CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021330/S-004

Name: Commit® (nicotine polacrilex) Lozenge

Sponsor: GlaxoSmithKline Consumer Healthcare

Approval Date: November 22, 2005

This supplemental new drug application provided for a new cherry flavored Commit® (nicotine polacrilex) Lozenge.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021330/S-004

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Approvable Letter	
Labeling	**X**
Division Director's Memo	
Labeling Review(s)	**X**
Medical Review(s)	
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology / Toxicology Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology & Biopharmaceutics Review(s)	**X**
Other Review(s)	
Administrative and Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021330/S-004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-330/S-004

GlaxoSmithKline Consumer Healthcare
Attention: Iris Shelton
Assistant Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Shelton:

Please refer to your supplemental new drug application dated July 22, 2005, received July 22, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Commit® (2mg and 4mg nicotine polacrilex) Lozenge.

We also acknowledge receipt of your submission dated November 2, 2005.

This supplemental new drug application proposes a new cherry flavor.

We have completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on July 22, 2005.

In addition, we remind you to make the following agreed upon labeling changes at the time of next printing or in 180 days, which ever comes first:

1. In the "Inactive ingredients" section, correct the spelling of the ingredient listed as "palm kernal oil" to "palm kernel oil."

2. Please be reminded that FDA recommended the following label revisions after review of SCP-003 (BL) for Commit Mint Lozenge, submitted 10/21/05:

    a. On vial labels and carton labels, revise the statement under the first vial graphic to read: "To open vial, push in child resistant band on the POPPAC with thumb."

    b. Revise sentence 2 in paragraph 2 on vial labels to read: "Discard vial after use."

    c. On vial labels, revise the first two sentences following the table to read: "Place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. Do not chew or swallow lozenge. Occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20–30 minutes)."

    d. Revise the first bullet under "Ask a doctor before use if you have" to read "a sodium-restricted diet."

We remind you to remove the word “New” from the label after 6 months of OTC marketing.

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Laura Shay, Regulatory Project Manager, at (301) 796-0994.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, MD
Acting Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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

/s/

Andrea Segal

11/22/2005 03:40:01 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

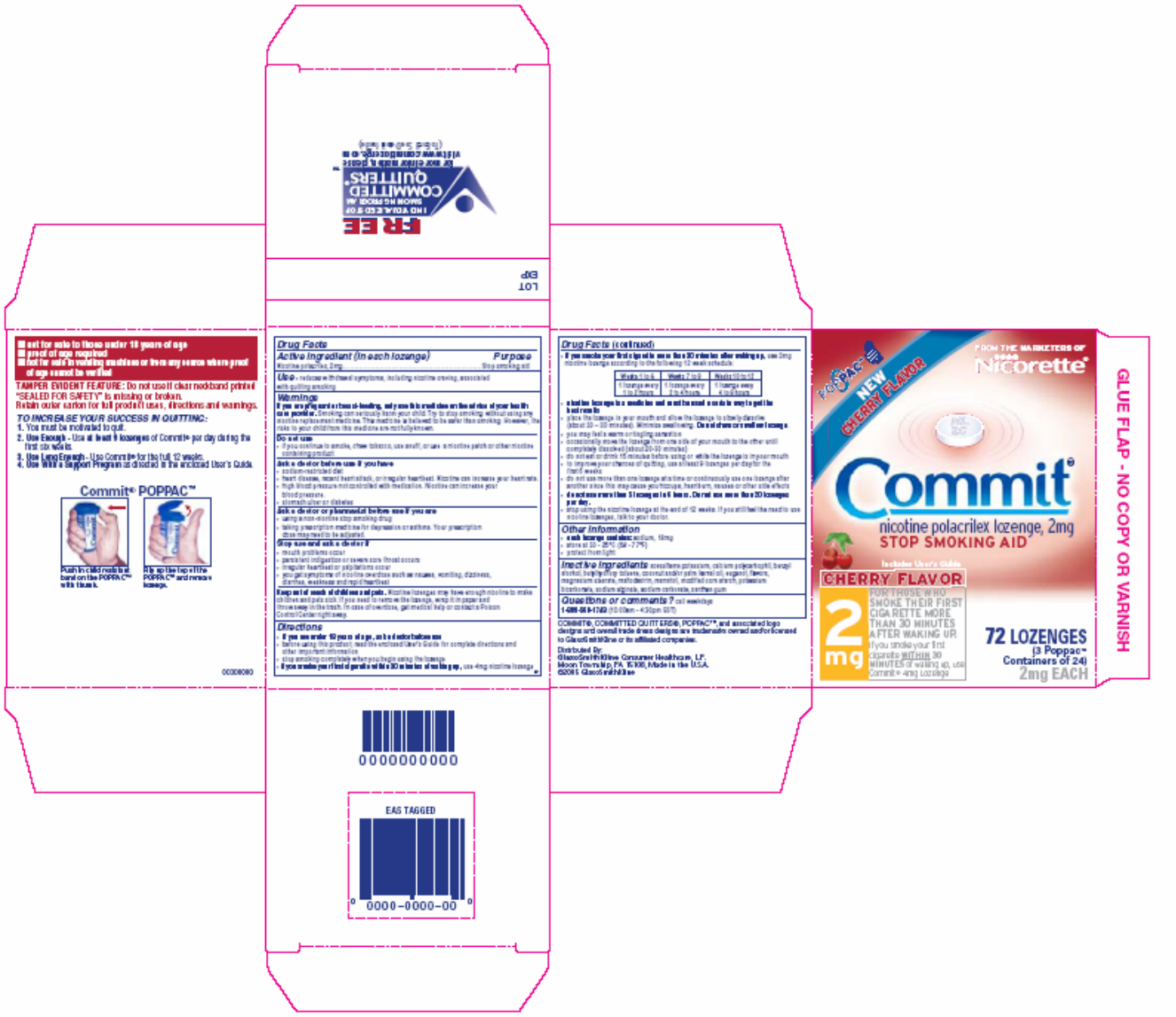
APPLICATION NUMBER:

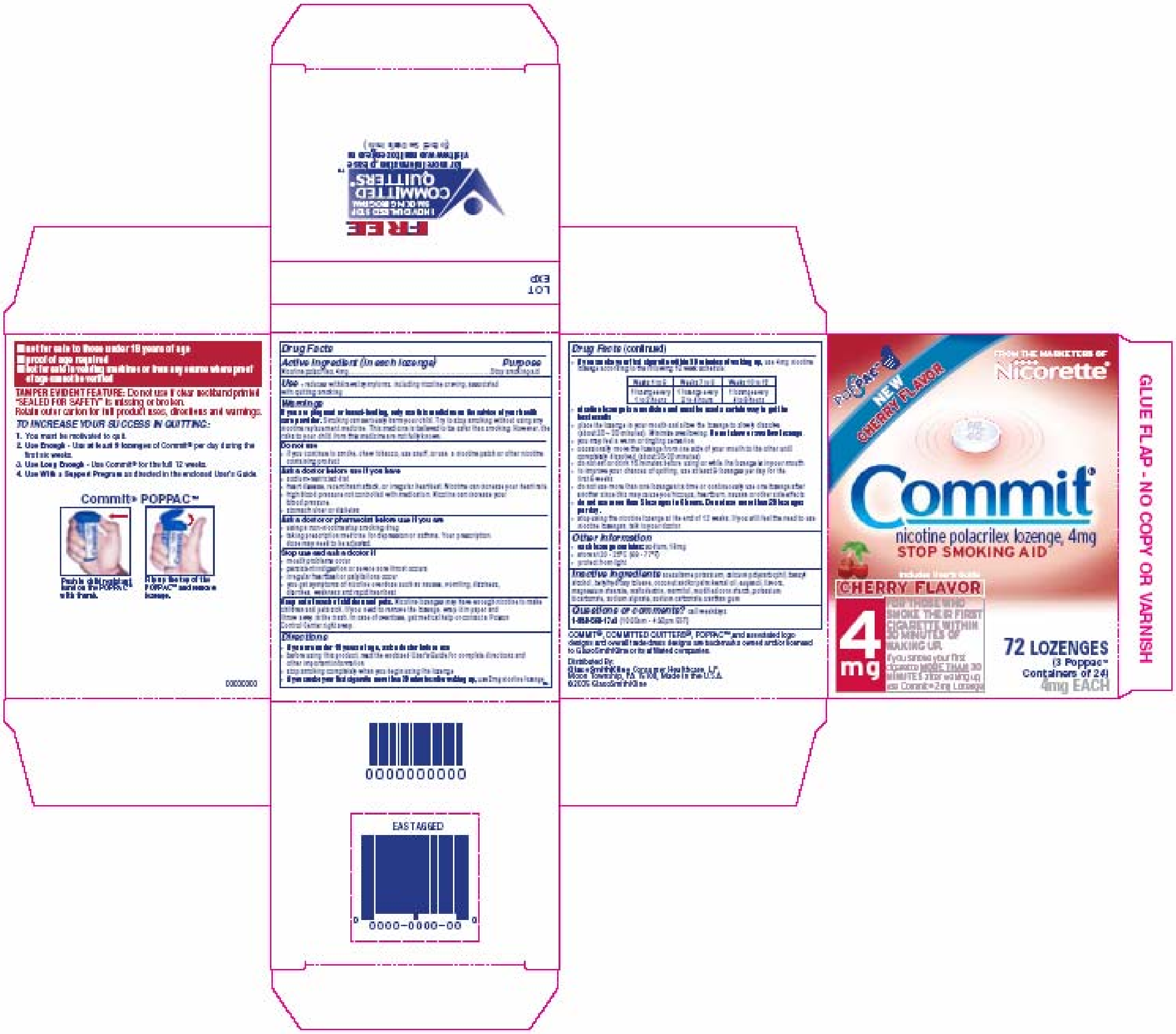
NDA 021330/S-004

LABELING


Commit® POPPAC™
Drug Facts
Active ingredient (in each lozenge)
Purpose
Use
Warnings
Do not use
Ask a doctor before use if you have
Ask a doctor or pharmacist before use if you are
Stop use and ask a doctor if
Keep out of reach of children and pets.
Directions
Drug Facts (continued)
Other information
Inactive ingredients
Questions or comments?
EAS TAGGED
0000-0000-00
FREE
EXP
LOT
Commit®
nicotine polacrilex lozenge, 2mg
STOP SMOKING AID
NEW CHERRY FLAVOR
CHERRY FLAVOR
2 mg
48 LOZENGES
(2 Poppac™ Containers of 24)
2mg EACH
GLUE FLAP - NO COPY OR VARNISH


Commit® POPPAC™
Drug Facts
Active Ingredient (In each lozenge)
Purpose
Uses
Warnings
Do not use
Ask a doctor before use if you have
Ask a doctor or pharmacist before use if you are
Stop use and ask a doctor if
Directions
Drug Facts (continued)
Other information
Inactive ingredients
Questions or comments?
FREE
LOT
EXP
0000000000
EAS TAGGED
0000-0000-00
FROM THE MARKETERS OF
Nicorette®
NEW
CHERRY FLAVOR
Commit®
nicotine polacrilex lozenge, 4mg
STOP SMOKING AID
CHERRY FLAVOR
4 mg
48 LOZENGES
(2 Poppac™ Containers of 24)
4mg EACH
GLUE FLAP - NO COPY OR VARNISH


Not for sale to those under 18 years of age
No proof of age required
Not for sale in vending machines or from any source where proof of age cannot be verified
TAMPER EVIDENT FEATURE: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken.
Retain outer carton for full product uses, directions and warnings.
TO INCREASE YOUR SUCCESS IN QUITTING:
1. You must be motivated to quit.
2. Use Enough - Use at least 9 lozenges of Commit® per day during the first six weeks.
3. Use Long Enough - Use Commit® for the full 12 weeks.
4. Use With a Support Program as directed in the enclosed User's Guide.
Commit® POPPAC™
Push in child resistant band on the POPPAC™ with thumb.
Flip open top of the POPPAC™ and remove lozenge.
00308080
Drug Facts
Active Ingredient (in each lozenge)
Purpose
Nicotine polacrilex, 2mg
Stop smoking aid
Use
Warnings
Do not use
Ask a doctor before use if you have
Ask a doctor or pharmacist before use if you are
Stop use and ask a doctor if
Keep out of reach of children and pets.
Directions
Drug Facts (continued)
Other Information
Inactive Ingredients
Questions or comments?
1-888-8Commit (8:00am - 4:30pm EST)
COMMIT®, COMMITTED QUITTERS®, POPPAC™, and associated logo designs and overall trade dress designs are trademarks owned and/or licensed to GlaxoSmithKline or its affiliated companies.
Distributed By:
GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108, Made in the U.S.A.
©2006 GlaxoSmithKline
LOT
EXP
0000000000
EAS TAGGED
0000-0000-00
FROM THE MARKETERS OF
Nicorette®
POPPAC™
NEW CHERRY FLAVOR
Commit®
nicotine polacrilex lozenge, 2mg
STOP SMOKING AID
CHERRY FLAVOR
2 mg
FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE MORE THAN 30 MINUTES AFTER WAKING UP.
If you smoke your first cigarette WITHIN 30 MINUTES of waking up, use Commit® 4mg Lozenge
72 LOZENGES
(3 Poppac™ Containers of 24)
2mg EACH
GLUE FLAP - NO COPY OR VARNISH


FREE
COMMITTED QUITTERS
LOT
EXP
TAMPER EVIDENT FEATURE: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken.
TO INCREASE YOUR SUCCESS IN QUITTING:
1. You must be motivated to quit.
3. Use Long Enough - Use Commit® for the full 12 weeks.
Commit® POPPAC™
00000000
Drug Facts
Active ingredient (in each lozenge)
Purpose
Use
Warnings
Do not use
Ask a doctor before use if you have
Ask a doctor or pharmacist before use if you are
Stop use and ask a doctor if
Directions
0000000000
EAS TAGGED
0000-0000-00
Drug Facts (continued)
Other information
Inactive ingredients
Questions or comments?
Distributed By:
FROM THE MARKETERS OF
Nicorette®
PopPac™
NEW CHERRY FLAVOR
Commit®
nicotine polacrilex lozenge, 4mg
STOP SMOKING AID
CHERRY FLAVOR
4 mg
FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE WITHIN 30 MINUTES OF WAKING UP.
72 LOZENGES
(3 Poppac™ Containers of 24)
4mg EACH
GLUE FLAP - NO COPY OR VARNISH


In case of overdose, get medical help or contact a Poison Control Center right away.
Retain outer carton for full product uses, directions and warnings. Discard after use.
Tamper Evident Feature: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken.
Distributed By:
GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108
Made in the U.S.A.
©2005 GlaxoSmithKline
00000XA
24 LOZENGES
Push in child resistant band on the POPPAC™ with thumb.
Flip up the top of the POPPAC™ and remove lozenge.
POPPAC™
Commit®
nicotine polacrilex lozenge, 2mg
STOP SMOKING AID
CHERRY FLAVOR
Directions:
Not for Individual Sale
Weeks 1 to 6
1 lozenge every 1 to 2 hours
Weeks 7 to 9
1 lozenge every 2 to 4 hours
Weeks 10 to 12
1 lozenge every 4 to 8 hours
Place the lozenge in your mouth and allow the lozenge to slowly dissolve. Occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 – 30 minutes). Do not eat or drink 15 minutes before using or while the lozenge is in your mouth.
Do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.
Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash.
76


In case of overdose, get medical help or contact a Poison Control Center right away.
Retain outer carton for full product uses, directions and warnings. Discard after use.
Tamper Evident Feature: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken.
Distributed By:
GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108
Made in the U.S.A.
©2005 GlaxoSmithKline
00000XA
24 LOZENGES
Push in child resistant band on the POPPAC™ with thumb.
Flip up the top of the POPPAC™ and remove lozenge.
POPPAC™
Commit®
nicotine polacrilex lozenge, 4mg
STOP SMOKING AID
CHERRY FLAVOR
Directions:
Not for Individual Sale
Weeks 1 to 6
1 lozenge every 1 to 2 hours
Weeks 7 to 9
1 lozenge every 2 to 4 hours
Weeks 10 to 12
1 lozenge every 4 to 8 hours
Place the lozenge in your mouth and allow the lozenge to slowly dissolve. Occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 – 30 minutes). Do not eat or drink 15 minutes before using or while the lozenge is in your mouth.
Do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.
Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash.
77

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021330/S-004

LABELING REVIEWS

Office of Non-prescription Products - Labeling Review for an NDA Supplement

NDA 21-330 / SCF-004

Submission Date:	July 22, 2005
Drug product:	Commit Cherry Lozenge, 2mg and 4mg
Active ingredient:	nicotine polacrilex
Pharmacological category:	stop smoking aid
Sponsor/Contact:	Iris H. Shelton Assistant Director, Regulatory Affairs GlaxoSmithKline 1500 Littleton Road Parsipanny, NJ 07054-3884 (973) 889-2167
Labeling submitted:	2mg carton labels: 48-ct (two 24-ct vials), 72-ct (three 24-ct vials) 4mg carton labels: 48-ct (two 24-ct vials), 72-ct (three 24-ct vials) 2mg vial label 4mg vial label 2mg and 4mg User's Guide
Reviewer:	Reynold Tan
Review date:	November 7, 2005
Project manager:	Laura Shay

Background: The sponsor submitted this supplemental new drug application for a new cherry-flavored formulation of their Commit Lozenge. The sponsor reported that this new Commit Cherry Lozenge met the current specifications of the approved Commit Mint Lozenge (S-002, approved 2/13/04). Commit Cherry Lozenge is packaged in 24-ct "Poppac" vials, in either a 48-ct carton (two vials) or a 72-ct carton (three vials). The sponsor proposed the "Poppac" vial enclosure system for the Commit Mint Lozenge in supplement SCP-003 (submitted 4/22/05 and 10/21/05). After review of SCP-003, FDA communicated several recommended label revisions to the sponsor in a 10/19/05 fax (see Reviewer's Recommendations below).

Reviewer's Comments:

1) The only differences between currently submitted labels for Commit Cherry Lozenge and Commit Mint Lozenge labels in SCP-003 are the following:

a) The statement "NEW CHERRY FLAVOR" replaces the statement "NEW & IMPROVED MINT FLAVOR" in the upper left-hand corner of the principal display panel.

Comment: This change is acceptable.

b) The tablet graphic is embossed with "NL 2C," instead of "NL 2S."

Comment: This change is acceptable.

c) The "Inactive ingredients" section lists the appropriate inactive ingredients for the new cherry-flavored formulation.

Comment: This change is acceptable. However, the ingredient listed as "palm kernal oil" should be properly spelled "palm kernel oil."

2) The sponsor did not yet incorporate any of the revisions (1-4) that FDA recommended following review of SCP-003. FDA communicated these recommended revisions to the sponsor in a 10/19/05 fax, and the sponsor agreed to make these revisions at the time of next printing or 180 days, whichever comes first.

Reviewer's Recommendations: The following comments can be conveyed to the sponsor:

1) In the "Inactive Ingredients" sections, correct the spelling of the ingredient listed as "palm kernal oil" to "palm kernel oil."

2) Please be reminded that FDA recommended the following label revisions after review of SCP-003 (BL) for Commit Mint Lozenge, submitted 10/21/05:

1. On vial labels and carton labels, revise the statement under the first vial graphic to read: "To open vial, push in child resistant band on the POPPAC with thumb."
2. Revise sentence 2 in paragraph 2 on vial labels to read: "Discard vial after use."
3. On vial labels, revise the first two sentences following the table to read: "Place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. Do not chew or swallow lozenge. Occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20–30 minutes)."
4. Revise the first bullet under "Warnings" to read "a sodium-restricted diet."

FDA communicated these recommended revisions to the sponsor in a 10/19/05 fax. The sponsor agreed to make these revisions at the time of next printing or 180 days, whichever comes. The sponsor should also apply these label revisions to the new Commit Cherry Lozenge.

Reynold Tan, Ph.D.	Helen Cothran, B.S.
IDS/Chemist	IDS/Team Leader

Table of Contents
NDA 21-330
COMMIT Cherry 2mg and 4mg Lozenge
NDA Supplement
Supplement - Prior Approval

Description	Electronic Archival Copy Folder/Filename
Item 2 - Table of Contents	labeling\labeltoc.pdf
Item 2 - Draft Labeling	labeling\ndaitem2.pdf
26103XA Commit User's Guide	labeling\usrguide.pdf
COMMIT 48ct 2mg Carton	labeling\com48ct2.pdf
COMMIT 48ct 4mg Carton	labeling\com48ct4.pdf
COMMIT 72ct 2mg Carton	labeling\com72ct2.pdf
COMMIT 72ct 4mg Carton	labeling\com72ct4.pdf
COMMIT 2mg 24ct Vial	labeling\commit2m.pdf
COMMIT 4mg 24ct Vial	labeling\commit4m.pdf

Note: Page numbers for each document are located in the lower left corner of each page.

Following this page, 34 pages withheld in full - draft labeling (b)(4)

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

/s/

Reynold Tan
11/10/2005 03:13:43 PM
INTERDISCIPLINARY

Helen Cothran
11/14/2005 09:10:09 AM
INTERDISCIPLINARY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021330/S-004

CHEMISTRY REVIEWS

Chemistry Review #1	**1. Division** HFD-560	**2. NDA/Supp. Number** 21-330/SCF-004
3. Name and Address of Applicant GlaxoSmithKline Attention: Iris H. Shelton Assistant Director, Regulatory Affairs 1500 Littleton Road Parsippany, NJ 07054-3884		**4. Date of** **Subm.** **Stamp** **User Fee** 7/22/05 7/26/05 11/26/05
5. Name of Drug Nicotine Polacrilex	**6. Nonproprietary Name** Nicotine	
7. Supplement Provides for: A cherry flavored Commit® Lozenge.		**8. Amendment(s)** 11/2/05
9. Pharmacological Category	**10. How Dispensed** OTC	**11. Related Documents** DMF (b) (4)
12. Dosage Form: Lozenge	**13. Potency(ies):** 2 mg and 4 mg	
14. Chemical Name and Structure see USAN		

15. **Comments**:

The firm developed a cherry flavored product in an effort to improve flavor and provide consumers with alternative nicotine replacement therapy lozenge options. All other excipients and manufacturing processes are identical to spearmint lozenge (supplement 002). There are no changes to the manufacture and control of the drug substance. The changes made are the change of the spearmint flavor to cherry flavor and aspartame to Acesulfame potassium.

The acceptance criteria for impurity (b) (4) is the currently approved.

A total of 3 full production batches for 2 mg and 4 mg strengths were placed on stability. Satisfactory 6 months of stability data for these batches were provided.

16. Conclusions and Recommendations: Recommend Approval.

17. Name	**Signature**	**Date**
Bart Ho Review Chemist		November 4, 2005

Following this page, 16 pages withheld in full - (b)(4)

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

/s/

Bartholomew Ho
11/4/2005 02:23:16 PM
CHEMIST

John Smith
11/4/2005 02:29:33 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021330/S-004

PHARMACOLOGY AND TOXICOLOGY REVIEWS

FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Rheumatology Products
HFD-170, 10903 New Hampshire Avenue, Silver Spring, MD 20993

CONSULTATION

Date:	November 22, 2005
To:	Laura Shay, Project Manager Office of Nonprescription Products HFD-560
Through:	Rigoberto Roca, M.D. Deputy Division Director, DAARP
From:	R. Daniel Mellon, Ph.D. Supervisory Pharmacologist, DAARP
Subject:	**NDA 21-330** **Prior Approval Supplement** **Commit® Cherry (nicotine polacrilex)** **2 mg and 4 mg Lozenge**
Date of Submission:	July 22, 2005
Date Response Requested (Priority):	November 22, 2005

Background: GlaxoSmithKline has submitted this supplement for a Cherry Flavored Commit lozenge in an effort to improve flavor. The Office of Nonprescription Products requested a review of the pre-clinical data contained in this prior approval chemistry supplement. The full submission is located in the Electronic Document Room under N21330/S004 22-July-2005.

The following table lists the quantitative composition of the Cherry Lozenge (Table 4.A.2-1 of the Sponsor's submission).

Table 4.A.2-1
Quantitative Composition of Nicotine Polacrilex Cherry Lozenges

Ingredient Name	Composition (mg/lozenge)	
	2 mg lozenge	4 mg lozenge
(b) (4)		
Total lozenge weight	1253.70	1253.70
1 (b) (4)		
2		
3		

Pharmacology Toxicology Assessment of Proposed Formulation

For the cherry formulation, the Sponsor has substituted acesulfame potassium for the aspartame that was used in the spearmint lozenge. Acesulfame potassium is listed in the Inactive Ingredient Database for Approved Drug Products. In addition, the CFR 21 (172.800) indicates that Acesulfame K may be safely used as a sweetening agent in chewing gum with no limits on the maximum amount other than the amount should not exceed that reasonably required to accomplish the intended effect. There are no preclinical concerns regarding this excipient.

The Cherry (b) (4) Flavor ((b) (4)) in the new formulation replaces the Mint (b) (4) that was approved for the Spearmint flavored lozenge. Current DMFs have been filed by the manufacturers of these flavoring agents. In his review dated November 4, 2005, Dr. Bart Ho, the Review Chemist, noted that the DMFs are adequate.

The Sponsor states the following:

> The flavors, (b) (4) are certified by the manufacturers to comply with the requirements of the Food, Drug and Cosmetic Act and contain only ingredients which are listed as approved for use in a regulation of FDA, are listed as being generally recognized as safe on the FEMA [Flavor and Extract Manufacturers Association] GRAS lists and/or are foods. The sweetener, acesulfame potassium, is designated by FDA as a substance that may be safely used as a sweetening agent in food when used at a level not exceeding the amount reasonably required to accomplish the intended effect. Exposure to these excipient ingredients from use of the Application Product at the recommended dosage presents no significant toxicological risk.

Following discussion with Dr. Ho regarding the chemical composition of the flavoring agents and the designation of GRAS by FEMA, the flavoring agents appear to be adequately qualified for safety in the drug product. The remaining ingredients in the Cherry Lozenge formulation are identical to those found in the approved Spearmint Lozenge.

Impurity Specifications

The Sponsor proposed the following release and stability specifications for impurities/degradation products (modified from Table 4.A.2-9 and Table 4.A.2-10):

Impurity/Degradation Products	*Release Specification 2 mg Lozenge*	*Release Specification 4 mg Lozenge*
(b) (4)		
Individual unspecified impurities		
Sum of all impurities		

Impurity/Degradation Products	*Stability Specification 2 mg Lozenge*	*Stability Specification 4 mg Lozenge*
		(b) (4)
Individual unspecified impurities		
Sum of all impurities		

The above specifications are consistent with those in the approved spearmint lozenge and are acceptable for this drug product.

The Sponsor also provided a summary of recently published studies that provide additional characterization of the potential toxicity of nicotine. Although these publications suggest that nicotine may contribute to diverse toxicity (including reproductive, developmental, and genetic toxicity), the risks associated with continued smoking would far outweigh the risks associated with exposure to nicotine in this form as part of a smoking cessation program.

Overall recommendations: From the pharmacology toxicology perspective, the specifications for the levels of impurities in the drug product are acceptable for this drug product's indication. There are no preclinical concerns with the use of acesulfame potassium. According to the Sponsor, the (b) (4) flavoring agents, Cherry (b) (4) flavor (b) (4) have been evaluated by the Flavor and Extract Manufacturers Association (FEMA) and designated GRAS. Both DMFs are adequate according to the Chemistry Reviewer. Therefore, from the nonclinical perspective, supplement S004 can be approved.

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

/s/

R. Daniel Mellon
11/22/2005 01:06:30 PM
PHARMACOLOGIST

Rigoberto Roca
11/22/2005 01:08:30 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021330/S-004

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-330 (SCF 004)
Submission Date	7/22/2005
Brand Name	Commit® Cherry Lozenge (2 mg and 4 mg)
Generic Name	Nicotine Polacrilex
Reviewer	Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCPB Division	DCPB2
OND Division	ONP/DNCE
Sponsor	GlaxoSmithKline
Submission Type	Supplement-Prior Approval

Executive Summary

Nicotine as a nicotine replacement therapy is available in many different formulations, such as polacrilex chewing gum (Nicorette), transdermal patch, inhaler, nasal spray and lozenge.

GlaxoSmithKline has approved mint-flavored nicotine lozenges marketed as Commit™ (NDA 21-330, Oct 31, 2002) Lozenges in 2- and 4-mg strength and spearmint-flavored nicotine lozenges in 2- and 4-mg strength (NDA 21-330, supplement 002).

This supplement was submitted to allow for a change in flavor of Commit® (Nicotine Polacrilex) Lozenge (2 mg and 4 mg) to a cherry flavor in an effort to improve flavor and provide consumers with alternative nicotine replacement therapy lozenge options. All other excipients and manufacturing processes are identical to spearmint lozenge (supplement 002). There are no changes to the manufacture and control of the drug substance.

The flavor change of the formulations for the new product is below the limits previously supported with the *in vivo* PK studies and the new flavor lozenges meet current lozenge specifications. Based upon this and agreement to restrict other formula variations, the Sponsor proposed (letter dated 5/9/03), and FDA agreed (letter dated 6/2/03) that establishment of bioequivalence for new flavor variations using in-vitro dissolution comparisons with the original, approved Nicotine Polacrilex Lozenges was acceptable.

In this supplement, the Sponsor included the comparative *in vitro* dissolution data as the basis of this application. The model independent approach that uses a difference factor (f_1) and a similarity

factor (f_2) to compare the dissolution profiles was used to determine the similarity between the dissolution profiles of the original and new flavor formulations.

The results of the f_1 and f_2 testing along with a visual examination of the data reveal that the change in flavor has had little if any effect on the release of nicotine from the lozenge. These data support that the proposed cherry-flavored products are similar to the currently marketed Commit® Lozenge (2 mg and 4 mg) products.

Recommendations

Form a Clinical Pharmacology and Biopharmaceutics perspective, this supplemental NDA 21-330 is acceptable.

_____

Lei Zhang, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology and Biopharmaceutics II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: _____

Suresh Doddapaneni, Ph.D.
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology and Biopharmaceutics II
Office of Clinical Pharmacology and Biopharmaceutics

Review of *In Vitro* Release Data

Study Report: Comparison of the In Vitro Nicotine Release Profiles of (b) (4) Lozenges and (b) (4) Cherry Lozenges

Objective: This study was conducted to compare the *in vitro* dissolution profiles of (b) (4) Cherry Nicotine Lozenges versus (b) (4) Nicotine Lozenges in three different dissolution media. The results from this study are used to ensure that the dissolution profiles of the two products are comparable.

(Reviewer's Note: The formulation of (b) (4) Lozenge is the same as the original lozenge formulation and the formulation for (b) (4) Cherry lozenges is the same as the proposed cherry-flavored lozenge formulation (Table 1, and Tables A1 and A2 in Appendix).)

Formulation Comparison:

As compared with those of (b) (4) Nicotine Lozenges, the formulations of (b) (4) Cherry Lozenges are changed in the flavor (b) (4) and the amount of flavor used.

Expressed as percentage (w/w) of total formulation, the content of flavor (b) (4) is (b) (4)% in (b) (4) Lozenge and (b) (4)% in (b) (4) Cherry Lozenge (Table 1).

Table 1. Formulations of (b) (4) (Cherry) versus Formulations of (b) (4) (Original).

Ingredient Name	QCS Reference No.	2 mg (b) (4) MFC#10449-002-0002	4 mg (b) (4) MFC# 10449-003-0002	2 mg Cherry MFC# MFC50418	4 mg Cherry MFC# MFC50420
(b) (4)					
TOTALS		1200.000	1200.000	1253.70	1253.70

Lots Tested:

Test (2 batches each):

2 mg Nicotine Lozenges ((b) (4) Cherry), MFC 50418, Batch#9057XP-4001 and 9057XP-4003

4 mg Nicotine Lozenges (Cherry), MFC 50420, Batch#9059XP-4001 and 9059XP-4003

Reference (1 batch each):

2 mg Nicotine Lozenges ((b) (4)), MFC 10449-002-0002, Batch# 9003FP4025

4 mg Nicotine Lozenges ( ), MFC 10449-003-0002, Batch# 9005FP4058

Methods:
Dissolution method (C-1926.07) was used for comparison studies of the Nicotine Lozenges. This method uses USP phosphate buffer at pH 7.4 as dissolution media and the dissolution test is conducted at 37 ± 0.5°C in 900 mL of dissolution media. The specifications for *in vitro* dissolution tests for Nicotine Lozenges in pH 7.4 phosphate buffer is presently given as no more than (b)(4)% LC Release at 1 hour and no less than (b)(4)% LC Release at 8 hours. The dissolution comparison tests were performed following method C-1926.07 with the modifications in different media used. Three dissolution media were used: 0.1 N hydrochloric acid, Acetate Buffer at pH 4.5 and Phosphate Buffer at pH 7.4. The time points for dissolution comparison were set at 1, 3, 6, and 8 hours. 12 individual dosage units of the reference product ((b) (4)) and test product ((b) (4) Cherry) were used for testing. For all media tested, automated sample collections were used. The total dissolution volume was 900 mL and the media were replaced after sample withdrawal at every set time point.

The model independent approach that uses a difference factor (f_1) and a similarity factor (f_2) to compare the dissolution profiles was used. For the two dissolution curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values in the range of 0 – 15 and f_2 values in the range of 50 – 100 ensure sameness or equivalence of the two curves and, thus, of the performance of the two products.

Results:
Overall the results from in vitro testing of different lots of nicotine products under different media gave reproducible results across strengths (See Tables A3-A8, Appendix).

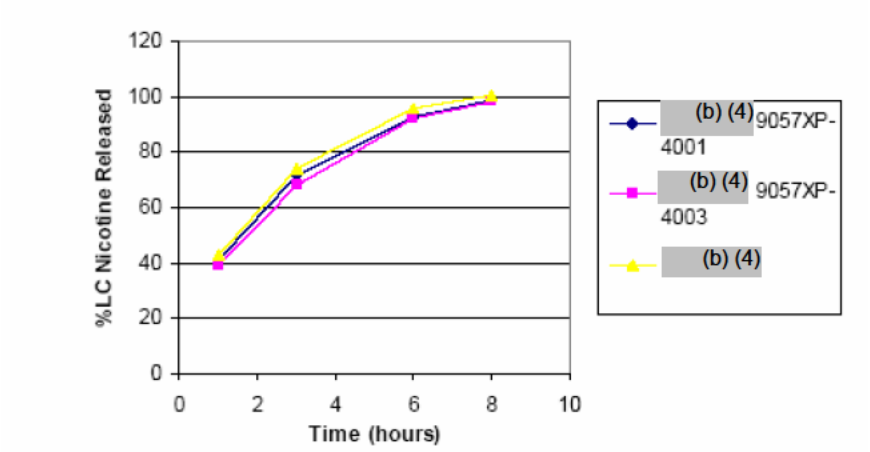
In terms of f_1 and f_2 testing, the following results were obtained:

Table 2. The Difference (f_1) and Similarity (f_2) Factors between (b) (4) and (b) (4)

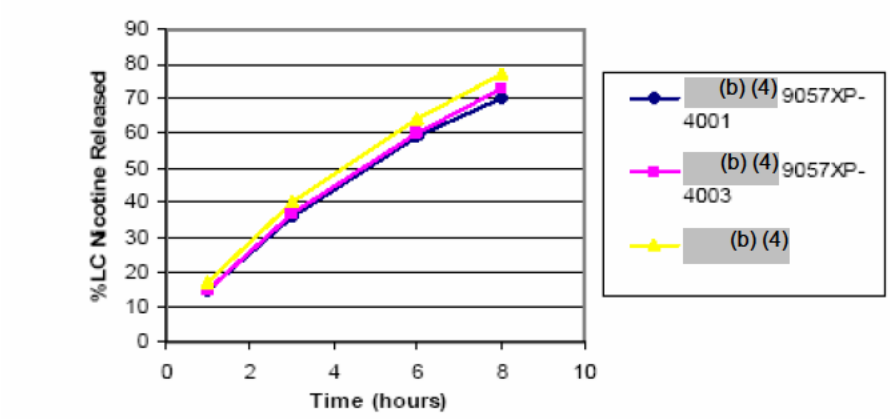
Formulation	Batch #	Difference Factor f_1 (Acceptance Criteria: 0 - 15)			Similarity Factor f_2 (Acceptance Criteria: 50 - 100)		
		Dissolution Media			Dissolution Media		
		0.1 N HCL	pH 4.5	pH 7.4	0.1 N HCL	pH 4.5	pH 7.4
(b) (4) 2 mg vs (b) (4) 2mg	9057XP-4001	3	9	4	80	65	73
	9057XP-4003	5	7	5	67	73	70
(b) (4) 4 mg vs (b) (4) 4mg	9059XP-4001	3	13	4	80	59	75
	9059XP-4003	1	8	4	91	70	75

The Difference Factors (f_1) and the Similarity Factors (f_2) between (b) (4) Lozenges and (b) (4) Lozenges in all three dissolution media meet the FDA acceptance criteria (0 – 15 for difference factors and 50 – 100 for similarity factors), indicating that the dissolution profiles for (b) (4) and (b) (4) are similar.

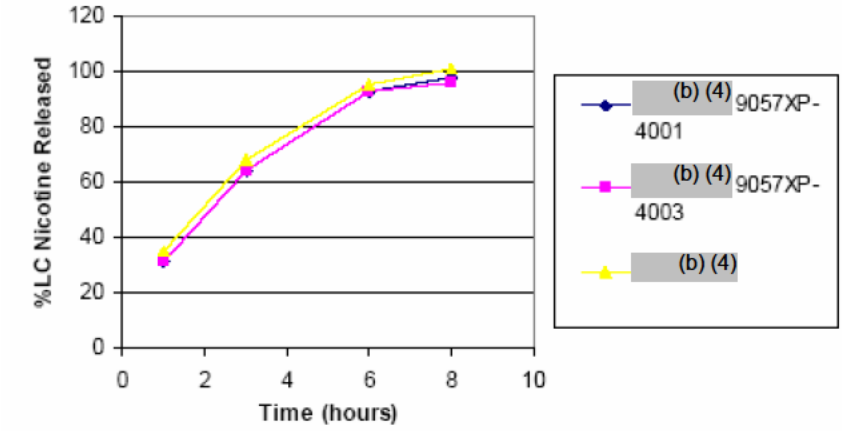
In vitro nicotine release profiles for the proposed cherry-flavored lozenge products and the original lozenge products are shown in Figures 1 and 2.



a) 0.1 N HCl

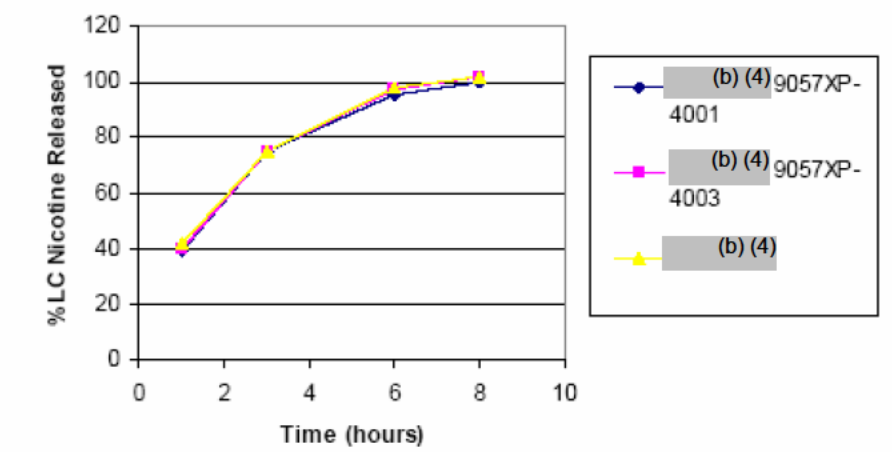


b) Acetate Buffer pH 4.5

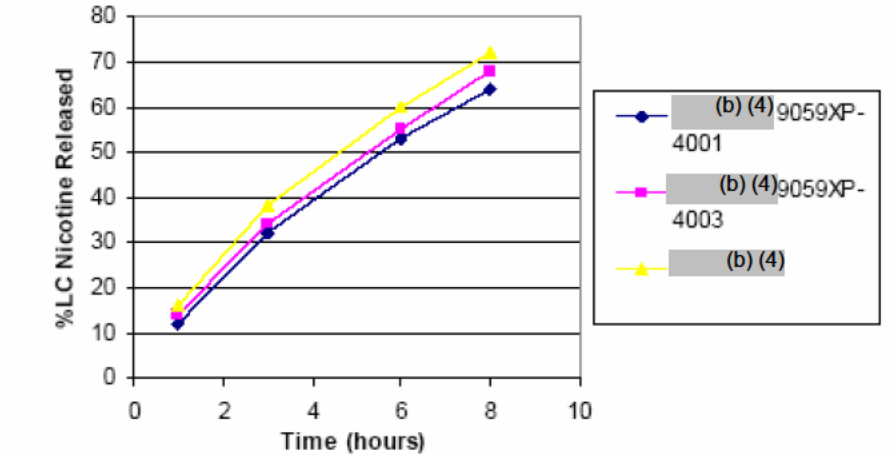


c) Phosphate Buffer pH 7.4

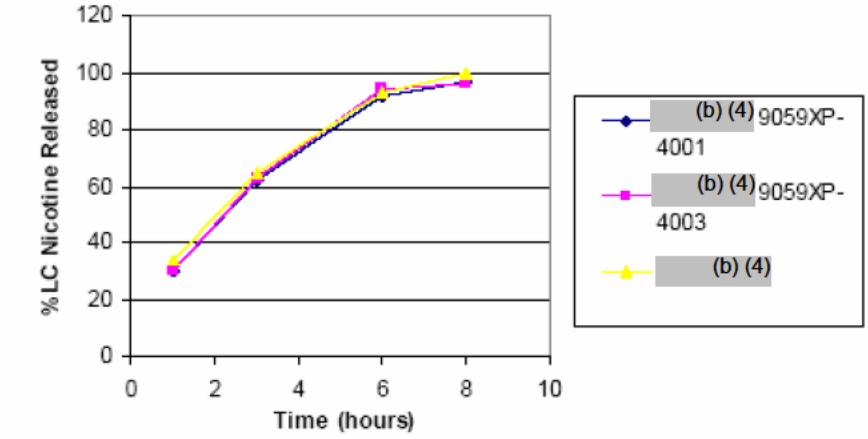
Figure 1. Dissolution Profiles of 2 mg Nicotine Products in pH 1 (a), 4.5 (b) and 7.4 (c) Media.



a) 0.1 N HCl



b) Acetate Buffer pH 4.5



c) Phosphate Buffer pH 7.4

Figure 2. Dissolution Profiles of 4 mg Nicotine Products in pH 1 (a), 4.5 (b) and 7.4 (c) Media.

Conclusions:

The changes in the formulations from (b) (4) (original) Nicotine Lozenge to (b) (4) (Cherry-Flavored) Lozenge did not affect the *in vitro* dissolution performance of the products. The dissolution profiles of (b) (4) and (b) (4) are similar in all three dissolution media tested.

Appendix.

Table A1.

Table 3. The components and composition of the original mint-flavored 2- and 4-mg Commit Lozenges are provided below:

Ingredients	Composition (mg/lozenge)	
	2 mg strength	4 mg strength
(b) (4)		
Total Weight	1200.00	1200.00

Table A2.

Quantitative Composition of Nicotine Polacrilex Cherry Lozenges

Ingredient Name	Composition (mg/lozenge)	
	2 mg lozenge	4 mg lozenge
(b) (4)		
Total lozenge weight	1253.70	1253.70
(b) (4)		

Table A3. Dissolution Profile of 2mg Nicotine Products in 0.1N HCl.

TIME (hour)	2 mg Cherry Batch# 9057XP-4001 LNB# G9460/13 and G9460/20				2 mg Cherry Batch# 9057XP-4003 LNB# G9460/26 and G9460/32				2 mg (b) (4) Batch# 9003FP4025 LNB#G9295/115 and G9287/140			
	%LC Nicotine Release			%RSD	%LC Nicotine Release			%RSD	%LC Nicotine Release			%RSD
	Set1	Set2 (b) (4)	Mean		Set1	Set2 (b) (4)	Mean		Set1	Set2 (b) (4)	Mean	
1			41	1.8			39	1.0			43	2.1
3			72	1.3			68	1.8			74	2.5
6			93	1.8			92	2.2			96	1.6
8			99	1.7			98	1.9			101	1.3

Table A4. Dissolution Profile of 2mg Nicotine Products in Acetate Buffer pH 4.5.

TIME (hour)	2 mg Cherry Batch# 9057XP-4001 LNB# G9473/11 and G9473/16				2 mg Cherry Batch# 9057XP-4003 LNB# G9473/21 and G9473/26				2 mg (b) (4) Batch# 9003FP4025 LNB#G9322/43 and G9322/57			
	%LC Nicotine Release			%RSD	%LC Nicotine Release			%RSD	%LC Nicotine Release			%RSD
	Set1	Set2	Mean		Set1	Set2	Mean		Set1	Set2	Mean	
1	(b) (4)		15	6.7	(b) (4)		15	4.8	(b) (4)		17	4.2
3			36	2.9			37	3.3			40	6.1
6			59	2.2			60	2.1			64	6.2
8			70	2.1			73	2.1			77	4.5

Table A5. Dissolution Profile of 2mg Nicotine Products in Phosphate Buffer pH 7.4.

TIME (hour)	2 mg Cherry Batch# 9057XP-4001 LNB# G9442/22 and G9442/112 %LC Nicotine Release			%RSD	2 mg Cherry Batch# 9057XP-4003 LNB# G9442/33 and G9460/6 %LC Nicotine Release			%RSD	2 mg (b) (4) Batch# 9003FP4025 Aiken %Lc Nicotine Release			%RSD
	Set1	Set2	Mean		Set1	Set2	Mean		Set1	Set2	Mean	
1	(b) (4)		31	3.7	(b) (4)		31	3.8	(b) (4)		35	2.2
3			64	2.9			64	3.3			68	2.1
6			93	1.7			93	2.3			95	0.9
8			98	1.6			96	2.9			101	1.0

Table A6. Dissolution Profile of 4mg Nicotine Products in 0.1N HCl.

TIME (hour)	4 mg Cherry Batch# 9059XP-4001 LNB# G9442/127 and G9460/38				4 mg Cherry Batch# 9059XP-4003 LNB# G9460/44 and G9461/78				4 mg (b) (4) Batch# 9005FP4058 LNB#G9287/146 and G9286/134			
	%LC Nicotine Release			%RSD	%LC Nicotine Release			%RSD	%LC Nicotine Release			%RSD
	Set1	Set2	Mean		Set1	Set2	Mean		Set1	Set2	Mean	
1	(b) (4)		39	1.3	(b) (4)		40	2.6	(b) (4)		42	1.6
3			75	4.3			75	3.6			75	1.9
6			95	2.7			97	3.5			98	1.1
8			100	2.1			102	3.6			102	1.2

Table A7. Dissolution Profile of 4mg Nicotine Products in Acetate Buffer pH 4.5.

TIME (hour)	4 mg Cherry Batch# 9059XP-4001 LNB# G9460/76 and G9460/83				4 mg Cherry Batch# 9059XP-4003 LNB# G9473/31 and G9460/89				4 mg (b) (4) Batch# 9005FP4058 LNB#G9322/51 and G9322/62			
	%LC Nicotine Release			%RSD	%LC Nicotine Release			%RSD	%LC Nicotine Release			%RSD
	Set1	Set2	Mean		Set1	Set2	Mean		Set1	Set2	Mean	
1	(b) (4)		12	16.4	(b) (4)		14	13.7	(b) (4)		16	4.2
3			32	5.2			34	5.6			38	3.8
6			53	4.1			55	5.0			60	3.6
8			64	4.1			68	3.8			72	2.5

Table A8. Dissolution Profile of 4mg Nicotine Products in Phosphate Buffer pH 7.4.

TIME (hour)	4 mg Cherry Batch# 9059XP-4001 LNB# G9442/42 and G9442/117 %LC Nicotine Release			%RSD	4 mg Cherry Batch# 9059XP-4003 LNB# G9442/52 and G9442/122 %LC Nicotine Release			%RSD	4 mg (b) (4) Batch# 9005FP4058 Aiken %LC Nicotine Release			%RSD
	Set1	Set2	Mean		Set1	Set2	Mean		Set1	Set2	Mean	
1	(b) (4)		30	3.6	(b) (4)		30	2.2	(b) (4)		34	3.3
3			62	2.6			63	1.6			65	1.6
6			92	0.9			94	0.8			93	1.7
8			97	1.4			96	2.6			100	1.5

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

/s/

Lei K Zhang
11/17/2005 11:44:52 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
11/17/2005 11:52:40 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021330/S-004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-330/S-004

PRIOR APPROVAL SUPPLEMENT

GlaxoSmithKline Consumer Healthcare
Attention: Iris Shelton
Assistant Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Shelton:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Commit® (2mg and 4mg nicotine polacrilex) Lozenge

NDA Number: 21-330

Supplement number: 004

Date of supplement: July 22, 2005

Date of receipt: July 22, 2005

This supplemental application proposes a new cherry flavor.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 20, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 22, 2005.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Office of Nonprescription Products, HFD-560
Attention: Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products, HFD-560
Attention: Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions, call Laura Shay, Regulatory Project Manager, at (301) 827-2274.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Acting Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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

/s/

Leah Christl

8/17/2005 11:20:56 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Div. of Anesthetic, Critical Care, and Addiction Drug Prod.
HFD-170
PharmTox

FROM:
Laura Shay, PM
HFD-560
Office of Nonprescription Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 27, 2005		21-330	Prior Approval Chemistry Suppl.	July 22, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Commit® Lozenge		Nicotine Replacement Product	October 26, 2005

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
- X 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 X OTHER (SPECIFY BELOW): Pharmtox

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
- X PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the pre-clinical data contained in this prior approval chemistry supplement for a new cherry flavored Commit® lozenge. Thank you.

The full submission is in the EDR: under N21330/S004 SCS 22-July-2005

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

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

/s/

Curtis Rosebraugh

7/28/05 08:23:15 AM