Lewis, Mary

From: Lewis, Mary
Sent: Thursday, December 18, 2008 9:33 AM
To: 'Iris.H.Shelton@gsk.com'
Cc: Lewis, Mary
Subject: NDA 22-360; MDS received a 483 b(4)

Hi Iris,

We think it is not likely that the PDUFA goal date will be affected, but we cannot commit to it. You should submit it as soon as you can.

Thank you.

Mary

Mary M. Lewis, RN, BSN
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Phone: 301-796-0941

-----Original Message-----
From: Iris.H.Shelton@gsk.com [mailto:Iris.H.Shelton@gsk.com]
Sent: Friday, December 12, 2008 2:25 PM
To: Lewis, Mary
Subject: NDA 22-360

Hi Mary,
This is regarding NDA 22-360. We were advised by MDS, who conducted the BE Study (S3010567) they received a 483 with observations regarding the bioanalytical portion of the study.
To address this, GSK is proceeding with a reanalysis of samples. We intend to submit this data as an amendment to the subject NDA by 2/18/09 (prior to the final review quarter). We would appreciate confirmation that this is acceptable to the Agency and will not impact the PDUFA action date of 5/18/09.

Please let me know if you need any additional information. Thanks in advance for your prompt handling.

Regards,
Iris

Iris H. Shelton
GlaxoSmithKline Consumer Healthcare

973-889-2167

Lewis, Mary

From: Lewis, Mary
Sent: Tuesday, December 16, 2008 10:47 AM
To: 'Iris.H.Shelton@gsk.com'
Subject: NDA 22-360; Commit Mini Lozenge; Information Request letter
Attachments: Email IR to GSK 121608.pdf

Hi Iris,

This IR letter was sent out yesterday. We look forward to your response. Please confirm you have received this email with attachment.

I still haven't heard a response to your question about the MDS, 483 and submitting information to us by 2/18/09.

Mary

Mary M. Lewis, RN, BSN
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Phone: 301-796-0941
Fax: 301-796-9899
Email: Mary.1.Lewis@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-360

INFORMATION REQUEST LETTER

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

Dear Ms. Shelton:

Please refer to your July 18, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Commit® Mini (2 mg and 4 mg, nicotine polacrilex) lozenge.

We are reviewing your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Clarify the proposed proprietary name of your product. The dosage form has been stated several different ways throughout the submission (Commit Mini Mint Lozenges; Commit Mini Lozenge; Mini Mint Lozenges, etc.). Also, clarify if it is your intent to include the word "lozenge" as part of the proprietary name.
2. On the inner container label submitted for NDA 22-360 you have termed the package configuration a "vial". Is that correct or did you mean to use the term "[redacted]" as used in NDA 21-330? b(4)
3. Are you planning to manufacture the mini lozenge only in mint flavor, or will you be manufacturing all seven flavors that are approved under NDA 21-330?
4. Do you intend to discontinue the currently marketed Commit lozenge if the Commit Mini lozenge is approved? If you do intend to discontinue the current Commit lozenge, what will the timeframe be?
5. Please provide justification for the use of the new flavoring system, especially at the level you propose to use for the following ingredient: [redacted]. For more information, please refer to the FDA guidance entitled "Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients". b(4)

If you have any questions, call Mary Lewis, Regulatory Health Project Manager, at 301-796-0941.

Sincerely,

{See appended electronic signature page}

Melissa Hancock Furness
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/

Melissa Furness
12/15/2008 05:13:28 PM

Lewis, Mary

From: Iris.H.Shelton@gsk.com
Sent: Friday, December 12, 2008 2:25 PM
To: Lewis, Mary
Subject: NDA 22-360

Hi Mary,
This is regarding NDA 22-360. We were advised by MDS, who conducted the BE Study (S3010567) they received a 483 with observations regarding the bioanalytical portion of the study.
To address this, GSK is proceeding with a reanalysis of samples. We intend to submit this data as an amendment to the subject NDA by 2/18/09 (prior to the final review quarter). We would appreciate confirmation that this is acceptable to the Agency and will not impact the PDUFA action date of 5/18/09.

Please let me know if you need any additional information. Thanks in advance for your prompt handling.

Regards,
Iris

Iris H. Shelton
GlaxoSmithKline Consumer Healthcare
973-889-2167

Lewis, Mary

From: Iris.H.Shelton@gsk.com
Sent: Tuesday, November 18, 2008 9:17 AM
To: Lewis, Mary
Subject: Re: NDA 22-360; Commit Mini Mint Lozenge; need for information
Attachments: dataset information 2.PDF

Hi Mary,

Attached is the information for Study 466.

With respect to the other 2 studies, 329 and 320, they used nicotine polacrilex gum as the control. Therefore, they did not capture time to first cigarette as this product is based on number of cigarettes per day.

Please let me know if you need any additional information.

Regards,
Iris

"Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>

17-Nov-2008 14:49

To Iris.H.Shelton@gsk.com
cc
Subject NDA 22-360; Commit Mini Mint Lozenge; need for information

Hi Iris,

Thank you for sending this information. One thing is missing from 3 of the study reports.

You didn't tell us time to first cigarette in minutes on the following studies:
466
339
320

Please send at your earliest convenience.
Thank you.

Mary

From: Iris.H.Shelton@gsk.com [mailto:Iris.H.Shelton@gsk.com]
Sent: Monday, November 17, 2008 1:49 PM
To: Lewis, Mary
Subject: Re: NDA 22-360; Commit Mini Mint Lozenge; need for information

Hi Mary,
The information requested may be found in the reports. To facilitate review, I've provided copies in the attachment. Please contact me if you need any further information.

Regards,
Iris

"Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>

10-Nov-2008 13:38

To Iris.H.Shelton@gsk.com
cc
Subject NDA 22-360; Commit Mini Mint Lozenge; need for information

Hi Iris,

We need the following information from the 3 Phase I and 3 Phase II studies:

- the number of cigarettes smoked per day per subject
- the time in minutes only to the first cigarette smoked per subject

If you can get that to us within the next two weeks we would appreciate it.

Thank you.

Mary

Data Listing 2.17
Smoking History

Subject Number	Study Period	On Average, How Many Cigarettes Smoked Per Day In Last Year?	From Waking, How long Until First Cigarette? (Minutes)
1	Screen	7	15
2	Screen	20	15
3	Screen	14	30
4	Screen	40	10
5	Screen	20	15
6	Screen	14	10
7	Screen	18	10
8	Screen	20	10
9	Screen	5	30
10	Screen	3	30
11	Screen	14	20
12	Screen	13	15
13	Screen	20	5
14	Screen	14	20

(Continued)

Note: Treatment A = 4 mg nicotine polacrilex mini lozenge
Treatment B = 4 mg nicotine polacrilex standard lozenge

Data Listing 2.17
Smoking History

Subject Number	Study Period	On Average, How Many Cigarettes Smoked Per Day In Last Year?	From Waking, How long Until First Cigarette? (Minutes)
15	Screen	20	15
16	Screen	20	15
17	Screen	20	10
18	Screen	33	15
19	Screen	17	10
20	Screen	20	15
21	Screen	14	30
22	Screen	30	25
23	Screen	30	5
24	Screen	20	5
25	Screen	30	5
26	Screen	16	30
27	Screen	4	30
28	Screen	20	15

Note: Treatment A = 4 mg nicotine polacrilex mini lozenge
Treatment B = 4 mg nicotine polacrilex standard lozenge

Program: DM_P14:[HLAA40514.STSAS.LIS]LIS_SHQ.SAS

Source: ShqAA40514.sas7bdat

Lewis, Mary

From: Lewis, Mary
Sent: Monday, November 17, 2008 2:49 PM
To: 'Iris.H.Shelton@gsk.com'
Subject: NDA 22-360; Commit Mini Mint Lozenge; need for information

Hi Iris,

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You didn't tell us time to first cigarette in minutes on the following studies:
466
339
320

Please send at your earliest convenience.
Thank you.

Mary

From: Iris.H.Shelton@gsk.com [mailto:Iris.H.Shelton@gsk.com]
Sent: Monday, November 17, 2008 1:49 PM
To: Lewis, Mary
Subject: Re: NDA 22-360; Commit Mini Mint Lozenge; need for information

Hi Mary,
The infomation requested may be found in the reports. To facilitate review, I've provided copies in the attachment. Please contact me if you need any further information.

Regards,
Iris

"Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>

10-Nov-2008 13:38

To Iris.H.Shelton@gsk.com
cc
Subject NDA 22-360; Commit Mini Mint Lozenge; need for information

Hi Iris,

We need the following information from the 3 Phase I and 3 Phase II studies:

- the number of cigarettes smoked per day per subject
- the time in minutes only to the first cigarette smoked per subject

If you can get that to us within the next two weeks we would appreciate it.

Thank you.

Mary

Study Report	Table
S2300319	 319
S2300320	 320
S2300339	 339
S3010445	 445
S3010466	 466
S3010567	 567

Lewis, Mary

From: Iris.H.Shelton@gsk.com
Sent: Wednesday, November 12, 2008 2:24 PM
To: Lewis, Mary
Subject: Re: NDA 22-360; Commit Mini Mint Lozenge; need for information
Follow Up Flag: Follow up
Flag Status: Red

Hi Mary,
We'll try to include this with the submittion of the data tabulations for the Phase 1 studies.

Regards,
Iris

"Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>

10-Nov-2008 13:38

To Iris.H.Shelton@gsk.com
cc
Subject NDA 22-360; Commit Mini Mint Lozenge; need for information

Hi Iris,

We need the following information from the 3 Phase I and 3 Phase II studies:

- the number of cigarettes smoked per day per subject
- the time in minutes only to the first cigarette smoked per subject

If you can get that to us within the next two weeks we would appreciate it.

Thank you.

Mary

Lewis, Mary

From: Iris.H.Shelton@gsk.com
Sent: Tuesday, October 28, 2008 3:55 PM
To: Lewis, Mary
Subject: Re: NDA 22-360 Commit Mini Mint Lozenge; request for information

Hi Mary,
This is to follow up on our discussion:

1) PDF files of the reports will be sent today via overnight mail and you should receive these by noon tomorrow
2) The official report submission in e-CTD format containing reports, data listings and data tabulations will be submitted next week.
3) The contents files (define.doc) for these studies are being generated and will be submitted upon completetion as a separate submission.

Thanks for your assistance.
Iris

"Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>

28-Oct-2008 13:38

To Iris.H.Shelton@gsk.com
cc
Subject NDA 22-360 Commit Mini Mint Lozenge; request for information

Hi Iris,

Can you tell me the status of our receiving this information. Thanks.

Mary

From: Iris.H.Shelton@gsk.com [mailto:Iris.H.Shelton@gsk.com]
Sent: Monday, October 20, 2008 10:37 AM
To: Lewis, Mary
Subject: Re: NDA 22-360 Commit Mini Mint Lozenge; request for information

Hi Mary,
I'm getting the team together to address this. Also, the response to the 9/29 request regarding packaging, will be sent out tomorrow.
Regards
Iris

"Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>

20-Oct-2008 09:55

To Iris.H.Shelton@gsk.com

cc "Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>

Subject NDA 22-360 Commit Mini Mint Lozenge; request for information

Hi Iris,

One of my reviewers needs the following information for this NDA:

Details of the Phase I studies are mentioned in the ISS, but it isn't complete. We have found "summaries" but not any protocol or study reports. You reference "section 2.7.1", but we can't find the data in that section. We need full study reports on these three Phase I studies (S2300319, S2300339 and S2300320), particularly any information regarding extent of exposure (one of these was apparently a multi-dose trial), the protocol details, adverse events and dropouts.

We would appreciate it if you can get this to us as soon as possible.

Thanks.

Mary

Mary M. Lewis, RN, BSN
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Phone: 301-796-0941
Fax: 301-796-9899
Email: Mary.1.Lewis@fda.hhs.gov

Lewis, Mary

From: Iris.H.Shelton@gsk.com
Sent: Tuesday, October 28, 2008 1:59 PM
To: Lewis, Mary
Subject: Re: NDA 22-360 Commit Mini Mint Lozenge; request for information

Hi Mary,
We're in the process of re-configuring the reports into e-ctd format, as they were previously used for EU submission.The reports should be availble for submission by next week. If you prefer receiving PDF files for these reports, we can provide these earlier. Please let me know which you prefer and we'll provide accordingly. Thanks
Iris

"Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>

28-Oct-2008 13:38

To Iris.H.Shelton@gsk.com
cc
Subject NDA 22-360 Commit Mini Mint Lozenge; request for information

Hi Iris,

Can you tell me the status of our receiving this information. Thanks.

Mary

From: Iris.H.Shelton@gsk.com [mailto:Iris.H.Shelton@gsk.com]
Sent: Monday, October 20, 2008 10:37 AM
To: Lewis, Mary
Subject: Re: NDA 22-360 Commit Mini Mint Lozenge; request for information

Hi Mary,
I'm getting the team together to address this. Also, the response to the 9/29 request regarding packaging, will be sent out tomorrow.
Regards
Iris

"Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>

20-Oct-2008 09:56

To Iris.H.Shelton@gsk.com
cc "Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>
Subject NDA 22-360 Commit Mini Mint Lozenge; request for information

Hi Iris,

One of my reviewers needs the following information for this NDA:

Details of the Phase I studies are mentioned in the ISS, but it isn't complete. We have found "summaries" but not any protocol or study reports. You reference "section 2.7.1", but we can't find the data in that section. We need full study reports on these three Phase I studies (S2300319, S2300339 and S2300320), particularly any information regarding extent of exposure (one of these was apparently a multi-dose trial), the protocol details, adverse events and dropouts.

We would appreciate it if you can get this to us as soon as possible.

Thanks.

Mary

Mary M. Lewis, RN, BSN
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Phone: 301-796-0941
Fax: 301-796-9899
Email: Mary.1.Lewis@fda.hhs.gov

Lewis, Mary

From: Iris.H.Shelton@gsk.com
Sent: Tuesday, October 21, 2008 11:00 AM
To: Lewis, Mary
Subject: Re: NDA 22-360; Commit Mini Mint Lozenge; a question

Hi Mary,
That information will be submitted today.
Regards,
Iris

"Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>

21-Oct-2008 10:56

To Iris.H.Shelton@gsk.com
cc
Subject NDA 22-360; Commit Mini Mint Lozenge; a question

Hi Iris,

See attached page 3 of your 10/3/08 letter in response to our 9/29/08 letter. Can you tell me the status of when we can look for the information on the tamper-evident feature; exact lozenge counts per vial and the annotated specifications for the "Drug Facts" labels?

Thanks.

Mary

[attachment "Page 3 of 100308 GSK cover letter.pdf" deleted by Iris H Shelton/PAR/CH/SB_PLC]

respectively marketed Commit Lozenges. The safety data obtained in the studies comparing the Mini Mint Lozenges 2mg and 4mg to the marketed Commit Lozenges demonstrated a generally similar pattern of adverse events for all of the formulations. Although the Mini Mint Lozenges are smaller in size than the currently marketed Commit formulations and dissolves in approximately half the time, it is important to note that all the lozenge formulations are intended to be moved around the mouth until completely dissolved, unlike for other formulation (such as nicotine gums and sublingual tablets) which are placed in one particular location for some or all of the time they are being used. This movement will most likely disperse the nicotine around the lining of the mouth thus mitigating any local increase in nicotine concentration. If such an increase had an impact on tolerability of the product this would likely be seen as reports of adverse events related to the mouth, throat or gastrointestinal track. As noted in the report feew incidences of such events were reported.

3. **Plan for pediatric studies for ages 10-17.**

As per e-mail from the Agency, this will be addressed as part of the 4-month safety update for NDA 22-360. This safety update will also address the letter of August 19, 2008 to GSK for NDA 21-330, Commit lozenge, regarding pediatric post marketing study commitment and Agency Guidelines.

We also acknowledge receipt of Agency letter dated 9/29/08 requesting GSK submit the following:

1. Provide a description of and manufacturing information for the tamper-evident feature
2. Specify the exact lozenge counts per vial which you plan to market for the proposed Commit Mini lozenges, 2 mg and 4 mg
3. Submit annotated specifications for the "Drug Facts" labels

Please be advised that GSK will provide a response to this request under separate cover, in a timely manner.

Lewis, Mary

From: Iris.H.Shelton@gsk.com
Sent: Monday, October 20, 2008 10:37 AM
To: Lewis, Mary
Subject: Re: NDA 22-360 Commit Mini Mint Lozenge; request for information

Hi Mary,
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Iris

"Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>

20-Oct-2008 09:55

To Iris.H.Shelton@gsk.com
cc "Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>
Subject NDA 22-360 Commit Mini Mint Lozenge; request for information

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One of my reviewers needs the following information for this NDA:

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Thanks.

Mary

Mary M. Lewis, RN, BSN
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Phone: 301-796-0941
Fax: 301-796-9899
Email: Mary.1.Lewis@fda.hhs.gov

APPEARS THIS WAY
ON ORIGINAL

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: OND/PMHS Attention: Rosemary Addy			FROM *(Name, Office/Division, and Phone Number of Requestor)*: ONP Mary M. Lewis, RPM x60941	
DATE 10/3/08	IND NO.	NDA NO. 22-360	TYPE OF DOCUMENT new NDA	DATE OF DOCUMENT 7/18/08
NAME OF DRUG Commit Mini Mint Lozenge	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG NRT	DESIRED COMPLETION DATE 1/29/09

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 2a MEETING
- ☐ END-OF-PHASE 2 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

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 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
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: NDA 22-360, Commit Mini Mint Lozenge 2 mg and 4 mg is seeking indication "reduce withdrawal symptoms, including nicotine craving associated with quitting smoking". The sponsor is requesting a waiver for the pediatric population 0 - 10 years of age; and a deferral of greater than or equal to 10 - 17 years of age. Reasoning for waiver and deferrals are attached. Please note: The original Commit Lozenge, NDA 21-330, has a peds review in DFS regarding GSK has not completed their PREA requirements for postmarketing commitment. ONP has sent GSK a letter in reference to this peds review and what they need to do at this time for that NDA. With regard to the new NDA are there any other studies you think would be required and what would those studies be?

Attachments via separate email: 7/18/08 cover letter, deferral and waiver justifications; NDA 22-360 Peds Page DFS'd 10/1/08 and cc'd to Rosemary Addy. I don't know if you need these but I am attaching them: Original Commit Lozenge NDA 21-330 Peds Review from 3/4/08 and ONP PMC 4F letter from 8/19/08.

SIGNATURE OF REQUESTOR Mary M. Lewis, RPM x 60941	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND 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/

Mary Lewis
10/3/2008 03:58:22 PM

DSI

Lewis, Mary

From: Patague, Yolanda
Sent: Wednesday, October 01, 2008 3:29 PM
To: Montgomery, Carl J; Thompson, Teresa C; Thorsky, John W
Cc: Biswas, Gopa; Skelly, Michael F; Yau, Martin K; Vaccari, Leslie; Kaufman, Linda; Doddapaneni, Suresh; Lewis, Mary
Subject: High Priority BE Inspection assignment FACTS#978500 NDA# 22-360
Importance: High
Attachments: NDA 22-360 FACTS 978500 assignment.pdf

FACTS#	978500	b(4)
NDA#	22-360	
EIR DUE:	1/23/2009	
DSI Contact:	Gopa Biswas Ph.D. 301-796-4167	

Yolanda Patague
Public Health Analyst
FDA/CDER/Office of Compliance
Division of Scientific Investigations
yolanda.patague@fda.hhs.gov
301-796-3388

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 26, 2008

TO: Director, Investigations Branch
Kansas District Office
11630 W. 80th St.
Lenexa, KS 66214

FROM: C.T. Viswanathan, Ph.D. Martin K. Yau
Associate Director (Bioequivalence)
Division of Scientific Investigations

SUBJECT: FY 2008, **High Priority, CDER User Fee NDA,** Pre-Approval Data Validation Inspection, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 22-360
DRUG: Commit (nicotine polacrilex) Mini Mint Lozenges 2mg and 4mg.
SPONSOR: Glaxo-Smith-Kline Healthcare

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence study. **Due to the user fee deadline, the inspections should be completed by January 23, 2009. A DSI scientist with specialized knowledge will participate in the inspection at MDS Pharma Services, Lincoln to provide scientific and technical expertise.**

Study Number: S3010567

Study Title: "A Single Dose Bioequivalence Study of 2mg and 4mg Mini Nicotine Lozenges"

Clinical Site: MDS Pharma Services,
621 Rose Street,
Lincoln, NE 68502

Clinical Investigator: James C. Kisicki, MD
TEL/FAX: 1-402-476-2811/1-402-476-7598

Following identification of the investigator, background materials will be forwarded directly.

Headquarters Contact Person: Gopa Biswas, Ph.D.
(301) 796-4167

cc:
DSI/Vaccari
DSI/Biswas/Patague/CF
OND/ONP/DNCE/Mary Lewis
OTS/OCP/DCP2/Doddapaneni
HFR-SW350/Montgomery (BIMO)
Draft: GB 9/26/08
Edit: SS 9/30/08, MKY 9/30/08
DSI: 5900; O:\BE\assign\bio22360.doc
FACTS ID: 978500

b(4)

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

TO *(Division/Office)*:	FROM:
CDER OSE CONSULTS	Mary M. Lewis, RPM ONP/DNCE x60941

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9/29/08		22-360	New NDA	7/18/08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Commit Mini Mint Lozenge for 2mg and 4 mg	Standard		12/29/08

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/SPECIAL INSTRUCTIONS: Please review the proposed trade name in this NDA.
The DMEPA reviewer, when assigned, will be added to all team and labeling meetings. Please attend as warranted. The submission is available via the EDR: \\CDSESUB1\EVSPROD\NDA022360\0000. Labels can be found in the EDR, and I will email the labels to DMEPA from my folder.

PDUFA DATE: May 18, 2009
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA 22-360
HFD-560/Division File
HFD-560/RPM
HFD-560/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)		
Mary M. Lewis x60941	☒ DFS ONLY	☐ MAIL	☐ HAND

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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

/s/

Mary Lewis
9/29/2008 04:47:35 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-360

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

Dear Ms Shelton:

Please refer to your new drug application (NDA) dated July 18, 2008, received July 18, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Commit Mini Mint (2 mg and 4 mg, nicotine polacrilex) lozenge.

We also refer to your submission dated September 9, 2008, and your email dated September 16, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the goal date is May 18, 2009.

During our filing review of your application, we identified the following potential review issues:

The application did not contain:

1. a complete Integrated Summary of Safety
2. information regarding local safety of the mini lozenge in the mouth
3. your plan for pediatric studies for ages 10-17
4. the lozenge counts per vial that you plan to market for the 2 mg and 4 mg mini lozenge
5. annotated specifications for all "Drug Facts" labels
6. a description of and manufacturing information for the tamper-evident feature

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We remind you of your agreements below:

1. As stated in your email dated September 16, 2008, you have agreed to submit the following information:

a. Integrated Summary of Safety by October 6, 2008.
This should include updated safety review for the currently marketed Commit lozenges as well as any worldwide data for the new formulation. Safety data from the following data bases to be submitted are:
- FDA Adverse Event Reporting System (AERS)
- World Health Organization International Drug Monitoring Program
- Literature Review
- Drug Abuse and Overdose Data – to included American Association of Poison Control Centers (AAPCC), Drug Abuse Warning Network (DAWN)

b. Information regarding local safety of the mini lozenge in the mouth by October 6, 2008.
c. Your pediatric drug development plan for children 10-17 years old by November 18, 2008.

We also request that you submit the following information:

1. Provide a description of and manufacturing information for the tamper-evident feature.
2. Specify the exact lozenge counts per vial which you plan to market for the proposed Commit Mini lozenges, 2 mg and 4 mg.
3. Submit annotated specifications for the "Drug Facts" labels.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients below the age of 10 years. We also acknowledge receipt of your request for a deferral of pediatric studies for this application for pediatric patients 10 to 17 years old.

If you have any questions, call Mary Lewis, Regulatory Project Manager, at (301) 796-0941.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D.
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
9/29/2008 12:21:54 PM

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: September 25, 2008

TO: Ct Viswanathan, Branch Chief
Bioequivalence Investigations Branch
Division of Scientific Investigations

FROM: Mary M Lewis, Regulatory Health Project Manager, Division of Nonprescription Clinical Evaluation

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 22-360
Commit® (nicotine polacrilex) Mini Mint Lozenges 2mg and 4mg

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Sponsor protocol #S3010567	Clinical Site (James C. Kisicki, MD, MDS Pharma Services, 621 Rose Street, Lincoln, NE 68502; Phone (402) 476-2811; Fax (402) 476-7598	Analytical Site / MDS Pharma Services, 621 Rose Street, Lincoln, NE 68502;

b(4)

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **February 23, 2009**. We intend to issue an action letter on this application by **May 18, 2009**.

Should you require any additional information, please contact Mary M. Lewis, at 301-796-0941.

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/s/

Mary Lewis
9/25/2008 04:51:34 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION		
NDA # 22-360 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: nicotine polacrilex Established/Proper Name: Nicorette mini lozenge Dosage Form: 2 mg and 4 mg		Applicant: GlaxoSmithKline Agent for Applicant (if applicable):
RPM: Mary M. Lewis		Division: Division of Nonprescription Clinical Evaluation

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	May 18, 2009
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application[2] Characteristics	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): 5 ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC • Comments: **THIS IS A 505 (b)(1).**	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: PMHS states PREA is not necessary.	1/26/09; does not require PREA
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV certification**, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.
  Answer the following questions for **each** paragraph IV certification:

(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

If "Yes," skip to question (4) below. If "No," continue with question (2).

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	4/29/09
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 5/13/09 AP
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	7/18/08 User's Guide
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert (Patient Information Guide) ☐ Instructions for Use ☒ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	7/18/09
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	[redacted]
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	2/10/09 & 4/22/09 + 5/13/09 mm
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEDP ☐ DRISK ☐ DDMAC ☐ CSS ☐ Other reviews
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	 4/2/09 4/27/09 acceptable
[redacted]	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	4/29/09
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	[redacted]
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☒ None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	☒ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☐ Not applicable
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☐ Not applicable
• Regulatory Briefing *(indicate date)*	☐ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg
• EOP2 meeting *(indicate date)*	☐ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	T-con Mtg Minutes 4/14/09
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 5/18/09
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
Clinical Information	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	3/23/09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	In clinical review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
Clinical Microbiology	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics	☒ None
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology	☐ None
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 4/2/09
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None 2/25/09
Nonclinical	☐ None
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 3/27/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☐ None requested
CMC/Quality	☐ None
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 4/7/09 ✓ 5/15/09
• BLAs only: Facility information review(s) *(indicate dates)*	☒ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: 12/2008 ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER	Date completed: ☐ Acceptable ☐ Withhold recommendation
o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Requested ☐ Accepted ☐ Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Lewis, Mary

From: Iris.H.Shelton@gsk.com
Sent: Tuesday, September 16, 2008 2:40 PM
To: Lewis, Mary
Subject: Re: NDA 22-360; Mini Lozenge; in reference to your questions today about our 9/15/08 email sent to you yesterday
Importance: High
Attachments: Email to GSK 091508 ISS.pdf

Hi Mary,
Reference is made to your request below. This is to inform you of GSK's commitment to provide the information in the timings requested by FDA. Items 1 and 2 will be submitted by Oct. 6, 2008 and Item 3 will be provided by Nov. 18, 2008.

Regards,
Iris

"Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>

16-Sep-2008 14:09

To Iris.H.Shelton@gsk.com
cc "Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>
Subject NDA 22-360; Mini Lozenge; in reference to your questions today about our 9/15/08 email sent to you yesterday

Hi,

In reference to your question, do all these need to be sent to the FDA within the next 3 weeks: regarding numbers 1 and 2 in the attached email, we want that information sent to us within 3 weeks.

With regard to number 3, your submitting the following information: "Plan for pediatric studies for ages 10-17" our response is twofold:

- Send this pediatric plan by the time of the 4-month safety update
- Also see our August 19, 2008 letter to GSK for NDA 21-330, Commit Lozenge, regarding pediatric post marketing study commitment and our guidelines

Please respond to this email today with your commitment to provide this information.

Thank you.

Mary

Mary M. Lewis, RN, BSN
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Phone: 301-796-0941
Fax: 301-796-9899
Email: Mary.1.Lewis@fda.hhs.gov

Lewis, Mary

From:	Lewis, Mary
Sent:	Tuesday, September 16, 2008 2:10 PM
To:	'Iris.H.Shelton@gsk.com'
Cc:	Lewis, Mary
Subject:	NDA 22-360; Mini Lozenge; in reference to your questions today about our 9/15/08 email sent to you yesterday
Importance:	High
Attachments:	Email to GSK 091508 ISS.pdf

Hi,

In reference to your question, do all these need to be sent to the FDA within the next 3 weeks: regarding numbers 1 and 2 in the attached email, we want that information sent to us within 3 weeks.

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Please respond to this email today with your commitment to provide this information.

Thank you.

Mary

Mary M. Lewis, RN, BSN
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Phone: 301-796-0941
Fax: 301-796-9899
Email: Mary.1.Lewis@fda.hhs.gov

Lewis, Mary

From: Iris.H.Shelton@gsk.com
Sent: Tuesday, September 16, 2008 2:06 PM
To: Lewis, Mary
Subject: Fw: NDA 22-360; Mini Lozenge; email transmittal
Attachments: Email to GSK 091508 ISS.pdf

Mary,
We've been informed that there were e-mail issues in our system and this one was identified as not having gone through. Therefore, I am resending just in case you didn't receive. Sorry for any inconvenience.
Regards,
Iris

---- Forwarded by Iris H Shelton/PAR/CH/SB_PLC on 09/16/2008 02:05 PM ----

Iris H Shelton/PAR/CH

16-Sep-2008 08:15

To "Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>
cc
Subject Re: NDA 22-360; Mini Lozenge; email transmittal Link

Hi Mary,
Reference is made to your request below for ISS and safety information. This is to inform you that GSK will address this information and submit it to the Agency within three weeks as requested.
Regards,
Iris

"Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>

15-Sep-2008 15:57

To Iris.H.Shelton@gsk.com
cc "Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>
Subject NDA 22-360; Mini Lozenge; email transmittal

Hi Iris,

Please see that attached email. Please respond that you have received this email.

We need you to respond to us as early as possible tomorrow.

Thank you.

Mary

Mary M. Lewis, RN, BSN
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Phone: 301-796-0941
Fax: 301-796-9899
Email: Mary.1.Lewis@fda.hhs.gov

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products

EMAIL TRANSMITTAL SHEET

DATE: September 15, 2008

To: Iris H. Shelton Assistant Director, Regulatory Affairs	**From:** Mary M. Lewis, RN Regulatory Project Manager
Company: GlaxoSmithKline Consumer Healthcare, L.P.	Office of Nonprescription Products
E-mail: Iris.H.Shelton@gsk.com	**E-mail:** Mary.1.Lewis@fda.hhs.gov
Phone number: 973-889-2167	**Phone number:** 301-796-094

Subject: NDA 22-360: Incomplete NDA submission – Integrated Summary of Safety Required within 3 weeks of this email.

Total no. of pages including cover: 3

Document e-mailed: X YES

The NDA submission for Commit Mini Lozenge (22-360) is incomplete as specified in 21 CFR 314.50(d)(5). Specifically, it does not include an Integrated Summary of Safety section. In order for us to assess safety of the proposed new formulation, you should submit the following information:

1. Integrated Summary of Safety.
   This should include an updated safety review for the currently marketed Commit lozenges as well as any worldwide data for the new formulation. Safety data from the following databases should be submitted:

   - FDA Adverse Event Reporting System (AERS)
   - World Health Organization International Drug Monitoring Program
   - Literature Review
   - Drug Abuse and Overdose Data – to include American Association of Poison Control Centers (AAPCC), Drug Abuse Warning Network (DAWN)

2. Information regarding local safety of the mini lozenge in the mouth (as discussed at the January 29, 2008 meeting)

3. Plan for pediatric studies for ages 10-17.

You should provide this report to us within three weeks from the date of this email.

An ISS is required at the time of the NDA submission. If not included, the lack of the ISS can be a reason to refuse to file an application.

Please respond to this e-mail by Tuesday, September 16, 2008, with your commitment to provide this information.

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

/s/

Mary Lewis
9/15/2008 03:51:02 PM
CSO

Mary Lewis
9/15/2008 03:51:38 PM
CSO

LABELING FILING CHECKLIST FOR A NEW NDA/BLA

Drug Name: Commit Mini Mint (nicotine polacrilex) lozenges 2 mg and 4 mg	**Applicant:** GlaxoSmithKline	**Letter Date:** July 18, 2008
NDA Number: 22 360	**NDA Type:** N-000	**Stamp Date:**

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comments
1	Is Index sufficient to locate necessary labeling?	√		
2	Has labeling for all SKUs been submitted (e.g., blister card, pouch, immediate container, carton label and package insert labeling, etc)?	√		
3	Does the submission contain the annotated specifications for the "Drug Facts" label?		√	
4	Is a new trade name being proposed? If multiple trade names, is the RLD trade name identified?	√		

Any Additional Comments:

Mary S. Robinson, MS — 9/11/2008
Reviewing Regulatory Review Chemist — Date

Debbie L. Lumpkins
Supervisor/Team Leader — Date

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
9/11/2008 03:20:37 PM
INTERDISCIPLINARY

Debbie Lumpkins
9/11/2008 03:21:35 PM
INTERDISCIPLINARY

Lewis, Mary

From: Lewis, Mary
Sent: Friday, August 29, 2008 12:30 PM
To: 'Iris.H.Shelton@gsk.com'
Cc: Lewis, Mary; Abraham, Elaine G
Subject: RE: FW: NDA 22-360; mini mint lozenge; information request deadline dates
Follow Up Flag: Follow up
Flag Status: Red

Thanks Iris.

Another request: please explain why the BE clinical study report says something different about the manufacturing site, and make necessary corrections in the clinical study report.

Thank you.

Mary

From: Iris.H.Shelton@gsk.com [mailto:Iris.H.Shelton@gsk.com]
Sent: Friday, August 29, 2008 11:41 AM
To: Lewis, Mary; Abraham, Elaine G
Subject: Re: FW: NDA 22-360; mini mint lozenge; information request deadline dates
Importance: High

Mary/Elaine,
Provided is the response to item #1. We will also be formally submitting this along with responses to itmes #2 and 3.

Provide formulation and manufacturing (date, site and batch size) information for each drug product clinical batch (including standard lozenges) used in the clinical BE study S3010567. We have noted discrepancies between Module 2 (p. 6 of 7, Section 2.3.P.2 Pharmaceutical Development) and Module 5 (pp.15-16 of 166, clinical study report for study S3010567 regarding manufacturing site.

All supplies were manufactured in GSK's facility in Aiken, S.C. The standard lozenges were packaged at that site as well. The Mini Mint lozenges were packaged in our facility in Parsippany, N.J. Provided below is a chart containing the batch information requested.

Drug Product Batch number	Strength	Date of Manufacture	Manufacturing Site	Batch size
GSK5583B011	2mg mini lozenge	14 Feb 2008	Aiken, South Carolina, USA	[redacted]
GSK5584B011	4mg mini lozenge	14 Feb 2008	Aiken, South Carolina, USA	[redacted]

b(4)

Lot number 8A21	2mg standard lozenge	24th/25th Nov 2007	Aiken South Carolina, USA	[redacted]
Lot number 8A07	4mg standard lozenge	25th/26th Oct and/or 11th/12 Dec 2007	Aiken South Carolina , USA	[redacted]

b(4

Regards,
Iris H. Shelton
973-889-2167

"Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>

26-Aug-2008 13:03

To Iris.H.Shelton@gsk.com
cc
Subject FW: NDA 22-360; mini mint lozenge; information request deadline date:

Iris,

It was my mistake not to put these dates in the letter. My apologies. The timeline for this information request is as follows:

1: we would like your response by September 4, 2008. (I will be out of the office that week. Please email your response to: Elaine Abraham who is covering for me at that time. Her email address is: elaine.abraham@fda.hhs.gov

#'s 2 and 3: we would like your response by September 12, 2008, if not sooner.

Mary

From: Lewis, Mary
Sent: Tuesday, August 26, 2008 12:51 PM
To: 'Iris.H.Shelton@gsk.com'
Subject: NDA 22-360; mini mint lozenge; information request

Hi Iris,

Attached is an information request letter. You will also receive this letter via the mail system, but I'm emailing you a copy so we can get a response as soon as possible.

Thank you.

Mary

Mary M. Lewis, RN, BSN
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Phone: 301-796-0941
Fax: 301-796-9899
Email: Mary.1.Lewis@fda.hhs.gov

[attachment "IR CMC Emailed to GSK 082608,pdf.pdf" deleted by Iris H Shelton/PAR/CH/SB_PLC]

"EMF <fda.hhs.gov>" made the following annotations.

This message was sent by GlaxoSmith Kline across the Internet in encrypted form

==========

Lewis, Mary

From: Lewis, Mary
Sent: Tuesday, August 26, 2008 4:50 PM
To: 'Iris.H.Shelton@gsk.com'
Subject: RE: FW: NDA 22-360; mini mint lozenge; information request deadline dates

Iris,

Provide what you believe is needed to support your NDA, and we will review it.

Thank you.

Mary

From: Iris.H.Shelton@gsk.com [mailto:Iris.H.Shelton@gsk.com]
Sent: Tuesday, August 26, 2008 2:55 PM
To: Lewis, Mary
Subject: Re: FW: NDA 22-360; mini mint lozenge; information request deadline dates
Importance: High

Hi Mary,
We're in the process of reviewing the request and have a question regarding item 2 regarding method validation reports.

For methods 1925 and 1927 the reports were provided for both 2 and 4mg. Would you like for us to also submit for the 1.5mg?

Test Method 1926 was provided and only applies to the 2 and 4mg utilizing USP 1. It was not validated for the 1.5mg which utilizes the USP 3 method. Please clarify what we need to provide.
Thanks
Iris

"Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov>
26-Aug-2008 13:03

To Iris.H.Shelton@gsk.com
cc
Subject FW: NDA 22-360; mini mint lozenge; information request deadline date

Iris,

It was my mistake not to put these dates in the letter. My apologies. The timeline for this information request is as follows:

1: we would like your response by September 4, 2008. (I will be out of the office that week. Please email your response to: Elaine Abraham who is covering for me at that time. Her email address is: elaine.abraham@fda.hhs.gov

#'s 2 and 3: we would like your response by September 12, 2008, if not sooner.

Mary

From: Lewis, Mary
Sent: Tuesday, August 26, 2008 12:51 PM
To: 'Iris.H.Shelton@gsk.com'
Subject: NDA 22-360; mini mint lozenge; information request

Hi Iris,

Attached is an information request letter. You will also receive this letter via the mail system, but I'm emailing you a copy so we can get a response as soon as possible.

Thank you.

Mary

Mary M. Lewis, RN, BSN
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Phone: 301-796-0941
Fax: 301-796-9899
Email: Mary.1.Lewis@fda.hhs.gov

[attachment "IR CMC Emailed to GSK 082608,pdf.pdf" deleted by Iris H Shelton/PAR/CH/SB_PLC]

"EMF <fda.hhs.gov>" made the following annotations.

This message was sent by GlaxoSmith Kline across the Internet in encrypted form

==========

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-360

INFORMATION REQUEST LETTER

GlaxoSmithKline
GlaxoSmith Kline Consumer Healthcare, L.P.
Attention: Iris H. Shelton
Assistant Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms Shelton:

Please refer to your July 18, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Commit Mini Mint (2 mg and 4 mg, nicotine polacrilex) lozenge.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide formulation and manufacturing (date, site and batch size) information for each drug product clinical batch (including standard lozenges) used in the clinical BE study S3010567. We have noted discrepancies between Module 2 (p. 6 of 7, Section 2.3.P.2 Pharmaceutical Development) and Module 5 (pp. 15-16 of 166, clinical study report for study S3010567) regarding manufacturing site.

2. Provide method validation reports and data to support drug product methods C1925, C1926, C1927, and the three microbial methods included in drug product specification.

3. Provide a copy of the production scale master batch record for each proposed drug product.

If you have any questions, call Mary Lewis, Regulatory Health Project Manager, at 301-796-0941.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
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
8/26/2008 12:41:10 PM

Lewis, Mary

From: Lewis, Mary
Sent: Monday, August 11, 2008 11:39 AM
To: 'Iris.H.Shelton@gsk.com'
Subject: RE: NDA 22-360- NDA Acknowledgement Letter

My apologies. Yes the goal date is May 18, 2009.

Mary

From: Iris.H.Shelton@gsk.com [mailto:Iris.H.Shelton@gsk.com]
Sent: Monday, August 11, 2008 11:27 AM
To: Lewis, Mary
Subject: RE: NDA 22-360- NDA Acknowledgement Letter

Hi Mary,
We received the acknowledgement letter for NDA 22-3360 and noticed that it did not include a goal date. Would appreciate if you could let us know if the goal date has been assigned.
Thanks

Iris
GSK 973-889-2167

"EMF <fda.hhs.gov>" made the following annotations.

This message was sent by GlaxoSmith Kline across the Internet in encrypted form
==========

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-360

NDA ACKNOWLEDGMENT

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

Dear Ms Shelton:

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

Name of Drug Product: Commit Mini Mint (2 mg and 4 mg, nicotine polacrilex) lozenge

Date of Application: July 18, 2008

Date of Receipt: July 18, 2008

Our Reference Number: NDA 22-360

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 16, 2008, in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved.

Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call Mary Lewis, Regulatory Project Manager, at (301)796-0941.

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
8/1/2008 11:26:54 AM

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

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

July 18, 2008

NDA 22-360

Dr. Andrea Leonard-Segal
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: New Drug Application - Original
Commit® (nicotine polacrilex) Mini Mint 2mg and 4mg Lozenge

Dear Dr. Leonard-Segal,

In accordance with Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50, GlaxoSmithKline (GSK) hereby submits an original New Drug Application (NDA) for Commit® (nicotine polacrilex) Mini Mint Lozenges 2mg and 4mg. This NDA is to provide for a smaller version of Commit®, Nicotine Polacrilex Lozenges, 2mg and 4mg, currently marketed by GSK under an approved NDA 21-330. This application incorporates cross-references to NDA 21-330 for Commit® as agreed in our January 29,2008 meeting with the Agency.

Please contact me at (973) 889-2167 if you have any questions on the information provided in this submission.

Sincerely,
Iris H. Shelton
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

June 24, 2008

GlaxoSmithKline

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

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

Wachovia Bank
Attn: Food and Drug Administration, Lockbox 70963
1525 West WT Harris Blvd., Room NC0810
Charlotte, NC 28262

Re: **NDA 22-360- Nicotine Polacrilex Mini Mint Lozenges, 2 & 4mg**
User Fee I.D. Number PD3008214

Dear Sir/Madam,

Please find an enclosed user fee check in the amount of $589,000 for GlaxoSmithKline Consumer Healthcare's (GSK) NDA 22-360 for Nicotine Polacrilex Mini Mint lozenges 2mg and 4mg. Also enclosed is the User Fee Cover Sheet (Form FDA 3397).

Please contact me at 973-889-2167 if you have any questions.

Sincerely,

[redacted]is H. Shelton
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare L.P.

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

GLAXOSMITHKLINE CONSUMER HEALTHCARE LP
Iris Shelton
GLAXOSMITHKLINE CONSUMER HEALTHCARE 1500 LITTLETON ROAD
PARSIPPANY NJ 07054-3884
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

22-360

2. TELEPHONE NUMBER

973-889-2167

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[ ] YES [X] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.
IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[ ] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

NDA 21-330

3. PRODUCT NAME

Commit Mini Mint Lozenge (Nicotine Polacrilex Lozenge)

6. USER FEE I.D. NUMBER

PD3008214

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

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

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

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

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

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

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 Drive, Room 3046
Rockville, MD 20852

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

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Iris M Shelton	ASSISTANT DIRECTOR Regulatory Affairs	April 1, 2008

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION

$569,000.00

Form FDA 3397 (03/07)

Close Print Cover sheet

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-330

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

Dear Ms Shelton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Commit® (2 mg and 4 mg, nicotine polacrilex) lozenge.

We also refer to the meeting between representatives of your firm and the FDA on January 29, 2008. The purpose of the meeting was to discuss your future submission of a supplemental NDA under the referenced NDA for reformulated 2 mg and 4 mg nicotine polacrilex lozenges.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mary Lewis, Regulatory Project Manager, at (301) 796-0941.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Enclosure

FOOD AND DRUG ADMINISTRATION

Meeting Date and Time:	January 29, 2008
Meeting Type:	B
Meeting Category:	NDA
Meeting Location:	FDA/White Oak 10903 New Hampshire Avenue Room 1419 Silver Spring, MD 20993
Application Number:	NDA 21-330
Product Name:	Commit® (2 mg and 4 mg, nicotine polacrilex) lozenge
Received Briefing Package:	December 29, 2007
Meeting Requestor:	Iris H. Shelton, M.S. Assistant Director Regulatory Affairs
Meeting Chair:	Andrea Leonard-Segal, M.D. Director Division of Nonprescription Clinical Evaluation
Meeting Recorder:	Mary M. Lewis Regulatory Project Manager

FDA Attendees:

Division of Nonprescription Clinical Evaluation
Andrea Leonard-Segal, M.D., Director
Joel Schiffenbauer, M.D., Deputy Director
Daiva Shetty, M.D., Medical Team Leader
Christina Chang, M.D., Medical Reviewer

Office of New Drug Quality Assessment, Division of Pharmaceutical Evaluation
Liang Zhou, Ph.D., Pharmaceutical Assessment Lead
Steve Hathaway, Ph.D., Chemistry Reviewer

Office of Clinical Pharmacology
David Lee, Ph.D., Clinical Pharmacology Reviewer

External Attendees

GlaxoSmithKline
Rick Chan, Ph.D. Director, New Product Development
Mitchell Kotler, Ph.D. Group Leader, Biostatistics
Rajesh Mishra, M.D., Ph.D. Director, Medical Affairs
David Schifkovitz Director, Regulatory Affairs
Iris H. Shelton, M.S. Assistant Director, Regulatory Affairs

1.0 BACKGROUND:

GlaxoSmithKline's (GSK) Commit® (2 mg and 4 mg, nicotine polacrilex) lozenge was approved (NDA 21-330) on October 31, 2002 for adults 18 years of age and older, to reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking. Since that time there have been several supplements approved for additional flavors and package changes.

GSK submitted a meeting request to the FDA on October 31, 2007 requesting a meeting to discuss their future submission of an NDA for reformulated 2 mg and 4 mg mini nicotine polacrilex lozenges. According to the December 29, 2007 meeting package, GSK proposes to reformulate the 2 and 4 mg lozenges resulting in a smaller-sized lozenge. GSK proposes to market this smaller lozenge _____ with the name "Mini Lozenge". b(4)

2.0 DISCUSSION:

Preliminary responses to the questions enclosed in the December 29, 2007 Meeting Package were sent to GlaxoSmithKline via email on January 25, 2008.

Following introductions, the meeting agenda consisted of Power Point slides (attached) by GSK and further discussion based on the preliminary responses from the FDA and reference to GSK Power Point slides. The questions from GSK appear below followed by the preliminary FDA responses in italics. For questions where no additional discussion is indicated, neither GSK nor FDA raised any additional issues pertaining to the questions.

2.1 Questions and FDA Preliminary Responses:

Question 1:

Does the Agency have any questions/comments regarding formulation rationale of the smaller size nicotine mini mint 2 mg and 4mg lozenges?

FDA Preliminary Response:

We have determined that the proposed mini-lozenge formulations are new formulations and cannot be considered to be equivalent to the approved lozenges with respect to the chemistry (CMC) information. As a result, full CMC documentation will be required for these new formulations.

The proposed mini lozenges represent new formulations for the following reasons:

- ***Significant size discrepancy: the mini lozenge is approximately [redacted] the size of the original lozenge.*** b(4)
- ***Ingredients common to the mini and original lozenges were not reduced proportionally in the proposed mini lozenges.***
- [redacted] b(4)
- ***The mini-lozenges are not chemically equivalent to the original lozenges under USP Dissolution test conditions.***

If you do not meet the criteria in CFR 320.31 an Investigational New Drug application (IND) will be required prior to initiating any studies with a new formulation in the United States.

Additional Discussion:

GSK agreed to provide a full chemistry package to support the mini lozenge. GSK asked for further clarification as to why a new NDA needed to be submitted. FDA reiterated the above listed chemistry reasons to explain why the proposed mini lozenge is a significant change from the previously approved formulation and is considered to be a new formulation. GSK acknowledged that, given the above characteristics, this will be a new formulation and a new NDA will be submitted.

Question 2:

Does the Agency agree that a demonstration of bioequivalence between the current Commit® lozenge and 2 mg and 4 mg mini mint nicotine lozenges is sufficient for sNDA review and approval?

FDA preliminary response:

The proposed mini lozenge differs in quantitative composition from the original lozenge (see response to question 1) to the extent that the submission of a new NDA would be required for this

new formulation. The submission of a supplemental NDA (sNDA) is not appropriate for the proposed changes.

Demonstration of bioequivalence between the proposed mini lozenges and the currently marketed Commit® lozenges may be sufficient, as long as the proposed formulation does not raise any efficacy or safety concerns (see below). Whether the studies already conducted are adequate for approval is ultimately a review issue.

The pharmacokinetic profile submitted in this briefing package is incomplete. You did not provide information on the overall shape of the plasma profiles (e.g., T_{max}) from the bioequivalence studies. Additional information (e.g., individual profiles and parameters, assay results) will also be needed in the overall assessment to determine whether the two formulations (mini vs. original) are bioequivalent.

It is unclear whether a reduced dissolution time would decrease the T_{max} for the mini lozenges, even though the C_{max} data appeared comparable between the new and original formulations. If the T_{max} differs substantially from that of the original formulation, the ability of the mini lozenge to relieve craving may be affected. This in turn may influence the dosing regimen and thus have efficacy implications.

Whether local nicotine concentration in the mouth would be temporarily higher from the mini lozenge relative to the original lozenge due to faster dissolution in the mouth would also need to be explained. In the event that local nicotine concentration is temporarily higher for this new formulation, safety data would be needed. In addition, an analysis of the amount ingested (unintended route of administration) would need to be conducted. Orally administered nicotine may have safety implications. We strongly encourage you to provide complete pharmacokinetic data for FDA review.

You would need to explain the apparent discrepancy in AUC and C_{max} between the original 2 and 4 mg lozenges used in the current submission and those submitted in the original NDA of December 15, 2000.

Additional Discussion:

GSK responded to FDA's comment on T_{max} that the mini lozenge dissolves faster but achieves similar overall exposure as the original lozenge formulation. GSK explained that nicotine is absorbed through swallowing even though they don't know how much nicotine would be swallowed. However, GSK commented that most of the nicotine is absorbed through the buccal mucosa and that the diffusion rate across buccal mucosa may be slower and therefore C_{max} is not higher. FDA expressed concerns about whether the increase in concentration of the active ingredient and the buccal reservoir of nicotine would impact safety, specifically regarding local effects in the mouth, and requested that GSK provide more information on absorption and local safety in their next submission. GSK agreed to provide all these data.

FDA asked why the two pharmacokinetic (PK) studies did not show dose proportionate response to AUC and C_{max}. FDA also asked about the discrepancy in AUC and Cmax between the 2 and

4 mg original lozenge formulations used in currently submitted studies (S3010445 and S3010466) and those from the original NDA. These points reflected FDA's overall concern about whether the current development plan can use these PK data for bridging. GSK stated that the 2 mg PK study was done in a population in India where lower weights and differences in diet could have influenced the results. Therefore, GSK felt that the 2 mg PK data should be bridgeable. FDA expressed concern about this and asked GSK to provide data to support it.

GSK asked if it would help if the study was performed in the U.S. population. FDA stated that a study in the U.S. population would provide data that would be more reassuring. FDA inquired whether GSK would consider conducting a study in the U.S. population to compare the 2 mg vs. 4 mg mini lozenges directly to see if they get a dose-proportionate response. In addition, the 2 mg original lozenge could be used as a comparator. GSK responded that they would take this into consideration and would provide a protocol for FDA review.

Question 3:

Recognizing the inherent differences in the sizes of the original and mini mint lozenges, does the Agency agree with the proposed dissolution specifications for Commit® mini mint 2 mg and 4 mg nicotine polacrilex lozenges?

FDA preliminary response:

Determination of the adequacy of the test and acceptance criteria is a review issue.

Additional Discussion:

GSK asked if they need to do additional studies besides a ——— dissolution study. FDA responded that we need to see the details of the dissolution method for review before any decision can be reached. FDA noted that the original dissolution method resulted in a different dissolution profile for the mini lozenges, which it was noted, appeared to be the reason for revision of the method. The rationale for the proposed change from a ——— dissolution test to a ——— test is unclear. To determine if a ———, is acceptable, GSK needs to provide a proposal and data to support their approach.

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Question 4:

Does the Agency agree with GSK proposal and data support for the 2 mg and 4 mg lozenges involving bracketing stability data from stability studies on the 1.5 mg and 4 mg mini mint lozenges?

FDA preliminary response:

Yes, we agree. Use of the 1.5 mg mini lozenge stability data to support the 2 mg strength is acceptable. The application should contain a description of the post-approval stability plan commitment for the mini lozenges, including the plan for the 2 mg strength.

Question 5:

Does the Agency agree with the proposed content (scope) and format of data to be provided as an eCTD submission for this sNDA?

FDA preliminary response:

Submission of an NDA, not sNDA, will be required to support the marketing of the proposed mini lozenge (see responses to questions 1 and 2). You have not provided an outline of the proposed submission in this briefing package.

The requirements for the content of an NDA are not different for an eCTD from those for a paper submission. These are described in 21 CFR 314.50.

The submission should be organized based on the 5 modules in the CTD:

- *Module 1: administrative and prescribing information*
- *Module 2: CTD summary documents*
- *Module 3: information on quality*
- *Module 4: nonclinical study reports*
- *Module 5: clinical study reports*

Information that is identical to the current 2 mg and 4 mg lozenges may be included by reference to the approved NDA or an approved NDA supplement. Any reference should be as comprehensive as possible and include submission date, volume information, page numbers, etc. With respect to the CMC portion, the proposed application should contain full information on any new excipients or flavorants used in the formulation, including the identities of the suppliers and the raw material specifications for each. Manufacturing process information should be provided, including master and executed batch records for both strengths, as well as detailed manufacturing process descriptions and flowcharts. In-process controls and criteria should be described. The regulatory specifications for the mini-lozenges should be provided, including both release and stability specification as applicable.

For specific technical questions, you are referred to the electronic submission coordinator at esub@cder.fda.gov

We refer you to the Agency's 4/19/2006 Guidance for Industry on eCTD submissions: http://www.fda.gov/cder/regulatory/ersr/ectd.htm

We also refer you to the guidance document developed by ICH M2 Expert Working Group for details: www.ich.org

Additional Discussion:

GSK asked if with regard to an eCTD submission do they need to cross reference broadly or specifically. FDA responded that using the NDA as their reference is acceptable, but with regard to the chemistry section GSK should be explicit in referencing information. Information that is

unchanged between formulations (e.g. suppliers, tests, specifications for common excipients) can be cross-referenced, but information specific to the proposed dosage form should be provided in detail (for example: new flavorant information, detailed manufacturing descriptions, test methods and specifications, stability data, etc.)

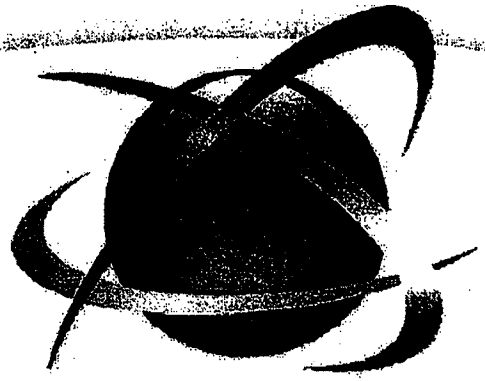
GSK asked if the name "mini lozenge" is acceptable as a statement of identity. FDA responded that the term 'mini' is not included in the Data Standard Manual as a dosage form descriptor and an alternative identifying statement would need to be proposed. FDA indicated that incorporation of "mini" might be more appropriate as part of the proprietary/trade name but that the final trade name would have to be reviewed and that FDA could not comment beyond that at this meeting. GSK indicated that they would include a proposed name for their product in their next submission.

3.0 ACTION ITEMS

1. GSK will take the recommendations from FDA under consideration.
2. GSK will submit a full chemistry package to FDA.

4.0 ATTACHMENTS

GlaxoSmithKline Power Point slides.



RadicalR&D

Accelerate Innovation

Pharmacokinetics of Mini Nicotine Lozenge vs Standard Nicotine Lozenge

GlaxoSmithKline Presentation at the FDA meeting, Jan 29th, 2008

gsk GlaxoSmithKline

Summary of Baseline-Adjusted Nicotine Pharmacokinetic Variables

Study: S3010445 (2mg)

Parameter	Means*		Ratio: Mini/Standard	
	Mini	Standard	Estimate	90% CI
C_{max} (ng/ml)	6.88	6.58	104.66%	[96.70%,113.27%]
$AUC_{(0-t)}$ (ng*hr/ml)	26.91	27.31	98.55%	[88.57%,109.66%]

Study: S3010466 (4mg)

Parameter	Means*		Ratio: Mini/Standard	
	Mini	Standard	Estimate	90% CI
C_{max} (ng/mL)	7.23	7.61	95.0%	[87.4%,103.3%]
$AUC_{(0-t)}$ (ng*hr/mL)	24.39	25.63	95.2%	[89.8%,100.9%]

*Geometric adjusted means calculated by exponentiating adjusted mean log

RadicalR&D

Difference in Tmax: Mini Lozenge and Standard Lozenge

Study	Mean (hr)	Median (hr)	P-Value*
S3010445 (2mg)	**-0.019**	**0.000**	**0.9753**
S3010466 (4mg)	**0.215**	**0.168**	**0.1215**

*Based on Signed-Rank Test

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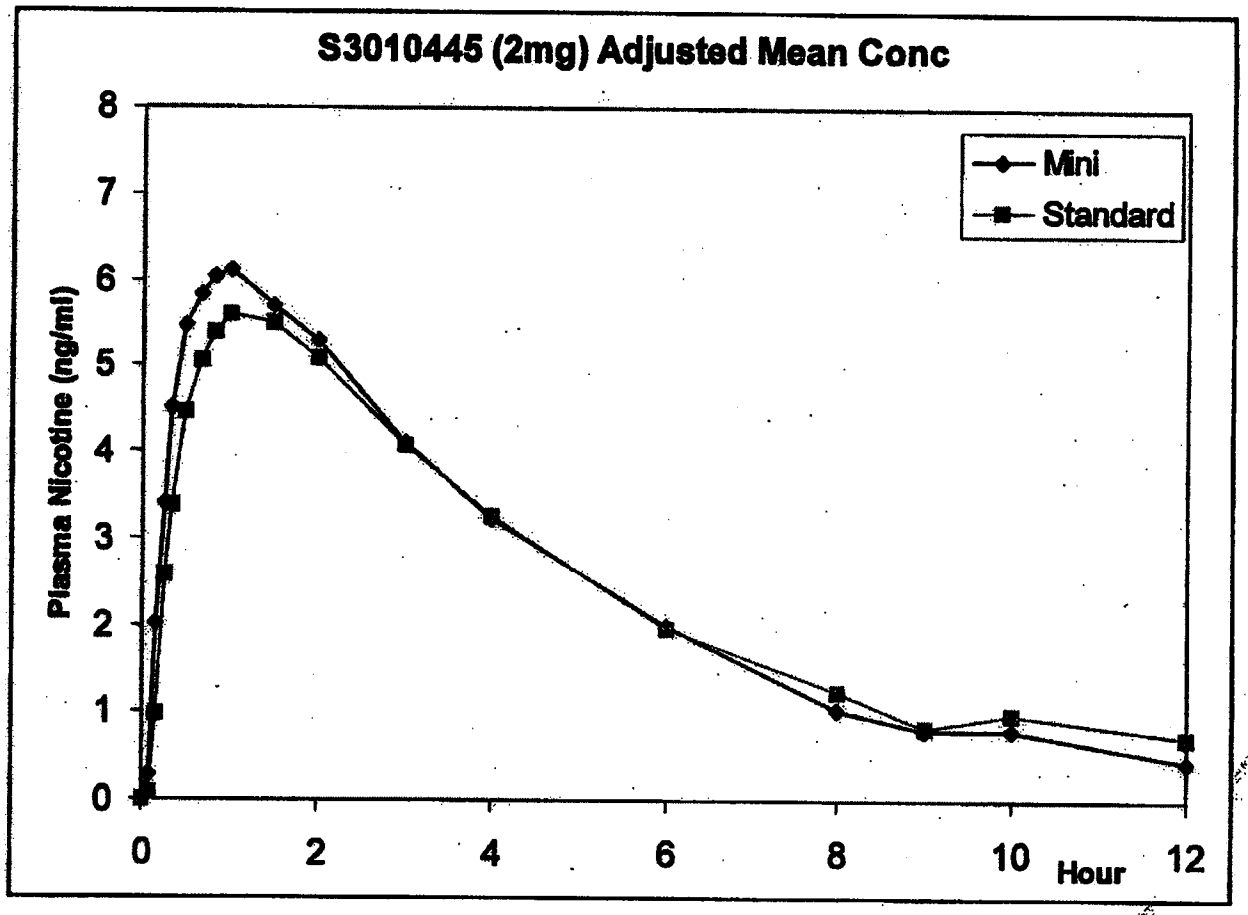
Pharmacokinetic Profile of 2 mg Mini Lozenge vs 2 mg Standard Lozenge



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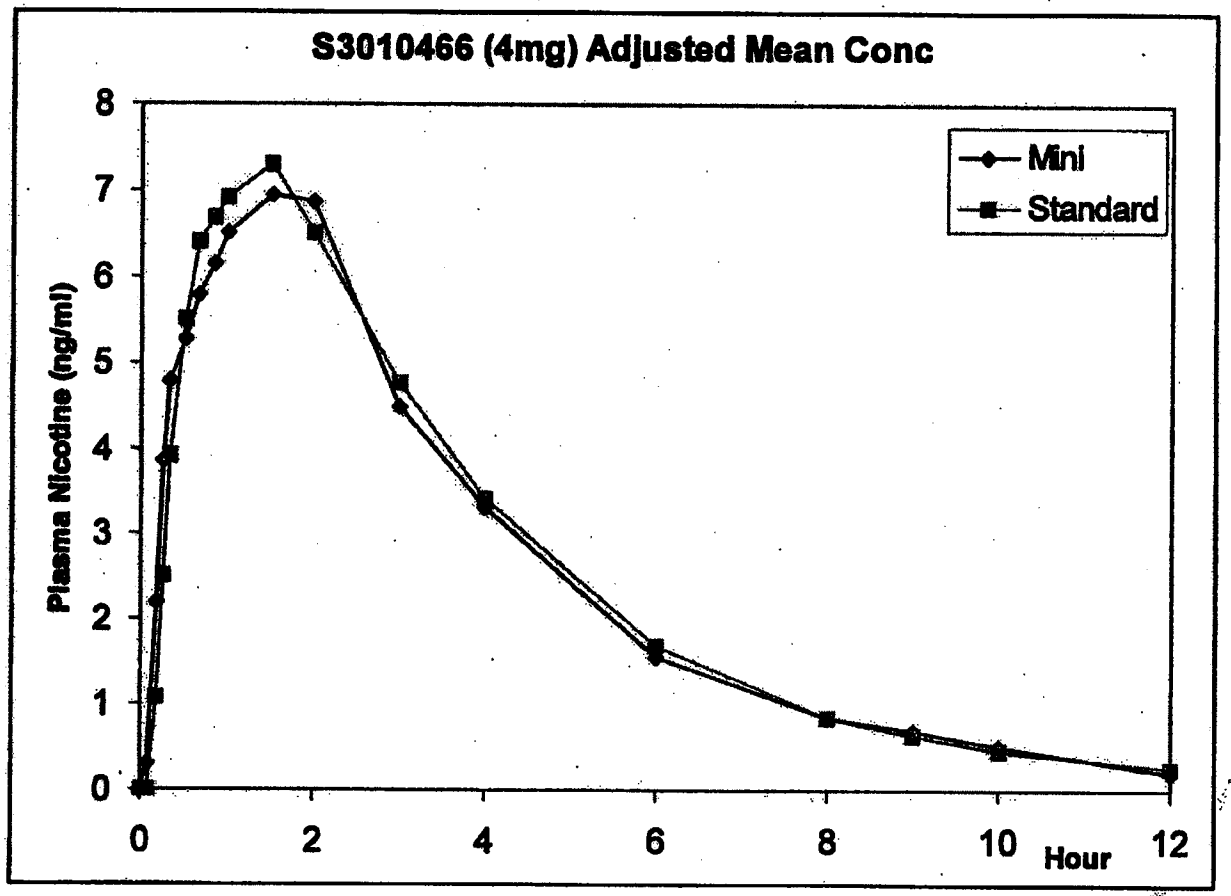
Pharmacokinetic Profile of 4 mg Mini Lozenge vs 4 mg Standard Lozenge



RadicalR&D

Dose Proportionality of Commit Lozenge: 4mg vs. 2mg from historical data

Study	Parameters	Ratio: 4mg/2mg	
		Estimate	90% CI
S1410190 (Aiken)	C_{max}	184.5%	[172.6%, 197.2%]
	$AUC_{(0-t)}$	218.1%	[201.3%, 236.3%]
S1410190 (Crawley)	C_{max}	169.1%	[158.1%, 180.8%]
	$AUC_{(0-t)}$	190.3%	[175.6%, 206.3%]
S1740163	C_{max}	171.6%	[162.8%, 180.8%]
	$AUC_{(0-t)}$	200.0%	[188.7%, 212.1%]

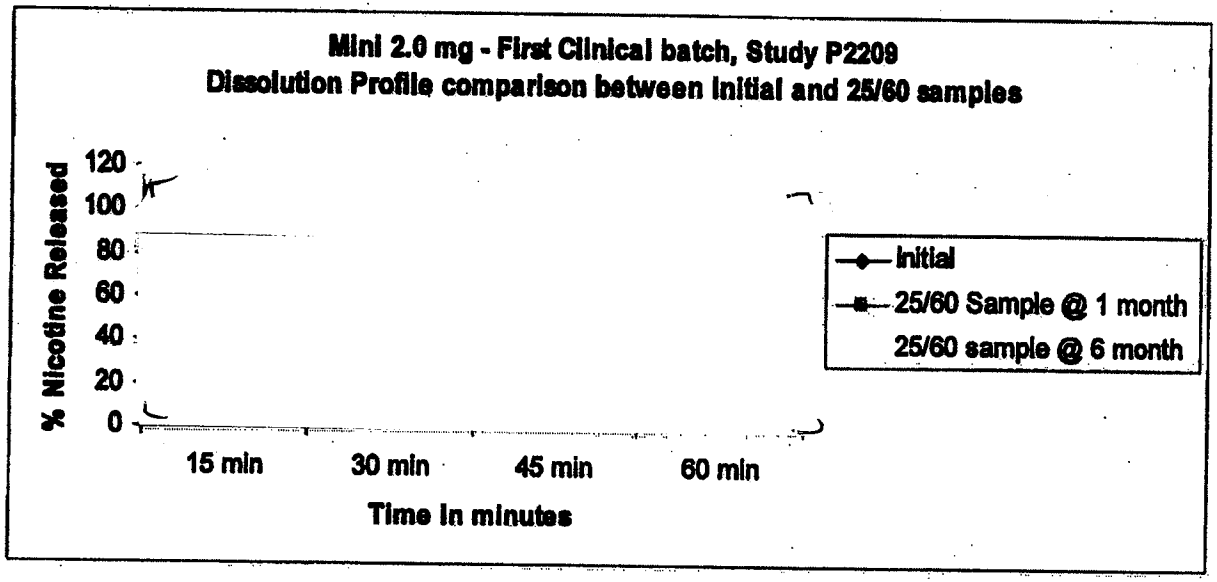
*Geometric adjusted means calculated by exponentiating adjusted mean log

RadicalR&D

Dissolution Testing

- Formulation similar to Commit lozenge
- Non-disintegrating tablet formulation
- Dissolution Method III
  - Target [redacted] test for QA efficiency b(4)
  - Mini lozenge dissolves within 15' in buccal cavity

Comparison of USP 3 Dissolution Profiles of 2.0 mg Mini first clinical Batch @ different stability time points



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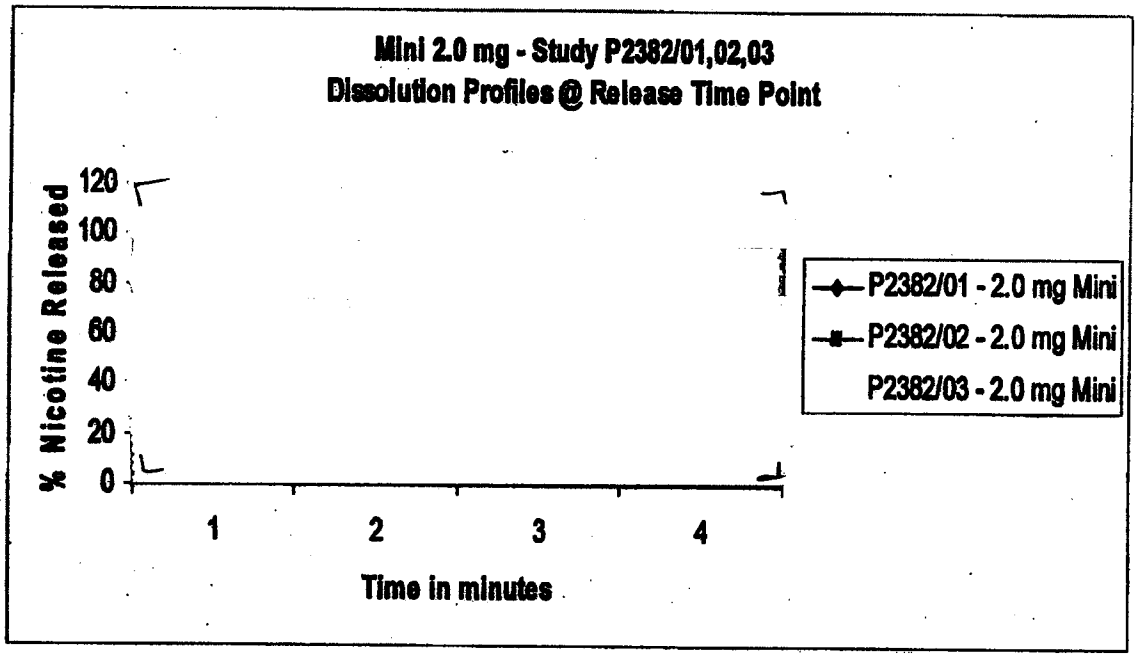
Dissolution Profiles of three recent 2.0 mg Mini batches @ Release time point



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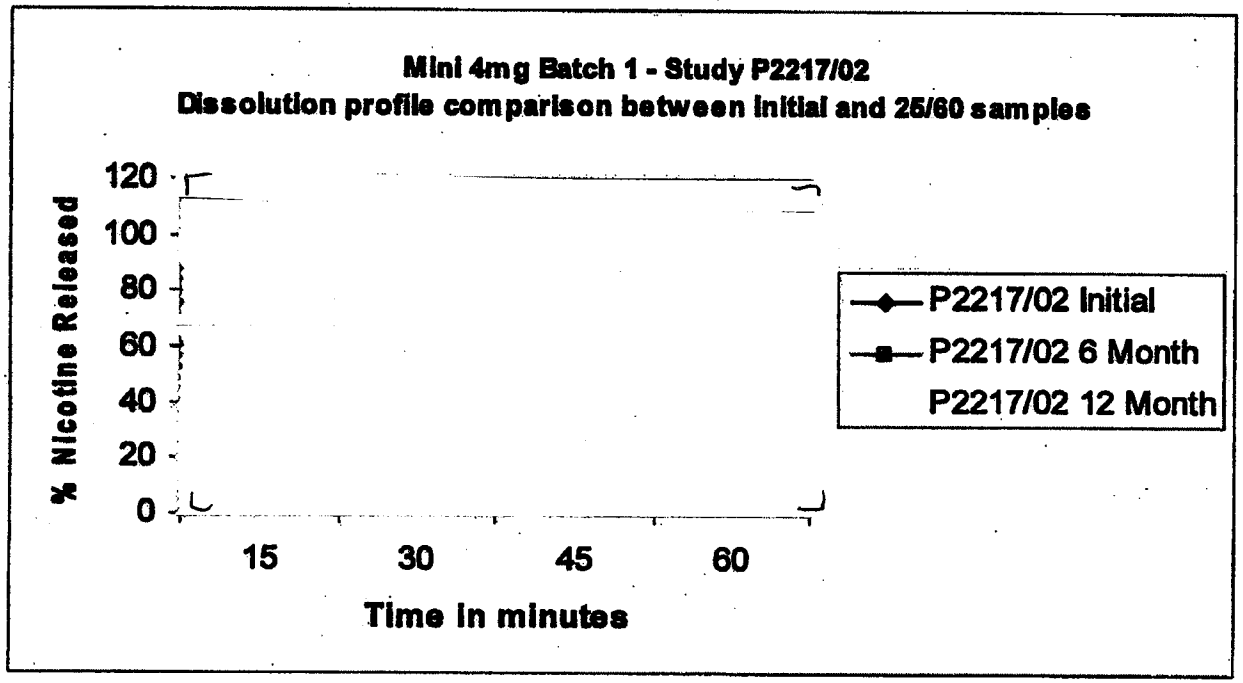
Comparison of USP 3 Dissolution Profiles of 4.0 mg Mini Batch 1 @ different stability time points



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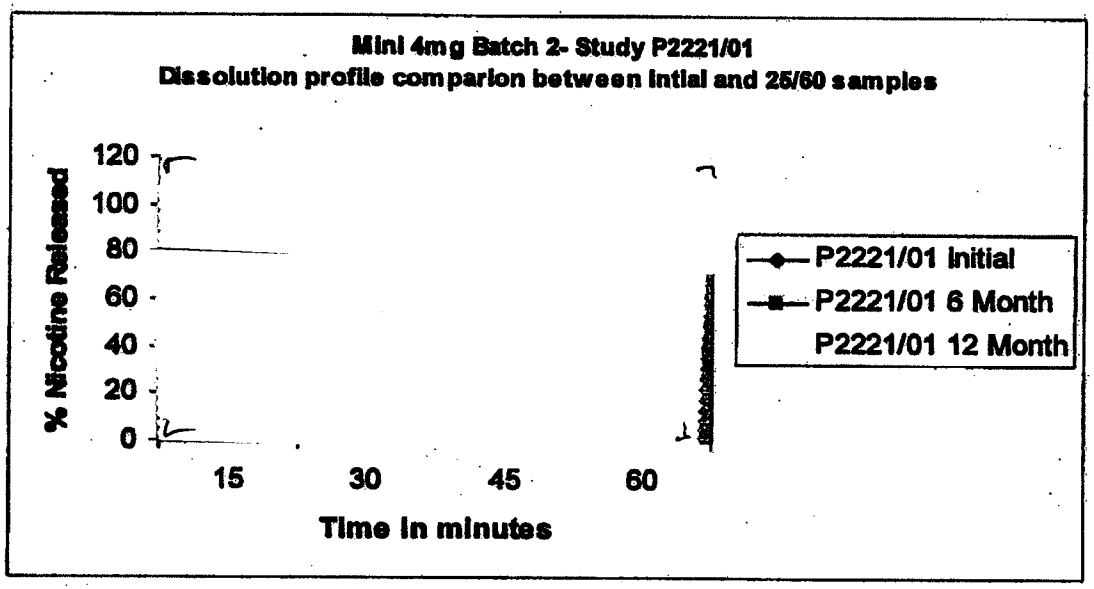
Comparison of USP 3 Dissolution Profiles of 4.0 mg Mini Batch 2 @ different stability time points



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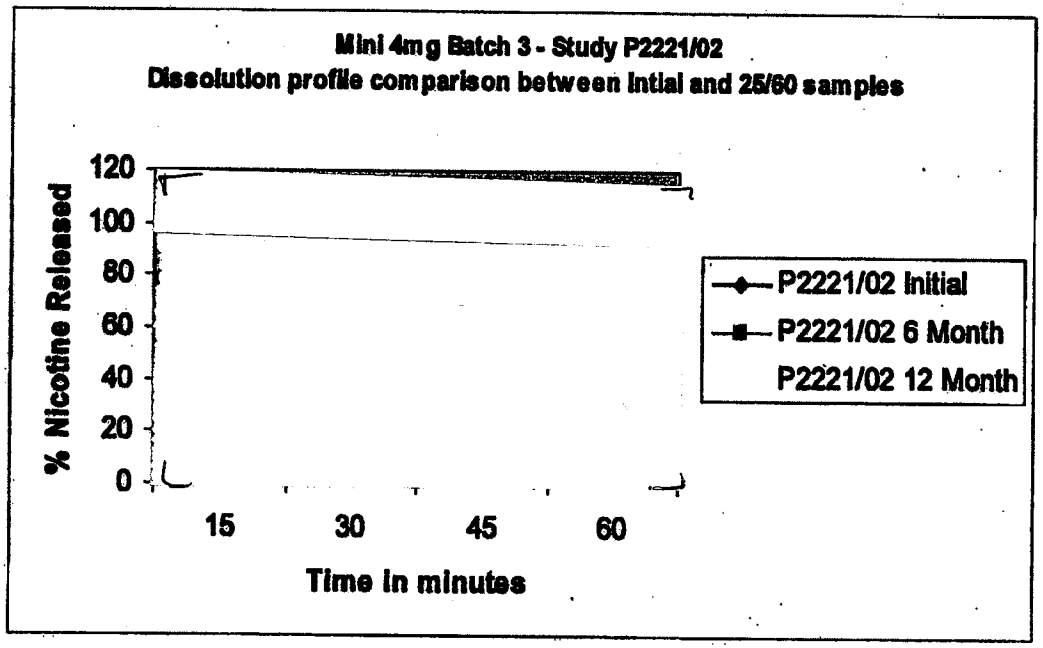
Comparison of USP 3 Dissolution Profiles of 4.0 mg Mini Batch 3 @ different stability time points



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Proposal

- [ ]dissolution specification b(4)
- Complete dissolution in 45' to 1 hour
- Non-disintegrating solid dose form
- Drug progressively released by erosion and not disintegrated

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/s/

Andrea Segal
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