreases if the directions for use are not followed (chewed and swallowed as opposed to dissolving in the mouth). Study S1410092 compared a single dose 3 mg lozenge to 4 mg nicotine gum. The 3 mg nicotine lozenge was found to be bioequivalent to the 4 mg gum. In study S1410091, 2 mg or 4 mg nicotine lozenge administered every 90 minutes for 9 doses were compared to 2 mg or 4 mg nicotine gum administered every 60 minutes for 13 doses. The C_{max} and AUC $_{0 \rightarrow t}$ were approximately 20% and 25% lower respectively for the lozenge dosage regimen. In summary, the following observations can be made:

- The 4 mg nicotine gum is bioequivalent to a 3 mg nicotine lozenge.
- The 4 mg lozenge delivers approximately 25% more nicotine compared to the nicotine gum.
- The 4 mg nicotine lozenge is not bioequivalent to the 4 mg nicotine gum.
- Dosing the 4 mg nicotine lozenge every 90 minutes provides lower nicotine levels compared to the nicotine gum dosed every 60 minutes.

The biopharmacology reviewer recommended different dissolution specifications than those proposed by the sponsor.

[3] The formulations of the lozenge in these studies were slightly different from the to be marketed formulation. The chemistry review notes that these differences were not substantiated and should not impact on the bioavailability.

Clinical Efficacy and Safety

The sponsor conducted a single efficacy study to support the application. Study S1410043 was a randomized, double-blind, placebo controlled, multi-center, multi-national, parallel arm study in subjects with few underlying medical conditions. Subjects who fulfilled the entrance criteria were randomized to nicotine lozenge 2 mg, 2 mg placebo lozenge, 4 mg nicotine lozenge or 4 mg placebo lozenge. The subjects were stratified to the 2 or 4 mg lozenge based on whether they smoked within 30 minutes of waking in the morning. Those who smoked their first cigarette within the 30 minutes were randomized to the 4 mg or 4mg placebo lozenge. Those who smoked their first cigarette after 30 minutes were randomized to the 2 mg or 2mg placebo lozenge. This criteria for dose selection deviates from the previous criteria used (#cigarettes per day) for stratification with other products. Lozenges were self-titrated based on cravings according to the following schedule.

Week	Recommended Dosing Schedule
0 - 6	• 1 lozenge every 1 - 2 hours • no more than 5 lozenges in a 6 hour period • no more than 20 lozenges per day
6 - 10	• 1 lozenge every 2 - 4 hours
10 - 12	• 1 lozenge every 4 - 6 hours
12 - 24	• Use occasionally

Abstinence from smoking was confirmed by measuring carbon monoxide levels. The primary measure of efficacy was the 6 week abstinence rate.

The study randomized 1818 subjects fairly evenly among the four treatment arms [2 mg nicotine (N = 459), 2 mg placebo (N = 458), 4 mg nicotine (N = 451), 4 mg placebo]. The study enrolled approximately 55% female subjects and 94% Caucasians. At 12 weeks, 177 subjects were using the 4 mg lozenge. By week 6, 26% (59 of 225) of the subjects still using the 4 mg lozenge used greater than 10 lozenges per day.[4] It is noteworthy to point out that 16% of the subjects were lost to follow-up and 15% withdrew consent. There is inadequate exposure at through the 12 week time point. The study failed to enroll an ethnically diverse population.

After 6 weeks of treatment, the smoking cessation rates for the 4 mg and 2 mg nicotine lozenges were significantly better than the placebo controls. This effect continued through the 12-week visit. After 12 weeks, the use of the lozenge declined dramatically so that it is difficult to determine the impact on long-term abstinence rates. The design of the study was not adequate to assess the benefit of long-term treatment up to 24 weeks. Table 1 lists the 6-week and 12-week abstinence rates.

Table 1. Smoking Cessation Rates at 6, 12 and 24 weeks. (ITT Population)

	2 mg nicotine	2 mg placebo	4 mg nicotine	4 mg placebo
6 weeks	46.0% (211/459)	29.7% (136/458)	48.7% (219/450)	20.8% (94/451)
	< .0001		< .0001	
12 weeks	34.4% (158/459)	21.6% (99/458)	35.3% (159/450)	14.0% (63/451)
	< .0001		< .0001	
24 weeks	24.2% (111/459)	14.4% (66/458)	23.6% (106/450)	10.2% (46/451)

[4] Total patient exposure as a function of time is presented in Dr. Winchell's review.

The nicotine lozenge was associated with a higher incidence of gastrointestinal symptoms compared to placebo. Most notably, nausea, heartburn and hiccups appear to be associated with the use of the product.

The Sponsor submitted labeling for the 2 mg and 4 mg nicotine lozenge that includes directions for use not studied in the efficacy trial. They propose an initial regimen of 1 lozenge every [redacted] 2 hours, with no more than [redacted] per day. It is unclear how the data from their efficacy study can be extrapolated to support the proposed dosing regimen.

The data supports the use of the time of first morning cigarette as the criteria for dosage strength selection.

Consumer Marketing and Label Comprehension

The sponsor conducted a consumer marketing study (S1410065), two label comprehension studies (2117, 2204) and a home use study (1410154). The results of these studies do not help overcome the concerns raised previously regarding the efficacy and safety of these products. The results from the consumer marketing study suggest that nicotine gum may be the preferable dosage form compared to the lozenge for many of the different ethnic groups studied[5]. In the labeling comprehension studies, approximately 80% of respondents correctly self-selected the appropriate dosage strength. There was also a high understanding of how often the product could be used although there is room for improvement in the low literacy group[6]. From the Home Use study, it is difficult to conclude much of anything because approximately 30% of the subjects were lost to follow-up.

Chemistry

The chemistry review outlines numerous deficiencies involving the qualification of impurities, identification and qualification of degradation products, stability specifications and drug master files. There are also two of five inspections pending. The deficiencies noted in the chemist's review warrant an approvable action.

Labeling

Aside from the directions for use, most of the comments on labeling are not major and should be easily resolvable. The sponsor will need to incorporate the latest pregnancy warning labeling.

[5] U.S. born subjects were the only group who preferred the lozenge over the gum.
[6] See Table B-6 in Dr. Linda Hu's review: 70% of the low literacy subjects knew the correct frequency.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Charles Ganley
10/18/01 05:28:40 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 8

❖❖❖

Confidential,
Commercial Information

(T)

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: August 18, 2001	**DUE DATE:** September 21, 2001	**OPDRA CONSULT #:** 01-0186

TO: Cynthia McCormick, M.D.
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

THROUGH: Judith Milstein, Project Manager
HFD-170

PRODUCT NAME: Commit Lozenge [redacted] (Nicotine Polacrilex Lozenge) 2 mg and 4 mg **NDA #:** 21330	**MANUFACTURER:** GlaxoSmithKline Pharmaceuticals **SPONSOR:** GlaxoSmithKline Healthcare

SAFETY EVALUATOR: David Diwa, Pharm.D.

SUMMARY: In response to a consult from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), OPDRA conducted a review of the proposed proprietary names Commit Lozenge [redacted] Commit Lozenge [redacted] to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not recommend use of the name Commit Lozenge [redacted] or Commit Lozenge [redacted] We believe that the firm should revise the name to read [redacted] in order to minimize the risk of confusion.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-032

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 12, 2001

NDA NUMBER: 21-330

NAME OF DRUG: Commit Lozenge [redacted] or
Commit Lozenge [redacted]
(Nicotine Polacrilex Lozenge) 2 mg and 4 mg

NDA HOLDER: GlaxoSmithkline Consumer Healthcare
Parsippany, NJ 07054-3884

I INTRODUCTION

This consult is written in response to an expedited request from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) for assessment of the tradenames Commit Lozenge [redacted] and Commit Lozenge [redacted] (Nicotine Polacrilex Lozenge).

The sponsor, GlaxoSmithKline Consumer Healthcare proposes to market Nicotine Polacrilex Lozenges over-the-counter (OTC) for the management of withdrawal symptoms associated with quitting smoking.

PRODUCT INFORMATION

Commit Lozenge [redacted] Commit Lozenge [redacted] is a compressed [redacted] form containing Nicotine within an [redacted] (Nicotine Polacrilex USP) that is formulated into a slow dissolving oral lozenge. The product systemically delivers nicotine primarily through the buccal mucosa. The Nicotine Polacrilex Lozenge will be marketed in 2 mg and 4 mg oral lozenges for OTC nicotine replacement therapy.

APPEARS THIS WAY
ON ORIGINAL

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3,4] as well as several FDA databases[5] and Thomson & Thomson's SAEGIS™ database[6] for existing drug names which sound alike or look alike to Commit Lozenge [redacted] Commit Lozenge [redacted] to a degree where potential confusion between drug names could occur. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[7]. There was one identified product (Promit), which posed concern for look-alike/sound-alike confusion with the proposed names.

A. EXPERT PANEL OPINION

OPDRA gathered professional opinions from safety evaluators regarding the proprietary name Commit Lozenge [redacted] and Commit Lozenge [redacted] The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The panel was concerned with the use of the terms [redacted]. They were most concerned with the reference to an already existing formulation. The panel questioned if this was a different formulation for an already marketed product. In addition, they were concerned about the look-alike/sound-alike qualities between "Commit" and Promit. DDMAC expressed no concerns regarding the promotional aspect of the names.

B. SAFETY EVALUATOR RISK ASSESSMENT.

The expert panel believed that the look-alike and sound-alike qualities between Promit and "Commit" posed the risk of confusion. Promit (Dextran-1) is collodial plasma volume expander that is used as an adjunct to Dextran. The usual adult dose is 20 mL 1-2 minutes before the intravenous infusion of dextran. The product is available as a 20 mL intravenous volume expander in 150 mg/mL strength. While Promit is an injectable dosage, the

---

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] Drug Information Handbook 1999-2000, Lacy CF, Armstrong LL, Goldman MP, Lance LL (eds) Lexi-Comp Inc, Hudson

[5] The Established Evaluation System [EES], the Labeling and Nomenclature [LNC] database of proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[6] Data provided by T&T's SAEGIS ™ online service available at www.thomson-thomson.com

[7] WWW location http://www.uspto.gov/tmdb/index.html. The US Patent & Trademark Office Trade Mark Electronic Search System (TESS)

proposed product an oral lozenge. The products have different indications and are no likely to be stored in close proximity. Moreover, Promit is mostly used in institutional care settings and is available by prescription only, while Commit Lozenge [redacted] Commit Lozenge [redacted] will be available OTC. The likelihood of a mix-up between these two products is therefore minimal.

The names Commit Lozenge [redacted] Commit Lozenge [redacted] may cause confusion because they make reference to nicotine chewing gum and a dermal patch as if they are the source of the lozenge. The active ingredient for the lozenge is Nicotine Polacrilex not Nicorette or Nicoderm CQ. A search of the Orange Book identified three approved applications for marketed Nicotine Polacrilex containing products (see below). These products are all buccal nicotine delivery chewing gums. Two of the applications bear the proprietary names Nicorette and Nicorette (mints).

The Orange Book also lists an approved application for 3 strengths for Nicoderm CQ extended release transdermal patch. While the active ingredient in Nicoderm CQ is nicotine, it is not formulated [redacted] (Nicotine Polacrilex USP) as in Nicorette and the proposed product. Furthermore, the term "transdermal" refers to a different delivery mechanism and could cause confusion if used in conjunction with an oral lozenge.

OTC Nicotine buccal delivery chewing gums

Appl #	Drug Name	Active Ingredient	Strength	Applicant
018612	Nicorette	Nicotine Polacrilex	EQ 2 mg base	SmithKline
018612	Nicorette (Mint)	Nicotine Polacrilex	EQ 2 mg base	SmithKline
020066	Nicorette	Nicotine Polacrilex	EQ 4 mg base	SmithKline
020066	Nicorette (Mint)	Nicotine Polacrilex	EQ 4 mg base	SmithKline
074507	Nicotine Polacrilex	Nicotine Polacrilex	EQ 2 mg base	Watson Lab
074707	Nicotine Polacrilex	Nicotine Polacrilex	EQ 4 mg base	Watson Lab

OTC Transdermal Nicotine Replacement Products

Appl #	Drug Name	Active Ingredient	Strength	Applicant
020165	Nicoderm CQ	Nicotine	14 mg/24 hrs	Aventis
020165	Nicoderm CQ	Nicotine	21 mg/24 hrs	Aventis
020165	Nicoderm CQ	Nicotine	7 mg/24 hrs	Aventis

OTC nicotine replacement products sold under the proprietary name Nicorette are chewing gums. The proposed product is being introduced as a therapeutic alternative for those who desire to quit smoking and are interested in a different dosage form. The new slow dissolving oral lozenge should be sucked rather than chewed. Therefore we are concerned that the term [redacted] " may lead to improper use and delivery of the product.

Currently, the agency is opposed to having two different proprietary names for the same active ingredient. In this particular case, OPDRA believes that the product should be named [redacted].

APPEARS THIS WAY
ON ORIGINAL

III. RECOMMENDATIONS

We do not recommend use of the name " Commit Lozenge [redacted] " or "Commit Lozenge [redacted] ". We believe that the firm should revise the name to read " [redacted] ".

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph. at 301-827-3231.

David Diwa, Pharm.D.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Diwa
9/21/01 11:01:51 AM
PHARMACIST

Jerry Phillips
9/21/01 11:19:27 AM
DIRECTOR

Martin Himmel
9/21/01 01:59:43 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

FROM EDR submission dated February 26, 2002

Response to FDA Advice Letter of 15-Feb-2002:

Item 5 – Post-Marketing Study Commitment

APPEARS THIS WAY
ON ORIGINAL

GlaxoSmithKline commits to conducting the following two post-marketing studies (Phase IV Commitments) to further assess and confirm the safety of the nicotine polacrilex 2 mg and 4 mg lozenge.

(a) GSK will conduct a study in subjects with relative contraindications for use (underlying diseases such as diabetes mellitus or cardiovascular disease) who may be directed by their physician to use a nicotine product. Study number will be determined in order to provide 200 – 300 subjects on active product. Study will be fielded within [redacted] days of approval based on design that will be shared with FDA Division(s) for feedback prior to initiation. GSK estimates [redacted], for completion of this study.

[redacted]

APPEARS THIS WAY
ON ORIGINAL

19.A Financial Certification

In accordance with 21 CFR 54.4(a)(1), a completed Form FDA 3454, certifying to the absence of financial interests and arrangements as defined in 21 CFR 54.2, is included on the following pages for all applicable investigators who participated in a covered study.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Please Refer to List of Investigators on the following pages	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME David Schifkovitz	TITLE Director, Regulatory Affairs
FIRM/ORGANIZATION SmithKline Beecham Consumer Healthcare	
SIGNATURE David Schifkovitz	DATE 12/8/00

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99) Created by Electronic Document Services/USDHHS: (301)443.2454 EF

APPEARS THIS WAY
ON ORIGINAL

Study Number N96016

Study Number S1410091

[ ]

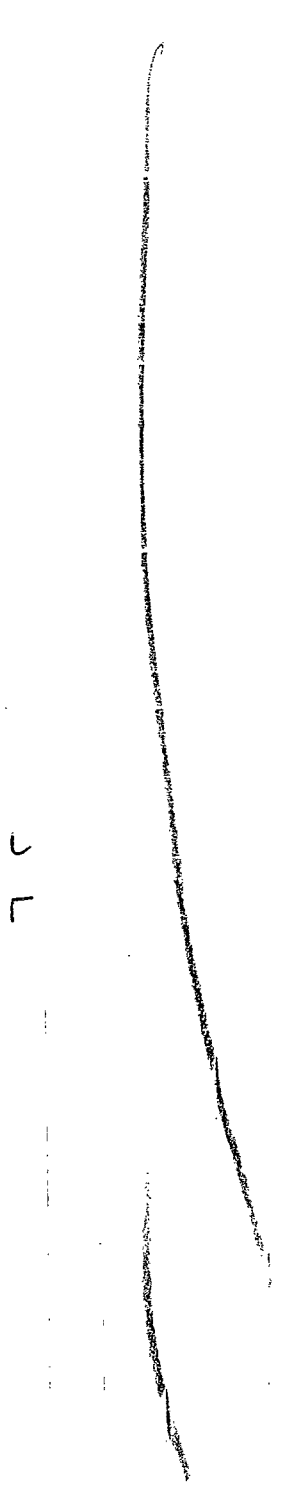
Study Number S1410092

[ ]

Study Number N98001

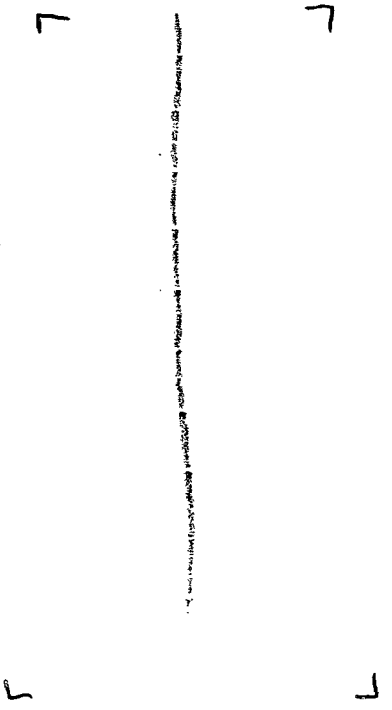
[ ]

APPEARS THIS WAY
ON ORIGINAL



APPEARS THIS WAY
ON ORIGINAL

Study Number S1410043 (continued)



Study Number S1410065

APPEARS THIS WAY
ON ORIGINAL

Study Number S1410089

Study Number S1410090

——— has an on-going consultation agreement with SmithKline Beecham. However, he was not directly involved in the treatment or evaluation of research subjects in the clinical study. His involvement was limited to protocol design.

19.A Financial Certification

In accordance with 21 CFR 54.4(a)(1), a completed Form FDA 3454, certifying to the absence of financial interests and arrangements as defined in 21 CFR 54.2, is included on the following pages for all applicable investigators who participated in a covered study.

Item 19.
Financial Information

21 CFR § 54.4(a)(1) and (3)
21 CFR 314.50(k)

19.B Financial Disclosure

In accordance with 21 CFR 54.4(a)(3), all clinical investigators that were involved in the conduct of a covered study as part of this new drug application were evaluated to determine whether completion of Form FDA 3455, disclosing any financial interests and arrangements as defined in 21 CFR 54.2, was required. SmithKline Beecham has determined that this section is not applicable as no investigator has satisfied the requirements of this section.

Item 19.
Financial Information

21 CFR § 54.4(a)(1) and (3)
21 CFR 314.50(k)

Introduction

In accordance with the final rule that was published in the federal register dated 2/2/98, and effective on 2/2/99, this section provides information (if applicable) concerning the compensation to, and financial interests of, clinical investigators directly involved in the treatment and evaluation of subjects enrolled in clinical studies that are used to establish the safety and efficacy of a product. The requirements of this section applies to the following "covered clinical studies" (as defined in 21 CFR 54.2(e)) that are included in both the Clinical section (Item 8) and Human Pharmacokinetics & Bioavailability section (Item 6) of this NDA submission:

ITEM 6 HUMAN PHARMACOKINETICS & BIOAVAILABILITY

Pilot Studies

Study Number N98001	A pilot, single-dose pharmacokinetic study of nicotine following oral of a 2mg nicotine lozenge and 2mg Nicortte® gum in healthy adult volunteers
Study Number N96016	A pilot, single-dose pharmacokinetic study of nicotine following oral administration of a 4mg nicotine lozenge and 4mg Nicorette® gum in healthy adult volunteers

Bioequivalence Studies

Study Number S1410092	A single center, open-label, single-dose, randomized, two-way crossover study to determine the bioequivalence of a 3mg nicotine lozenge and 4mg Nicorette® gum

APPEARS THIS WAY
ON ORIGINAL

Pharmacokinetic/Bioavailability Studies

Study Number S1410091	An open-label, multiple-dose, randomized, four-way crossover study to determine the steady state pharmacokinetics of 2mg and 4mg nicotine lozenge and 2mg and 4mg Nicorette® gum
Study Number S1410090	A single-dose pharmacokinetic study of a 4mg nicotine lozenge to determine the effects of potential misuse

ITEM 8 CLINICAL SECTION

Placebo Controlled Studies

Study Number S1410043	A multi-center, randomized, double-blind, placebo controlled, parallel group study to measure the efficacy and safety of nicotine polacrilex lozenges (2mg and 4mg) in smoking cessation

Product Sensory

Study Number S1410065	A randomized, open-label, two-way crossover study to measure subject expectations and acceptance of nicotine polacrilex lozenge compared to Nicorette® (nicotine polacrilex) gum in heavy smokers

Abuse Liability

Study Number S1410089	Nicotine polacrilex lozenge abuse liability study Adolescent Appeal

Please note that the Label Comprehension Study (Study Number 2117) included in the Clinical Section (Item 8) of this NDA submission was designed to assess the user's ability to understand and follow the labeling of the nicotine polacrilex lozenge product. This study is not critical to the establishment of the safety and efficacy of the product under study. Therefore, the sponsor has determined that this study is not subject to the requirements of financial certification and

disclosure as it does not constitute a "covered clinical study" per 21 CFR 54.2(e) for the reason stated above.

Section 8.A.1.b of this NDA contains a list of investigators by protocol, who participated in the conduct of each "Covered Clinical Study." This table is also being provided on the following pages for reference purposes.

APPEARS THIS WAY
ON ORIGINAL

(K)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

17 pages

(K)

APPENDIX D

Batch Analysis Data for Residual [redacted]

Residual [redacted] in commercial batches of [redacted] has been monitored by [redacted] Individual levels of residual [redacted] were consistently [redacted] Details of the results obtained including appropriate batch information will be provided in a separate note or in the next DMF annual update.

APPEARS THIS WAY
ON ORIGINAL

[ ]

Telefax

To: Victoria Kao, Regulatory Project Mgr [ ]

Company: FDA

Telefax no.: 301-443-7068 [ ]

From: [redacted]

Copy to:

Date: October 23, 2002

Number of pages
incl. this cover page: 7

Subject: [redacted] Response of 15 October 2002

Dear Ms. Kao,

Attached is our response to your question regarding the [redacted] response.

APPEARS THIS WAY
ON ORIGINAL

[ ]

[ ]

[ ]

October 23, 2002

Victoria Kao
Regulatory Project Manager
U.S. Food and Drug Administration
Division of Anesthetic, Critical Care and
Addiction Drug Products
5600 Fishers Lane
Room 9B-45, HFD-170
Rockville, MD 20857

Dear Ms. Kao:

[redacted] has periodically monitored pesticide levels in its Nicotine USP manufacturing process over the past 10 years in both the [redacted] as well as the finished API, Nicotine USP. No pesticides have been detected at the limit of detection in any of these samples.

Recently [redacted] obtained confirmation from its tobacco grower that no pesticides are used in cultivating the special grade of tobacco crop. (Exhibit 5 of 15 Oct 2002 Response). To periodically confirm this commitment, [redacted] monitors 25% of the annual shipments of tobacco dust for over 40 organophosphate pesticides and over 34 chlorinated pesticides. An example of this monitoring is attached. (Exhibit 6 of 15 Oct 2002 Response).

If you need any additional information or clarification, please feel free to give me a call.

Sincerely

[redacted]

APPEARS THIS WAY
ON ORIGINAL

Chief Compliance Officer

Attachments

[redacted]

IMTS # 8985

MEETING MINUTES

NDA #:	21-330
Sponsor:	GlaxoSmithKline (GSK)
Drug Product:	Nicotine lozenge 2 mg and 4 mg

Meeting Package Submission:	May 10, 2002
Meeting Date:	May 23, 2002

Background

FDA sent an advice letter to GlaxoSmithKline dated February 15, 2002. The letter identified what the sponsor needs to provide to respond to safety issues raised in the approvable letter dated October 19, 2001. One of the requirements is for the sponsor to commit to conducting two post-marketing studies (Phase 4 commitments). The first Phase 4 study is to be conducted on subjects with contraindications for use.

GlaxoSmithKline requested this teleconference to discuss their submission dated May 10, 2002, for the second Phase 4 study. The sponsor submitted two proposals for the adverse event trial: a telephone questionnaire trial; The sponsor prefers the telephone method for gathering data.

Meeting Attendees

FDA Division of OTC Drug Products

Charles Ganley, M.D.	Division Director
Linda Katz, M.D., M.P.H.	Deputy Director
Linda Hu, M.D.	Medical Officer
Helen Cothran	Team Leader
Mary Robinson, M.S.	IDS reviewer
Elaine Abraham	Project Manager

Division of Biometrics III

Laura (Hong) Lu, Ph.D.	Statistician

(P)

THIS SECTION WAS DETERMINED NOT TO BE RELEASABLE

3 pages

(P)

[ ]

Telefax

To: Victoria Kao, Regulatory Project Mgr [ ]

Company: FDA

Telefax no.: 301-443-7068 [ ]

From: [redacted]

Copy to:

Date: October 28, 2002

Number of pages
incl. this cover page: 2

Subject: [redacted]

APPEARS THIS WAY
ON ORIGINAL

October 28, 2002

Victoria Kao
Regulatory Project Manager
U.S. Food and Drug Administration
Division of Anesthetic and Critical Care and
Addiction Drug Products
5600 Fishers Lane, Room 09B-45
Rockville, MD 20857

Re: [redacted]

Dear Ms. Kao:

As stated in [redacted] October 23, 2002 letter, the Nicotine USP production process has been monitored for pesticides periodically over the past 10 years. All results have been negative. This monitoring is in addition to the tobacco grower's confirmation that pesticides are not used in cultivating the special grade of tobacco required in the [redacted] This commitment has been previously sent to the Agency, as have exemplary pesticide monitoring results.

During a telephone conference October 25, 2002 with reviewers Drs. Theadorakis and Koble, and again on October 28, 2002 with Project Manager Victoria Kao, routine monitoring for pesticides in the final API was suggested. Accordingly, [redacted] will monitor pure nicotine for pesticides quarterly. In addition, 25% of the annual shipments of tobacco dust will be monitored for pesticides.

Pesticide analysis is performed by contract laboratories. Methods and specifications for pesticides will be forwarded to your office in approximately 14 days once they have completed the approval process.

[redacted] is the authorized agent for [redacted]

Sincerely,

[redacted]

APPEARS THIS WAY
ON ORIGINAL

[redacted]

Director, Regulatory Affairs

[ ]

Telefax

To: Victoria Kao, Regulatory Project Mgr [ ]

Company: FDA

Telefax no.: 301-443-7068

From: [redacted] [ ] [ ]

Copy to:

Date: October 25, 2002

Number of pages
incl. this cover page: 2

Subject: [redacted]

APPEARS THIS WAY
ON ORIGINAL

October 25, 2002

Victoria Kao
Regulatory Project Manager
U.S. Food and Drug Administration
Division of Anesthetic and Critical Care and
Addiction Drug Products
5600 Fishers Lane, Room 09B-45
Rockville, MD 20857

Re: [redacted]

Dear Ms. Kao:

As stated in [redacted] October 23, 2002 letter, the Nicotine USP production process has been monitored for pesticides periodically over the past 10 years. All results have been negative. This monitoring is in addition to the tobacco grower's confirmation that pesticides are not used in cultivating the special grade of tobacco required in the [redacted] This commitment has been previously sent to the Agency, as have exemplary pesticide monitoring results.

During a telephone conference yesterday with reviewers Drs. Theadorakis and Koble, routine monitoring for pesticides in the final API was suggested. Accordingly, [redacted] will monitor pure nicotine for pesticides quarterly for one year, then adjust this frequency based on results obtained. Similarly, [redacted] will continue for one year after which the value of this program will be re-evaluated and adjusted accordingly.

Pesticide analysis is performed by contract laboratories. Methods and specifications for pesticides will be forwarded to your office in approximately 14 days once they have completed the approval process.

[redacted] is the authorized agent for [redacted]

Sincerely,

[redacted]

[redacted], Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL