RECORD OF TELEPHONE CONVERSATION

Date:	**7/8/02**
Project Manager:	**Elaine Abraham**
Subject:	**Labeling questions**
NDA:	**N 21-330**
Product Name:	**Nicotine lozenge**
Sponsor:	**David Schifkovitz, GlaxoSmithKline**
Phone No:	**(973) 889-2509**

Background:

The Division of Over-the-Counter Drug Products provided GlaxoSmithKline with labeling comments on the nicotine lozenge via fax on July 1 and 3, 2002. Mr. Schifkovitz called with a few additional questions.

Discussion:

After discussing with the team leader, I called the sponsor with the following response:

1) Keep the following phrase in the back panel directions: "Do not chew or swallow lozenge."

2) The parenthetical phrase "about 20-30 minutes" referring to how long the lozenge should be allowed to dissolve, appears in bulleted statements 7 and 9. The sponsor can delete this from bullet 9.

HFD-560/Abraham
C:\word\N21-330 nicotine loz labeling tcon.doc

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/s/

Elaine Abraham
10/17/02 09:49:56 AM
CSO

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Q

Number of Pages Redacted 7 pages

❖❖❖

Confidential,
Commercial Information

Q

Teleconference 8-24-02

Re: N21-330 nicotine lozenge · [redacted]

Attendees:

GSK

David Schifkovitz &
Other manufacturing personnel

FDA

Dale Koble, Ph.D.
Mike Theodorakis, Ph.D.
Victoria Kao, B.S.

To address the applicant's [redacted] The Sponsor agreed to [redacted]

The Sponsor will provide [redacted] The submission will be faxed ASAP and be followed by hard copy.

Memo prepared by Victoria Kao 8-24-02

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/s/

Victoria Kao
10/24/02 04:25:57 PM
CSO

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Approval based on this labeling submission

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

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

August 30, 2002

NDA 21-330

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

Re: Revised Labeling Reflecting Agreements from July 1-3, 2002 FAX Communications
NDA 21-330 (nicotine polacrilex lozenge 2mg & 4 mg)

Dear Dr. McCormick,

Please refer to the above referenced NDA for nicotine polacrilex lozenges (2 mg & 4 mg) currently under final review by your Division. Enclosed please find electronic and paper copies of labeling for the above referenced products. The revisions incorporate the changes agreed to by FDA and GlaxoSmithKline FAX communications that occurred between July 1 –3, 2002. Copies of the FAXES covering the agreements on label changes were also submitted as general correspondence on July 8, 2002.

In addition to the artwork for carton, blister and User's Guide, a summary of changes to labels submitted under the March 12, 2002 amendment is also provided. This summary covers all points discussed in the July 1-3 FAXES.

Please note that planned carton sizes include a 72 count and a 168 count. The content and layout for both sizes are identical with the exception of net contents declaration. The 72 count will be used for general distribution and is the size that includes the Phase IV telephone questionnaire enrollment form. The 168 count package size will be limited in distribution to the "club store" class of trade.

Please contact my office at 973-889-2509 with any questions.

Sincerely,

David Schifkovitz
Director, Regulatory Affairs

cc: Victoria Kao (Desk Copy -2)
Regulatory Project Manager
Division of Anesthetic Critical Care and Addiction Drug Products

Elaine Abraham (Desk Copy -1)
Regulatory Project Manager
Division of Over-The-Counter Drug Products

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Number of Pages Redacted 29

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Draft Labeling
(not releasable,

(L)

(M)

Number of Pages Redacted 57

❖❖❖

Confidential,
Commercial Information

(M)

Teleconference of Memo 10/10/02

Re: N21-330 Nicotine Lozenge

Attendees:

[redacted]

[redacted] Ph.D.
Etc.

FDA

Dale Koble, Ph.D.
Mike Theodorakis, Ph.D.
Victoria Kao, B.S.

This was a teleconference to discuss Sponsor's pending response to Agency's issued October 19, 2001, and September 25, 2002, deficiency letters for DMF [redacted]

The deficiencies listed in October 19, 200, letter were discussed point by point.

The main discussion points were as follows:

1. [redacted]

2. [redacted]

3. [redacted]

Memo prepared by Victoria Kao 10/21/02

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/s/

Victoria Kao
10/21/02 02:00:18 PM
CSO

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GlaxoSmithKline

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

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

October 15, 2002

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

Re: NDA 21-330
Amendment #15
Response to October 9, 2002 Questions From Dr. M. Theodorakis

Dear McCormick,

Please refer to the March 11, 2002 Amendment #11 for the above referenced New Drug Application for nicotine polacrilex 2 mg and 4 mg lozenge. Refer also to five questions that were provided to GSK on October 9, 2002 (enclosed) in a meeting between GSK representatives and FDA. Enclosed please find our responses to the five questions.

This amendment is provided in electronic format. The enclosed CD-ROM has been confirmed to be virus-free using Norton AntiVirus Corporate Edition, version 7.61.930, scan engine 4.1.0.15, updated 10/9/2002.

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. If you have questions about the operation of electronic version, please contact Gregory Smith, Director of Regulatory Operations at (973) 889-2540.

Sincerely,

David Schifkovitz
Director of Regulatory Affairs – Smoking Control
GlaxoSmithKline Consumer Healthcare

cc: Victoria Kao, Division of Anesthetic, Critical Care and Addiction Drug Products (2 Desk Copies)

Laura Shay, Division of Over The Counter Drug Products (1 Desk Copy)

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	October 15, 2002
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	Commit Lozenge

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

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 #15 – GSK Response to Oct 9 2002 Questions from Dr. M. Theodorakis

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
X	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)
	20. OTHER *(Specify)*

CERTIFICATION

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

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 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**	**October 15, 2002**

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

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FORM FDA 356h (4/00)

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

REQUEST FOR CONSULTATION

TO (Division/Office): Jerry Phillips
Associate Director, Medication Error Prevention
Office of Drug Safety, HFD-400
(Rm. 15B-03, PKLN Bldg.)

FROM:
Charles Ganley

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/22/02		21-330		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nicotine Polacrilex Lozenge	Urgent	Nicotine Replacement	October 23, 2002

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

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

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Re-address the Trade name Commit, the first review was requested August 21, 2001

Information Faxed on 10/21/02

PDUFA DATE: November 1, 2002
ATTACHMENTS: Label in EDR under NDA 21-330, August 30 2002 submission
CC:
Archival IND/NDA 21-330
HFD-560RPM

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

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/s/

Charles Ganley
10/22/02 01:34:20 PM

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

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Memo of Teleconference 10-24-02

Re: DMF [redacted] for review of N21-330 nicotine lozenge

Attendees:

[redacted]

FDA

Dale Koble, Ph.D.
Mike Theodorakis, Ph.D.
Victoria Kao, B.S.

The discussion centered on Agency's fax dated October 22, 2002 and [redacted] faxed response dated October 23, 2002.

Agency's comments on October 22, 2002 were as follows:

Provide a specification (a test, test method, and acceptance criterion) for [redacted] and a regular testing schedule for this test. This test should be performed on the drug substance, [redacted]

To the DMF holder's October 23, 2002 faxed response, Agency made the following comments during this telecon:

In addition to the commitment to monitor [redacted]

[redacted] will fax their response to this request later today.

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/s/

Victoria Kao
10/24/02 02:57:35 PM
CSO

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Food and Drug Administration
Center for Drug Evaluation and Research
Division of OTC Drug Products
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: October 24, 2002

To: Dave Schifkovitz	**From:** Laura Shay, MS, RN, C-ANP Regulatory Project Manager
Company: GlaxoSmithKline	Division of Over-the-Counter Drug Products
Fax number: 973-889-2390	**Fax number:** (301) 827-2315
Phone number: 973-889-2509	**Phone number:** (301) 827-2274

Subject: Labeling Comments NDA 21-330 (nicotine polacrilex lozenges)

Total no. of pages including cover: 2

Document to be mailed: ☐ YES ☑ NO

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We have attached reviewer's comments related to the labeling submitted August 30, 2002.

The labeling revisions submitted for the 2 mg and 4 mg Commit™ nicotine polacrilex lozenge for the 72 and 168 count cartons, User's Guide and blister pack included in this submission are in accordance with the agency's requested revisions discussed in the March 12, 2002, July 1-3, 2002, and July 8, 2002, correspondences, except for the following:

1. Carton back, under ***Directions***, bullet 11, place a period at the end of the second sentence.

2. User's Guide, Page 9, under the heading CUTTING BACK ON YOUR Commit™ LOZENGE USAGE, paragraph 1, bold the sentence that reads **"Stop Using Commit™ Lozenge at the end of week 12."**

3. Provide the graphic specifications used for the Drug Facts labeling (e.g.,type and font sizes, bullet sizes, hairline sizes, barline sizes, etc.) in accordance with 21 CFR 201.66(d).

In order to ensure a timely action for this new drug application, we request that you respond to the issues listed below as soon as possible. You can fax your labeling changes to Laura Shay at (301) 827-2315.

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/s/

Laura Shay
10/24/02 05:27:07 PM
UNKNOWN

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ON ORIGINAL

Teleconference Memo 10/25/02

Re: DMF [redacted] for review of N21-330 nicotine lozenge

Attendees:

[redacted]

[redacted]

FDA

Dale Koble, Ph.D.
Mike Theodorakis, Ph.D.
Victoria Kao, B.S.

This was a teleconference to further clarify the [redacted]

The Agency clarified that DMF holder should not have at will discretion to change the frequency of the monitoring for either the [redacted] All proposals to modify the monitoring plans would first need to be reviewed by the Agency.

[redacted] said that he will forward the comments for discussion internally and fax (with a hard copy follow up to Division and DMF file) the Agency a response on Monday 10/27/02.

Memo prepared by Victoria Kao 10-25-02

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/s/

Victoria Kao
10/25/02 06:18:42 PM
CSO

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

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

October 25, 2002

NDA 21-330

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

Re: NDA 21-330 (nicotine polacrilex lozenge 2mg & 4 mg)
Commitment for Label Revisions

Dear Dr. McCormick,

Please refer to our August 30, 2002 submission of revised labeling with changes made as per FAX comments of July 1 –3, 2002. Refer also to the label comments from FDA received via FAX on October 24, 2002, a copy of which is enclosed.

GlaxoSmithKline Consumer Healthcare commits to implementing the changes requested in items # 1 and 2 of the October 24, 2002 FAX at the next printing of these components.

The specifications used for carton Drug Facts labeling are enclosed in accordance with 21 CFR 201.66(d).

APPEARS THIS WAY
ON ORIGINAL

Please contact my office at 973-889-2509 with any questions.

Sincerely,

David Schifkovitz
Director, Regulatory Affairs

cc: Victoria Kao (Desk Copy -1)
Regulatory Project Manager
Division of Anesthetic Critical Care and Addiction Drug Products

Laura Shay (Desk Copy -2)
Regulatory Project Manager
Division of Over-The-Counter Drug Products

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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	**October 25, 2002**
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	**Commit Lozenge**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*

CODE NAME *(If any)*

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
Labeling Commitment and Specifications

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 ——

FORM FDA 356h (4/00)

APPEARS THIS WAY
ON ORIGINAL

This application contains the following items: *(Check all that apply)*	
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	3. Summary (21 CFR 314.50 (c))
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	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)
	20. OTHER *(Specify)*

CERTIFICATION

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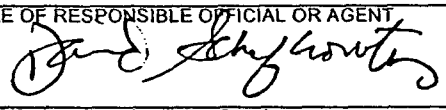
1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations 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** **Director, Regulatory Affairs**	**October 25, 2002**

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

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The text and graphic specifications used in the Drug Facts portion of both the 72 count and 168 count Commit 2 mg and 4 mg Lozenge are as follows:

Title	DRUG FACTS	9.25 pt Helvetica, Bold, Italics
Headings	Use,Warnings	8.5 pt Helvetica, Bold, Italics
Subheadings	Do not use	6.5 pt Helvetica, Bold
Text	If you are...	6.5 pt Helvetica, 7 pt leading
Bullets		5.25 pt Helvetica
Box Barline		1.5 pt
Barlines		1.5 pt
Hairline		.43 pt

Received Oct 25, 2002

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

Tel. 973 889 2100
Fax. 973 889 2399
www.gsk.com

October 25, 2002

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

Re: NDA 21-330
Amendment #16
Revisions per October 24, 2002 Telecon with Dr. M. Theodorakis

Dear McCormick,

Please refer to the March 11, 2002 Amendment #11 for the above referenced New Drug Application for nicotine polacrilex 2 mg and 4 mg lozenge. Refer also to five questions that were provided to GSK on October 9, 2002 in a meeting between GSK representatives and FDA and our October 13, 2002 response to these questions as Amendment #15. A teleconference between Drs. Theodorakis and Koble and representatives of GSK took place on October 25, 2002 to discuss the Agency request for [redacted] It was agreed in the teleconference that the [redacted] These revisions are reflected in the enclosed specifications and sampling plan.

This amendment is provided in electronic format. The enclosed CD-ROM has been confirmed to be virus-free using Norton AntiVirus Corporate Edition, version 7.61.930, scan engine 4.1.0.15, updated 10/9/2002.

APPEARS THIS WAY
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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. If you have questions about the operation of electronic version, please contact Gregory Smith, Director of Regulatory Operations at (973) 889-2540.

Sincerely,

David Schifkovitz
Director of Regulatory Affairs – Smoking Control
GlaxoSmithKline Consumer Healthcare

cc: Victoria Kao, Division of Anesthetic, Critical Care and Addiction Drug Products (2 Desk Copies)

Laura Shay, Division of Over The Counter Drug Products (1 Desk Copy)

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	**October 25, 2002**
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	**Commit Lozenge**

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

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 #16 – Revised Specifications and Sampling Plan

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

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See attached

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IND 56,295, DMF — DMF —

FORM FDA 356h (4/00) EF

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
David Schifkovitz	**David Schifkovitz** **Director, Regulatory Affairs**	**October 25, 2002**

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

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Rockville, MD 20852-1448

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4.A.2.k Specifications and Analytical Methods for the Drug Product

Sampling Plan and Testing

[redacted]

Sample Number	Lozenge Count	Weight of Produced Lozenges
1	[redacted]	[redacted]
2		
3		
4		
5		
6		

Note: Theoretical batch size = [redacted] lozenges and [redacted]

Individually assay 5 lozenges from each Sample Number resulting in 30 individual lozenge content uniformity results. Results must pass USP Content Uniformity.

Specifications – Release

The regulatory specifications that have been established for both the 2 mg and 4 mg nicotine polacrilex lozenges, which must be met prior to the release of the finished drug products by the sponsors Aiken manufacturing facility are shown in Table 4.A.2.k-1.

(R)

Number of Pages Redacted 2 pages

❖❖❖

Confidential,
Commercial Information

(R)

Division Director Memorandum

NDA #: 21-330
Drug Name: nicotine polacrilex lozenge
Sponsor: Glaxo Smith Kline
Correspondence Date: 5-01-02
Date Agency Received: 5-01-02
Type of Document: response to approvable letter
Date: 10-28-02

Background

The sponsor received an approvable letter on 10-15-01 that outlined chemistry, labeling and clinical deficiencies. The submission is a complete response to those deficiencies.

Conclusion/ Recommendation

The sponsor provided a sufficient response to all of the deficiencies and the application should be approved. The sponsor has agreed to conduct two phase IV studies to assess safety post-marketing. They should also increase the size of the generic name on the principal display panel.

Chemistry

All pending chemistry issues have been resolved to the satisfaction of the chemists.

Clinical

The sponsor provided information on the bioavailability of the nicotine gum using differing methods of chewing, the cardiovascular effect of nicotine as a function of concentration, the safety data from the United Kingdom for the product, and safety information on the patch. The following comments address this data:

- There does appear to be slight differences in the bioavailability of the nicotine gum depending on the method of chewing. This could account for some variation of nicotine levels in the actual use versus the controlled trial setting.
- There does appear to be a flat dose response for the cardiovascular effect of nicotine but the temperature response does not appear to be flat.
- There are no serious adverse events reported to date with OTC nicotine lozenge.

There are limitations on the pharmacodynamic information provided. The flat dose response is based on average data and there may be consumers who are outliers. Additionally, there may be some pharmacodynamic effects that do not have a flat dose response that are of clinical importance. Because there is a long marketing history of nicotine products, this gives a lot of reassurance of the safety. There seems to be reasonable data to support the approval of the product from a safety perspective but it is reasonable to have the sponsor to commit to phase IV safety studies. These were discussed with the sponsor and they agreed to conduct two phase IV safety studies. One study will focus on subjects who have relative contraindications for use and the other will attempt to obtain safety data from a general population of users in a proactive manner.

Labeling

During this review cycle, the sponsor and agency agreed on final labeling for the product. The sponsor incorporated Directions that were consistent with the directions in their primary efficacy studies. The product name was not agreed upon in the first review cycle. The sponsor subsequently submitted the name Commit Lozenge. HFD-170, HFD-560 and Office of Drug Safety found the name to be acceptable. The Office of Drug Safety (ODS) had several additional comments regarding the principal display panel (PDP). First, ODS wanted the sponsor to change the phrase "From the Marketers of Nicorette" to [redacted] because distributor is included in 21 CFR 201.1. Unless the sponsor agrees with this change, we probably have little regulatory authority to force them to do it. 21 CFR 201.1(h)(5) permits the use of "Marketed by ____". This is close to the "marketers" language. Second, ODS did not

want the word "Nicorette" to be juxtaposition near the Commit name. In their review of the original NDA, they recommended that " ' would be an acceptable name. The sponsor has already de-emphasized the "Nicorette" name on the PDP based on previous feedback. Consequently, it would be difficult for us to force additional concessions at this time. The primary labeling reviewer did not have problems with the current PDP. Third, ODS questioned the use of the American Cancer Society endorsement. The Agency has permitted these types of endorsements on labeling of OTC drug products.

The sponsor should be asked to increase the type size of the generic name of the product.

Charles J. Ganley, M.D.

cc: orig.
HFD-560
HFD-560 /project manager / C. GANLEY

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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
10/29/02 04:25:27 PM
MEDICAL OFFICER

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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 APPROVAL MEMO

TO: File, NDA 21-330

THROUGH: Bob A. Rappaport, M.D.
Acting Division Director
Division of Anesthetic, Critical Care and Addiction Drug Products

FROM: Celia Winchell, M.D.
Medical Team Leader
Addiction Drug Products

DATE: October 30, 2002

RE: Commit (Nicotine Polacrilex Lozenges, 2 mg and 4 mg)
Glaxo SmithKline Consumer Health Care

This memorandum documents for the file the basis of the Division's regulatory decision concerning NDA 21-330, Nicotine Polacrilex Lozenges, 2 mg and 4 mg, submitted by Glaxo SmithKline Consumer Health Care as a direct-to-OTC application for use as an aid to smoking cessation

Action: This application may be approved.

Recommendation on Phase 4 Studies:

Two Phase 4 studies have been recommended by the Division of Over-the-Counter Drug Products, and protocols have been submitted to the IND and agreed upon between the OTC division (which will assume responsibility for the NDA after approval) and the sponsor. These include:

1. A study to be conducted 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.

2. A study to solicit adverse event information (using leaflets enclosed in packages).

Summary of Review Issues:

Background:

This is the second submission for NDA 21-330, Nicotine Polacrilex Lozenge. Nicotine Polacrilex Lozenge (2 mg and 4 mg) is a buccally delivered nicotine replacement product intended for use as an aid to smoking cessation. The clinical development program consisted of pharmacokinetic characterization of the product, comparison to the approved nicotine polacrilex gum (Nicorette) also marketed by the sponsor, and a single placebo-controlled clinical efficacy and safety trial, and a brief, open-label "usage" study best characterized as a market research study. The NDA was first submitted on 12/20/00, as a direct-to-OTC application. The application rested in part on reference to previous agency findings concerning the safety of Nicorette gum; however, the lozenge was not bioequivalent to the gum and delivered approximately 25% more nicotine than the analogous doses of Nicorette gum (also available in 2 mg and 4 mg strengths). Although the efficacy of the tested regimen was demonstrated, the agency concluded that there was insufficient evidence of safety of the 4-mg lozenge to permit approval of the product for OTC use. Furthermore, there were a number of deficiencies the chemistry, manufacturing, and controls section of the application.

An approvable letter was issued on 10/12/01. The letter identified several chemistry deficiencies, including:

Clinically, the initial action letter requested additional safety data from 150 - 200 subjects exposed to the 4-mg nicotine lozenge over a 12-week period. However, after an end-of-review meeting (12/12/01), Dr. Charles Ganley, the Director of the Division of Over-the-Counter Drug Products (with concurrence from HFD-170), issued a revision to the approvable letter stipulating the following safety information would be needed for the response to the safety issues raised during the first review cycle:

1. Provide data and information on nicotine concentrations comparing the metronome chewing method with ad lib chewing for nicotine gum
2. Provide information on the maximum concentrations achieved with single and repeat dosing

with various nicotine products (e.g., gum, transdermal).

3. Provide information to support the flat dose response curve for the systemic effects.
4. Provide adverse event reports from countries already marketing the lozenge over-the-counter, behind the counter or by prescription.
5. Agree to two post-marketing studies (Phase IV commitments) to further assess safety:
   a) Conduct a study in subjects with relative contraindications for use (i.e. subjects who have underlying diseases such as diabetes mellitus but are instructed by their physician to use a nicotine product).
   b) Conduct a study soliciting adverse event information

Clinical Deficiency #1 was intended to shed further light on the pharmacokinetic data from the comparison between the lozenge and the Nicorette gum. Deficiency #3 was intended to provide support for the sponsor's contention, made at the end-of-review meeting, that the dose-response curve for cardiovascular and endocrine effects of nicotine was flat, and that, therefore, there was little risk associated with exceeding the dose currently marketed.

The approvable letter also noted the Agency's objections to the proposed proprietary trade name, and provided preliminary labeling comments.

The resubmission addresses the issues noted above, all of which appear to have been satisfactorily resolved in this review cycle.

Clinical Issues: Efficacy:

No new efficacy information was submitted in this response. The original submission provided evidence of efficacy of nicotine polacrilex lozenge at the tested regimen.

The finding of efficacy was based in part on reference to findings concerning Nicorette, and was further supported by a single placebo-controlled clinical trial involving 1818 subjects. Participants were assigned to either the 2-mg lozenge or 4-mg lozenge (based on a measure of level of nicotine dependence) and self-titrated their use according to parameters provided in a simulated OTC label and user's guide. The full-dose treatment period was 6 weeks, followed by an additional 6 week tapering period and a 3 month period of occasional prn use. No concomitant behavioral support was provided.

Success was defined as self-reported abstinence from smoking from the end of week 2 to the end of week 6 (the last month of full-dose treatment), CO-verified at weeks 4 and 6. Additional analysis at the end of taper and end of study were performed (with CO verification at week 12 and month 6). Results are shown below.

	2 mg		4 mg	
Continuous Quit Rate (% abstinent continuously since week 2)	Active N = 459	Placebo N = 458	Active N = 450	Placebo N = 451
6 week	46%	30%	49%	21%
12 week	34%	22%	35%	14%
6 months	24%	14%	24%	10%

All comparisons to placebo were statistically significant.

A single trial was considered adequate demonstration of efficacy because nicotine has proven superior to placebo in a variety of clinical studies encompassing different doses, dosage forms, routes of administration, and levels of concomitant behavioral support.

Clinical Issues: Safety

The safety information in this resubmission was reviewed by the Division of Over-the-Counter Drug Products and was judged adequate to address the safety concerns raised in the original review.

The material submitted in response to the safety issues raised in the approvable letter included:

- Data on how bioavailability of the Nicorette gum is affected by metronome-paced vs. ad lib chewing, in order to better understand the comparative study of lozenge vs. Nicorette (which used metronome-paced chewing).
- Pharmacokinetic comparisons to other marketed nicotine products.
- A literature review and supporting references concerning the purported flat dose-response to nicotine.

- Literature cardiovascular effects of nicotine patches in smokers with coronary artery disease.
- Foreign post-marketing data on the nicotine lozenge.

These were reviewed by Dr. Jin Chen, of the Division of Over-the-Counter Drug Products, who also examined the FDA database of post-marketing safety information for nicotine replacement products.

Dr. Chen concluded that:

- Based on the review of information about the effect of metronome-paced chewing, the differences in C_{max} (8% higher with the lozenge) and AUC (27% higher with lozenge) in PK study N96016 may be overestimates of what would occur compared to ad-lib chewing.
- Cross-study comparisons of pharmacokinetic profiles of various nicotine replacement products suggested that the 4-mg nicotine lozenge at single and multiple dosing regimens appears to produce slightly higher total systemic nicotine exposure (AUC) than, but may be comparable to, the currently marketed OTC products, 4-mg nicotine gum and nicotine patches.
- Certain cardiovascular effects (heart rate and blood pressure) demonstrated a flat dose-response to nicotine, but others (e.g. microcirculation) did not. Furthermore, a 3.5-hour between doses interval (which would be commonly exceeded in clinical use of the lozenge after the first 6 weeks) completely restored nicotinic cardiovascular effects, suggesting transient tolerance.
- Three clinical studies (two randomized control trials and one case-series study) from literature reports showed that nicotine patches (15 mg, 21 mg) did not induce significant cardiac toxicity in smokers with coronary artery disease and with or without concurrent cigarette smoking; however, due to higher Cmax and faster nicotine delivery (shorter T_{max}) from the lozenge compared to nicotine patch at multiple dosing regimens, this finding may not be relevant to the lozenge, and does not obviate the need for Phase 4 study of smokers with cardiovascular diseases, as recommended by the Agency in the previous review cycle.
- The 3-month post-market spontaneous AE reports on the nicotine lozenge (2-mg and 4-mg) marketed in UK showed no serious AEs associated with nicotine lozenge. The general spectrum of AEs associated with nicotine lozenges appeared similar to that from the clinical trial submitted in the original NDA. Users of the 4-mg nicotine lozenge experienced more adverse events than those using the 2-mg lozenge after adjusted with distribution of each dosage form.
- Post-marketing AE reports retrieved from the FDA spontaneous AE report database (from 1984-1994) showed no serious adverse events associated with Rx nicotine gum or Rx nicotine patch in a 10-years period preceding the 1996 OTC switch.

Chemistry Issues:

The approvable letter listed [redacted]

[redacted]

by both the sponsor and [redacted]. All issues were satisfactorily resolved. A brief summary of the issues and their manner of resolution, as per reviews by Michael Theodorakis, Ph.D., reviewing chemist, is as follows:

1. Regarding the drug substance:

[redacted]

2. Regarding the drug product:

[redacted]

- The sponsor was also asked to revise the regulatory specifications for acceptance of the drug product to include reporting specification, identification, and qualification limits in a manner consistent with ICH guidelines for impurities in drug products. This has been satisfactorily addressed.

- The sponsor was asked to revise the acceptance criteria for the dissolution specifications, and provided a satisfactory response to this issue.

3. EERs were issued for four facilities and all were acceptable as of July 8, 2002.

Nomenclature:

The Office of Drug Safety objected to the proposed proprietary tradenames, Commit Lozenge [redacted] Commit Lozenge. [redacted] noting that these names might "cause confusion because they make reference to nicotine chewing gum and a dermal patch, as if they are the source of the lozenge." The packaging has been revised to retain the name "Commit" but to clarify that the product is "from the marketers of" Nicorette. Dr. Ganley's memo will address the acceptability of the current presentation. HFD-170 has no objection to the current proposed proprietary tradename or trade dress.

Labeling:

The carton and user's guide have been revised in response to Agency comments and are satisfactory to HFD-170.

Status of pediatric studies and pediatric plan:

GSK has requested a deferral of submission of data concerning the safety and effectiveness of the nicotine polacrilex lozenge in the pediatric population. The sponsor is undertaking a pediatric program described as being "designed to (1) monitor adolescent trends in smoking initiation and cessation, (2) monitor adolescent nicotine replacement therapy (NRT) use in the OTC marketplace, (3) compile and evaluate current expert opinion in the area of NRT use for adolescent smoking cessation and (4) monitor, guide and support clinical investigations of NRT use for adolescent smoking cessation. [GSK] believe[s] this approach is practical, adds to the body of knowledge, and avoids a rush to judgement in this area." The pediatric plan described lists studies being "supported" (not sponsored) by GSK, and a protocol for a PK study of various NRTs in adolescents.

A deferral is acceptable. Many unanswered questions regarding the design of efficacy trials in adolescents remain, yet the demonstration of efficacy in this population is essential, as the agency does not feel extrapolation from adult efficacy studies is appropriate. In light of the current legal status of the Pediatric Rule, the agency cannot require GSK to perform safety and efficacy studies in adolescents, but will inform the sponsor that such studies would be required if the pediatric rule were in force. This is in line with Center policy to inform sponsors of pediatric requirements so that they will be prepared should the Agency decide to appeal the recent court decision striking down the Pediatric Rule.

Studies in adolescents (10-16) may be deferred, while studies in younger pediatric groups may be waived.

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/s/

Celia Winchell
10/30/02 01:59:30 PM
MEDICAL OFFICER

Bob Rappaport
10/30/02 02:14:03 PM
MEDICAL OFFICER

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Number of Pages Redacted 52

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Draft Labeling
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: July 3, 2002

To: David Schifkovitz	**From:** Elaine Abraham
Company: GlaxoSmithKline	Division of Over-the-Counter Drug Products
Fax number: (973) 889-2244	**Fax number:** (301) 827-2316
Phone number: (973) 889-2509	**Phone number:** (301) 827-2301

Subject: N 21-330 Labeling Review

Total no. of pages including cover: 3

Comments: Comments on User's Guide and Response to GSK 7/2/02 Fax

Document to be mailed: ☐ YES ☑ NO

Message: Please refer to your new drug application NDA 21-330 amendment dated March 12, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nicotine Polacrilex Lozenges 2 mg and 4 mg.

We have attached reviewer's comments on the user's guide and our response to your fax of July 2, 2002.

Attachment

Reviewer's Recommendations on User's Guide:

1. User's Guide, page 33, item 2.

   Revise the paragraph beginning with the phrase [redacted] ." to the following:

   > **Commit™** Lozenges do contain nicotine, however there is probably less nicotine in your daily dose of lozenges than in your cigarettes. **Commit™** Lozenges give you enough nicotine to help you combat the physical withdrawal symptoms so you can cope with the mental side of stopping smoking. Also, since the nicotine from the lozenges goes into your blood stream more slowly, it produces less of the effects of nicotine that people find rewarding. In fact, when used as directed in the 12 week program, **Commit™** Lozenges gradually wean you off your dependence for both nicotine and cigarettes.

2. User's Guide, page 33, item 3.

   Revise the paragraph beginning with [redacted] to the following by omitting the first sentence:

   > **3. Can Commit™ Lozenges do any harm?**
   > Some people with conditions like heart disease or people taking prescription medicine for asthma or depression should not use this product without talking to their doctor – check the IMPORTANT WARNINGS on page 3. You may also experience side effects such as hiccups, mouth or throat irritation, heartburn or other stomach problems such as nausea especially if **Commit™** Lozenges are chewed or swallowed. In any case, **Commit™** Lozenges do not contain the tar, carbon monoxide, and other toxins present in cigarette smoke.

FDA's Comments on July 2, 2002 GlaxoSmithKline Fax:

3. Back Panel:

Paragraph § 201.66	Description of Paragraph	Comments
(c)(5)(vii)	**Warnings**, under **Stop use and ask a doctor if"**	Insert new bullet 4 to read: "[bullet] persistent indigestion or severe sore throat occurs"
(c)(5)(x)	Keep out of reach of children warning	After the second sentence, add the following disposal statement: "If you need to remove the lozenge, wrap in paper and throw away in the trash."
(c)(6)	**Directions**—bullet 7	Revise to state placement of the lozenge as follows: "place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20–30 minutes). Minimize swallowing."
(c)(6)	**Directions**—bullet 8	Delete the phrase [redacted] and revise bullet 8 to read: "[bullet] you may feel a warm or tingling sensation"

4. User's Guide:

Page(s)	Description (User's Guide Page Number)	Comments
23	Page 3, **Keep out of reach warning**	Insert after the second sentence: "If you need to remove the lozenge, wrap in paper and throw away in the trash."
24	Page 4, under the heading **"THE PROGRAM,"** paragraph 3,sentence 3.	Revise sentence 3 as follows: "Place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20–30 minutes). Minimize swallowing."
24	Page 4, under the heading **"THE PROGRAM,"** paragraph 3, sentence 5.	Delete the phrase [redacted] and revise to read: "[bullet] you may feel a warm or tingling sensation"
27	Page 7, under the heading **USING Commit™ LOZENGES PROPERLY,** paragraph 4 (item 1), sentences 2 through 4	Revise to read: "Place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20–30 minutes). Minimize swallowing. **Do not chew or swallow the lozenge."**

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/s/

Elaine Abraham
7/3/02 03:50:31 PM
CSO

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Number of Pages Redacted 32

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Draft Labeling
(not releasable,

Linda Katz, M.D.	Division Deputy Director
Helen Cothran, B.S.	Microbiologist and Team Leader
Mary Robinson, M.S.	Regulatory Review Chemist
Dan Keravich	Regulatory Project Manager

Background: SBCH is developing a 2mg and 4 mg nicotine polacrilex lozenge, with the intention of filing an NDA as an application for direct-to-OTC marketing.

Objectives: To obtain advice/agreements on the presentation of the clinical data, and structure/content of the overall NDA.

Discussion: Each one of the questions posted by the sponsor in their briefing package was addressed as follows:

Questions #1, And #2 were addressed simultaneously.

Question #1. In light of the additional summary data from the pivotal study, does the Agency agree that the clinical plan implemented for nicotine polacrilex lozenges is adequate to support an OTC marketing application?

Question #2. The Agency expressed initial concerns regarding incremental exposure associated with the use of the 4 mg lozenge. The safety profile emerging from our pivotal trial is very encouraging and consistent with previous experience for other oral form of NRT. What additional analysis, if any, would be required to address this issue?

The Division of Over the Counter Drug Products expressed that there is no objection to the filing of the NDA for direct-to-OTC marketing for the 2 mg lozenge. However, there are insufficient data to substantiate the proposed labeling and safety for the 4 mg lozenge direct-to-OTC marketing.

SBCH's pivotal trial randomized 450 subjects to the 4 mg lozenge arm with instructions to use up to 20 lozenges/day and up to 12 weeks of usage. No indication is given in the briefing package on how many subjects used that maximum dose, nor is information regarding the safety profile of those subjects.

In order to comply with current standards for safety data for OTC formulations, SBCH will need to provide safety data on the 4 mg lozenge, for at least 300 subjects, using the product beyond the labeled time for administration. That translates into a minimum of 300 subjects at the completion of the study, who used 20 lozenges/day for 12 weeks (as the label indicates), and follow-up for 6 months of sufficient number of patients to be able to assess long-tem safety.

The following options were discussed with SBCH in order to address the insufficient safety information available for the 4 mg lozenge.

1. Submit the NDA as an Rx application, while acquiring additional safety information for the 4 mg lozenge. Dr. McCormick indicated that there are sufficient safety data to file the NDA for both the 2mg and 4 mg lozenge as Rx formulations.

2. Conduct a safety study prior to submitting the application. The safety study should be large enough to ensure that a sufficient number of subjects will complete 12 months of treatment at the high end of the dose recommended in the label. This could be done either through requiring a certain level of use (rather than having subjects use the product prn within parameters), or by identifying characteristics of subjects likely to use the product at a higher daily dose, and enriching the study population for those subjects.

3. Determining whether it is possible to modify the dosing recommendations, without departing from the doses actually used by the participants in the efficacy trial, so that the total daily dose falls within the range of total daily nicotine exposure from 4 mg Nicorette Gum. This will require analysis of safety issues to determine whether total daily exposure is the proper measure of risk, or whether Cmax from each incremental dose is more appropriate. Furthermore, it is possible that changes in the label which create directions significantly different from those tested will require a Label Comprehension Study.

SBCH's representatives indicated they will consider the Agency's recommendations while re-assessing their data.

During the meeting, SBCH presented the simulated pharmacokinetic data where 1 lozenge is given every 60 min according to the proposed labeling claim (use 1 lozenge every 1-2 hours), and compared with the multiple-dose PK data obtained from study # s1410091 (1 lozenge every 90 min). The simulated C_{max} level observed in this simulation is approximately 30-35 ng/ml for the 4 mg lozenge, which is lower than the estimated value reported previously (40-45 ng/ml reported in the March 15, 2000 submission). The Agency indicated that the simulation study where 1 lozenge is given every 60 min, for both the 2 mg and 4 mg lozenge, and the estimated steady-state drug levels and PK parameters (C_{max}, T_{max} and $AUC_{0\text{-}60\ min}$) have to be included in the submission, including a rationale to address the discrepancy between the two estimated C_{max} values reported (30-35 ng/ml vs. 40-45 ng/ml).

Question #3. Does the Agency agree with SBCH's proposal for analysis and presentation of efficacy data from the pivotal study?

The Agency agrees on the analysis and presentation of the safety and efficacy data, and specifically on the outcomes broken out both by treatment group, TTFC (Time to First Cigarette), and CPD (Cigarettes Per Day). Each data table should include all three of these for each subject.

Tables should break out the number of subjects using the product at various levels of lozenge per day, by duration. Lozenge use should be reported by subject, rather than only as group medians.

Question #4. Does the Agency agree with SBCH's electronic submission proposal as outlined in the briefing document.

The Electronic submission of the NDA should follow CDER's guidelines on electronic submissions. A copy can be found at www.fda.gov/cder/guidance/index.htm.

The following additional information, not provided at the time of the meeting, is also needed.

1. Electronic version of the labeling.

2. Electronic version of the user's guide. It should include annotated sources of information as well as highlighted differences between the proposed user's guide and the text of Nicoderm/Nicorette materials.

Question #5. Does the Agency have any comments or recommendations on proposed NDA table of contents?

SBCH needs to ensure that the following information is included in the submission

1. Financial Disclosure certification.
2. Pediatric section that conforms to Pediatric Rule.

3. Simulation of individual PK profiles and estimation of their PK parameters (e.g.,C_{max}, AUC) for both 2 and 4 mg lozenges when given every 60 min and a summary table of the estimated mean (± standard deviation) PK parameters for both strengths, plus a graph of the mean (± standard deviation) plasma profiles. (see Question #1 and #2).

4. Electronic versions of labeling and user's guide.

Question #6. Agency reaction to the appropriateness of "time to first cigarette" in OTC labeling as a tool for assessing tobacco dependency and dosage allocation.

The studies conducted by SBCH were designed to use "time to first cigarette" as a tool for assessing tobacco dependency and dosage allocation. Therefore, the Agency concurs with SBCH in that assessment.

Question #7. Is the Agency aware of any critical issues to be addressed in the NDA relative to the safety and efficacy of nicotine polacrilex lozenges (2 mg and 4 mg) as an OTC smoking cessation aid?

Refer to Question #1 and #2

Judit Milstein, Regulatory Project Manager

Celia Winchell, M.D., Medical Team Leader concurrence

CC:
Archival: IND 56,295

HFD-170/Division File
HFD-170/C. Winchell
HFD-170/D. Koble
HFD-170/T. Permutt
HFD-170/A.Chen
HFD-170/J.Milstein

HFD-870/J. Hunt

HFD-560/L. Katz/H. Cothran/M.Robinson/D.Keravich.

Drafted by: J.M. 10-5-00
Reviewed by: C. Winchell 10-5-00, L. Katz 10-5-00, C.Schumaker 10-6-00, A. Chen 10-10-00, 10-30-00.
Initialized by: electronic confirmation C.Winchell, L.Katz.
Final:

File: E:\I56,295 Nicotine lozenge\minutes of the meeting 3.doc

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/s/

Celia Winchell
11/3/00 04:11:24 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

IND 56,295

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

Attention: Robert M. Harris
Assistant Director, Regulatory Affairs

MAY 1 1 2000

Dear Mr. Harris:

Please refer to the telecon between representatives of your firm and FDA on Tuesday, April 11, 2000. The purpose of the meeting was to discuss the development for a new oral dosage form for nicotine polacrilex lozenge, and the potential direct to OTC switch.

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

If you have any questions, call me at (301) 827-7440.

Sincerely,

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

Enclosure: Minutes of the telecon

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cc:
Archival IND 58,995
HFD-170/Div. Files
HFD-170/J.Milstein
HFD-170/C. Schumaker

Drafted by: jrm/March 23, 2000
Initialed by:
final:
filename: N:\cso\milstein\I56295 Nic Polacrilex Loz\minutes sent.doc

GENERAL CORRESPONDENCE (MINUTES SENT)

MEMORANDUM OF TELECON

DATE: April 11, 2000 IMTS# 5478

MAY 1 1 2000

APPLICATION NUMBER: IND 56,295

BETWEEN:

Name: Scott Coapman, Associate Director, New Product Development
Jae Choi, Pharm. D., Assistant Director, Medical Affairs
Carolyn Dresler, M.D., Director, Medical Affairs
Robert Harris, Assistant Director, Regulatory Affairs
Eva Krusinska, Ph. D., Director, Biostatistics & Data Management
[redacted]
[redacted]
Elizabeth Rappaport, M.D., Vice President and Director of Medical, Regulatory and Toxicology
Martin Steiner, Ph. D., Project Director

Phone: 1-800-813-0615 , Participant Code 89544
Representing: SmithKline Beecham, Consumer Healthcare (SBHC)

AND

Name: Cynthia G. McCormick, M.D., Division Director
Celia Winchell, M.D., Medical Team Leader
Tien-Mien Chen, Ph.D., Clinical Pharmacology and Biopharmaceuticals reviewer
Judit Milstein, Regulatory Project Manager
Representing the Division of Anesthetic, Critical Care, and Addiction Drug Products HFD-170
Charles J. Ganley, M.D., Division Director
Ling Chin, M.D., Medical Officer
Rosemary Cook, Supervisory Project Management
Dan Keravich, Regulatory Project Manager
Representing the Division of Over the Counter Drug Products (OTC), HFD-560

After a brief introduction by Dr. Elizabeth Rappaport, explaining the highlights of SBHC program, and Dr. McCormick's invitation for a formal pre-NDA meeting in the near future, the questions posted by SBHC in their briefing package were addressed.

Question # 1. Does the Agency agree that the clinical development plan implemented for nicotine polacrilex lozenges is adequate to support a marketing application?

SBHC proposed development plan has basically all the safety and efficacy elements to support an R_x application, even though the database of 400 patients would barely satisfy the safety arm of the application.
Another concern arises from the 4 mg, single dose, pharmacokinetic (PK) study, where preliminary evaluation indicates the levels of nicotine delivered exceeds any level of current nicotine replacement therapies (NRT's).

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Question # 2. Does the Agency agree conceptually with taking nicotine polacrilex lozenges directly to the OTC market?

The Agency agrees that the 2 mg lozenge could go directly to OTC market, however, several concerns arose for the 4 mg lozenge as follows:

1. From a preliminary evaluation of the labeling, there seems to be no difference with the labeling for the Nicorette mint, therefore, the question arises if there is need for a different formulation considering that there is no presumed advantage in the use of the lozenge.

2. Does the 4 mg lozenge demonstrate more efficacy than the 4 mg gum? If the lozenge is less efficacious than the gum, what is the justification for the higher dose?

3. The Agency's experience indicates that it would be easier to get nicotine out of the lozenge than out of the gum; therefore, more data would be needed (e.g., from an actual use trial, with patients using both 4 mg gum and smoking, or from a PK comparison of gum and lozenge in ad-lib use, rather than metronome-paced, use) to assure that the nicotine delivered by the 4 mg lozenge doesn't exceed the safety ceiling currently accepted for NRT's.

4. If the 3 mg lozenge is bio-equivalent to the 4 mg gum, how can it be expected that the 4 mg lozenge would deliver less or equal nicotine than the 4 mg gum?

5. All NRT products currently marketed provide for a 10-12 week treatment. The Agency will need justification and substantiation for the additional 12 weeks proposed by the SBHC plan.

Question # 3. Does the Agency agree that an in vivo BE study can be waived based on the minor formulation differences (i.e., different drug substance source) and comparable in vitro dissolution profiles exhibited between the pivotal clinical trial formulation s ant the to-be- marketed drug product formulations?

Since the proposed formulation change is less than 0.5% of total weight, the request is acceptable provided that adequate *in vitro* dissolution data are submitted.
It will be necessary to select an appropriate (i.e., more optimal) dissolution test and set specifications which would reflect dissolution situation *in vivo*. Therefore, additional information on dissolution profile comparisons of nicotine lozenges (of both sources), using different media and/or methods is needed (see SUPAC IR for reference). The sponsor agreed.

Judit Mintstein
Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

Concur

MD 5-11-02

/S/

cc: Original IND 56,295
HFD-170/Div. File
HFD-170/Judit Milstein/C.Schumaker
HFD-170/A. Chen/R.Uppoor
HFD-170/C. Winchell

c-sig

Drafted by: J. Milstein 5-1-2000
Initialized: A. Chen 5-9-2000 /C.Winchell 5-9-2000
Request for comments was sent to the OTC division on 4-30-2000 and 5-7-2000. No Response was received
File:N:\ CSO\MILSTEIN\I56295 Nic Polacrilex Loz\minutes of the meeting 4-11-00v3.doc

TELECON

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Consumer Healthcare
P.O. Box 1467
Pittsburgh, PA
15230

Tel. 412 928 1000
www.gsk.com

Debarment Certification

Pursuant to Section 306(k) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not employ the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

Janice McSherry

January 31, 2001
Date

Janice McSherry
Senior Counsel

APPEARS THIS WAY
ON ORIGINAL

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Last printed by MCSHEJ00 on 02/01/01 8:46 AM

NDA 21-330 NICOTINE POLACRILEX LOZENGES 2 AND 4 MG

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application:

	YES	NO
CLINICAL:		
(1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	YES	
(2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	YES	
(3) On its face, is the clinical section of the NDA legible so that substantive review can begin?	YES	
(4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	*	

No dose ranging study was done but PK, BE, and BA studies (S1410091, S1410092, N98001, and N96016, See Item 3.H.4.a, pp. 452-453) were done comparing the lozenge to Nicorette gum and on this basis the doses were selected.
The sponsor states that the choice of the 2 and 4 mg dose were based on current marketed doses for nicotine gum as well as the above mentioned studies. [Item 3.4.4, p. 24-25.]

Although the 3mg lozenge was found in studies to be equivalent to the 4mg gum, the sponsor of the 4mg lozenge.

(5) On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?	*	

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Implicit in the answer to Questions 1 and 2 in the 10-4-00 meeting minutes, the sponsor was allowed to do one AWC study.

(6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling? YES

The trial is a randomized, double-blind, placebo-controlled, parallel group study.

The suggested treatment regimen in the pivotal trial does not exactly match up with the label directions. [Item 5.3, pp. 62-63, and Item 2 labeling, p. 29.] The differences are minor and, if anything, are more restrictive in the label than in the study protocol. This reviewer believes this issue should be handled as a labeling rather than a filing issue.

The trial provided for initial use of the gum in a range of 1-2 hours. The label states initial use should be in a range of — -2 hours.

The trial suggests maximum of 20 lozenges/day. The label suggests a maximum of — lozenges/day.

The trial suggests a minimum initial use of 9 lozenges/day. The label suggests a minimum of —

The trial suggests 1-2 lozenges/day from week 12 to the 6th month. The label suggests stopping the use of the lozenge after 12 weeks.

(7) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested'? YES

There is only one pivotal study and one indication. The datasets appears to be complete.

(8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the-extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling'? YES

(9) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division') YES

All datasets include the variables requested in the 10-4-00 meeting:

1. *Time to first cigarette*
2. *Treatment group*
3. *Cigarettes per day*

They have also provided a breakout of subjects using product at various levels of lozenge /day reported by subject rather than group medians. [See Table 9.2.1.1 and Section 3H Summary, Table 3.H.2.c-1, p. 439, Table 3.H.4.c-1, p.455, and Table 3.H.3.e.-1, p. 446]

CLINICAL:	YES	NO
(10) Has the application submitted a rationale for assuming the applicability of foreign data in the submission to the US population?	YES*	

On 1-29-01 the sponsor replied by FAX to our inquiry about the rationale for the applicability of foreign data. The sponsor wanted to make sure they could obtain a sufficient number of demographically correct persons who desired to quit smoking with a nicotine lozenge. Analyses were performed to make sure that critical smoking characteristics were consistent between the two countries. They also stated that, "the similarity of genetic and social heritage between the US and the UK are obvious and not in question. Analyses were repeatedly performed examining the potential differences in findings between the countries... The data from both countries were handled in a uniform manner." The sponsor feels that the rationale was included throughout the study report for S141003.

(11) Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division? N/A

(12) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? YES

(13)Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product? YES

See item 3.C, pp. 56-57

(14)Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package? NO

The sponsor provided annotated sources of information as requested in the 10-4-00 meeting in Section 3.A.1. of the application summary. Highlighted differences with the text of Nicoderm/Nicorette materials were not provided because the sponsor feels the text was essentially different.

It should be noted that the label does state in the Warnings Section that you should not use this product if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing products.

In the pivotal trial concomitant smoking, smoking of other substances during or 30 days prior to the study, and use of other NRT or other smoking control products during the same time frame was not allowed. [Item 3.4.7, p.26.]

The suggested treatment regimen in the pivotal trial does not exactly match up with the label directions. [Item 5.3, pp. 62-63, and Item 2 labeling, p. 29.] This is the same comment as for Question 6. This reviewer believes this issue should be handled as a labeling rather than a filing issue.

(15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? NO

In 10-4-00 meeting we asked sponsor, in order for them to get a direct OTC switch to:

1. *Do a 12-month safety study. The pivotal study allowed subjects to remain in the trial for up to 12 month post-quit but the study report only contains 6-month safety data.*
2. *Reduce dosing recommendations to within the range of total daily exposure for 4mg Nicorette gum as in 10-4-00 minutes.*
3. *OR ELSE, while getting safety data, and come in with an R_x application for the 4mg dose.*

The sponsor has not chosen any of these options. We will consult with OTC.

(16) From a clinical perspective, is this NDA fileable? If "no", please state below why it is not. YES

/S/ 2-1-01

Harold Blatt, D.D.S.
Reviewing Medical Officer
Date

/S/ 2/2/01

Celia Winchell, M.D.
Supervisory Medical Officer
Date

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45 DAY MEETING CHECKLIST
(Answer Yes or No to the questions below)

FILEABILITY:

On initial overview of the NDA application: **20-714**

PHARMACOLOGY AND TOXICOLOGY:

(1) On its face, is the pharmacology section of the NDA organized in a manner to allow substantive review to begin? Yes

(2) Is the pharmacology section of the NDA indexed and paginated in a manner to allow substantive review to begin? N/A

(3) On its face, is the pharmacology section of the NDA legible so that substantive review can being? N/A

(4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetics studies, etc)? N/A

(5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies using the marketed product or to explain why such repetition should be required? N/A

(6) Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57? No

(7) Has the sponsor submitted all special studies/data requested by the Division during Pre-submission discussions with the sponsor? N/A

(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted rationale to justify the alternative route? N/A

(9) Has the sponsor submitted a statement(s) that all the pivotal Pharm/Tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? N/A

(10)Has the sponsor submitted a statement(s) that the Pharm/Tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? N/A

(11) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. Yes

Thomas Papoian, Ph.D.
Supervisory Pharmacologist
Feb. 9, 2001

/s/

Thomas Papoian
2/9/01 03:10:39 PM
PHARMACOLOGIST

APPEARS THIS WAY
ON ORIGINAL

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

REQUEST FOR CONSULTATION

TO (Division/Office):	FROM:
HFD-009 (Controlled Substances Staff), Corinne Moody	HFD-170 (Division of Anesthetic, Critical Care, and Addiction Drug Products), Dr. Cynthia McCormick

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2-21-01		NDA 21-330	Electronic submission	December 15, 2000

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nicotine Polacrilex Lozenge	medium	Nicotine addiction	May 1, 2001

NAME OF FIRM: Glaxo SmithKline

REASON FOR REQUEST

I. GENERAL

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

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the following studies for abuse liability and abuse potential, especially as it relates to OTC marketing and adolescent misuse.

1. Protocol I410089 " An Abuse Liability trial comparing abuse potential of nicotine polacrilex lozenge (placebo, 2 mg, 3 mg, and 4 mg), d-amphetamine (20 mg/70kg), Nicorette nicotine gum, and a confectionary lozenge.
2. Nicotine Polacrilex Lozenge Teen Exploratory-Qualitative teen research study examining detailed reactions/impressions obtained from concept presentations on nicotine Lozenge.

If you have any questions, please contact Judit Milstein, Regulatory Project Manager, at 301-827-7440. Please cc: all written responses to Judit Milstein, Dan Keravich (HFD-540), and Aleta Crane. Thank you for your assistance.

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

/s/

Judit Milstein
2/22/01 12:19:19 PM

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a. Protocol 1410089 entitled " An Abuse Liability trial comparing abuse potential of nicotine polacrilex lozenge (placebo, 2 mg, 3 mg, 4 mg), d-amphetamine (20 mg/70kg), Nicorette nicotine gum, and a confectionary lozenge."

b. Nicotine Polacrilex Lozenge Teen Exploratory- Qualitative teen research study examining detailed reactions/impressions obtained from concept presentations on nicotine lozenge

21-330

Review for abuse liability and abuse potential especially as it relates to OTC marketing & adolescent misuse!

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ON ORIGINAL

NDA 21-330
Nicotine Polacrilex Lozenge
GlaxoSmithKline

No DSI inspections were requested.

Judit Milstein
8-31-01

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ON ORIGINAL

Labeling Review
Addendum
Division of OTC Drug Products, HFD-560

NDA #: 21-330	**Sponsor:** GlaxoSmithKline (formerly SmithKline Beecham) Consumer Healthcare
Drug Product: Nicotine Polacrilex Lozenges , 2 mg and 4 mg	**# of Stock Keeping Units in Submission:** 4
Submission Date: December 15, 2000	**Review Date:** April 4, 2001
Type of Submission: NDA	**Reviewer:** Mary S. Robinson, HFD-560

Addendum

The sponsor proposed [redacted] as the maximum number of lozenges to be taken per day. However, the directions for use in the supporting efficacy and safety clinical trials allowed a maximum of 20 lozenges per day. Therefore, the following changes to be made in the labeling reflect those trials and supercede the changes stated where indicated in the above reference review dated April 4, 2001 for Nicotine Polacrilex Lozenges, 2 mg:

Back Panel (2 and 4 mg Starter Kit and Refill) (attachment 1, pages 18, 22, 26, and 30)

Paragraph § 201.66	Description of Paragraph	Comments
(c)(6)	**Directions**—bullet 13	Revise to read: "do not use more than 20 lozenges a day."

User's Guide (attachment 1)

Page(s)	Description (User's Guide Page)	Comments
40	Page 10, Chart—	The information following the chart needs to be revised to read: "Do not exceed 5 lozenges in 6 hours. **Do not use more than 20 lozenges per day.** [redacted] lozenge at the end of 12 weeks (3 months)."
40	Page 11, paragraph 1	Revise last sentence to read: "But do not exceed the recommended maximum daily dosage of 20 lozenges per day."
47	Page 19, under **COPING AFTER QUITTING**, chart	Make chart consistent with carton label chart, and chart on page 10 of User's guide by: (1) changing [redacted] to "1-2 hours" and (2) Adding following after the chart: "Do not exceed 5 lozenges in 6 hours. **Do not use more than 20 lozenges per day.** [redacted] lozenge at the end of 12 weeks (3 months)."

Reviewer's Comments

The sponsor needs to make the changes and revisions as stated in this review as stated before this application is approved. These comments can be conveyed to the sponsor.

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

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

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ON ORIGINAL

cc:
NDA 21330
HFD-170: JMilstein
HFD-560: CGanley/LKatz/HCothran/LChin/MRobinson/DKeravich
HFD-560: Division/File team 4 binder with labeling
R/D: MRobinson
DOC ID: C:\Data\Nicotine Lozenge\21330Nicotine Lozenge Label Addendum12-15-01.doc

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

/s/

Mary Robinson
10/10/01 01:20:21 PM
INTERDISCIPLINARY

Helen Cothran
10/10/01 04:44:36 PM
INTERDISCIPLINARY

APPEARS THIS WAY
ON ORIGINAL

(J)

Number of Pages Redacted 38

❖❖❖

Draft Labeling
(not releasable,

(J)

SPONSOR MEETING ATTENDEES

Meeting Date: October 4, 2000 IMTS#

Location: Parklawn Building, Potomac Conference Room

IND : 56,295

Sponsor: SmithKline Beecham Consumer Healthcare

Type of Meeting: Pre NDA, for a direct to OTC switch

Meeting Chair: Celia Winchell, M.D., Medical Team Leader
Division of Anesthetics, Critical Care and
Addiction Drug Products, HFD-170

SKB Consumer Healthcare	Title
Steven Burton	Head of Smoking Control and Strategic Development and Medical Promotion
Scott Coapman	Associate Director, New Product Development
Carolyn Dressler, M.D.	Director, Medical
Robert Harris	Assistant Director, Regulatory Affairs
Eva Krusinska, Ph.D.	Director , Biostatistics
David Schifkovitz	Director, Regulatory Affairs
[redacted]	[redacted]
Martin Steiner, Ph.D.	Project Director
Kenneth Strahs, Ph.D.	Vice President/Therapeutic Category Head-Smoking Control
Paul A. Wardle	Senior Brand Equity Manager
FDA HFD-170	Title
Cynthia G. McCormick M.D.	Division Director
Celia Winchell, M.D.	Medical Team Leader
Kenneth Hastings, Ph.D.	Pharm. Tox. Supervisor
Dale Koble, Ph.D.	Acting Chemistry Team Leader
Tom Permutt, Ph. D.	Team Leader, Biostatistics
Albert Chen, Ph.D.	Clinical Pharmacology and Biopharmaceutics Acting Team Leader
Judit Milstein	Regulatory Project Manager
John Hunt (HFD-870)	Division Deputy Director
FDA HFD-560	

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ON ORIGINAL