CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 22360/S-008

Name: Nicorette (nicotine polacrilex) Mini Mint Lozenge

Sponsor: GlaxoSmithKline Consumer Healthcare, L.P.

Approval Date: February 14, 2014

This "Prior Approval" supplemental application proposes revision of dissolution specifications for Nicorette (nicotine polacrilex) Mini Mint Lozenge, 2 mg and 4 mg.

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APPLICATION NUMBER:

NDA 22360/S-008

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APPLICATION NUMBER:

NDA 22360/S-008

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22360/S-008

APPROVAL LETTER

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

Dear Ms. Shelton:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 18, 2013, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nicorette (nicotine polacrilex) Mini Mint Lozenge, 2mg and 4mg.

This "Prior Approval" supplemental application proposes revision of dissolution specifications for Nicorette (nicotine polacrilex) Mini Mint Lozenge, 2 mg and 4 mg.

We have completed our review of this supplemental new drug application. This supplement is approved.

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

If you have any questions, call Rebecca McKnight, Regulatory Project Manager, at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

Ramesh Raghavachari, Ph.D.
Branch Chief, Branch IX
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
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/

RAMESH RAGHAVACHARI
02/14/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22360/S-008

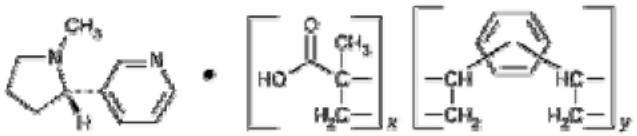
CHEMISTRY REVIEWS

CHEMISTRY REVIEW
OF **SUPPLEMENT**

1. ORGANIZATION: ONDQA – Division of Post-Marketing Evaluation
2. NDA Number: **22360**
3. SUPPLEMENT NUMBER/DATE: **S008 (PA)**
   Letter date: October 18, 2013
   Stamp date: October 18, 2013
4. AMENDMENT/ REPORTS/DATE: **none**
5. RECEIVED BY CHEMIST: **October 30, 2013**

6. APPLICANT NAME & ADDRESS: GlaxoSmithKline Consumer Healthcare L.P.
1500 Littleton Road
Parsippany, NJ 07054-3884

7. NAME OF DRUG: Nicorette® Mini Mint
8. NONPROPRIETARY NAME: nicotine polacrilex
9. CHEMICAL NAME/STRUCTURE: Nicotine polacrilex is a nicotine complex with a weak carboxylic cation-exchange resin prepared from methacrylic acid and divinylbenzene.
$[(C_4H_6O_2)x(C_{10}H_{10})y](C_{10}H_{14}N_2)$



10. DOSAGE FORM(S): Oral Lozenge; to maximize nicotine released and absorbed by the oral mucosa. Nicorette Mini Mint Lozange is a medicine not a candy and must be used in a certain way to get the best results.
11. POTENCY: 2 mg/lozenge piece and 4 mg/lozenge piece in mint flavor
12. PHARMACOLOGICAL CATEGORY: Stop smoking aid; reduces withdrawal symptoms including nicotine craving, associated with quitting smoking.
13. HOW DISPENSED: ____ (R_x) X (OTC)
14. RECORDS & REPORTS CURRENT: X Yes ____ No
    REVIEW RECORDS & REPORTS CURRENT X Yes ____ No
15. RELATED IND/NDA/DMF: None

16. SUPPLEMENT PROVIDES FOR: Revised dissolution specifications for Nicorette (nicotine polacrilex) 2 mg and 4 mg Mini Mint Lozenge.

17. COMMENTS: GlaxoSmithKline Consumer Healthcare L.P. (GSKCH) NDA 22360 for Nicorette (nicotine polacrilex) 2 mg and 4 mg Mini Mint Lozenge (NMML) was approved May 19, 2009. GSKCH has submitted a Prior Approval Supplement (PAS) proposing to revise the dissolution specifications. On December 20, 2013 the FDA acknowledged that the supplement application would be reviewed as PAS 22360/S008. The Initial Quality Assessment (IQA) for 22360/S008 is shown in Attachment 1.

NB: The IQA notes 22360/S008 cross references a number of applications/DMFs. The cross-referenced applications/DMFs are not considered directly relevant to the proposed changes. Thus, the cross-referenced applications/DMFs are not evaluated for this review.

Background

On April 27, 2010, GSKCH and the FDA held a Type B Meeting to discuss the process for establishing revised dissolution specifications for NMML. GSKCH noted that during the validation and pre-launch commercial manufacture of NMML the dissolution profiles shifted for both strengths of NMML as compared to the profiles established from the clinical and pivotal batches. This resulted in nine failing batches. GSKCH determined the root cause of the batch failures was the use of a new batch of sodium alginate NF ((b) (4) from a new supplier, (b) (4). All lots of NMML manufactured using sodium alginate NF (b) (4) supplied by (b) (4) passed. (b) (4) is the

supplier of sodium alginate NF described in the original NDA. At the time of the meeting with the FDA GSKCH was in possession of the (b) (4) supply of (b) (4) sodium alginate NF, and (b) (4) was no longer manufacturing (b) (4). GSKCH stated that their intention was to qualify a new sodium alginate NF supplier. GSKCH noted that the approved NMML dissolution specifications were based on the dissolution analysis of NMML (clinical and pivotal stability batches) manufactured using (b) (4) sodium alginate NF.

NB: Alginate is a natural product, found in a wide variety of brown seaweeds. It is a structural polysaccharide, made up of a linear block copolymer of α-L-guluronic acid (G) and β-D-mannuronic acid (M) (Attachment 2). The block structure varies in size and sequence. Heterogeneous random blocks may also be present. The type of block structure is influenced by seaweed species, growing conditions and seasonal changes. The block structure ultimately dictates the cross-linking properties of alginate in the presence of metals ions such as calcium. It is this property of alginates, namely to cross link through metal ions (such as calcium) to form hydrogel, which is commonly employed as a mechanism to achieve controlled-release of drugs in oral solid dosage forms. The variable nature of alginate can influence the behavior of alginate when used as an excipient in solid oral dosage forms.

GSKCH has included in 22360/S008 the FDA Meeting Minutes for the April 27, 2010 meeting. See DARRTS entry, dated May 25, 2010 by Dr. Joel Schiffenbauer, MD, (Deputy Director-Division of Nonprescription Clinical Evaluation (on April 27, 2010)) for 22360/S008 for the FDA Meeting Minutes. In addition to agreeing to submit a PAS for the revised dissolution specifications, the following **Decisions (Agreements)** were agreed to:

- GSKCH will provide information on the quality and variability of sodium alginate.
- GSKCH will provide adequate release and 6 months of accelerated stability data as part of the PAS.

The FDA Meeting Notes records the following additional FDA's recommendations to convey to GSKH:

- How many lots (NMML) have been manufactured to date.
- How many lots (NMML) failed to meet the dissolution acceptance criteria.
- At which stage(s) of the dissolution test these failures occurred.
- FDA would like to see any data available from dissolution tests of products after extended storage under stability conditions.
- FDA wants to know if there are any manufacturing site related correlations in the dissolution results.
- The individual data (dissolution) for the nine failing batches should be provided.
- With regard to the individual data for the nine failing batches (NMML), FDA requests that GSKCH provide all of the data, including the upper and lower limits as well as the average, rather than composite mean dissolution data.
- FDA will require data (dissolution) from three batches (NMML), in order to assess batch-to-batch variability.
- FDA would like to see any information on alginate (i.e., what batch-to-batch variability of naturally derived sodium alginate would most affect NMML).

NDA 22360/S008 provides the data that addresses the **Decisions (Agreements)** reached at the April 27, 2010 meeting. In addition, 22360/S008 provides appropriate supporting data that adequately address the majority of FDA's recommendations.

NB: The FDA Meeting Minutes records GSKHC's intention to respond to the FDA's preliminary responses in a follow-up correspondence. GSKHC's follow-up correspondence or GSKHC's Meeting Notes are not available in DARRTS.

Proposed Dissolution Method and Specifications for NMML

The current and proposed dissolution method and specifications for both NMML and Nicorette Lozenge (NDA 21330) are described in Attachment 3. As described above the proposed changes to the dissolution method and specifications are driven by the chemical variability in naturally derived sodium alginate excipient, sourced from different suppliers. The original supplier (b) (4) of sodium alginate NF is no longer available. GSKCH has

identified (b) (4) as the new supplier of sodium alginate NF. The proposed changes in sodium alginate supplier do not change the approved NMML formulation.

GSKCH has updated NMML release and stability specifications to reflect the proposed dissolution specifications. GSKHC's has described the development of the new dissolution method and specifications in Section **3.2.P.2.2 Formulation Development**. GSKCH provided justifications of the new dissolution method and specifications in Section **3.2.P.5.6 Justification of Specification**. The changes proposed in 22360/S008 do not impact the process and equipment used to manufacture NMML or the approved NMML container closure system.

Justification New Dissolution Method and Specifications for NMML

Per the **Decisions (Agreements)**, GSKCH has included in Section **3.2.P.2.2 Formulation Development** a description of the 2009 compliance problem with respect to the NMML USP I dissolution test data collected during process validation and initial commercial manufacture ((b) (4) batches/strength). GSKCH has provided the individual dissolution data for these batches. As indicated above, GSKCH has traced dissolution failure to the natural chemical variability in the sodium alginate NF excipient. GSKCH does not believe the variability in the NMML USP I dissolution test data is a true measure of the clinical performance of NMML. GSKCH has proposed a NMML USP III (reciprocating cylinders) dissolution method and revised NMML dissolution specifications (Attachment 3) which the applicant believes more accurately reflects the fact that for both NMML and Nicorette Lozenge, nicotine absorption through the ora-mucosal tissues is permeation-limited rather than dissolution limited. This is consistent with the fact that the two products have the following differences: size (not strength) (Attachment 4), 2) dissolution profile (Attachment 5) and 3) in-vivo dissolution time (Attachment 6). However, despite these differences NMML and Nicorette Lozenge are bioequivalent. The bioequivalence study (S3010567) was evaluated in the original NDA 22360 review. See DARRTS entry, dated March 23, 2009 by Priscilla Callahan-Lyon, MD (Clinical Reviewer-Division of Nonprescription Clinical Evaluation) for 22360 with an approval recommendation

GSKCH has adequately described the dissolution data for the failed NMML validation batches. GSKCH has adequately described their root cause analysis of these failures to be due to the chemical variability in the sodium alginate NF excipient, and the resultant differences in the chemistry of sodium alginate NF (due to different suppliers) shifted the dissolution behavior of NMML. GSKCH was adequately described how this chemical variability affects the function of sodium alginate NF in NMML, which in turn affects how nicotine is released. These explanations will not be, however they are available in Section **3.2.P.2.2 Formulation Development**.

GSKCH is proposing a more relevant dissolution test, namely USP III (reciprocating cylinders) vs. USP I (paddle), and a new specification (Q= (b) (4) at 60 minutes). The proposed dissolution method and specifications are based on GSKHC's understandings of the following:

- variability of sodium alginates
- nicotine release mechanisms of NMML
- clinical performances of NMML
- long term stability of NMML
- requirements of the dissolution method as a quality control for NMML release and stability
- process capability of manufacturing NMML of consistent quality

Per the **Decisions (Agreements)**, GSKCH has provided in Section **3.2.P.2.2 Formulation Development**, 24 months ICH dissolution stability test results using both the USP I and USP III dissolution methods. For this study (Protocol P2518), six batches of NMML were manufactured using three lots of (b) (4) sodium alginate NF and three lots of nicotine polyacrilex. The 150 minutes stability time point replaces 120 minutes because GSKCH anticipated slower dissolution for NMML manufactured using (b) (4) sodium alginate NF. The batch analysis of the three lots of (b) (4) sodium alginate NF shows that the three excipient lots are of similar quality. GSKCH has provided distribution plots for the USP I and USP III dissolution data

collected on the six batches of NMML. The dissolution data distribution plots for NMML manufactured using (b) (4) sodium alginate NF are shown in Attachment 7. The mean and SD for USP I and USP III dissolution data are listed below.

Mean Values and SD for Dissolution Stability Test Results (Protocol P2518)

USP I			USP III
30 minutes	**60 minutes**	**150 minutes**	**60 minutes**
29.67 ± 2.79	49.91 ± 4.6	95.48 ± 4.88	98.05 ± 3.27

GSKCH has provided in Section **3.2.P.2.2 Formulation Development** 36 months of ICH dissolution stability test results using both the USP I and USP III dissolution methods. This study (Protocol 2402) used the six NMML batches representing the clinical and pivotal stability batches. As described above these batches were manufactured using (b) (4) sodium alginate NF. According to GSKCH the SD (variability) for study P2518 using (b) (4) sodium alginate NF are similar to the SD observed in study P2402 up to two years using NMML manufactured using the original (b) (4) sodium alginate NF. However, the mean value for percentage released for each time point for NMML manufactured with (b) (4) sodium alginate NF is slightly lower ((b) (4)%) compared to NMML manufactured with (b) (4) sodium alginate NF. According to GSKH, this is because (b) (4) sodium alginate NF has (b) (4) and (b) (4) than (b) (4) sodium alginate NF.

GSKCH has provided the appropriate stability data requested at the April 27, 2010 meeting. The data distribution (variability) of the USP I and USP III dissolution methods are comparable. An examination of the dissolution data generated by the proposed USP III dissolution method shows several data points would fail stage I testing (i.e., (b) (4)%). An examination of Protocol P2518 dissolution data shows no dissolution failures after 24 months on long term storage and a single dissolution value less than (b) (4)% ((b) (4)%) when sample is stored at 30ºC/75%RH. No dissolution failures were seen for sample stored for 12 months (complete) at 40ºC/75%RH.

GSKCH describes a (b) (4) The description and GSKHC's explanation of the root cause of the (b) (4) effect seen in NMML dissolution results is provided in Section **3.2.P.2.2 Formulation Development**. GSKCH has adequately described and provided a plausible explanation of the impact (b) (4) (b) (4) has on NMML dissolution results over time. The USP III (reciprocating cylinders) dissolution method and revised NMML dissolution specifications is able to detect significant dissolution change due to the (b) (4) (b) (4) changes in the NMML (b) (4)

As shown in Attachment 3, GSKCH proposes to replace the NMML USP I dissolution test with a USP III (reciprocating cylinders) method, and replace the dissolution specification for NMML. The reason for the proposed changes is the fact that NMML (specifically the 2 mg lozenge) has failed to meet the dissolution specification at 60 and 120 minutes using the USP I dissolution test. GSKCH has provided the following justifications for the USP III dissolution method with Q= (b) (4) at 60 minutes time point for NMML:

- USP III dissolution method at 60 minutes demonstrates the same degree of dissolution completion as the USP I dissolution method
- USP III dissolution method is more relevant to the clinical dissolution than the USP I dissolution method in terms of release mechanism and dissolution duration.
- USP III dissolution method is sensitive and demonstrated to detect significant product change that could influence product performance and change product quality.
- USP III dissolution method provides some degree of physical erosion (b) (4) (b) (4), which allows NMML to release nicotine more similar to the actual usage of the drug product.

- The actual in vivo dissolution time for NMML is 10-20 minutes, USP III dissolution at 60 minutes is more biorelevant to clinical performance of NMML and bioequivalent to Nicorette Lozenges.

GSKCH has provided in Section **3.2.P.2.2 Formulation Development** and Section **3.2.P.5.6 Justification of Specification** descriptions of studies performed to support the justification that USP III dissolution method has adequate discrimatory powers and sensitivity to detect any changes in the NMML, such as (b) (4) (b) (4) or change in the amount of (b) (4) (b) (4) GSKCH has provided data, which shows the proposed dissolution specification is sensitive to detect dissolution failure upon long-term stability storage of NMML ((b) (4)) while its potency remains above (b) (4)LC. GSKCH has provided sufficient and adequate data to demonstrate that USP III dissolution method and single point dissolution specification is sensitive to detect changes in the NMML formulation at release and during long-term stability. The long-term stability data (Protocol P2518) demonstrates the USP III dissolution method accommodates the inherent variability of the natural excipient sodium alginate NF. Thus, USP III dissolution method is suitable to be used as a quality control tool to evaluate the pharmaceutical performance (i.e., batch-to-batch uniformity) of both NMML and Nicorette Lozenge.

Supporting the USP III dissolution method for NMML release and stability is the fact that the USP III dissolution test with specification Q=(b) (4) at 60 minutes is used for release and stability testing of NMML (1.5 mg and 4 mg) for European markets. GSKCH has been manufacturing NMML for the European market since 2008, and all finished product has met specifications that includes using USP III dissolution method as a quality control test. The commercial manufacture process capability for the manufacture of NMML in the US and European markets are shown in Attachment 8. A Ppk of (b) (4) for the proposed US dissolution specification of Q=(b) (4) adequately demonstrates that the current commercial manufacturing process is a highly capable process with the proposed dissolution specification for NMML manufactured using (b) (4) sodium alginate. GSKCH has also performed process capability analysis for USP III dissolution method with specification Q=(b) (4) using the long term stability data generated in Protocol P2518 and Protocol 2402/2 years (Attachment 9). Ppk of (b) (4), which is greater than (b) (4), demonstrates that the proposed specification is within the commercial process capability with a consistent quality. Both process capability calculations demonstrate the NMML manufacture process is a highly capable process to achieve the proposed dissolution specification USP III Q=(b) (4)% at 60 minutes.

The NMML has been shown to be bioequivalent (S3010567) with Nicorette Lozenges for both the 2 mg and 4 mg strength. GSKCH has provided a summary of the bioequivalence study (S301567) in Section **3.2.P.2.2 Formulation Development**. In order to investigate the in-vitro dissolution (USP I) and the in-vivo absorption relationship, the in-vivo function is estimated from the mean plasma concentrations using the Wagner-Nelson equation. The scaled in-vitro dissolution profiles were used to analyze in-vitro and in-vivo relationship (IVIVR) for both NMML and Nicorette lozenges and strengths. GSKCH concludes that IVIVR for both NMML and Nicorette Lozenges illustrates that the in-vivo absorption of nicotine is permeation-limited and not dissolution-limited. Evaluation of the applicant's analysis of the IVIVR will be performed in the biopharm review of 22360/S008. On October 22, 2013, Ms. Rebecca McKnight (Project Manger-ONDQA postmarketing) requested a Biopharm review of 22360/S008.

Validation of USP III Dissolution Method

GSKCH has provided in **Appendix E** the USP III dissolution method for NMML, namely method C-1961 One Hour Release Profile of Nicotine from Lozenges, Version 5.0 (Issue Date December 5, 2006). The method is validated as a QC release and stability-indicating assay for the following formulations of nicotine lozenges:

(b) (4)

Method validation of C-1961 is available in validation reports: VR-C1961-01, VR-C1961-02, VR-C1961-03, VR-C1961-05 and VR-C1961-07. The method C-1961 is adequate for it intended use.

Nanotechnology product evaluating questions are appended to this review (Attachment 10).

18. CONCLUSIONS & RECOMMENDATIONS: Recommend issuing approval letter from a CMC standpoint, pending Biopharm approval.

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Lorenzo Rocca	Signed Electronically	

20. BRANCH CHIEF NAME	SIGNATURE	DATE COMPLETED
Ramesh Raghavachari	Signed Electronically	

cc:
RRaghavachari
LRocca
RMcKnight

F/T by: LRocca, File: C:Data\LR\Supplement\n22360pm_Nicorette_Lozenge\S008(PA)\S008Review1.doc

Attachment 1
IQA for 22360/S008

PI assign

Gautam-Basak, Mamta

From: Gautam-Basak, Mamta
Sent: Monday, October 28, 2013 11:41 AM
To: McKnight, Rebecca
Subject: RE: Supplement Triage for NDA 22360/S-008, Nicorette Lozenge - IQA completed

This PAS provides for revised dissolution specifications for mini lozenges 2 mg and 4 mg. This supplement is filed as per advice at the meeting held on 4/27/2010. Steve Hathaway/Patrick Marroum attended the meeting from the CMC/Biopharm standpoint.
Stability data (both at accelerated and storage temperature condition) provided need to be reviewed. Meeting minutes (4/27/2010, in DARRTs as well provided in submission) should be reviewed to make sure data is provided as advised.

Note: This application also cross references the following applications/DMFs:

NDA 21-330 Nicorette (formerly Commit) (Nicotine Polacrilex) lozenges 2mg and 4mg and approved flavor supplements; mint (S002 and S003), cherry (S004) and cappuccino (S007). In addition, Prior Approval Supplement for the replacement drug substance (S010)
IND 56,295 Nicotine Polacrilex Lozenge

DMF (b) (4)
DMF
DMF
DMF
DMF

- Mamta

From: McKnight, Rebecca
Sent: Tuesday, October 22, 2013 4:47 PM
To: Gautam-Basak, Mamta
Subject: Supplement Triage for NDA 22360/S-008, Nicorette Lozenge

PDUFA DATE: February 18, 2014

Submitted as: Electronic

Applicant submit supplement as: PAS

ONDQA received date: October 21, 2013

Assigned to Lorenzo

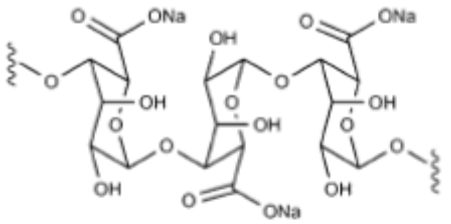
10/28/13

1

Attachment 2
Sodium Alginate Sequences

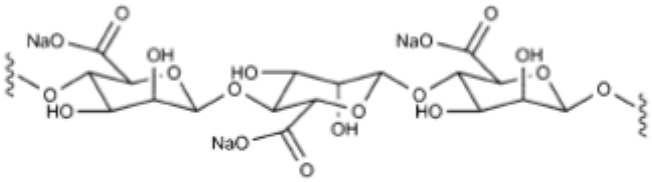
Homogeneous *G* sequence

—(*G*)$_n$—



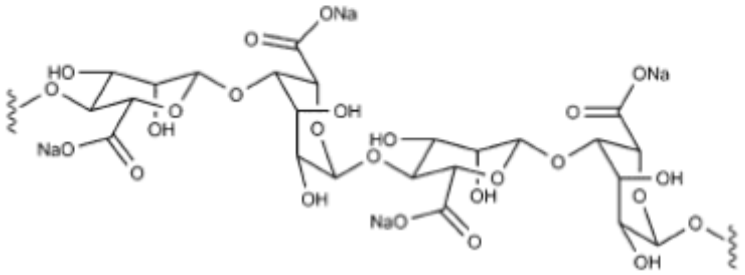
Homogeneous *M* sequence

—(*M*)$_n$—



Heterogeneous *MG* sequence

—(*MG*)$_n$—



Attachment 3
Current and Proposed Dissolution Method and Specifications for NMML

Proposed Method

- Apparatus: USP apparatus III (reciprocating cylinders)
- Media: 250 ml/phosphate buffer pH 7.4
- Temperature: 37 ± 0.5 °C
- Dipping speed: 20 dpm
- Sampling volume: 5 mL manually
- Profile time points: 15, 30, 45, and 60 minutes
- Specification time point: Q=(b) (4)% at 60 minutes

Current Method

- Apparatus: USP apparatus I
- Media: phosphate buffer pH 7.4
- Temperature: 37 ± 0.5 °C
- Rotation speed: 100 rpm
- Sampling volume: 2 mL manually
- Dissolution specification time points

i. Nicorette® lozenges – 1, 3, and 6 hour (NDA 21-330)

ii. Mini Mint lozenges – 30, 60, and 120 minutes (NDA 22-360)

Dissolution Specifications for Nicorette® and Mini Mint Lozenges

Nicorette®	60 minutes (1 hour)	180 minutes (3 hour)	360 minutes (6 hour)
Upper limit		(b) (4)	
Lower limit			

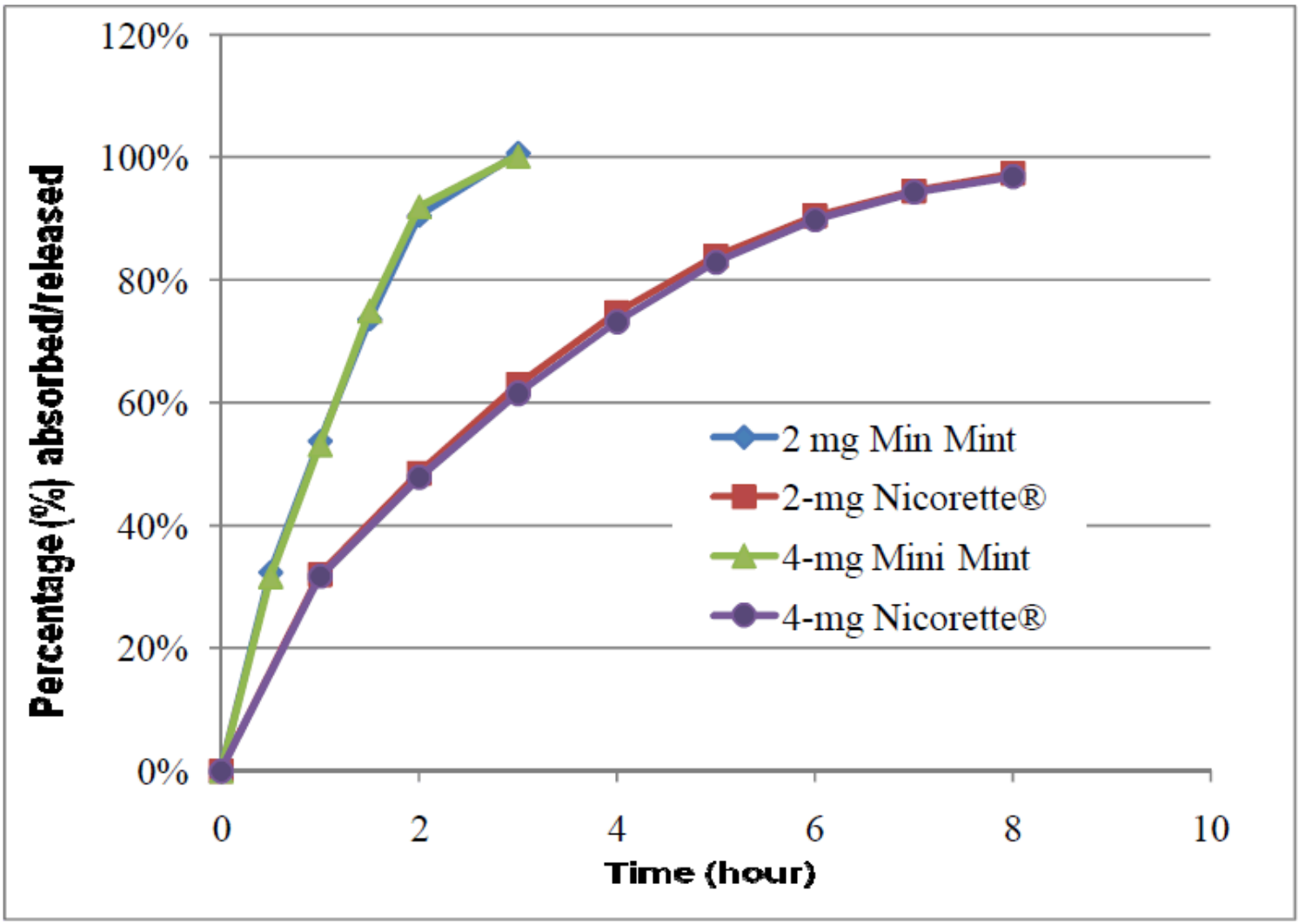
Mini Mint	30 minutes	60 minutes	120 minutes
Upper limit		(b) (4)	
Lower limit			

Attachment 4
Formulations of NMML and Nicorette Lozenges

Excipients	Mini Mint		Nicorette®	
	2-mg	4-mg	2-mg	4-mg
[redacted]				
Total weight (mg)	250.000	250.000	1200.00	1200.00

(b) (4)

Attachment 5
Comparison of In-Vitro Dissolution Profiles for the 2-mg and 4-mg NMML and Nicorette Lozenges

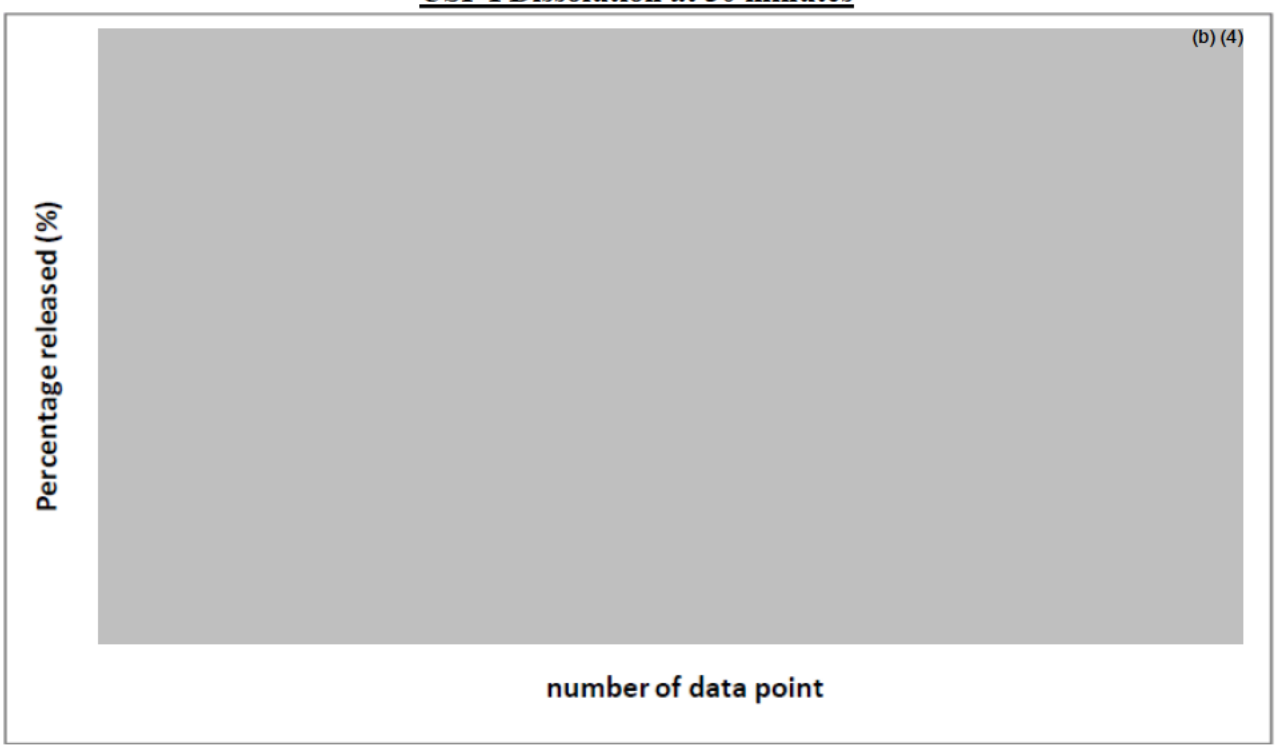


Attachment 6
The In-Vivo Dissolution Time of NMML and Nicorette Lozenges

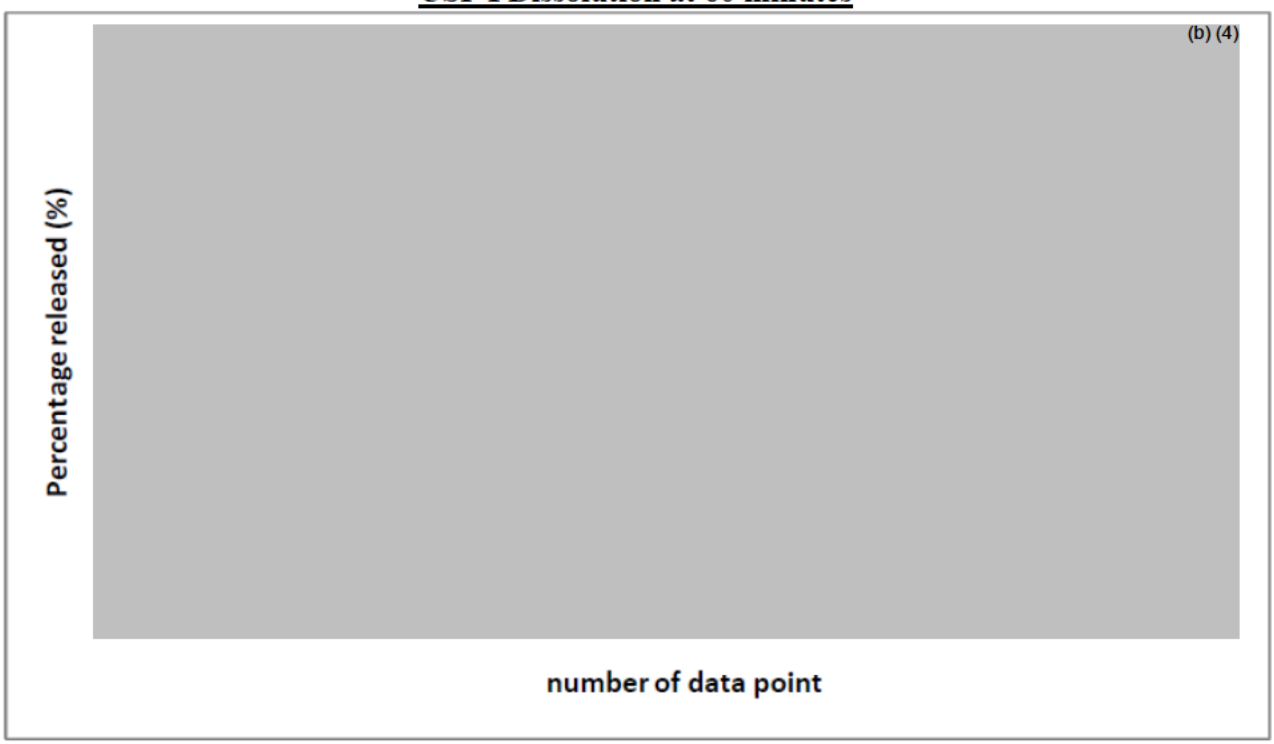
Dissolution time in oral cavity (min)	2-mg		4-mg	
	Mini Mint	Nicorette®	Mini Mint	Nicorette®
Mean	12.5	25.0	11.2	25.6
Std	5.2	8.3	3.9	11.1
Minimum	3	12	4	10
Maximum	26	51	24	57

Attachment 7
NMML Dissolution Data Distribution for Study P2518
(b) (4)

USP I Dissolution at 30 minutes



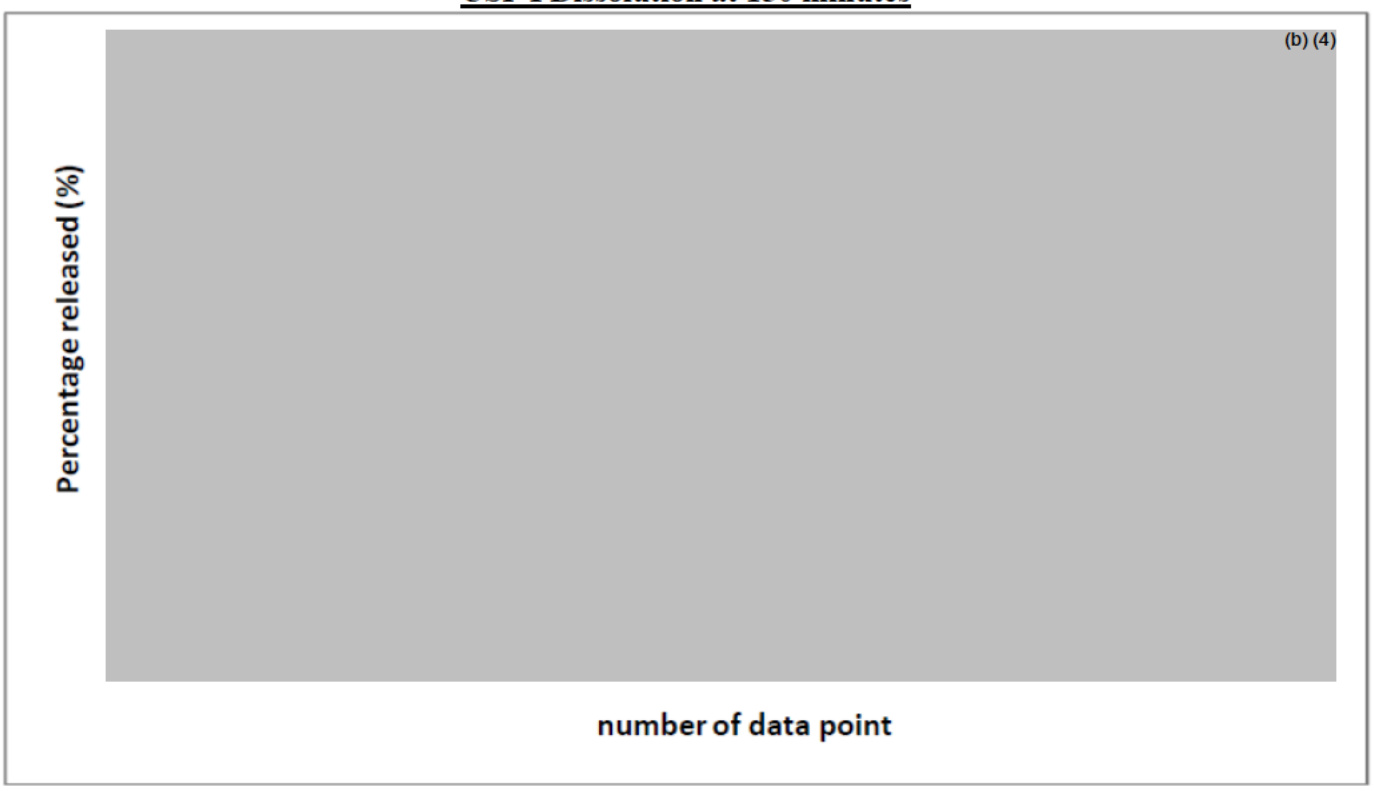
USP I Dissolution at 60 minutes



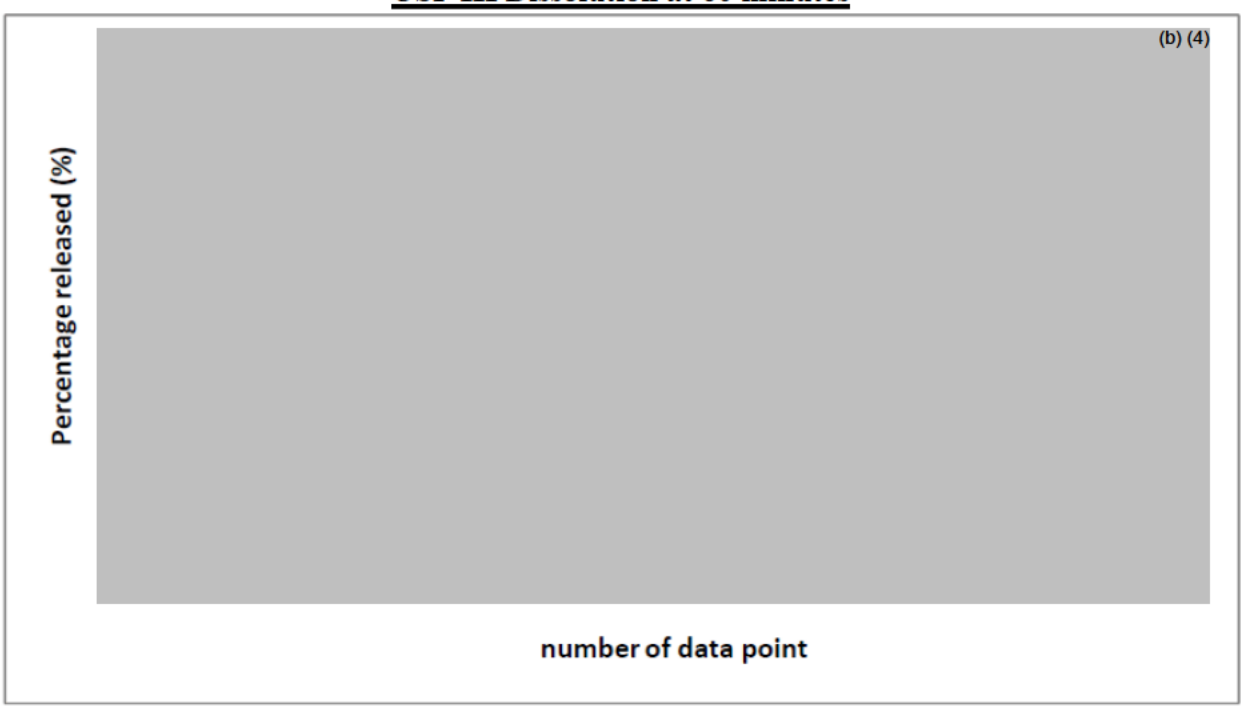
Attachment 7, continued
NMML Dissolution Data Distribution for Study P2518

(b) (4)

USP I Dissolution at 150 minutes



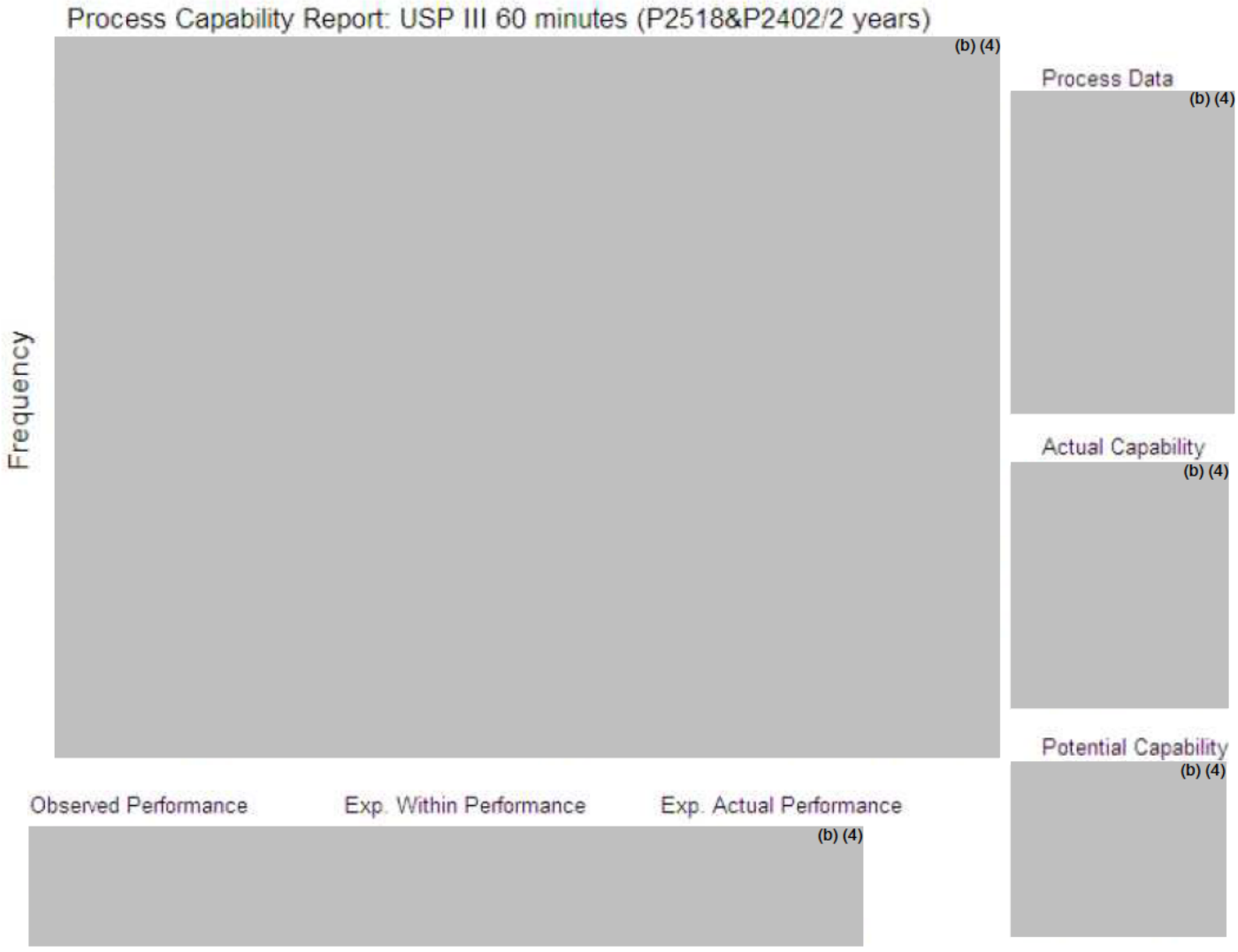
USP III Dissolution at 60 minutes



Attachment 8
USP III Dissolution Data Analysis and Process Capability Analysis

	USP III Dissolution Data for Mini Mint 4 -mg Lozenges	
Numbers of batches	(b) (4)	
Mean	99.59%	
Standard Deviation (actual)	2.01%	
Maximum	(b) (4)	
Minimum		
	USP III Dissolution Data and Process Capability Analysis	
	EU specification Q (b) (4)	Proposed Specification Q (b) (4)
Ppk	(b) (4)	(b) (4)
Ppl		
Sigma level		

Attachment 9
Process Capability Analysis for USP III (b) (4)%
(Q (b) (4)%) at 60 Minutes



Attachment 10

Attachment A: Nanotechnology product evaluating questions:

1, This review contains new information added to the table below: _____Yes; ____X__No Review date: _____
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes_____; No_____ ; Maybe (please specify)_____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____ 3 b) What is the source of the nanomaterial?
4) Is the nanomaterial a reformulation of a previously approved product? Yes No
5) What is the nanomaterial functionality? Carrier_____; Excipient_____; Packaging_____ API_____; Other_____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble **(**e.g., gold nanoparticle**)** in an aqueous environment? Soluble _____; Insoluble_____
7) Was particle size or size range of the nanomaterial included in the application? Yes_____(Complete 8); No_____ (go to 9).
8) What is the reported particle size? Mean particle size_____ ; Size range distribution_____; Other_____
9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____
11) List all methods used to characterize the nanomaterial?_____ _____

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/s/

LORENZO A ROCCA
02/03/2014

RAMESH RAGHAVACHARI
02/04/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22360/S-008

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
NDA Number	22-360/S-08	**Reviewer**	Assadollah Noory, Ph.D.
Stamp Date	10/18/2013	**Team Leader**	Tapash Ghosh, Ph.D.
Type of Submission	PAS	**Acting Supervisor**	Richard Lostritto, Ph.D.
Clinical Division	DNCE		
Sponsor	GSK		
Trade Name	Nicorette		
Generic Name	Nicotine polacrilex		
Dosage Form	2mg and 4mg Mini Mint Lozenge		
Indication	To reduce withdrawal symptoms in quitting smoking		
Rout of Administration	Buccal		

SUMMARY: GSK submitted this prior approval supplement (PAS) for the approval of a new dissolution methodology and specification for Nicorette Mini Mint lozenges. The original dissolution method was USP apparatus I. The proposed dissolution methodology uses USP apparatus III, the reciprocating cylinder. In a Type B Meeting on April 27, 2010 the Agency recommended that the Sponsor submitted data supporting the proposed dissolution method and/or specification change in a prior approval supplement for review. The Sponsor presented an extensive documentation for their proposed dissolution methodology. According to the sponsor, the data supports the change to USP apparatus III.

RECOMMENDATION: ONDQA-Biopharmaceutics has completed the review of data supporting the new dissolution methodology proposed by the Sponsor for NDA 22360/S-08. The proposed use of USP apparatus III, reciprocating cylinder, is acceptable to use in dissolution method for Nicorette Mini Mint lozenges. ONDQA-Biopharmaceutics recommends the approval of the new dissolution methodology and specification proposed by the Sponsor as described in the following table for product release and stability period:

Apparatus	**USP III (reciprocating cylinder)**
Agitation	**20 dip/minute**
Dissolution Medium	**Phosphate buffer pH 7.4**
Volume	**250 mL**
Specification	**Q=(b) (4) % at 60 minutes**

Assadollah Noory, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph. D.
Team Leader
Office of New Drug Quality Assessment

Background:

Nicorette Mini Mints 2mg and 4mg lozenge (NDA 22-360) were approved on May 18, 2009 based on bioequivalence to Nicorette® lozenge. Both Nicorette® lozenge and Nicorette Mini Mint lozenge are manufactured from (b) (4) varies as the source of sodium alginate changes. A change in the dissolution profiles was seen during validation and pre-launch of commercial production where nine (2-mg) lots failed the Stage 1 dissolution specification. The Sponsor determined that the cause was a change in the supplier of sodium alginate, from (b) (4) to (b) (4) This information was presented to FDA on April 27, 2010. The Agency recommended that the Sponsor submit data supporting a different dissolution method and/or specification in a prior approval supplement for review.

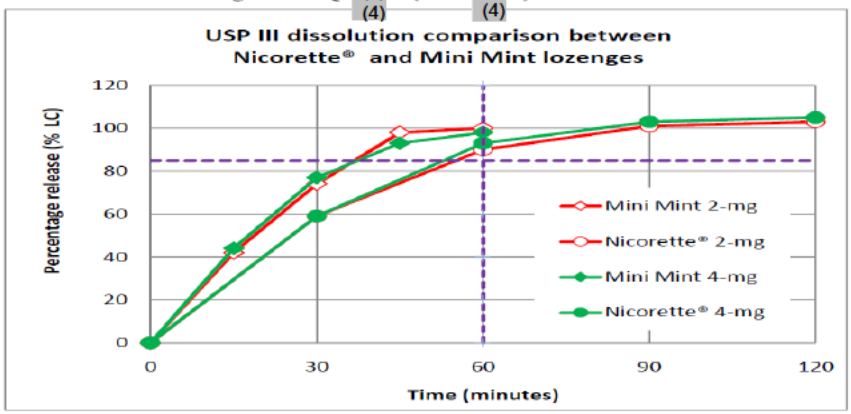
Dissolution Methodology and Justification:

GSK provided extensive data in support of their new proposed dissolution methodology including comparison of bio-batches, ability to detect significant changes, and ability to assure process capability. In the original dissolution method USP apparatus I was used but in the proposed dissolution methodology USP III (reciprocating cylinder) has been proposed. Along with the proposed change in dissolution method, new dissolution specification has been proposed also. The following table contains the current and the proposed dissolution methodologies and specifications.

Dissolution Method for nicotine Mini Mint lozenge		
	Current Method	**Proposed Method**
Apparatus	**USP 1**	**USP III**
Agitation	**100 rpm**	**20 dip/minute**
Medium	**Phosphate buffer pH 7.4**	**Phosphate buffer pH 7.4**
Volume	**900 mL**	**250 mL**
Specification	**Q=(b) (4) % in 120 minutes**	**Q=(b) (4) % in 60 minutes**

A comparison of dissolution of Mini Mint and Nicorette bio-batch using the proposed methodology is shown in the following figure.

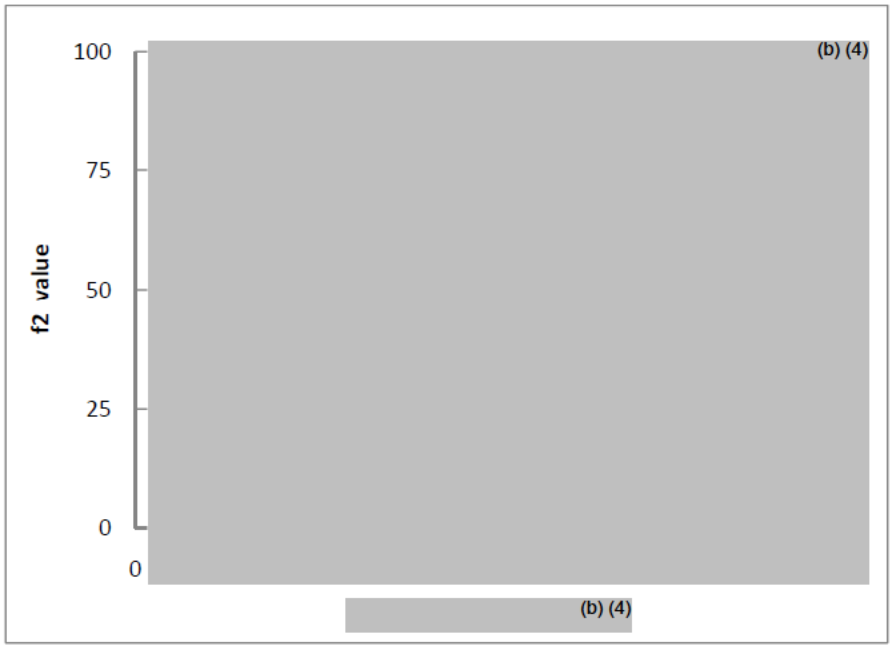
Figure 1
USP III dissolution (mean of six) comparison between Nicorette® and Mini Mint Lozenges with Q= (b)(4)% (NLT (b)(4)%) at 60 minutes



Both products showed comparable release at 60 minutes.

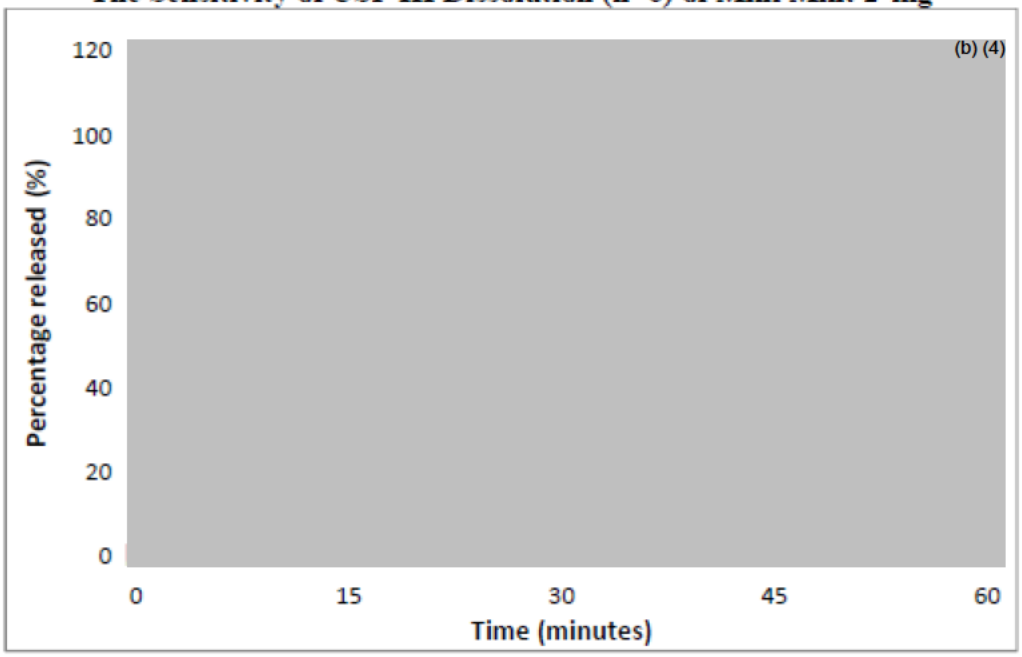
The proposed dissolution method was able to detect significant changes in (b) (4) (b) (4) in the (b) (4) and in changes in the (b) (4) (b) (4) as demonstrated in the following figures.

Figure 2
Similarity Factor (f_2) as a Function of (b) (4)



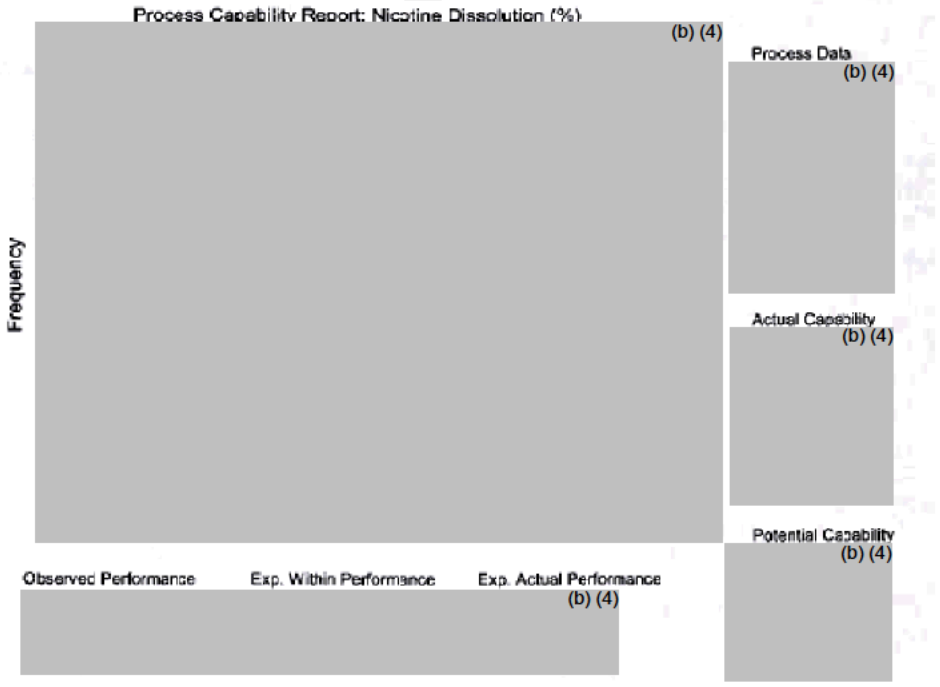
The ability to detect changes in the (b) (4) is illustrated in the following figure.

Figure 27
The Sensitivity of USP III Dissolution (n=6) of Mini Mint 2-mg



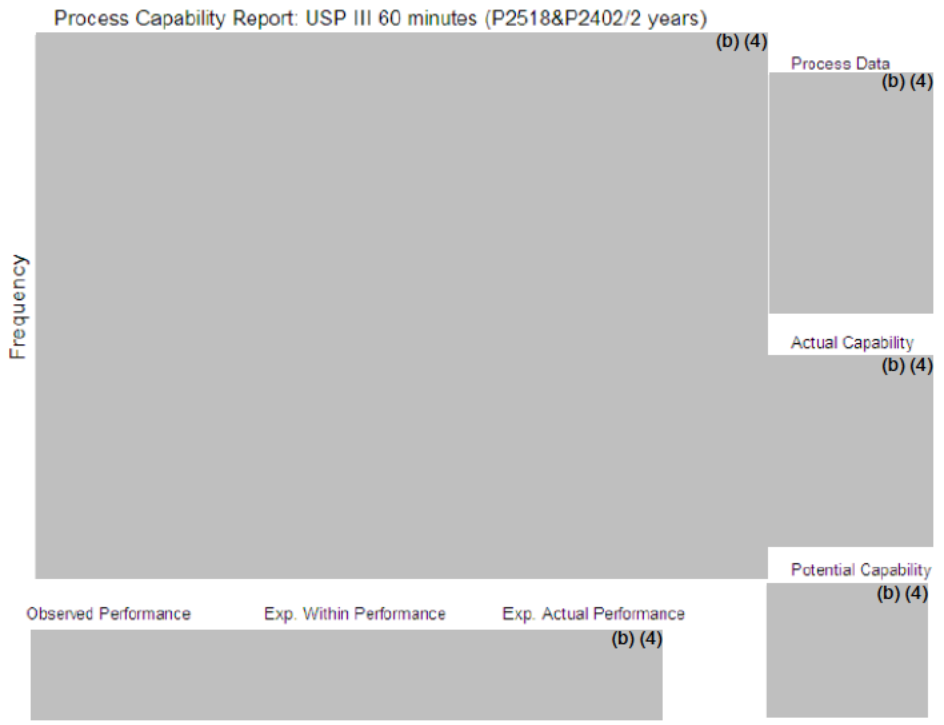
To demonstrate process capability (b) (4) lots (1.5 and 4 mg Mini Mint lozenges) manufactured for the European market in 2011 and 2012 using (b) (4) and tested using the USP apparatus III at 60 minutes showed a mean dissolution of 99.59% (2.01% SD) and range of (b) (4)-(b) (4)% for the 4-mg lozenge. The process capabilities against EU dissolution specification, which is Q (b) (4) at 60 minutes has a PPK (a capacity index for manufacturing process performance) of (b) (4) and sigma level of (b) (4). With the specification of (b) (4)%, the PPK is (b) (4) with a sigma level of (b) (4) shown in the following figure.

Process Capability Analysis for Mini Mint 4-mg Lozenge with USP III Dissolution Specification (Q (b) (4)% at 60 Minutes)



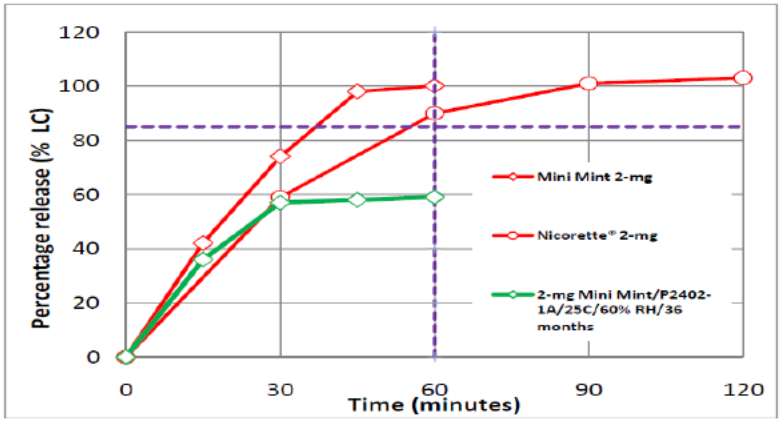
In the US, process capability analysis was performed using long term stability batches. Using USP III with a specification of (b) (4)% resulted in a PPK = (b) (4) with a sigma level of (b) (4) with a mean dissolution of 99.06% ± 2.93 shown in the following figure.

Process Capability Analysis for USP III NLT (b) (4)%
(Q ((b) (4) %) at 60 Minutes



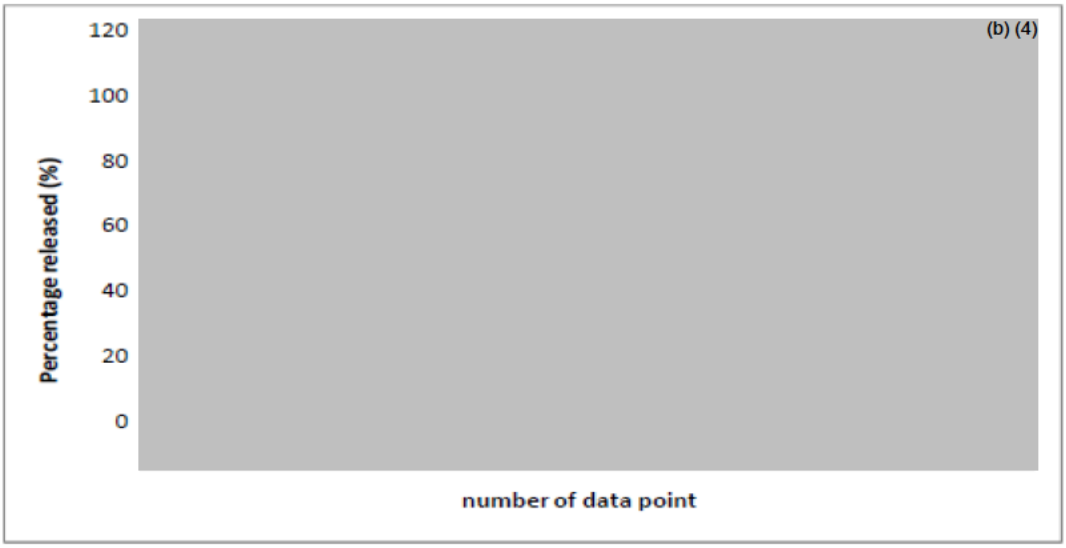
24 Month Stability at 25°C and 60% RH was conducted. Two bio-batches plus four pivotal batches manufactured with (b) (4) and stored under ICH stability conditions were tested using the proposed USP apparatus III method. The results are shown in the following figure.

Figure 4
Sensitivity of the Proposed Dissolution Specification for Stability Samples



Three years of long term stability data has been collected on the clinical and pivotal stability batches: (GSK5587B11/2mg, GSK5587B012/2-mg, GSK5587B13/2mg, GSK5588B011/4-mg, GSK5588B012/4-mg, and GSK5588B013/4-mg) using USP apparatus I and USP apparatus III dissolution methods. The distribution of USP I dissolution data at 120 minutes for both strengths (six batches and all three ICH conditions) are shown in the following Figure.

Figure 12
Data Distribution of USP I Dissolution at 120 minutes
(b) (4)



The distribution of USP III dissolution data at 60 minutes for both strengths is shown in the following figure.

Figure 13
Data Distribution of USP III Dissolution at 60 minutes
(b) (4)

Following the meeting with the Agency, six batches of Mini Mints (GSK5699B01 2-mg, GSK5699B02 2-mg, GSK5699B03 2-mg, GSK5700B01 4-mg, GSK5700B01 4-mg, and GSK5700B01 4-mg) along with three batches of Nicorette lozenge were manufactured with three lots of (b) (4) and placed under ICH conditions for 24 months. Data distribution with USP apparatus 1 at 150 minutes is shown in the following figure. The Agency suggested that the Sponsor evaluate the specification at 150 minutes using USP apparatus I. The mean was 95.48% ±4.88%.

Figure 17
Data Distribution of USP I Dissolution at 150 minutes

(b) (4)

The same lots were tested with USPIII at 60 minutes and the results are show in the following figure below. The mean was 98.05%±3.27%.

Figure 18
Data Distribution of USP III Dissolution at 60 minutes

(b) (4)

Reviewer Comment:

Based on the provided information, use of the USP apparatus III along with the proposed new dissolution specification (Q = (b) (4)% in 60 min) is acceptable for Nicorette Mini Mint lozenges using sodium alginate made by (b) (4) It is capable of detecting some differences due to manufacturing changes and stability conditions. USP apparatus III has been used in the EU for many years. Overall, the proposed dissolution method methodology and specification are acceptable.

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/s/

ASSADOLLAH NOORY
02/14/2014

TAPASH K GHOSH
02/14/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22360/S-008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 22360/S-008

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

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

Dear Ms. Shelton:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 22360

SUPPLEMENT NUMBER: S-008

PRODUCT NAME: Nicorette (nicotine polacrilex) 2mg and 4mg Mini Mint Lozenge

DATE OF SUBMISSION: October 18, 2013

DATE OF RECEIPT: October 18, 2013

This supplemental application proposes the following change(s): revised dissolution specifications.

The application was filed on December 18, 2013, in accordance with 21 CFR 314.101(a). The user fee goal date will be February 18, 2014.

SUBMISSION REQUIREMENTS

Cite the application number listed above 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 Non-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, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

Rebecca McKnight
Regulatory Health Project Manager
Division of New Drug Quality Assessment III
Office of New Drug Evaluation
Center for Drug Evaluation and Research

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/s/

REBECCA A MCKNIGHT
12/20/2013