CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 207868

Name: Nicotine Polacrilex Lozenges, 2 mg and 4 mg (Mini)

Sponsor: PLD Acquisitions LLC

Approval Date: February 07, 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA207868Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207868

APPROVAL LETTER

ANDA 207868

ANDA APPROVAL

PLD Acquisitions LLC, D/B/A Avema Pharma Solutions
609-2 Cantiague Rock Road
Westbury, NY 11590
Attention: Mehul Govani
Regulatory Affairs Manager

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 2, 2015, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Nicotine Polacrilex Lozenges, 2 mg and 4 mg (Mini).

Reference is also made to the complete response letter issued by this office on October 25, 2018, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for over-the-counter (OTC) use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Nicotine Polacrilex Lozenges, 2 mg and 4 mg (Mini), to be bioequivalent to the reference listed drug (RLD), Nicorette Mini Lozenges, 2 mg and 4 mg, of GlaxoSmithKline Consumer Healthcare (GlaxoSmithKline).

The RLD upon which you have based your ANDA, GlaxoSmithKline's Nicorette Mini Lozenges, 2 mg and 4 mg, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
8,501,164 (the '164 patent)	June 14, 2029
8,940,772 (the '772 patent)	April 30, 2029

Your ANDA contains paragraph IV certifications to each of the patents under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Nicotine Polacrilex Lozenges, 2 mg and 4 mg (Mini), under this ANDA. You have notified the Agency that PLD Acquisitions LLC, D/B/A Avema Pharma Solutions (PLD) complied with the requirements of section 505(j)(2)(B) of the FD&C Act and that no action for infringement was brought against PLD within the statutory 45-day period.

With respect to 180-day generic drug exclusivity, we note that PLD was the first ANDA applicant for Nicotine Polacrilex Lozenges, 2 mg and 4 mg (Mini), to submit a substantially complete

ANDA with a paragraph IV certification. Therefore, with this approval, PLD is eligible for 180 days of generic drug exclusivity for Nicotine Polacrilex Lozenges, 2 mg and 4 mg (Mini). This exclusivity, which is provided for under 505(j)(5)(B)(iv) of the FD&C Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA notifying the Agency within 30 days of the date of the first commercial marketing of this drug product or the RLD. If you do not notify the Agency within 30 days, the date of first commercial marketing will be deemed to be the date of the drug product's approval. See 21 CFR 314.107(c)(2).

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL

files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, Pharm.D.
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Sarah Kurtz

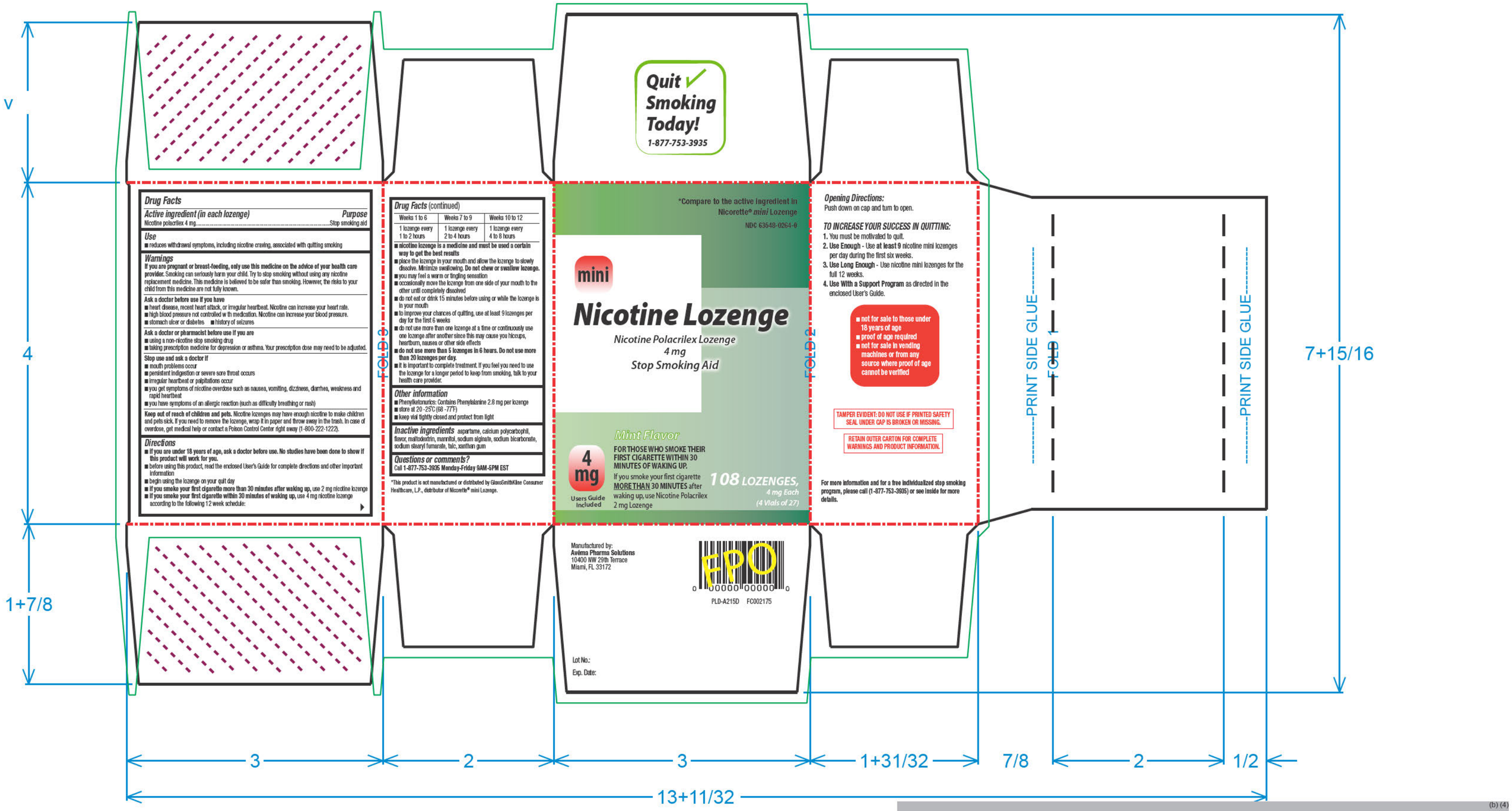
Digitally signed by Sarah Kurtz
Date: 2/07/2019 06:30:11PM
GUID: 54078879000a1b9e15dd31ed6f0343ca

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207868

LABELING



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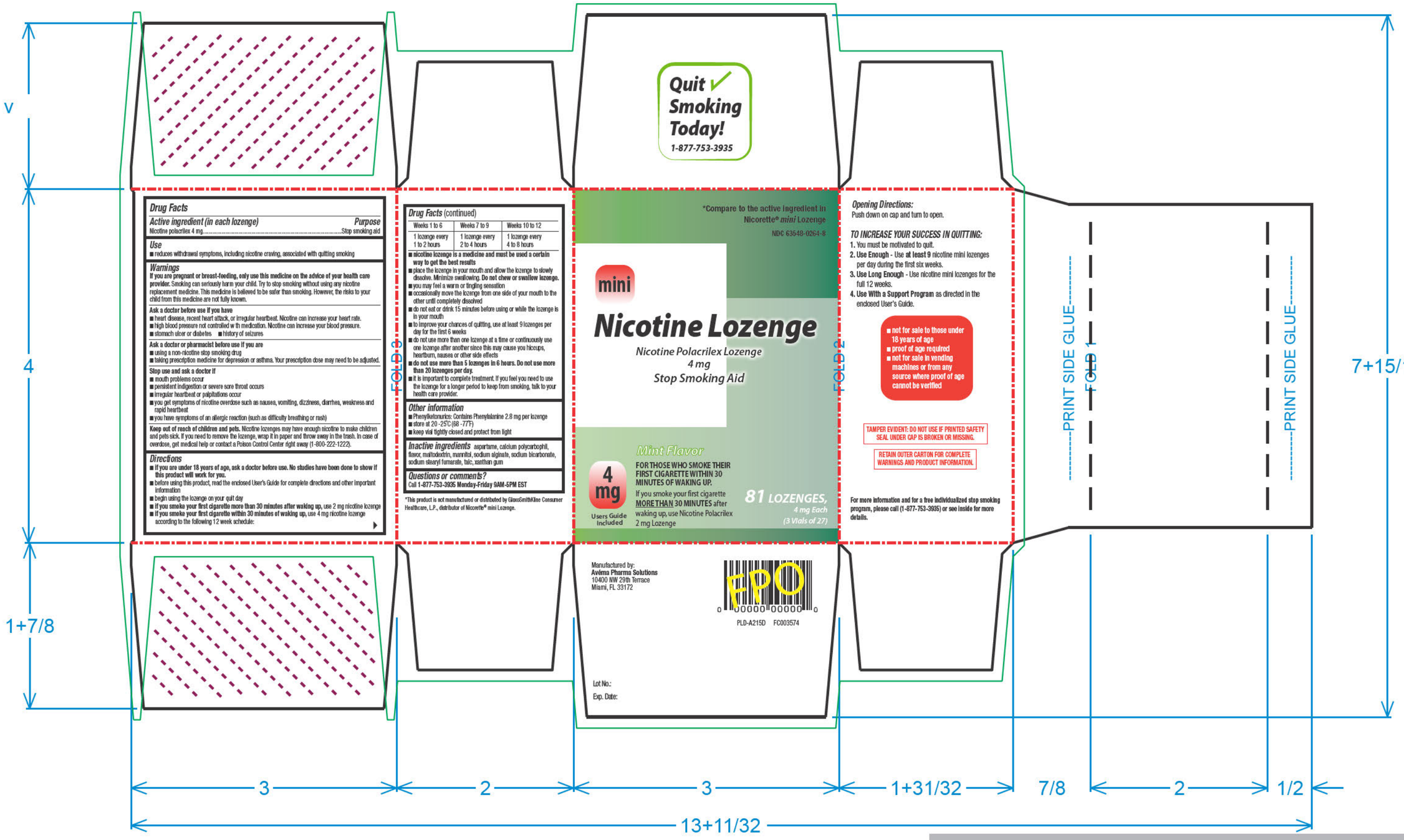
National Brand

(b) (4)



(b) (4)

National Brand

(b) (4)


mini
NDC 63548-0264-7
Mint Flavor
Nicotine Lozenge
Nicotine Polacrilex Lozenge
4 mg
Stop Smoking Aid
4 mg
27 LOZENGES
27 LOZENGES
In case of overdose, get medical help or contact a Poison Control Center right away (1-800-222-1222). Retain outer carton for full product uses, directions and warnings. Keep vial tightly closed and protect from light. Discard vial after use. Tamper Evident Feature: Do not use if printed safety seal under cap is broken or missing.
Store at 20-25°C (68-77°F).
Questions or comments? Call 1-877-753-3935
Manufactured by:
Aveima Pharma Solutions
10400 NW 29 th Terrace
Miami, FL 33172
PLO A215D
LB01648
Lot No.:
Exp. Date:

1.5 X 2.75

(b) (4)

*Compare to the active ingredient in Nicorette® *mini* Lozenge

NDC 63548-0264-7

mini

Nicotine Lozenge

Nicotine Polacrilex Lozenge
4 mg
Stop Smoking Aid

Mint Flavor

4 mg

FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE WITHIN 30 MINUTES OF WAKING UP.

If you smoke your first cigarette **MORE THAN 30 MINUTES** after waking up, use Nicotine Polacrilex 2 mg Lozenge

Users Guide Included

27 LOZENGES,
4 mg Each
(1 Vial of 27)

*This product is not manufactured or distributed by GlaxoSmithKline Consumer Healthcare, L.P., distributor of Nicorette® mini Lozenge.

TAMPER EVIDENT: DO NOT USE IF PRINTED SAFETY SEAL UNDER CAP IS BROKEN OR MISSING.

RETAIN OUTER CARD FOR COMPLETE WARNINGS AND PRODUCT INFORMATION.

Drug Facts

Active ingredient (in each lozenge) **Purpose**
Nicotine polacrilex 4 mg ..... Stop smoking aid

Use
■ reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings
If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Ask a doctor before use if you have ■ heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate. ■ high blood pressure not controlled with medication. Nicotine can increase your blood pressure. ■ stomach ulcer or diabetes ■ history of seizures

Ask a doctor or pharmacist before use if you are ■ using a non-nicotine stop smoking drug ■ taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if ■ mouth problems occur ■ persistent indigestion or severe sore throat occurs ■ irregular heartbeat or palpitations occur ■ you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat ■ you have symptoms of an allergic reaction (such as difficulty breathing or rash)

Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away (1-800-222-1222).

Directions ■ **If you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.** ■ before using this product, read the enclosed User's Guide for complete directions and other important information ■ begin using the lozenge on your quit day ■ **if you smoke your first cigarette more than 30 minutes after waking up,** use 2 mg nicotine lozenge ■ **if you smoke your first cigarette within 30 minutes of waking up,** use 4 mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

■ **nicotine lozenge is a medicine and must be used a certain way to get the best results** ■ place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. **Do not chew or swallow lozenge.** ■ you may feel a warm or tingling sensation ■ occasionally move the lozenge from one side of your mouth to the other until completely dissolved ■ do not eat or drink 15 minutes before using or while the lozenge is in your mouth ■ to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks ■ do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects ■ **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.** ■ it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.

Other information ■ Phenylketonurics: Contains Phenylalanine 2.8 mg per lozenge ■ store at 20 -25°C (68 -77F) ■ keep vial tightly closed and protect from light

Inactive ingredients aspartame, calcium polycarbophil, flavor, maltodextrin, mannitol, sodium alginate, sodium bicarbonate, sodium stearyl fumarate, talc, xanthan gum

Questions or comments?
Call **1-877-753-3935 Monday-Friday 9AM-5PM EST**

Opening Directions: Push down on cap and turn to open.

TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to qu t.
2. **Use Enough** - Use at least 9 nicotine mini lozenges per day during the first six weeks.
3. **Use Long Enough** - Use nicotine mini lozenges for the full 12 weeks.
4. **Use With a Support Program** as directed in the enclosed User's Guide.

For more information and for a free individualized stop smoking program, please call (1-877-753-3935) or see inside for more details.

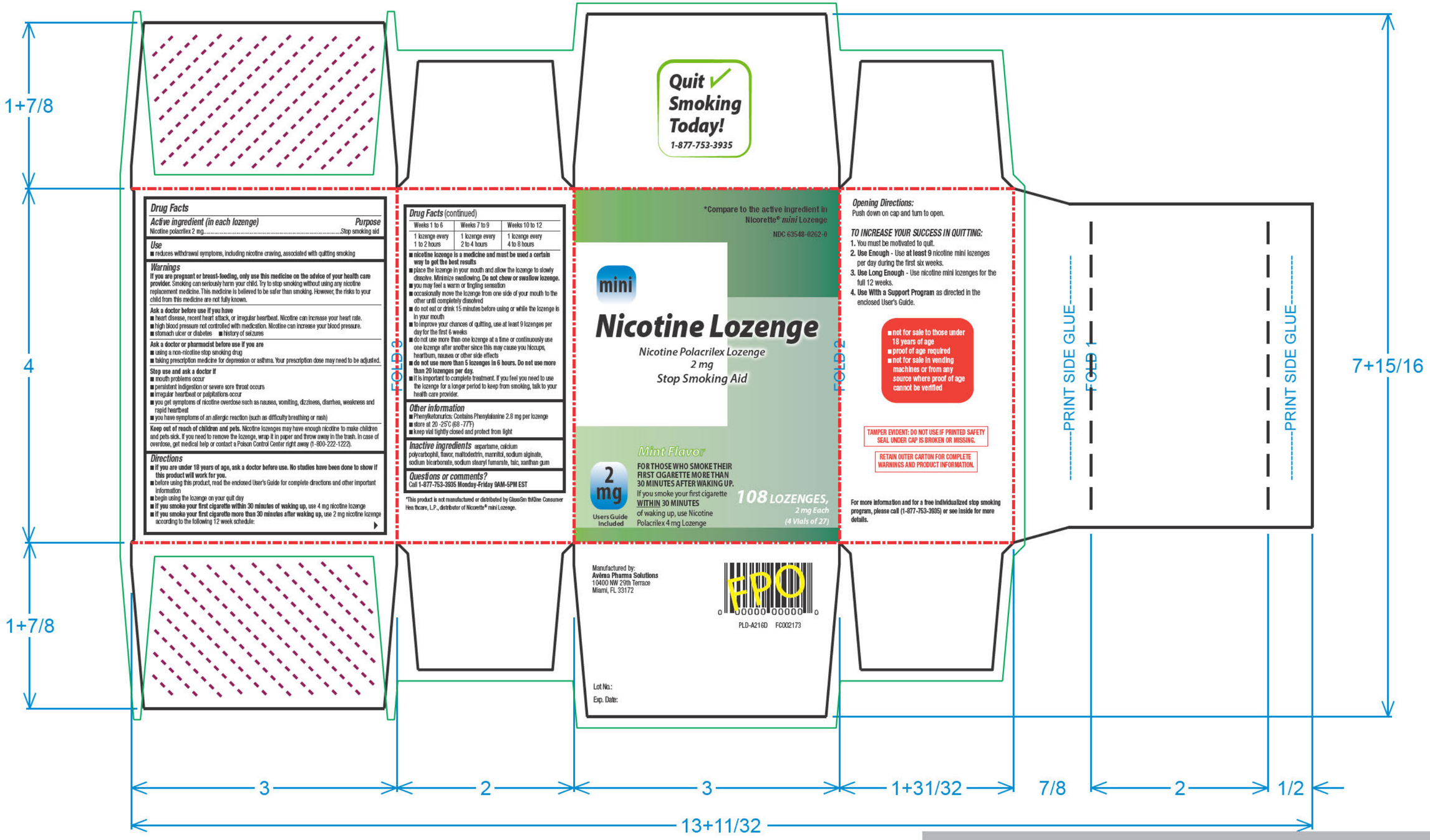
■ **not for sale to those under 18 years of age**
■ **proof of age required**
■ **not for sale in vending machines or from any source where proof of age cannot be verified**

Manufactured by:
Avéma Pharma Solutions
10400 NW 29th Terrace
Miami, FL 33172
PLD-A215D FC002219

Lot No.:
Exp. Date:

(b) (4)

National Brand



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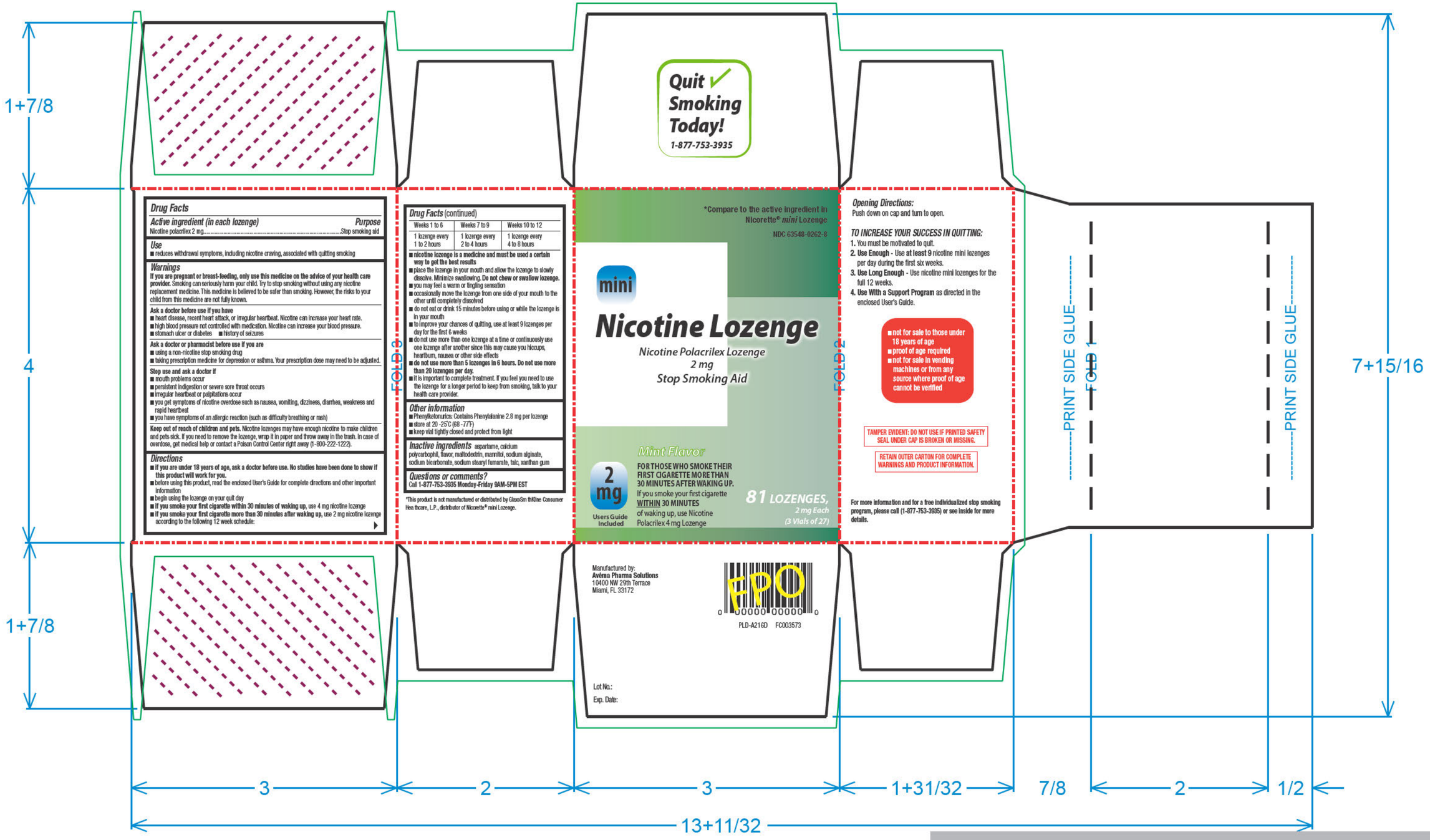
National Brand

(b) (4)



(b) (4)

National Brand

(b) (4)


mini
NDC 63548-0262-7
Mint Flavor
Nicotine Lozenge
Nicotine Polacrilex Lozenge
2 mg
Stop Smoking Aid
2 mg
27 LOZENGES
27 LOZENGES
In case of overdose, get medical help or contact a Poison Control Center right away (1-800-222-1222). Retain outer carton for full product uses, directions and warnings. Keep vial tightly closed and protect from light. Discard vial after use. Tamper Evident Feature: Do not use if printed safety seal under cap is broken or missing.
Store at 20-25°C (68-77°F).
Questions or comments? Call 1-877-753-3935
Manufactured by:
Aveima Pharma Solutions
10400 NW 29th Terrace
Miami, FL 33172
PLD A216D
LB001847
Lot No.:
Exp. Date:

1.5 X 2.75

(b) (4)

*Compare to the active ingredient in Nicorette® *mini* Lozenge

NDC 63548-0262-7

mini

Nicotine Lozenge

Nicotine Polacrilex Lozenge
2 mg
Stop Smoking Aid

Mint Flavor

2 mg

Users Guide Included

FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE MORE THAN 30 MINUTES AFTER WAKING UP.
If you smoke your first cigarette **WITHIN 30 MINUTES** of waking up, use Nicotine Polacrilex 4 mg Lozenge

27 LOZENGES,
2 mg Each
(1 Vial of 27)

*This product is not manufactured or distributed by GlaxoSmithKline Consumer Healthcare, L.P., distributor of Nicorette® mini Lozenge.

TAMPER EVIDENT: DO NOT USE IF PRINTED SAFETY SEAL UNDER CAP IS BROKEN OR MISSING.

RETAIN OUTER CARD FOR COMPLETE WARNINGS AND PRODUCT INFORMATION.

Drug Facts

Active ingredient (in each lozenge) Purpose
Nicotine polacrilex 2 mg.....Stop smoking aid

Use ■ reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Ask a doctor before use if you have ■ heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate. ■ high blood pressure not controlled with medication. Nicotine can increase your blood pressure. ■ stomach ulcer or diabetes ■ history of seizures

Ask a doctor or pharmacist before use if you are ■ using a non-nicotine stop smoking drug ■ taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if ■ mouth problems occur ■ persistent indigestion or severe sore throat occurs ■ irregular heartbeat or palpitations occur ■ you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat ■ you have symptoms of an allergic reaction (such as difficulty breathing or rash)

Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away (1-800-222-1222).

Directions ■ **If you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.** ■ before using this product, read the enclosed User's Guide for complete directions and other important information ■ begin using the lozenge on your quit day ■ **If you smoke your first cigarette within 30 minutes of waking up,** use 4 mg nicotine lozenge ■ **If you smoke your first cigarette more than 30 minutes after waking up,** use 2 mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

■ **nicotine lozenge is a medicine and must be used a certain way to get the best results** ■ place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. **Do not chew or swallow lozenge.** ■ you may feel a warm or tingling sensation ■ occasionally move the lozenge from one side of your mouth to the other until completely dissolved ■ do not eat or drink 15 minutes before using or while the lozenge is in your mouth ■ to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks ■ do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects ■ **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.** ■ it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.

Other information ■ Phenylketonurics: Contains Phenylalanine 2.8 mg per lozenge ■ store at 20 -25°C (68 -77°F) ■ keep vial tightly closed and protect from light

Inactive ingredients aspartame, calcium polycarbophil, flavor, maltodextrin, mannitol, sodium alginate, sodium bicarbonate, sodium stearyl fumarate, talc, xanthan gum

Questions or comments?
Call 1-877-753-3935 Monday-Friday 9AM-5PM EST

Opening Directions: Push down on cap and turn to open.

TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to quit.
2. **Use Enough** - Use at least 9 nicotine mini lozenges per day during the first six weeks.
3. **Use Long Enough** - Use nicotine mini lozenges for the full 12 weeks.
4. **Use With a Support Program** as directed in the enclosed User's Guide.

For more information and for a free individualized stop smoking program, please call (1-877-753-3935) or see inside for more details.

■ not for sale to those under 18 years of age
■ proof of age required
■ not for sale in vending machines or from any source where proof of age cannot be verified

Manufactured by:
Avima Pharma Solutions
10400 NW 29th Terrace
Miami, FL 33172

PLD-A216D FC002218

Lot No.:
Exp. Date:

(b) (4)

National Brand

Nicotine Polacrilex Lozenge

2 mg and 4 mg User's Guide

mini Lozenge

How to Use Mini Nicotine Polacrilex Lozenges and Tips to Help You Quit Smoking.

Avéma

Pharma Solutions

PLANNING YOUR SUCCESS

1) The key to accomplishing anything important is commitment. When it comes to quitting smoking, that is especially true. **Nicotine polacrilex lozenges** can help if you really want to quit. **Nicotine polacrilex lozenges** help reduce withdrawal symptoms including nicotine craving associated with quitting smoking.

2) Your chances of staying off cigarettes are much better if you start with at least 9 **nicotine polacrilex lozenges** daily. For best results, use the lozenges on a regular schedule (as outlined in this User's Guide).

3) Start using **nicotine polacrilex lozenges** on your quit date.

4) This User's Guide outlines a 12-week plan for **nicotine polacrilex lozenges.** Even though you may feel confident about your non-smoking status after a few weeks, it's important to stick with the plan to help you remain smoke free. Even a single cigarette can put you right back to square one.

5) **Nicotine polacrilex lozenges** work best when used together with a support plan. See page 11 for a toll-free support line for advice and tips to keep you committed to quitting.

6) After the first six weeks, start using fewer **nicotine polacrilex lozenges,** as directed in the instructions, gradually reducing your use over the next six weeks. If you feel the need to use the lozenges for a longer period to keep from smoking, talk to your health care provider.

7) If you have questions about using **nicotine polacrilex lozenges,** call toll-free 1-877-753-3935 Monday Friday 9AM to 5PM EST, or please talk to your pharmacist, or family doctor.

YES! YOU WANT TO QUIT.

Wonderful. You've made the most important decision of all, to stop smoking. And by choosing **nicotine polacrilex lozenges** to help you, you're starting on the right path. Now remember, using **nicotine polacrilex lozenges** doesn't just mean taking a **nicotine polacrilex lozenge.** It means setting and following a program like the one we suggest in this User's Guide.

Your own success depends on your effort, your level of addiction to tobacco, and your commitment to following your program.

LET'S FACE IT.

Quitting smoking isn't easy! You or someone you know may have tried unsuccessfully. That's okay. It's hard to stop smoking the first time you try. The important part is to learn from your previous attempts, consider what went wrong and keep trying to quit until you succeed. Look to this User's Guide for support as you undergo this terrific task. The guide includes important information on how to use **nicotine polacrilex lozenges** and also gives you tips to help you stop smoking. Refer back to it often for advice, answers, and encouragement to help you stay on track.

GET MOTIVATED. STAY MOTIVATED.

Everyone has a reason for quitting–whether you're concerned about your health, your appearance,

family or peer pressure, or the effect of secondhand smoke on your loved ones–all of the above, or something else entirely. Whatever your reasons, write them down. There's a wallet card inside the back cover of this User's Guide. Write your reasons on the card and carry it with you. When you have an urge to smoke or experience a difficult moment it can help you focus on your reasons for quitting. Lots of people quit with a co-worker, spouse or friend and use them as a quitting buddy. You can help each other out by providing extra encouragement in tough moments.

There may be support groups in your area for people trying to quit. Call your local chapter of the American Lung Association, American Cancer Society or American Heart Association for further information. Toll-free phone numbers are printed on the wallet card on the back cover of this User's Guide.

UNDERSTANDING THE DOUBLE-EDGED SWORD.
Smoking has two addictive components, a physical and a mental need for the nicotine in tobacco. You need to conquer both to succeed. **Nicotine polacrilex lozenges** can ease your physical nicotine addiction. But your readiness and resolve are necessary to help overcome the mental side of your cigarette dependence. So once you're ready, it's time to begin. But first, read and consider the following important warnings.

IMPORTANT WARNINGS
This product is only for those who want to stop smoking.

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child.

Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Ask a doctor before use if you have

- heart disease, recent heart attack or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcers or diabetes
- history of seizures

Ask a doctor or pharmacist before use if you are

- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if

- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness or rapid heartbeat
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)

Keep out of reach of children and pets.

Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

YOU'RE READY TO START.

Okay, you're ready. To become a non-smoker, start today. Now before you do anything else, you have a bit of planning to do. Read this User's Guide all the way through. You want to make sure you bought the right dose to start. If you typically smoke **your first cigarette within 30 minutes of waking up,** use the 4 mg **nicotine polacrilex lozenges.** If you smoke **your first cigarette more than 30 minutes after waking up,** use the 2 mg **nicotine polacrilex lozenges.**

Next, plan your quitting schedule. Get a calendar to follow your progress and mark the following four important dates (see the reminders on page 23 of this booklet).

THE PROGRAM

STEP 1. (Weeks 1-6) Starting on your quit date it's best to use at least 9 nicotine polacrilex lozenges each day, one every 1-2 hours.

First choose the day you plan to quit (make it soon). Place the Step 1 reminder on this date. That's the day you will start using **nicotine polacrilex lozenges** to calm your cravings for nicotine and help you stay smoke free. Prior to the quit date, get rid of all your cigarettes to remove temptations and make it more difficult to start smoking again.

Use a **nicotine polacrilex lozenge** every 1 to 2 hours and at least 9 lozenges each day for the first 6 weeks to help prevent unexpected cravings and improve your chances of quitting. **These aren't ordinary lozenges.** Place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. **Do not chew or swallow the lozenge.** You may feel a warm or tingling sensation.

Occasionally move the lozenge from one side of your mouth to the other until completely dissolved.

Remember to read the instructions on page 10 and 11 before you take your first nicotine polacrilex lozenge.

STEP 2. (The next three weeks, that is weeks 7-9). At the beginning of week 7 start using fewer nicotine polacrilex lozenges, one every 2-4 hours. After six weeks, you should wait a little longer between lozenges, one lozenge every two to four hours. This will help you gradually use fewer **nicotine polacrilex lozenges.** Put the Step 2 reminder on the first day of week 7 to help remind you when to start reducing the number of **nicotine polacrilex lozenges** you take.

STEP 3. (The last three weeks, that is weeks 10-12). At the beginning of week 10, reduce nicotine polacrilex lozenge use even further, one every 4-8 hours.

At the beginning of week 10 further decrease the number of **nicotine polacrilex lozenges** you use each day to reduce the amount of nicotine you get. You should do this by using one lozenge every 4 to 8 hours. Put the Step 3 reminder on the first day of week 10 so you know when you should be starting this last step to becoming smoke-and nicotine-free.

END. At the end of week 12 you'll complete nicotine polacrilex lozenge therapy.

Put the "EX-SMOKER" reminder on your calendar on the date 12 weeks after the day you stopped smoking and started using **nicotine polacrilex lozenges.**

BE PREPARED.

Since smoking is an addiction, it is hard to quit. Even after you stop, there will be times when you WANT a cigarette, sometimes strongly. (See also section on "Challenges To Watch For"). The best defense is to be prepared.

Plan now for handling tough times so you don't give in. For example: think about situations when you usually get a craving for cigarettes or where you think you might experience strong cravings. Try to avoid these situations where you can (for example, avoid spending time with smokers, or drinking alcohol, if those things tempt you to smoke).

Change your habits. For example, take your coffee break somewhere else. Take a walk. In other words, break the association between your usual habits and cigarettes.

If you do encounter a situation where you feel a strong craving, fight it! Take a break from the situation; keep yourself busy or distracted with other activities. Remind yourself why you want to quit, and above all, remind yourself that having "just one" really will hurt your goal of quitting!

To prepare for tough situations, assemble a "survival package"– items that can keep you distracted in case you get a craving. For example, you may include cinnamon gum or hard candy, relaxing music, and things to keep your hands busy like a smooth stone, paper clips, or a rubber ball.

Track your progress as you quit. Keep a journal. Write down how many pieces of **nicotine polacrilex lozenges** you use each day. Note if and when you get a craving. If you slip and have a cigarette, don't give up. Stop smoking again and get back on your program with **nicotine polacrilex lozenges.**

Establish your support network. Keep friends' and family members' phone numbers ready to get the moral support you need. Before quitting, ask friends and family to support and encourage you. Think of specific ways they can help.

Reward yourself. Set aside little gifts to yourself such as a CD or video, which you can earn by overcoming difficult hurdles.

HOW NICOTINE POLACRILEX LOZENGES WORK.

Nicotine polacrilex lozenges are a form of Nicotine Replacement Therapy. They deliver nicotine to your body, temporarily relieving craving and nicotine withdrawal symptoms when you quit smoking. But unlike cigarettes, **nicotine polacrilex lozenges** deliver a lower, steady level of nicotine to your blood. When used as directed, **nicotine polacrilex lozenges** help you regulate, control, and gradually reduce your body's craving for nicotine.

The good news is that **nicotine polacrilex lozenges** contain no tar or carbon monoxide, and therefore don't present the same medical risks as cigarettes.

However, the lozenges still deliver nicotine, the addictive ingredient in cigarettes. And for some people the nicotine in **nicotine polacrilex lozenges** can occasionally cause mouth or throat irritation, headaches, nausea, hiccups, upset stomach or dizziness.

USING NICOTINE POLACRILEX LOZENGES PROPERLY. Remember, **nicotine polacrilex lozenges aren't like ordinary lozenges such as cough drops.** This lozenge is designed to deliver nicotine into your system through the lining of your mouth, not in your stomach like most other medicines. It is important to minimize swallowing the dissolved medicine in these lozenges so that it can be properly absorbed in your mouth.

Do not use more than one lozenge at a time, or many lozenges one after another since this can cause hiccups, heartburn, nausea or other side effects.

Read all the following instructions before using **nicotine polacrilex lozenges.** Refer to them often to make sure you're using **nicotine polacrilex lozenges** correctly.

IMPORTANT: Don't worry or give up if you do not like the taste of the lozenge at first. Nicotine polacrilex lozenges are a medication, not a candy. Most people get used to the taste after a day or two. Remember, staying with the plan will help you quit. Begin using nicotine polacrilex lozenges on your quit date.

1) Remove the **nicotine polacrilex lozenge** from the immediate container. Place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. **Do not chew or swallow the lozenge.** You may feel a warm or tingling sensation.

2) Occasionally move the lozenge from one side of your mouth to the other side until completely dissolved.

To reduce cravings or urges to smoke and other withdrawal symptoms, use **nicotine polacrilex lozenges** according to the following dosage schedule.

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

Do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day. At the end of 12 weeks (3 months) you will have completed treatment.

FOR THE BEST CHANCE OF QUITTING, use **nicotine polacrilex lozenges** on a regular schedule, using at least 9 lozenges a day during the first 6 weeks. That will help your body better adjust to the lack of cigarettes and better help prevent cravings. Some people may need more lozenges to reduce their cravings. Do not exceed the recommended maximum daily dosage of 20 lozenges per day. Do not continuously use one lozenge after another, since this may cause you hiccups, heartburn, nausea or other side effects.

Do not eat or drink 15 minutes before using or while the lozenge is in your mouth.

CALL FOR HELP:

Quit ✓ Smoking Today!

1-877-753-3935

Quitting smoking can be difficult.

There are some easy steps that you can follow to help you in your efforts to quit smoking. Call our toll free support line for advice and tips to keep you committed to quitting.

CUTTING BACK ON YOUR NICOTINE POLACRILEX LOZENGE USAGE.

The whole reason for using **nicotine polacrilex lozenges** is to decrease and slowly eliminate your need for nicotine, while you control cravings. So, as the above schedule indicates, you should gradually reduce the amount of **nicotine polacrilex lozenges** you take per day. Some people find it easier to reduce by substituting ordinary sweets or sugar free candy for some of the **nicotine polacrilex lozenges** they would normally use. As time goes on, you can increase the number of pieces of candy as you further reduce your use of **nicotine polacrilex lozenges. It is important to complete treatment.** If you still feel the need to use **nicotine polacrilex lozenges** to keep from smoking after week 12, talk with your health care provider.

MAKE QUITTING EASIER ON YOURSELF.

Soon after your quit date, parties, bars, celebrations, and socializing may all tempt you to smoke. Please remember these tips to help you resist those urges and stay smoke-free.

The Day You Quit Smoking:

- Look to your family and friends for support. Let them know what to do or avoid doing to help you quit.
- Throw away ALL cigarettes, ashtrays, matches, and lighters. You don't need them. You don't want them and you want to make it difficult to go back.
- Keep yourself occupied. Take a walk. See a movie. See friends. Do anything to keep your mind off cigarettes.
- Calculate all the money you'll save by not buying

cigarettes. Probably well over $1,000 a year! $1,000 a year? Think of what you can spend it on!

- Know what situations are going to make you want to smoke. Plan now how you'll avoid them or deal with them so you don't smoke.
- Keep **nicotine polacrilex lozenges** next to your bed so you're prepared when you get up. A lot of people get cravings first thing in the morning.
- Make an appointment to see your dentist and get the tobacco stains cleaned off. While you're getting rid of the evidence of cigarettes in the house, do the same for your teeth. Have clothes or drapes that smell of smoking cleaned.
- Now that your house is smoke-free, try to spend most of your time in smoke-free environments.
- If you usually smoked with coffee or alcohol, try to keep away from them for now. Remember you are also trying to break a habit.
- Smoking is a "hands-on" habit. So use something else to occupy your hands: a rubber band or a pen.
- Now's a good time to get active. Find activities to take your mind off cigarettes and relax. Take up jogging, swimming, or walking.
- Don't stress out about gaining weight. Dieting now may weaken your efforts to quit smoking. Eat sensibly and exercise daily; drink large quantities of water and fruit juices; this can help your chances of staying smoke-free.
- Laugh. Watch a sitcom. Read a comic book. It really helps.

REMEMBER: Urges to smoke are temporary. They'll pass, even if you don't smoke.

WHAT YOU CAN EXPECT.

As you are successful at staying smoke-free, initially you will probably notice a few of the following typical withdrawal symptoms, so don't be surprised. Use of **nicotine polacrilex lozenges** reduces these symptoms, but may not eliminate them entirely. They will go away with time. Stay focused on your goal of becoming an ex-smoker. Research shows that if you manage to avoid all smoking in the first week (that means not having a single puff), your chances of success increase dramatically.

The First Few Days. You may feel nervous or irritable or have difficulty concentrating during the first few days after you quit smoking. Your body needs time to regain balance. Initially, you might feel a little out of sorts, get headaches, feel light-headed, or have trouble sleeping. Your smoker's cough may get worse before it improves. But fear not, it's a positive sign. Coughing helps clean your lungs of the tar residue you got from smoking.

After a Couple of Weeks. Your confidence and ability to cope with urges to smoke should be getting stronger. But don't be over-confident and think you can smoke just one cigarette. Even now, having even a single puff can lead to a return to smoking cigarettes regularly. Be prepared, and remember why you wanted to stop smoking.

Have you noticed that your sense of taste and smell has improved? You are probably coughing less and finding it easier to breathe. You've also probably noticed your withdrawal symptoms are subsiding (though don't worry if they're still there: they last

longer for some people). These are all positive signs that your body is getting used to your success at stopping smoking.

By The End of The First Month. You are less likely to have cravings for cigarettes as often. However sudden cravings may still happen, and when they do, be on your guard, as they can be strong and seem to come out of the blue. Be prepared for these challenging times. The key is do what you can so these unexpected cravings can't beat you. Keep focused on the ways non-smokers are more attractive than smokers. Their breath smells better. Their clothes and hair are fresher. Their teeth are cleaner and brighter. Their skin is less likely to wrinkle. Not smoking around children and your friends is also healthier for them too.

What If You Do Slip And Smoke?

"What if I relapse?" One cigarette is a slip-up, but it's not the end of the quit effort. Everybody slips at something. The key is this: forgive yourself and stop at that one cigarette. Don't let this slip ruin your good intentions; keep at your quit attempt. So, throw out your cigarettes and continue with your quit attempt, keeping in mind what went wrong and led to the slip.

If you do go back to smoking, certainly don't throw out your **nicotine polacrilex lozenges.** Keep them for the next time you're ready to quit. In fact research says that even if you are back to smoking regularly the best thing you can do is learn and try again.

Try to understand the reason you had those cigarettes that made you slip. That's important, because now you can plan better to deal with these moments next time.

It's true you stumbled, but don't think of yourself as having failed. Encourage yourself by treating the last attempt as a learning experience, even a "trial run" for the real thing.

Take a look at the usage instructions and check that you used the **nicotine polacrilex lozenges** correctly and for the full 12 weeks of the program. When you try again; make sure you use enough and the right way. That way you'll be best equipped to deal with the unexpected cravings.

Don't forget; quitting isn't easy and it takes practice to do anything. Stopping smoking is no different.

YOU'VE MADE IT

Once your twelve-week quitting program is over, you've taken your last **nicotine polacrilex lozenge.** Now you are both cigarette and nicotine-free.

Get up and give yourself a standing ovation. We mean it. Do you realize that you have just done a really difficult thing?

Now is a good time to think back on the process. Think of all your reasons for quitting smoking. Think of your goals. Think of how they're going to be a reality now.

Think of what you're going to do with your newly liberated cigarette money. The places you can now go smoke-free. Think of the extra time you may have added to your life and what you can do with it. And although you may still experience the occasional temptation, and cigarettes still want you back, think positively. Think forward. And consider yourself a proud non-smoker.

FREQUENTLY ASKED QUESTIONS.

1. When I stop smoking and start using nicotine polacrilex lozenges how will I feel?

Nicotine polacrilex lozenges help reduce cravings, but be prepared for some nicotine withdrawal symptoms. After you stop smoking they can begin almost at once and are normally at their strongest during the first three or four days. For some people, any of the following may occur:

- unexpected craving or urges for cigarettes
- anxiety, irritability, restlessness, mood changes, nervousness
- drowsiness
- trouble concentrating
- increased appetite and weight gain
- headaches, muscular pain, constipation, fatigue

Nicotine polacrilex lozenges are designed to reduce the craving for nicotine you used to satisfy with cigarettes. **Nicotine polacrilex lozenges** can also help provide relief from other withdrawal symptoms such as irritability and nervousness.

2. Are nicotine polacrilex lozenges just swapping one type of nicotine addiction for another?

Nicotine polacrilex lozenges do contain nicotine, however there is probably less nicotine in your daily dose of lozenges than in your cigarettes. **Nicotine polacrilex lozenges** give you enough nicotine to help you combat the physical withdrawal symptoms so you can cope with the mental side of stopping smoking. Also, since the nicotine from the lozenges goes into your bloodstream more slowly, it produces less of the effects of nicotine that people find rewarding. In fact, when used as directed in the

12-week program, **nicotine polacrilex lozenges** gradually wean you off your dependence for both nicotine and cigarettes.

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

4. Will I put on weight?
In the first couple of months after quitting smoking, some people do put on a few pounds. But think of it this way. Overall, you'll be healthier and look better. You can always tackle your weight by changing your diet and increasing the amount you exercise once you have gotten through the difficult part of stopping smoking.

5. Does taking nicotine polacrilex lozenges cost more than smoking?
If you normally smoke a pack and a half a day, your total cost of using **nicotine polacrilex lozenges** during the 12-week period is about the same as smoking. But guess what? After you've finished the **nicotine polacrilex lozenge** program all that money you used to spend on cigarettes is now savings. And think of the health issues you'll hopefully be able to avoid.

6. What if I have a cigarette and start smoking?
Don't panic. First, don't think badly of yourself. Throw away your cigarettes and forgive yourself. Then think about what went wrong and get back on track. In fact people who have already tried to stop smoking are more likely to be successful the next time.

CHALLENGES TO WATCH FOR.
Once you quit smoking, you are likely to experience periodic, and sometimes intense, temptations to smoke. Certain situations present special challenges. Some common ones include:

Stress and upset.
When you are feeling stressed or upset, you may think a cigarette will make everything better. It won't. Find other ways to relax and unwind.

The blues.
You may be especially vulnerable when you feel bored or blue. Remember that having a cigarette will just make you feel worse.

Smoking cues.
Seeing cigarettes or watching other people smoke can trigger temptation. Remember that you choose not to smoke anymore.

Alcohol.
Drinking and smoking seem to go together, and alcoholic beverages may weaken your resolve, making drinking dangerous to your quit effort. Avoid drinking early in your quit effort, and try to drink with non-smokers.

Automatic slips.
Sometimes you may find yourself preparing to smoke

without even realizing it. Watch out for those moments when your hand seems to 'automatically' reach for a cigarette.

Watch out for these situations: they can trigger a relapse. You probably know which one(s) are most dangerous for you; plan ahead to deal with the situation effectively. Always remember that you're trying to break a habit, and the most important thing is to do something to combat the urge in these situations.

COPING AFTER QUITTING.

The key to staying smoke-free is to prepare for and cope with challenges as they occur. If you find yourself tempted to smoke, do something! Here are some things to consider.

- Escape. Leave the situation, even for a few minutes. Most temptations don't last long.
- Distract yourself. Get your mind off smoking. Think of something else or get busy with something.
- Relax. Don't let stress get to you. Think of pleasant, relaxing things; breathe slowly and regularly. Let the stress drain out of you.
- Talk yourself out of it. What you say to yourself matters. So, remind yourself how important it is for you to quit; remind yourself you can't have just one; or just command yourself to STOP.

For more information please call toll-free
1-877-753-3935 Monday Friday 9AM to 5PM EST.

Manufactured by:
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Avéma
Pharma Solutions

Distributed by: Avéma Pharma Solutions. USA

Revision date: 08/2016
Item number

Place these reminders on your calendar:

AT BEGINNING OF WEEK #1 (QUIT DATE)

STEP 1

1 lozenge every 1 to 2 hours

AT BEGINNING OF WEEK #7

STEP 2

1 lozenge every 2 to 4 hours

STEP 3

1 lozenge every 4 to 8 hours

AT BEGINNING OF WEEK #10

EX-SMOKER

12 WEEKS AFTER QUIT DATE

WALLET CARD

My most important reasons to quit smoking are:

WALLET CARD

WHERE TO CALL FOR HELP:

American Lung Association 1-800-586-4872

American Cancer Society 1-800-227-2345

American Heart Association 1-800-242-8721

Quitting Buddy or Friend who has Quit

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PLD-A215D-216D
NS000042

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207868

LABELING REVIEW(s)

***** This document contains proprietary information that cannot be released to the public. Addendum Template for TL during Endorsement Process.*****

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	2/1/19
ANDA Number(s)	207868
Review Number	Addendum to Review #3
Applicant Name	PLD Acquisitions LLC D/B/A Avema Pharma Solutions
Established Name & Strength(s)	Nicotine Polacrilex Lozenges, 2 mg and 4 mg (Mini)
Proposed Proprietary Name	NA
Submission Received Date	08/19/2016
Primary Labeling Reviewer	Marshall Florence, PharmD.
Secondary Labeling Reviewer	Katherine Won

Review Conclusion

☒ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☐ Yes	☒ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

1. CHANGES FROM THE LAST REVIEW

a. This addendum is to revise the established name on the cover letter from "Nicotine Polacrilex Lozenges, 2 mg and 4 mg" to "Nicotine Polacrilex Lozenges, 2 mg and 4 mg (Mini)."

b. Also, we like to note the content of salt in the drug product. Per 21 CFR Sec. 201.64 Sodium labeling: (a) The labeling of over-the-counter (OTC) drug products intended for oral ingestion shall contain the sodium content per dosage unit (e.g., tablet, teaspoonful) if the sodium content of a single maximum recommended dose of the product (which may be one or more dosage units) is 5 milligrams or more.

(b) The sodium content shall be expressed in milligrams per dosage unit and shall include the total amount of sodium regardless of the source, i.e., from both active and inactive ingredients. The sodium content shall be rounded-off to the nearest whole number. The sodium content per dosage unit shall follow the heading "Other information" as stated in §201.66(c)(7).

(c) The labeling of OTC drug products intended for oral ingestion shall contain the following statement under the heading "Warning" (or "Warnings" if it appears with additional warning statements) if the amount of sodium present in the labeled maximum daily dose of the product is more than 140 milligrams: "Ask a doctor before use if you have [in bold type] [bullet]1 a sodium-restricted diet". The warnings in §§201.64(c), 201.70(c), 201.71(c), and 201.72(c) may be combined, if applicable, provided the ingredients are listed in alphabetical order, e g., a calcium or sodium restricted diet.

From the applicant's 1/23/2017 submission under module 3.2.P.1., the following sodium calculation is provided. Because it does not exceed 5 mg per lozenge and 140 mg with the maximum daily dose, the sodium amount of the warning statement is not necessary on the Drug Facts labeling.

Sodium Calculation:

The 3 main sources of sodium in this formulation are sodium alginate, sodium stearyl fumarate and sodium bicarbonate. Below is the molecular formula.

1. Na Alginate: (C6H7NaO6)n
2. Na Stearyl Fumarate: C22H39NaO4
3. Na Bicarbonate: NaHCO3

Nicotine Polacrilex 2 mg and 4 mg mini lozenges each contain (b) (4) of sodium alginate, (b) (4) of sodium stearyl fumarate and (b) (4) of sodium bicarbonate. Based on this the sodium is calculated as mentioned below:

1. (b) (4)
2.
3.

(b) (4)

As per 21 CFR 201.64 the labeling of over-the-counter (OTC) drug products intended for oral ingestion shall contain the sodium content per dosage unit (e.g., tablet, teaspoonful) if the sodium content of a single maximum recommended dose of the product (which may be one or more dosage units) is 5 milligrams or more.

There are no other changes to the review completed on 9/2/2016.

Katherine Won

Digitally signed by Katherine Won
Date: 2/01/2019 12:09:03PM
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LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	09/02/2016
ANDA Number(s)	207868
Review Number	3
Applicant Name	PLD Acquisitions LLC D/B/A Avema Pharma Solutions
Established Name & Strength(s)	Nicotine Polacrilex Lozenge, 2 mg and 4 mg
Proposed Proprietary Name	None
Submission Received Date	08/19/2016
Labeling Reviewer	Marshall Florence, PharmD.
Labeling Team Leader	Adolph Vezza

Review Conclusion

☒ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☐ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on (add date) based on your submission(s) dated (add date):

1. GENERAL COMMENTS
   Comment

2. CONTAINER LABEL
   a. Comment
   b. Comment
3. CARTON LABELING
4. PRESCRIBING INFORMATION
   a. Comment
   b. Subheading
      i. Comment
      ii. Comment
5. MEDICATION GUIDE
6. STRUCTURED PRODUCT LABELING (SPL)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with Choose an item. all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission dated August 19, 2016.

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).
Click here to enter text.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments: The below comments are from the labeling review C2 based on the submission dated 04/15/2016.

1. GENERAL COMMENT
   Please describe the child resistant feature of the container and add "Opening Directions" to be the same as the reference listed drug's labeling.

2. CARTON AND CARD LABEL
   a. Please revise your carton and container labeling to be in accordance with the most recently approved labeling for the reference listed drug, (RLD), Nicorette Mini Lozenge, NDA 022360/S-010 approved 09/30/2015.
   b. Please see "GENERAL COMMENT" above.
   c. Please change the presentation of the established name and expression of strength on the principal display panel such as:
      Nicotine Polacrilex Lozenge
      # mg
      Stop Smoking Aid

3. CONTAINER LABEL
   a. See comments 2a and 2c above.
   b. Please add a storage recommendation statement to the container label.
   c. Please add the "Questions?" and Poison Control Center phone number to the label for safety reasons.

4. PATIENT INFORMATION
   a. The established name of the drug product is considered a common noun and need not be capitalized unless dictated by sentence structure.
   b. Revise the established name to read as "nicotine polacrilex lozenge". (You may retain "mini" as a descriptor for the drug product but it should not be part of the established name of the drug product.)

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: All C2 revision requests were addressed adequately.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments: From the cover letter of the 08/19/2016 submission:

1. **General Comment**

Please describe the child resistant feature of the container and add "Opening Directions" to be the same as the reference listed drug's labeling.

Response 1:

"Push down on cap and turn to open" has been added as the opening directions which is consistent with what the child resistant cap of the container says.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA# /Supplement# (S-000 if original):** 022360/S-010 **Supplement Approval Date:** 09/30/2015 **Proprietary Name:** Nicorette Mini Lozenge **Established Name:** Nicotine polacrilex **Description of Supplement:** This "Prior Approval" supplemental new drug application provides for the addition of a seizure warning on the Drug Facts Label.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES** Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES** Does the Model Labeling have combined insert labeling for multiple dosage forms? **YES**

Reviewer Comments: All C2 revision requests were addressed adequately.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 022360 Supplement-10 approved 09/30/2015]


Nicorette
nicotine polacrilex lozenge, 2 mg
stop smoking aid
mini
Lozenge
Opening Directions:
Push in child resistant tab on the vial with thumb. Flip up the top of vial. Turn upside down and shake to remove lozenge.
Personalized Quit Plan
Visit www.nicorette.com to enroll in a free, personalized quit plan. Nicorette Committed Quitters® is a personalized stop smoking program that will help you understand your smoking habits and determine how to best overcome your cravings. Track, target, and tame your temptations with Nicorette Committed Quitters®. Only available at www.nicorette.com
Drug Facts
Active ingredient (in each lozenge) Purpose
Nicotine polacrilex, 2 mg Stop smoking aid
Use • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking
Warnings
If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.
Ask a doctor before use if you have
• heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
• high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
• stomach ulcer or diabetes
• history of seizures
Ask a doctor or pharmacist before use if you are
• using a non-nicotine stop smoking drug
• taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.
Stop use and ask a doctor if
• mouth problems occur
• persistent indigestion or severe sore throat occurs
• irregular heartbeat or palpitations occur
• you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
• you have symptoms of an allergic reaction (such as difficulty breathing or rash)
Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.
Direction
• If you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.
Drug Facts (continued)
• before using this product, read the enclosed User's Guide for complete directions and other important information
• begin using the lozenge on your quit day
• If you smoke your first cigarette within 30 minutes of waking up, use 4 mg nicotine lozenge
• If you smoke your first cigarette more than 30 minutes after waking up, use 2 mg nicotine lozenge according to the following 12 week schedule:
Weeks 1 to 6: 1 lozenge every 1 to 2 hours
Weeks 7 to 9: 1 lozenge every 2 to 4 hours
Weeks 10 to 12: 1 lozenge every 4 to 8 hours
• nicotine lozenge is a medicine and must be used a certain way to get the best results
• place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. Do not chew or swallow lozenge.
• you may feel a warm or tingling sensation
• occasionally move the lozenge from one side of your mouth to the other until completely dissolved
• do not eat or drink 15 minutes before using or while the lozenge is in your mouth
• to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
• do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
• do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.
• it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.
Other information
• each lozenge contains: sodium, 5 mg
• store at 20 - 25°C (68 - 77°F)
• keep vial tightly closed and protect from light
Inactive ingredients acesulfame potassium, calcium polycarbophil, flavors, magnesium stearate, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum
Questions or comments? call toll-free 1-888-569-1743 (English/Spanish) weekdays (9:00 am - 4:30 pm ET)
TO INCREASE YOUR SUCCESS IN QUITTING:
1. You must be motivated to quit.
2. Use Enough - Use at least 9 Nicorette® mini lozenges per day during the first six weeks.
3. Use Long Enough - Use Nicorette® mini lozenges for the full 12 weeks.
4. Use With a Support Program as directed in the enclosed User's Guide.
■ not for sale to those under 18 years of age
■ proof of age required
■ not for sale in vending machines or from any source where proof of age cannot be verified
TAMPER EVIDENT FEATURE: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken. Retain outer back panel for full product uses, directions and warnings.
NICORETTE, COMMITTED QUITTERS® and the NICORETTE sunburst design are registered trademarks of the GSK group of companies.
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Moon Township, PA 15108
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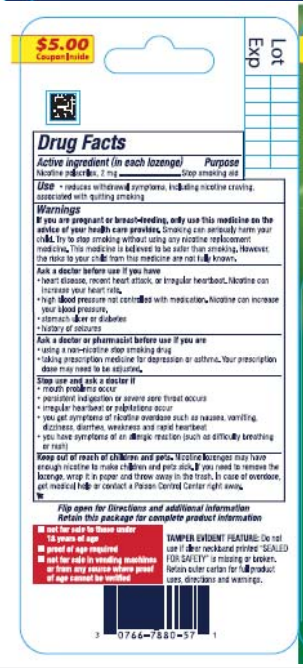
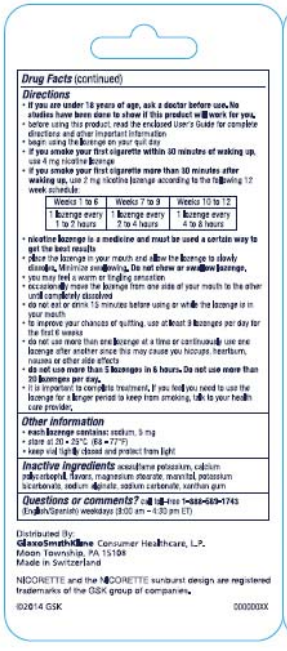
0766-7880-40
Lot
Exp


Nicorette
nicotine polacrilex lozenge, 2 mg
stop smoking aid
mini Lozenge
Mint
2 mg
FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE MORE THAN 30 MINUTES AFTER WAKING UP
135 LOZENGES, 2 mg Each
135 LOZENGES
2 mg Each (5 Vials of 27)


$5.00 Coupon Inside
Lot
Exp
Drug Facts
Active ingredient (in each lozenge) Purpose
Nicotine polacrilex, 2 mg Stop smoking aid
Use • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking
Warnings
If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.
Ask a doctor before use if you have
• heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
• high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
• stomach ulcer or diabetes
• history of seizures
Ask a doctor or pharmacist before use if you are
• using a non-nicotine stop smoking drug
• taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.
Stop use and ask a doctor if
• mouth problems occur
• persistent indigestion or severe sore throat occurs
• irregular heartbeat or palpitations occur
• you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
• you have symptoms of an allergic reaction (such as difficulty breathing or rash)
Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.
Flip open for Directions and additional information
Retain this package for complete product information
■ not for sale to those under 18 years of age
■ proof of age required
■ not for sale in vending machines or from any source where proof of age cannot be verified
TAMPER EVIDENT FEATURE: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken. Retain outer carton for full product uses, directions and warnings.
0766-7880-57


$5.00 Coupon Inside
NDC 0135-0501-04
gsk
Nicorette®
nicotine polacrilex lozenge, 2 mg
stop smoking aid
mini Lozenge
2 mg
FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE MORE THAN 30 MINUTES AFTER WAKING UP
If you smoke your first cigarette within 30 MINUTES of waking up, use Nicorette 4 mg Lozenge
20 LOZENGES
2 mg Each


Drug Facts (continued)
Directions
• If you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.
• before using this product, read the enclosed User's Guide for complete directions and other important information
• begin using the lozenge on your quit day
• If you smoke your first cigarette within 30 minutes of waking up, use 4 mg nicotine lozenge
• If you smoke your first cigarette more than 30 minutes after waking up, use 2 mg nicotine lozenge according to the following 12 week schedule:
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Weeks 7 to 9: 1 lozenge every 2 to 4 hours
Weeks 10 to 12: 1 lozenge every 4 to 8 hours
• nicotine lozenge is a medicine and must be used a certain way to get the best results
• place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. Do not chew or swallow lozenge.
• you may feel a warm or tingling sensation
• occasionally move the lozenge from one side of your mouth to the other until completely dissolved
• do not eat or drink 15 minutes before using or while the lozenge is in your mouth
• to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
• do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
• do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.
• it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.
Other information
• each lozenge contains: sodium, 5 mg
• store at 20 - 25°C (68 - 77°F)
• keep vial tightly closed and protect from light
Inactive ingredients acesulfame potassium, calcium polycarbophil, flavors, magnesium stearate, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum
Questions or comments? call toll-free 1-888-569-1743 (English/Spanish) weekdays (9:00 am - 4:30 pm ET)
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3. Use Long Enough - Use Nicorette® mini Lozenges for the full 12 weeks.
4. Use With a Support Program as directed in the enclosed User's Guide.
Opening Directions:
Push in child resistant tab on the vial with thumb. Flip up the top of vial. Turn upside down and shake to remove lozenge.
For more information and for a FREE individualized stop smoking program, please visit www.Nicorette.com or see inside for more details.
MANUFACTURER'S COUPON | EXPIRES 12/31/2017
SAVE $5.00
On Nicorette®
Mini Lozenge (81ct)
030766-074212

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph ? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	10/17/2016	No	NA	NA
PF	10/17/2016	No	NA	NA

Reviewer Comments:

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 9/2/2016.

Table 3 provides Orange Book patents for the Model Labeling (022360) and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter "Carve-out" or "None")
8501164	Jun 14, 2029			IV	09/16/2015	None
8940772	Apr 30, 2029			IV	09/16/2015	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments: From the cover letter of the 03/31/2016 submission:

> This patent amendment is to notify that no legal action was taken by the patent holder and the NDA holder within the 45-day period.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter "Carve-out" or "None")
NA					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments: None

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
aspartame, calcium polycarbophil, flavor, maltodextrin, mannitol, sodium alginate, sodium bicarbonate, sodium stearyl fumarate, talc, xanthan gum	aspartame, calcium polycarbophil, flavor, maltodextrin, mannitol, sodium alginate, sodium bicarbonate, sodium stearyl fumarate, talc, xanthan gum	**Acceptable**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Other information ■ Phenylketonurics: Contains Phenylalanine 2.8 mg per lozenge ■ store at 20 -25°C (68 -77°F) ■ keep vial tightly closed and protect from light	***Other information*** ■ Phenylketonurics: Contains Phenylalanine 2.8 mg per lozenge ■ store at 20 -25°C (68 -77°F) ■ keep vial tightly closed and protect from light	**Acceptable**

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Manufactured by: Avéma Pharma Solutions 10400 NW 29th Terrace, Miami, FL 33172	Manufactured by: Avéma Pharma Solutions 10400 NW 29th Terrace, Miami, FL 33172	**Acceptable**

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments: None

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments: None

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	1 vial: 27 lozenges	08/19/2016	Satisfactory
Blister	NA			
Carton	Draft	81 count carton: 3 vials of 27 108 count carton: 4 vials of 27	08/19/2016	Satisfactory
(Other – specify)	Draft	1 card: 1 vial of 27	08/19/2016	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	NA			
Medication Guide	NA			
Patient Information	Draft	Revision date: 08/2016	08/19/2016	Satisfactory
SPL Data Elements	NA	Revised: 6/2014	06/19/2014	Satisfactory

Adolph Vezza

Digitally signed by Adolph Vezza
Date: 10/21/2016 10 38:06AM
GUID: 508da70600028a9e6a494d73e6454d09

Marshall Florence

Digitally signed by Marshall Florence
Date: 9/07/2016 08:56:57AM
GUID: 55eefa420051b501ac3ced124279f785

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	07/24/2016
ANDA Number(s)	207868
Review Number	2
Applicant Name	PLD Acquisitions LLC D/B/A Avema Pharma Solutions
Established Name & Strength(s)	Nicotine Polacrilex Lozenge, 2 mg and 4 mg
Proposed Proprietary Name	None
Submission Received Date	04/15/2016
Labeling Reviewer	Marshall Florence, PharmD.
Labeling Team Leader	Adolph Vezza

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☐ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on July 26, 2016 based on your submission dated April 15, 2016:

1. GENERAL COMMENT

   Please describe the child resistant feature of the container and add "Opening Directions" to be the same as the reference listed drug's labeling.

2. CARTON AND CARD LABEL
   a. Please revise your carton and container labeling to be in accordance with the most recently approved labeling for the reference listed drug, (RLD), Nicorette Mini Lozenge, NDA 022360/S-010 approved 09/30/2015.
   b. Please see "GENERAL COMMENT" above.
   c. Please change the presentation of the established name and expression of strength on the principal display panel such as:

      Nicotine Polacrilex Lozenge
      # mg
      Stop Smoking Aid

3. CONTAINER LABEL
   a. See comments 2a and 2c above.
   b. Please add a storage recommendation statement to the container label.
   c. Please add the "Questions?" and Poison Control Center phone number to the label for safety reasons.

4. PATIENT INFORMATION
   a. The established name of the drug product is considered a common noun and need not be capitalized unless dictated by sentence structure.
   b. Revise the established name to read as "nicotine polacrilex lozenge". (You may retain "mini" as a descriptor for the drug product but it should not be part of the established name of the drug product.)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).
Click here to enter text.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments: The below comments are from the labeling review C1 based on the submission dated 06/19/2014.

1. GENERAL COMMENTS
   a. Revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Nicorette Mini Lozenge, NDA022360/S-010 approved 09/30/2015.
   b. Please revise the "revision date" to include an actual date including month and year.

2. CONTAINER (Vial), CARTON, and CARD LABELING
   See comment 1a above.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

-Please revise your carton and container labeling to be in accordance with the most recently approved labeling for the reference listed drug, (RLD), Nicorette Mini Lozenge, NDA 022360/S-010 approved 09/30/2015.

-Please describe the child resistant feature of the container and add "Opening Directions" to be the same as the reference listed drug's labeling.

-Revise and change the presentation of the established name and expression of strength on the principal display panel such as "Nicotine Polacrilex Lozenge; # mg; Stop Smoking Aid".

-Please add a storage recommendation statement to the container label.

-Please add the "Questions?" and Poison Control Center phone number to the label for safety reasons.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments: None

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO

If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA# /Supplement# (S-000 if original):** 022360/S-010 **Supplement Approval Date:** 09/30/2015 **Proprietary Name:** Nicorette Mini lozenge **Established Name:** Nicotine poll crilea **Description of Supplement:** xTih s" rior ApproPl lv h" ppleMentl Lneu m" g l pplicl tion proPmeh vør tTe l mmition owl heiz" re u l rning on tTe d r" g f l cth Dl Felb
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** . licCTere to enter teatb **Supplement Approval Date:** . licCTere to enter teatb **Proprietary Name:** . licCTere to enter teatb **Established Name:** . licCTere to enter teatb **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** . licCTere to enter teatb
☐ **OTHER (Describe):** . licCTere to enter teatb

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

-The established name of the drug product is considered a common noun and need not be capitalized unless dictated by sentence structure.

-Revise the established name to read as "nicotine polacrilex lozenge". (You may retain "mini" as a descriptor for the drug product but it should not be part of the established name of the drug product.)

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 022360 Supplement-10 approved 09/30/2015]


0000000000
Opening Directions:
Push in child resistant tab on the vial with thumb. Flip up the top of vial. Turn upside down and shake to remove lozenge.
Drug Facts (continued)
nicotine lozenge is a medicine and must be used a certain way to get the best results
• place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. Do not chew or swallow lozenge.
• you may feel a warm or tingling sensation
• occasionally move the lozenge from one side of your mouth to the other until completely dissolved
• do not eat or drink 15 minutes before using or while the lozenge is in your mouth
• to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
• do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
• do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.
• it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.
Other information
• each lozenge contains: sodium, 5 mg
• store at 20 - 25°C (68 - 77°F)
• keep vial tightly closed and protect from light
Inactive ingredients
acesulfame potassium, calcium polycarbophil, flavors, magnesium stearate, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum
Questions or comments?
call toll-free 1-888-569-1743 (English/Spanish) weekdays (9:00 am - 4:30 pm ET)
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Moon Township, PA 15108
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BONUS PACK
27 EXTRA PIECES
NDC 0135-0508-06
gsk
Nicorette®
nicotine polacrilex lozenge, 2 mg
stop smoking aid
mini
Lozenge
Mint
2 mg
FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE MORE THAN 30 MINUTES AFTER WAKING UP.
If you smoke your first cigarette WITHIN 30 MINUTES of waking up, use Nicorette 4 mg Lozenge
108 LOZENGES, 2 mg Each
(4 Vials of 27)
3 0766-7880-10 6
TO INCREASE YOUR SUCCESS IN QUITTING:
1. You must be motivated to quit.
2. Use Enough - Use at least 9 Nicorette® mini lozenges per day during the first six weeks.
3. Use Long Enough - Use Nicorette® mini lozenges for the full 12 weeks.
4. Use With a Support Program as directed in the enclosed User's Guide.
not for sale to those under 18 years of age
proof of age required
not for sale in vending machines or from any source where proof of age cannot be verified
TAMPER EVIDENT FEATURE:
Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken. Retain outer carton for full product uses, directions and warnings.
For more information and for a FREE individualized stop smoking program, please visit www.Nicorette.com or see inside for more details.
Drug Facts
Active ingredient (in each lozenge) Purpose
Nicotine polacrilex, 2 mg Stop smoking aid
Use • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking
Warnings
If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.
Ask a doctor before use if you have
• heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
• high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
• stomach ulcer or diabetes
• history of seizures
Ask a doctor or pharmacist before use if you are
• using a non-nicotine stop smoking drug
• taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.
Stop use and ask a doctor if
• mouth problems occur
• persistent indigestion or severe sore throat occurs
• irregular heartbeat or palpitations occur
• you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
• you have symptoms of an allergic reaction (such as difficulty breathing or rash)
Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.
Directions
• If you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.
• before using this product, read the enclosed User's Guide for complete directions and other important information
• begin using the lozenge on your quit day
• If you smoke your first cigarette within 30 minutes of waking up, use 4 mg nicotine lozenge
• If you smoke your first cigarette more than 30 minutes after waking up, use 2 mg nicotine lozenge according to the following 12 week schedule:
Weeks 1 to 6 | Weeks 7 to 9 | Weeks 10 to 12
1 lozenge every 1 to 2 hours | 1 lozenge every 2 to 4 hours | 1 lozenge every 4 to 8 hours

Nicorette®

nicotine polacrilex lozenge, 2 mg
stop smoking aid

mini
Lozenge

Opening Directions:
Push in child resistant tab on the vial with thumb.
Flip up the top of vial.
Turn upside down and shake to remove lozenge.

Personalized Quit Plan

Visit **www.nicorette.com** to enroll in a free, personalized quit plan. **Nicorette Committed Quitters®** is a personalized stop smoking program that will help you understand your smoking habits and determine how to best overcome your cravings. Track, target, and tame your temptations with **Nicorette Committed Quitters®.**
Only available at **www.nicorette.com**

Drug Facts

Active ingredient (in each lozenge) — **Purpose**
Nicotine polacrilex, 2 mg — Stop smoking aid

Use • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings
If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Ask a doctor before use if you have
- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes
- history of seizures

Ask a doctor or pharmacist before use if you are
- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if
- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)

Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

Direction
- **If you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.**

Drug Facts (continued)

- before using this product, read the enclosed User's Guide for complete directions and other important information
- begin using the lozenge on your quit day
- **if you smoke your first cigarette within 30 minutes of waking up,** use 4 mg nicotine lozenge
- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2 mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- **nicotine lozenge is a medicine and must be used a certain way to get the best results**
- place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation
- occasionally move the lozenge from one side of your mouth to the other until completely dissolved
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.**
- it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.

Other information
- **each lozenge contains:** sodium, 5 mg
- store at 20 - 25°C (68 - 77°F)
- keep vial tightly closed and protect from light

Inactive ingredients acesulfame potassium, calcium polycarbophil, flavors, magnesium stearate, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum

Questions or comments? call toll-free **1-888-569-1743** (English/Spanish) weekdays (9:00 am - 4:30 pm ET)

TO INCREASE YOUR SUCCESS IN QUITTING:
1. You must be motivated to quit.
2. **Use Enough** – Use at least 9 **Nicorette®** mini lozenges per day during the first six weeks.
3. **Use Long Enough** – Use **Nicorette®** mini lozenges for the full 12 weeks.
4. **Use With a Support Program** as directed in the enclosed User's Guide.

- **not for sale to those under 18 years of age**
- **proof of age required**
- **not for sale in vending machines or from any source where proof of age cannot be verified**

TAMPER EVIDENT FEATURE: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken. Retain outer back panel for full product uses, directions and warnings.

NICORETTE, COMMITTED QUITTERS and the NICORETTE sunburst design are registered trademarks of the GSK group of companies.

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Moon Township, PA 15108
Made in Switzerland
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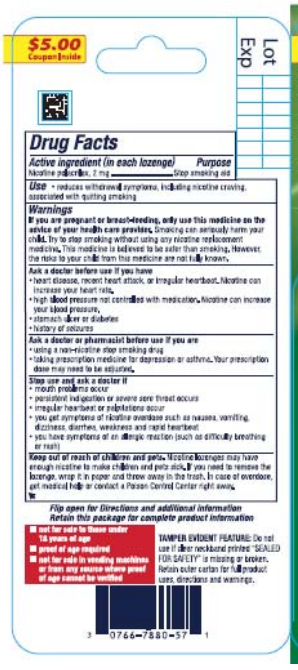
Lot
Exp


Nicorette
nicotine polacrilex lozenge, 2 mg
stop smoking aid
mini Lozenge
Mint
gsk
Includes User's Guide
2 mg
FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE MORE THAN 30 MINUTES AFTER WAKING UP.
135 LOZENGES, 2 mg Each
135 LOZENGES
2 mg Each (5 Vials of 27)


$5.00
Coupon Inside
Lot
Exp
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Flip open for Directions and additional information
Retain this package for complete product information
do not for sale to those under 18 years of age
proof of age required
not for sale in vending machines or from any source where proof of age cannot be verified
TAMPER EVIDENT FEATURE: Do not use if outer neckband printed "SEALED FOR SAFETY" is missing or broken. Retain outer carton for full product uses, directions and warnings.
3 0766-7880-57 1
$5.00
Coupon Inside
NDC 0135-0504-04
gsk
Nicorette
nicotine polacrilex lozenge, 2 mg
stop smoking aid
mini Lozenge
2 mg
FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE MORE THAN 30 MINUTES AFTER WAKING UP.
If you smoke your first cigarette WITHIN 30 MINUTES of waking up, use Nicorette 4 mg Lozenge
20 LOZENGES
2 mg Each


Drug Facts (continued)
Directions
• If you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.
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• occasionally move the lozenge from one side of your mouth to the other until completely dissolved
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• do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
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Other information
• each lozenge contains: sodium, 5 mg
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Inactive ingredients acesulfame potassium, calcium polycarbophil, flavors, magnesium stearate, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum
Questions or comments? call toll-free 1-888-669-1743 (English/Spanish) weekdays (8:00 am - 4:30 pm ET)
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For more information and for a FREE individualized stop smoking program, please visit www.Nicorette.com or see inside for more details.
MANUFACTURER'S COUPON | EXPIRES 12/31/2017
Nicorette
Nicorette
SAVE $5.00
On Nicorette®
Mini Lozenge (81ct)
030766-074212

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph ? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	k/25/2016	No	NA	NA
PF	k/25/2016	No	NA	NA

Reviewer Comments: None

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 7/25/2016.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
7501168	4" n 18J 2029			,I	09/16/2015	None
7980kk2	Apr 30J2029			,I	09/16/2015	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments: From the cover letter of the 03/31/2016 submission:

> This patent amendment is to notify that no legal action was taken by the patent holder and the NDA holder within the 45-day period.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments: None

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
l hpl rtl MeJcl lci" M poLVcl rFopTiLJ WL PorJMl ltomeatrinJMl nnitoLJhomi" M l lginl teJhomi" M Ficl rFonl teJhomi" M htel rVLẅMl rl teJtl lcJal ntTl n g" M	l hpl rtl MeJcl lci" M poLVcl rFopTiLJ WL PorJMl ltomeatrinJMl nnitoLJhomi" M l lginl teJhomi" M Ficl rFonl teJhomi" M htel rVLẅMl rl teJtl lcJal ntTl n g" M	**Acceptable**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Other information ■ Phenylketonurics: Contains Phenylalanine 2.8 mg per lozenge ■ store at 20 -25°C (68 -77°F) ■ keep vial tightly closed and protect from light	***Other information*** ■ Phenylketonurics: Contains Phenylalanine 2.8 mg per lozenge ■ store at 20 -25°C (68 -77°F) ■ keep vial tightly closed and protect from light	**Acceptable**

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
y l n" ẅct" remFV: APéMl " Tl rMl SoL" tionh 10800 NW 29tT xerrl ceJ y il MiJf D331k2	y l n" ẅct" remFV: APéMl " Tl rMl SoL" tionh 10800 NW 29tT xerrl ceJ y il MiJf D331k2	**Acceptable**

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments: None

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments: None

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	drl w	1 Pil L: 2k Lozengeh	08/15/2016	RePihe
Blister	NA			
Carton	drl w	71 co" nt cl rton: 3 Pil Lh ow 2k 107 co" nt cl rton: 8 Pil Lh ow 2k	08/15/2016	RePihe
(Other – Card)	drl w	1 cl rm 1 Pil Low2k	08/15/2016	RePihe
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	NA			
Medication Guide	NA			
Patient Information	drl w	RePihion m te: 08/2016	08/15/2016	RePihe
SPL Data Elements	NA	RePihem 6/2018	06/19/2018	Sl tihw ctorV

Adolph Vezza

Digitally signed by Adolph Vezza
Date: 8/05/2016 02:18:32PM
GUID: 508da70600028a9e6a494d73e6454d09

Marshall Florence

Digitally signed by Marshall Florence
Date: 7/30/2016 01:19:39PM
GUID: 55eefa420051b501ac3ced124279f785

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	02/17/2016
ANDA Number(s)	207868
Review Number	1
Applicant Name	PLD Acquisitions LLC D/B/A Avema Pharma Solutions
Established Name & Strength(s)	Nicotine Polacrilex Mini Lozenge, 2 mg and 4 mg
Proposed Proprietary Name	None
Submission Received Date	06/19/2014
Labeling Reviewer	Marshall Florence, PharmD.
Labeling Team Leader	Adolph Vezza

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☐ On Policy Alert List

TABLE OF CONTENTS

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on February 17, 2016 based on your submission dated June 19, 2014:

1. GENERAL COMMENTS
    a. Revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Nicorette Mini Lozenge, NDA022360/S-010 approved 09/30/2015.
    b. Please revise the "revision date" to include an actual date including month and year.

2. CONTAINER (Vial), CARTON, and CARD LABELING
    See comment 1a above.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission(s) dated (add date).

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).
Click here to enter text.

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

Has the ANDA been accepted for filing? YES
Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain.

Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

2.2 MODEL LABELING

2.2.1 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ MOST RECENTLY APPROVED NDA MODEL LABELING *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA RLD information.)* **NDA#/Supplement# (S-000 if original):** 022360/S-010 **Supplement Approval Date:** 09/30/2015 **Proprietary Name:** Nicorette mini lozenge **Established Name:** Nicotine Polacrilex **Description of Supplement:** This "Prior Approval" supplemental new drug application provides for the addition of a seizure warning on the Drug Facts Label.
☐ MOST RECENTLY APPROVED ANDA RLD LABELING **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:** Click here to enter text.
☐ TEMPLATE (e.g., BPCA, PREA, Carve-out): Click here to enter text.
☐ OTHER (Describe): Click here to enter text.

2.2.2 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: NDA 022360 Supplement-10 approved 09/30/2015 **)**


0000000000
Opening Directions:
Push in child resistant tab on the vial with thumb. Flip up the top of vial. Turn upside down and shake to remove lozenge.
Drug Facts (continued)
nicotine lozenge is a medicine and must be used a certain way to get the best results
• chew the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. Do not chew or swallow lozenge.
• you may feel a warm or tingling sensation
• occasionally move the lozenge from one side of your mouth to the other until completely dissolved
• do not eat or drink 15 minutes before using or while the lozenge is in your mouth
• to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
• do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
• do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.
• it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.
Other information
• each lozenge contains: sodium, 5 mg
• store at 20 - 25°C (68 - 77°F)
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BONUS PACK
27 EXTRA PIECES
NDC 0135-0508-06
gsk
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(4 Vials of 27)
3 0766-7880-10 6
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Only available at **www.nicorette.com**

Drug Facts

Active ingredient (in each lozenge) — ***Purpose***
Nicotine polacrilex, 2 mg ..... Stop smoking aid

Use • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Ask a doctor before use if you have
- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes
- history of seizures

Ask a doctor or pharmacist before use if you are
- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if
- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)

Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

Direction

- **If you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.**

Drug Facts (continued)

- before using this product, read the enclosed User's Guide for complete directions and other important information
- begin using the lozenge on your quit day
- **If you smoke your first cigarette within 30 minutes of waking up,** use 4 mg nicotine lozenge
- **If you smoke your first cigarette more than 30 minutes after waking up,** use 2 mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- **nicotine lozenge is a medicine and must be used a certain way to get the best results**
- place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation
- occasionally move the lozenge from one side of your mouth to the other until completely dissolved
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.**
- it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.

Other information

- **each lozenge contains:** sodium, 5 mg
- store at 20 - 25°C (68 - 77°F)
- keep vial tightly closed and protect from light

Inactive ingredients

acesulfame potassium, calcium polycarbophil, flavors, magnesium stearate, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum

Questions or comments?

call toll-free **1-888-569-1743** (English/Spanish) weekdays (9:00 am - 4:30 pm ET)

TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to quit.
2. **Use Enough** – Use at least 9 **Nicorette®** mini lozenges per day during the first six weeks.
3. **Use Long Enough** – Use **Nicorette®** mini lozenges for the full 12 weeks.
4. **Use With a Support Program** as directed in the enclosed User's Guide.

- **not for sale to those under 18 years of age**
- **proof of age required**
- **not for sale in vending machines or from any source where proof of age cannot be verified**

TAMPER EVIDENT FEATURE: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken. Retain outer back panel for full product uses, directions and warnings.

Distributed By:
GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108
Made in Switzerland

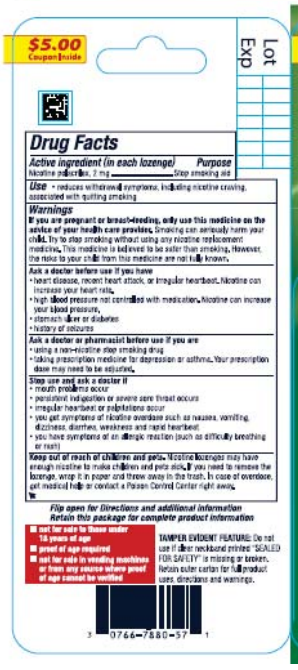
000000XX

000000

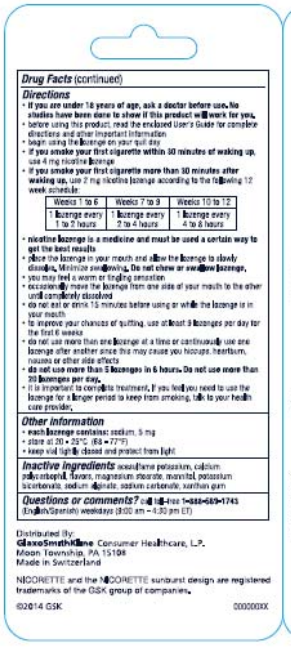
0766-7880-40

Lot
Exp


Nicorette
nicotine polacrilex lozenge, 2 mg
stop smoking aid
mini Lozenge
Mint
gsk
2 mg
FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE MORE THAN 30 MINUTES AFTER WAKING UP.
135 LOZENGES, 2 mg Each
135 LOZENGES
2 mg Each (5 Vials of 27)


$5.00
Coupon Inside
Lot
Exp
Drug Facts
Active ingredient (in each lozenge) Purpose
Nicotine polacrilex, 2 mg Stop smoking aid
Use
Warnings
Ask a doctor before use if you have
Ask a doctor or pharmacist before use if you are
Stop use and ask a doctor if
Keep out of reach of children and pets.
Flip open for Directions and additional information
Retain this package for complete product information
TAMPER EVIDENT FEATURE: Do not use if liner neckband printed "SEALED FOR SAFETY" is missing or broken. Retain outer carton for full product uses, directions and warnings.
0766-7880-57


$5.00
Coupon Inside
gsk
Nicorette
nicotine polacrilex lozenge, 2 mg
stop smoking aid
mini Lozenge
2 mg
FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE MORE THAN 30 MINUTES AFTER WAKING UP.
20 LOZENGES
2 mg Each


Drug Facts (continued)
Directions
Other information
Inactive ingredients
Questions or comments?
Distributed by:
GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108
Made in Switzerland
©2014 GSK


TO INCREASE YOUR SUCCESS IN QUITTING:
Opening Directions:
For more information and for a FREE Individualized stop smoking program, please visit www.Nicorette.com or see inside for more details.
MANUFACTURER'S COUPON EXPIRES 12/31/2017
SAVE $5.00
On Nicorette®
Mini Lozenge (81ct)
030766-074212

2.3 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	2/17/2016	No	NA	NA
PF	2/17/2016	No	NA	NA

2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 4/1/2016.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
8501164	Jun 14, 2029			IV	09/16/2015	None
8940772	Apr 30, 2029			IV	09/16/2015	None

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA					

2.5 MANUFACTURING FACILITY

Table 5 provides a description of the drug product manufacturing facility.

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of Facility ANDA Manufactured (Cite Source)	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information
From 3.2.P.3.1 PLD Acquisitions LLC D/B/A Avema Pharma Solutions 10400 NW 29th Terrace Miami FL 33172	Carton: Manufactured by: **Avéma Pharma Solutions** 10400 NW 29th Terrace Miami, FL 33172 Card: Manufactured by: **Avéma Pharma Solutions** 10400 NW 29th Terrace Miami, FL 33172 Label: Manufactured by: **Avéma Pharma Solutions** 10400 NW 29th Terrace Miami, FL 33172	Manufactured by: **Avéma Pharma Solutions** 10400 NW 29th Terrace, Miami, FL 33172 Distributed by: Avéma Pharma Solutions. USA

3. ASSESSMENT OF ANDA LABELING AND LABELS

The results for each material reviewed in this section provide the basis for the labeling comments to the applicant.

Is this product Rx or OTC? Please check one.

☐ Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE.)
☒ OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE)

3.1 RX (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **CLICK HERE**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **CLICK HERE**
Is the established name for this ANDA acceptable? **CLICK HERE**
Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **CLICK HERE**
Are the required USP recommendations reflected in the labeling? **CLICK HERE**
Is the applicant's "patent carve out" acceptable? **CLICK HERE**
Is the applicant's "exclusivity carve out" acceptable? **CLICK HERE**
Is the Manufacturer statement acceptable? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.1.1 RX: DESCRIPTION

We reviewed the DESCRIPTION section for accuracy (with input from the chemistry review, if appropriate) and acceptability from Labeling perspective. We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling Inactive Ingredients	**ANDA Labeling Inactive Ingredients**
Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling Memorandum of Understanding (MOU)? **CLICK HERE**
(Note: The MOU became effective on November 1, 2014. MOU does not apply to amendment reviews for ANDAs originally reviewed before November 1, 2014.)

If the chemistry review follows the MOU, labeling reviewer is not responsible for reviewing for accuracy of the DESCRIPTION section for chemical properties, system components of the drug product, etc. Please refer to the MOU, Appendix A, DESCRIPTION section for delineation of responsibilities. If chemistry review does NOT follow the MOU, labeling reviewer will follow the traditional review approach of reviewing the entire DESCRIPTION section.)

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? (If Chemistry follows the MOU, refer to the Labeling section of Chemistry review.) **CLICK HERE**
For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **CLICK HERE**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**

If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **CLICK HERE** Has the statement been verified by chemistry? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 7 and will be referred to the appropriate review discipline for evaluation.

Table 7: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	Click here to enter text.
ANDA Labeling	Click here to enter text.

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **CLICK HERE**
If the chemistry review does NOT follow the MOU, is the description (scoring, color and imprint) of the finished product in the HOW SUPPLIED section consistent with the information in Module 3.2.P.5.1 for Drug Product Specification? **CLICK HERE**
Does the ANDA require the same color coding as the Model Labeling? **CLICK HERE**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **CLICK HERE**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **CLICK HERE**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **CLICK HERE**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **CLICK HERE**
Is the storage or dispensing statement acceptable as compared to the USP? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.2 RX: MEDICATION GUIDE

Is Medication Guide required? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.1.3.

Reviewer Assessment:

Was Medication Guide submitted? **CLICK HERE**
Is the Medication Guide same as the model labeling, except for allowable differences? **CLICK HERE**
Does the Medication Guide meet the requirements of 21 CFR 208.20? **CLICK HERE**
Has the Applicant committed to provide a sufficient number of medication guides? **CLICK HERE**
Is the phonetic spelling of the proprietary or established name present? **CLICK HERE**
Is FDA 1-800-FDA-1088 phone number included? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.3 RX: OTHER PATIENT LABELING

Are other patient labeling required? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.

Reviewer Assessment:

Was other patient labeling submitted? **CLICK HERE**
Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.4 RX: CONTAINER LABEL

Was container label (other than Blisters) submitted? **CLICK HERE**
(For BLISTER labels go to section 3.1.5.)

We evaluated the container labels for the inclusion of all required statements and safety considerations.

Reviewer Assessment:

Is the established name acceptable? **CLICK HERE**
Is title case used in expressing the established name? **CLICK HERE**
Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **CLICK HERE**
Is container label too small to contain all required information? **CLICK HERE** If yes, does the container meet the "too small" exemption found in 21 CFR 201.10(j)? **CLICK HERE**

Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **CLICK HERE**

Is the following information properly displayed?

- Net quantity statement: **CLICK HERE**
- Route(s) of administration (other than oral): **CLICK HERE**
- Warnings (if any) or cautionary statements (if any): **CLICK HERE**
- Medication Guide Pharmacist instructions per 21 CFR 208.24(d): **CLICK HERE**
- Controlled substance symbol: **CLICK HERE**
- Usual Dosage statement: **CLICK HERE**
- Product strength equivalency statement: **CLICK HERE**
- NDC: **CLICK HERE**
- Bar code per 21 CFR 201.25(c)(2): **CLICK HERE**

Is the Manufacturer/Distributor/Packager statement acceptable? **CLICK HERE**
For foreign manufacturers, does the labeling have the country of origin? **CLICK HERE**
Are the required USP recommendations reflected on the label(s)? **CLICK HERE**
Is the storage or dispensing statement consistent with the How Supplied section of the insert? **CLICK HERE**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**

Are multiple strengths differentiated by use of different color or other acceptable means? **CLICK HERE**
Are the labels of related products differentiated to avoid selection errors? **CLICK HERE**
Does the ANDA require the same color coding as the Model Labeling? **CLICK HERE**

Are the requirements of 21 CFR 201.15 met for all required label statements? **CLICK HERE**
Are the requirements of 21 CFR 201.100 met for all required label statements? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

Is container for parenteral solution? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.2.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **CLICK HERE**
If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

Is container for solid injectable? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **CLICK HERE**
Are instructions for reconstitution and resultant concentration provided, if space permits? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

Is container a Pharmacy Bulk Package (parenteral preparations for admixtures)? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.1.5.

Reviewer Assessment:

Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **CLICK HERE**
Does the container label include graduation marks? **CLICK HERE**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.5 RX: UNIT DOSE BLISTER LABEL

Is container a Unit Dose Blister Pack? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.1.6.

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **CLICK HERE**
Do proprietary name, established name, strength, bar code, and manufacturer appear accurately on each blister cell? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Are the answers to the Container Label questions the same for the Carton Labeling? **CLICK HERE** If no, please explain the differences in the Reviewer Comments section.
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **CLICK HERE**
If country of origin is not on Container, does it appear on outer packaging labeling? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is the patient labeling the same as the model labeling, except for allowable differences? **YES**
Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **CLICK HERE**
Does "Questions?" have a toll-free number no less than 6 pt. font size per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" per 21 CFR 201.66 (c)(5)(vii)? **YES**
Did firm submit a Labeling Format Information Table to evaluate the font size? **CLICK HERE**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the established name for this ANDA acceptable? **YES**
Is title case used in expressing the established name? **YES**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **YES**
Is the following information properly displayed?
- Pharmacological category: **YES**
- Net quantity statement: **YES**
- Route(s) of administration (other than oral): **YES**
- Warnings (if any) or cautionary statements (if any): **YES**
- NDC: **YES**
- Bar code per 21 CFR 201.25(c)(2): **YES**

Is the Manufacturer/Distributor/Packager statement acceptable? **YES**
For foreign manufacturers, does the labeling have the country of origin? **NA**
Are the required USP recommendations reflected in the labeling? **NA**
Is the storage statement acceptable? **YES**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**
Are multiple strengths differentiated by use of different color or other acceptable means? **YES**
Are the labels of related products differentiated to avoid selection errors? **NA**

Reviewer Comments:
-Revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Nicorette Mini Lozenge, NDA022360/S-010 approved 09/30/2015.
-Please revise the "revision date" to include an actual date including month and year.

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
(b) (4)	ANDA Inactive Ingredients
	aspartame, calcium polycarbophil, flavor, maltodextrin, mannitol, sodium alginate, sodium bicarbonate, sodium stearyl fumarate, talc, xanthan gum

Reviewer Assessment:

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? **YES**
Are the inactive ingredients listed in alphabetical order? **YES**
For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **YES**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments: From 3.2.P.1:

Ingredient	Nicotine Polacrilex Mini 2.0mg Lozenges (mg/unit)	Nicotine Polacrilex Mini 4.0mg Lozenges (mg/unit)	Function
Nicotine Polacrilex	(b) (4)	(b) (4)	
Mannitol	(b) (4)		
Sodium Bicarbonate	(b) (4)		
Sodium Stearyl Fumarate	(b) (4)		
Maltodextrin	(b) (4)		
(b) (4)			
Calcium Polycarbophil			
Xanthan Gum	(b) (4)		
Aspartame			
Sodium Alginate	(b) (4)		
Talc	(b) (4)		
Total			

Under Other information the following statement is listed:
Phenylketonurics: Contains Phenylalanine 2.8 mg per lozenge.

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 9 and will be referred to the

appropriate review discipline for evaluation.

Table 9: Comparison of Model Labeling to ANDA finished product		
Model Labeling	***Other information*** • **each lozenge contains:** sodium, 5 mg • store at 20 - 25°C (68 - 77°F) • keep vial tightly closed and protect from light	
ANDA (enter source of information of product description on the right hand column; e.g., chemistry Review & date, Module 3.2.P.5.1)	***Other information*** ■ Phenylketonurics: Contains Phenylalanine 2.8 mg per lozenge ■ store at 20 -25°C (68 -77°F) ■ keep vial tightly closed and protect from light	

Reviewer Assessment:

Is the description (scoring, color and imprint) of the finished product consistent with the Drug Product Quality submission? **YES**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **YES**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**

Reviewer Comments: From 3.2.P.5.1 of 06/19/2014 submission:

(b) (4)

[redacted]

3.2.2 OTC: OTHER PATIENT LABELING

Are other patient labeling required? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Was other patient labeling submitted? **YES**
Is the patient labeling the same as the model labeling, except for allowable differences? **NO**

Reviewer Comments:
-Revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Nicorette Mini Lozenge, NDA022360/S-010 approved 09/30/2015.

3.3 CONTAINER/CLOSURE

We evaluated the container/closure system of this product to determine if special child-resistant packaging is required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.
Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **YES**
Are the tamper evident requirements met for OTC and Controlled Substances? (If quality review follows the chemistry-labeling MOU, obtain answer from Appendix D of chemistry review; if quality review does not follow the MOU, labeling reviewer is responsible for assessing for tamper evidence.) **YES**

For ophthalmic products:

Does this ophthalmic product cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **NO**

For parenteral products:

Is there text on the cap/ferrule overseal of this injectable product? **NA**
If YES, does text comply with the recommendations in USP General Chapter <1>? **NA**
What is the cap and ferrule color? **Click here to enter text.**
NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments: From 3.2.P.7:

Bottle Configuration	**2.0mg and 4.0mg Nicotine Polacrilex Lozenge**
Bottle	(b) (4)
Cap	
Desiccant	
IFC	

Tamper Evident Seal Information:

Description: (b) (4)

(b) (4)

3.4 CALCULATIONS FOR CONTENTS IN LABELING

Is calculation of ingredient(s) required? **NO**
If YES, go to Table 10 and Reviewer Assessment below, if NO go to section 3.5.

We verified the calculation on the following content.

Table 10: Ingredients		
Ingredient	**Stated Content**	**Location of the Information**
Click here to enter text.	Click here to enter text.	Click here to enter text.

(Note: For Rx products, if chemistry review follows the MOU, chemistry reviewer will verify the accuracy of the active and inactive ingredient amount(s) if information is in the DESCRIPTION and HOW SUPPLIED sections for all products, and additionally, DOSAGE AND ADMINISTRATION section for parenteral products. See Chemistry-Labeling MOU, Appendix A, Miscellaneous section for discussion on calculations.)

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **CLICK HERE**
Are the stated contents in the table above acceptable? **CLICK HERE**
Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per 21 CFR 201.323.
Did the chemistry reviewer verify the aluminum content? **CLICK HERE**
Are the labeling requirements met per 21 CFR 201.323? **CLICK HERE**

Reviewer Comments: None

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

We evaluated the SPL data elements to ensure they are consistent with the information submitted in the ANDA.

Table 11: ANDA Tablet/Capsule Size and Imprint		
Tablet/Capsule Strength	**ANDA Tablet/Capsule Size (mm) and imprint code from SPL**	**ANDA Tablet/Capsule Size (mm) and imprint code (Cite source of information such as the chemistry review that follows the MOU, Product Specification in 3.2.P.5.1, Commercial Batch Record in 3.2.P.3.3. etc.)**
2 mg	129; 10 mm	129; 10 mm
4 mg	131; 10 mm	131; 10 mm

Reviewer Assessment:

For solid oral dosage forms: Do size and imprint code from the SPL data elements match the information provided in the quality submission? **YES**
Are all the other data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **YES**

Reviewer Comments: None

4. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments: None

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other review discipline reviewer(s):

Reviewer Comments: None

6. SPECIAL CONSIDERATIONS

None

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 12 and 13 provide a summary of recommendations for each labeling piece analyzed in this review.

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	1 vial: 27 lozenges	06/19/2014	Revise
Blister	NA			
Carton	Draft	81 count carton: 3 vials of 27 108 count carton: 4 vials of 27	06/19/2014	Revise
(Other – Card)	Draft	1 card: 1 vial of 27	06/19/2014	Revise
Table 13 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	NA			
Medication Guide	NA			
Patient Information-User's Guide	Draft	Revision date: MM/YY14	06/19/2014	Revise
SPL Data Elements	NA	Revised: 6/2014	06/19/2014	Satisfactory

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207868

CHEMISTRY REVIEW(s)

Recommendation: APPROVABLE from CMC Perspective

ANDA:

☒ **Approval**

☐ **Information Request - Minor**

(_ days for applicant to response)

☐ **Complete Response - Minor**

☐ **Complete Response - Major**

(DMF, Labeling, BE, BP, and Facilities are adequate)

ANDA 207868

Review of Amendment dated 11/09/2018 (Review #4)

Drug Name/Dosage Form/Strength	Nicotine Polacrilex Mini Lozenges
Strength	2 mg, 4 mg
Reviewer(s)	Chandrasekar Manoharan
Applicant	PLD Acquisitions LLC, DBA Avema Pharma Solutions

PREVIOUS SUBMISSION(S) REVIEWED	DOCUMENT DATE
New ANDA (Original) - 1	06/19/2014
Quality Response to Information Request	09/17/2015
Resubmission to RTR*	12/02/2015
Quality/Response to information request	01/23/2017
Correspondence@	01/26/2017
Amendment to complete response letter	05/02/2017
Post complete response meeting request$	07/28/2017
Amendment to complete response letter	04/30/2018
Quality Response to Information Request	10/01/2018

* ANDA was RTR on 09/29/2015.

@ Submission only has verification statement in regards to 81 FR 69580.

$ Submission has quality information.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment to complete response letter	11/09/2018

REVIEW HISTORY

FINALIZED REVIEW	PRIMARY REVIEWER NAME	DOCUMENT DATE/LOCATION
Quality Review #1*	Chandrasekar Manoharan	02/08/2017/Panorama
Quality Review #2	Chandrasekar Manoharan	06/26/2017/Panorama
Quality Review #3	Chandrasekar Manoharan	10/19/2018/Panorama

* Review cycle had one IR and CR.

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Nicotine Polacrilex, 15%, USP	Adequate	06/22/2016 by Jayani R Perera Note: Review noted NAI.	NA

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Methods Validation	N/A		
Labeling	Adequate	10/21/2016	Marshall Florence
Biopharmaceutics	Adequate	01/25/2019	Okponanabofa Eradiri
Bioequivalence	Adequate	09/21/2018	Yi Zhang
Toxicology/Clinical	N/A		
EA	Categorical Exclusion	12/21/2016	Chandrasekar Manoharan
Radiopharmaceutical	N/A		
Samples Requested	Samples received	01/24/2017	Chandrasekar Manoharan

CONSULTS: *Completed and adequate*

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	Adequate	Levels of sodium stearyl fumarate, maltodextrin, and talc in the drug product are acceptable.	01/27/2017	Mi Young Yang
Other	N/A			

FACILITIES:

Overall Recommendation: Approve as of 01/03/2019			
Drug Substance			
Function	Site Information	FEI#	Status
(b) (4)			Approve 12/29/2015
			Status
			Approve 09/05/2018

[redacted] (b) (4)		

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is *approvable* from a CMC perspective. DMF, labeling, bioequivalence, biopharmaceutics, and facilities are adequate.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

I Drug Substance

Nicotine Polacrilex is an official USP drug substance. Nicotine Polacrilex 15% is a white to off-white free flowing powder. [redacted] (b) (4) [redacted] (b) (4) Due to the resinate characteristics of the drug substance, a defined molecular mass does not exist. Nicotine Polacrilex is practically insoluble in water and insoluble to slightly soluble in most common organic solvents. However, Nicotine in its base form is miscible in water and nonpolar solvents. Nicotine Polacrilex 15% does not exhibit polymorphism and isomerism. Nicotine Polacrilex is likely to be slightly hygroscopic. Nicotine has a pKa of 8.5.

Drug substance for this ANDA application is manufactured by [redacted] (b) (4), [redacted] (b) (4).

II Drug Product

Nicotine Polacrilex mini lozenge (2 mg and 4 mg) is a white, uncoated, oval shaped lozenge indicated for reducing withdrawal symptoms, including nicotine craving, associated with quitting smoking. This is an OTC drug product and a monograph is not established in USP. The 2 mg and 4 mg lozenges are top engraved with 129 and 131, respectively, and the bottom is plain. Each lozenge contains Nicotine Polacrilex equivalent to 2 mg or 4 mg of Nicotine. The inactive ingredients include: mannitol, sodium stearyl fumarate, sodium bicarbonate, calcium polycarbophil, peppermint flavor, sodium alginate, maltodextrin, aspartame, xanthan gum, and talc.

(b) (4)

[redacted]

Maximum Daily Dose (MDD): 80 mg

	Identification Threshold (IT)	Qualification Threshold (QT)
Drug Substance	0.10%	0.15%
Drug Product	0.2%	0.25%

B. Description of How the Drug Product is Intended to be Used

Nicotine Polacrilex mini lozenges are designed to dissolve slowly in the mouth. The lozenge should not be swallowed or chewed. The lozenge should be placed in the mouth and occasionally moved from side to side. The lozenge should be allowed to dissolve slowly (about 10 minutes) and swallowing should be minimized. Not more than 5 lozenges in 6 hours or more than 20 lozenges per day should be used.

C. Initial and Updated Risk Assessment: N/A

D. Basis for Approvability or Not-Approval Recommendation

Adequate.

Chemistry Review of Amendment dated 11/09/2018

The applicant responded to the complete response letter by submitting an amendment dated 11/09/2018. In the amendment, the applicant has proposed new dissolution acceptance criteria per recommendation from the Division of Biopharmaceutics. In this amendment review, the applicant's quality information is assessed, and all pertinent drug substance and drug product sections are updated.

2.3. S DRUG SUBSTANCE: Adequate

S.1 No Change; Adequate per Review #1

S.2 No Change; Adequate per Review #1

S.3 No Change; Adequate per Review #1

S.4 Adequate per Review #4

Drug substance specification:

Most recent drug substance specification (11/09/2018)

(b) (4)

[redacted]

***Reviewer's Assessment*: Adequate**
Nicotine Polacrilex is an official USP drug substance. The specifications set by the applicant are same as the drug substance manufacturer specifications.

Deficiency #1, Review #3a:
Please provide revised drug substance specification in Section 3.2.S.4.

Applicant's response in amendment dated 11/09/2018:
The revised drug substance specification is provided in Module 3.2.S.4.1.

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Chandrasekar Manoharan

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Date: 1/30/2019 12:40:35PM
GUID: 567431f7006e1e99507d87ad28722781

Suhas Patankar

Digitally signed by Suhas Patankar
Date: 1/30/2019 01:48:34PM
GUID: 508da70600028a4abf9ab8b19093cd0d

Recommendation:

ANDA:

☐ **Approval**

☐ **Information Request - Minor**

(_ days for applicant to response)

☒ **Complete Response - Minor**

☐ **Complete Response - Major**

(DMF, Labeling, BE, and Facilities are adequate; BP is inadequate)

ANDA 207868

Review of Amendment dated 10/01/2018 (Review #3a)

Drug Name/Dosage Form/Strength	Nicotine Polacrilex Mini Lozenges
Strength	2 mg, 4 mg
Reviewer(s)	Chandrasekar Manoharan
Applicant	PLD Acquisitions LLC, DBA Avema Pharma Solutions

PREVIOUS SUBMISSION(S) REVIEWED	DOCUMENT DATE
New ANDA (Original) - 1	06/19/2014
Quality Response to Information Request	09/17/2015
Resubmission to RTR*	12/02/2015
Quality/Response to information request	01/23/2017
Correspondence@	01/26/2017
Amendment to complete response letter	05/02/2017

* ANDA was RTR on 09/29/2015.

@ Submission only has verification statement in regards to 81 FR 69580.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Post complete response meeting request*	07/28/2017
Amendment to complete response letter	04/30/2018
Quality Response to Information Request	10/01/2018

* Submission has quality information.

REVIEW HISTORY

FINALIZED REVIEW	PRIMARY REVIEWER NAME	DOCUMENT DATE/LOCATION
Quality Review #1*	Chandrasekar Manoharan	02/08/2017/Panorama
Quality Review #2	Chandrasekar Manoharan	06/26/2017/Panorama

* Review cycle had one IR and CR.

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Nicotine Polacrilex, 15%, USP	Adequate	06/22/2016 by Jayani R Perera Note: Review noted NAI.	NA

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Methods Validation	N/A		
Labeling	Adequate	10/21/2016	Marshall Florence
Biopharmaceutics	Inadequate	10/16/2018	Tien-Mien Chen
Bioequivalence	Adequate	09/21/2018	Yi Zhang
Toxicology/Clinical	N/A		
EA	Categorical Exclusion	12/21/2016	Chandrasekar Manoharan
Radiopharmaceutical	N/A		
Samples Requested	Samples received	01/24/2017	Chandrasekar Manoharan

CONSULTS: *Completed and adequate*

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	Adequate	Levels of sodium stearyl fumarate, maltodextrin, and talc in the drug product are acceptable.	01/27/2017	Mi Young Yang
Other	N/A			

FACILITIES:

Overall Recommendation: Approve as of 09/17/2018			
Drug Substance			
Function	Site Information	FEI#	Status
(b) (4)			Approve 12/29/2015
			Status
			Approve 09/05/2018

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is *not approvable* from a CMC perspective. DMF, labeling, bioequivalence, and facilities are adequate. Biopharmaceutics is inadequate.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

I Drug Substance

Nicotine Polacrilex is an official USP drug substance. Nicotine Polacrilex 15% is a white to off-white free flowing powder. (b) (4) (b) (4) Due to the resinate characteristics of the drug substance, a defined molecular mass does not exist. Nicotine Polacrilex is practically insoluble in water and insoluble to slightly soluble in most common organic solvents. However, Nicotine in its base form is miscible in water and nonpolar solvents. Nicotine Polacrilex 15% does not exhibit polymorphism and isomerism. Nicotine Polacrilex is likely to be slightly hygroscopic. Nicotine has a pKa of 8.5.

Drug substance for this ANDA application is manufactured by (b) (4) (b) (4).

II Drug Product

Nicotine Polacrilex mini lozenge (2 mg and 4 mg) is a white, uncoated, oval shaped lozenge indicated for reducing withdrawal symptoms, including nicotine craving, associated with quitting smoking. This is an OTC drug product and a monograph is not established in USP. The 2 mg and 4 mg lozenges are top engraved with 129 and 131, respectively, and the bottom is plain. Each lozenge contains Nicotine Polacrilex equivalent to 2 mg or 4 mg of Nicotine. The inactive ingredients include: mannitol, sodium stearyl fumarate, sodium bicarbonate, calcium polycarbophil, (b) (4) flavor, sodium alginate, maltodextrin, aspartame, xanthan gum, and talc.

(b) (4)

(b) (4) Tamper-evident feature is provided by the seal placed on the neck of the bottle. For marketing the number of lozenges proposed per bottle is 27 for both strengths. A 24 month shelf-life is proposed and the recommended storage condition is 20 – 25 °C (68 – 77 °F).

Maximum Daily Dose (MDD): 80 mg

	Identification Threshold (IT)	Qualification Threshold (QT)
Drug Substance	0.10%	0.15%
Drug Product	0.2%	0.25%

B. Description of How the Drug Product is Intended to be Used

Nicotine Polacrilex mini lozenges are designed to dissolve slowly in the mouth. The lozenge should not be swallowed or chewed. The lozenge should be placed in the mouth and occasionally moved from side to side. The lozenge should be allowed to dissolve slowly (about 10 minutes) and swallowing should be minimized. Not more than 5 lozenges in 6 hours or more than 20 lozenges per day should be used.

C. Initial and Updated Risk Assessment: N/A

D. Basis for Approvability or Not-Approval Recommendation

Inadequate. The submitted information for the new drug product batch is not adequate to demonstrate acceptable quality.

Chemistry Review of Amendment dated 04/30/2018

The applicant responded to the complete response letter by submitting an amendment dated 04/30/2018. In the amendment, the applicant has addressed the deficiencies raised by the Division of Bioequivalence. The applicant repeated the pivotal fasting bioequivalence study by manufacturing a new drug product batch. Quality information (certificate of analysis for raw materials and finished product, executed batch record, and stability data) pertinent to the new drug product batch is provided. In this amendment review, the applicant's quality information is assessed, and all pertinent drug substance and drug product sections are updated.

2.3. S DRUG SUBSTANCE: Inadequate

S.1 No Change; Adequate per Review #1

S.2 No Change; Adequate per Review #1

S.3 No Change; Adequate per Review #1

S.4 Inadequate per Review #3a

Drug substance specification:

Most recent drug substance specification (01/23/2017)

(b) (4)

[redacted]

Retest: 12 months

Reviewer's Assessment*: *Inadequate

In the amendment dated 04/30/2018, COA for a new drug substance batch (CM031668) was provided and found to comply with specification. There are no changes in drug substance specification and analytical procedures.

(b) (4)

[redacted]

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Chemistry Branch Chief Name/Date: Suhas Patankar/ 09/18/2018; 9/20/2018; 10/06/2018; 10/19/2018
Project Manager Name/Date: Adrienne Belton

Chemistry Review #2
Chemist Name/Date: Chandrasekar Manoharan/ 06/19/2017
Chemistry Branch Chief Name/Date: Suhas Patankar/ 06/21/2017
Project Manager Name/Date: Adrienne Belton

Chemistry Review #1
Chemist Name/Date: Chandrasekar Manoharan/11/24/2016; 12/19/2016; 12/21/2016; 02/08/2017; 02/17/2017; 02/22/2017
Chemistry Branch Chief Name/Date: Suhas Patankar/ 12/11/2016; 12/21/2016; 02/16/2017; 02/17/2017; 2/23/2017
Project Manager Name/Date: Adrienne Belton

Chandrasekar Manoharan

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Date: 10/19/2018 08:36:29AM
GUID: 567431f7006e1e99507d87ad28722781

Suhas Patankar

Digitally signed by Suhas Patankar
Date: 10/19/2018 09:05:25AM
GUID: 508da70600028a4abf9ab8b19093cd0d

Recommendation:
ANDA:
☐ **Approval**
☐ **Information Request - Minor**
(_ days for applicant to response)
☐ **Complete Response - Minor**
☒ **Complete Response - Major**

(Labeling and DMF are adequate; BE and BP are inadequate; Facilities are Pending)

ANDA 207868

Review of Amendment dated 05/02/2017 (Review #2)

Drug Name/Dosage Form/Strength	Nicotine Polacrilex Mini Lozenges
Strength	2 mg, 4 mg
Reviewer(s)	Chandrasekar Manoharan
Applicant	PLD Acquisitions LLC, DBA Avema Pharma Solutions

PREVIOUS SUBMISSION(S) REVIEWED	DOCUMENT DATE
New ANDA (Original) - 1	06/19/2014
Quality Response to Information Request	09/17/2015
Resubmission to RTR*	12/02/2015
Quality/Response to information request	01/23/2017
Correspondence@	01/26/2017

* ANDA was RTR on 09/29/2015.
@ Submission only has verification statement in regards to 81 FR 69580.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment to complete response letter	05/02/2017

REVIEW HISTORY

FINALIZED REVIEW	PRIMARY REVIEWER NAME	DOCUMENT DATE/LOCATION
Quality Review #1*	Chandrasekar Manoharan	02/08/2017/Panorama

* Review cycle had one IR and CR.

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Nicotine Polacrilex, 15%, USP	Adequate	06/22/2016 by Jayani R Perera Note: Review noted NAI.	NA

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Methods Validation	N/A		
Labeling	Adequate	09/07/2016	Marshall Florence
Biopharmaceutics	Inadequate	06/06/2017	An-Chi Lu
Bioequivalence	Inadequate	06/13/2017	Yi Zhang
Toxicology/Clinical	N/A		
EA	Categorical Exclusion	12/21/2016	Chandrasekar Manoharan
Radiopharmaceutical	N/A		
Samples Requested	Samples received	01/24/2017	Chandrasekar Manoharan

CONSULTS: *Completed and adequate*

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	Adequate	Levels of sodium stearyl fumarate, maltodextrin, and talc in the drug product are acceptable.	01/27/2017	Mi Young Yang
Other	N/A			

FACILITIES:

Overall Recommendation: Pending as of 06/19/2017			
Drug Substance			
Function	Site Information	FEI#	Status
(b) (4)			Approve 12/29/2015
			Status
			Approve 01/07/2016

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is *not approvable* from a CMC perspective. DMF and labeling are adequate. Bioequivalence and biopharmaceutics are inadequate. Facilities are pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

I Drug Substance

Nicotine Polacrilex is an official USP drug substance. Nicotine Polacrilex 15% is a white to off-white free flowing powder. (b) (4) (b) (4) Due to the resinate characteristics of the drug substance, a defined molecular mass does not exist. Nicotine Polacrilex is practically insoluble in water and insoluble to slightly soluble in most common organic solvents. However, Nicotine in its base form is miscible in water and nonpolar solvents. Nicotine Polacrilex 15% does not exhibit polymorphism and isomerism. Nicotine Polacrilex is likely to be slightly hygroscopic. Nicotine has a pKa of 8.5.

Drug substance for this ANDA application is manufactured by (b) (4), (b) (4).

II Drug Product

Nicotine Polacrilex mini lozenge (2 mg and 4 mg) is a white, uncoated, oval shaped lozenge indicated for reducing withdrawal symptoms, including nicotine craving, associated with quitting smoking. This is an OTC drug product and a monograph is not established in USP. The 2 mg and 4 mg lozenges are top engraved with 129 and 131, respectively, and the bottom is plain. Each lozenge contains Nicotine Polacrilex equivalent to 2 mg or 4 mg of Nicotine. The inactive ingredients include: mannitol, sodium stearyl fumarate, sodium bicarbonate, calcium polycarbophil, (b) (4) flavor, sodium alginate, maltodextrin, aspartame, xanthan gum, and talc.

(b) (4)

(b) (4). Tamper-evident feature is provided by the seal placed on the neck of the bottle. For marketing the number of lozenges proposed per bottle is 27 for both strengths. A 24 month shelf-life is proposed and the recommended storage condition is 20 – 25 °C (68 – 77 °F).

Maximum Daily Dose (MDD): 80 mg

	Identification Threshold (IT)	Qualification Threshold (QT)
Drug Substance	0.10%	0.15%
Drug Product	0.2%	0.25%

B. Description of How the Drug Product is Intended to be Used

Nicotine Polacrilex mini lozenges are designed to dissolve slowly in the mouth. The lozenge should not be swallowed or chewed. The lozenge should be placed in the mouth and occasionally moved from side to side. The lozenge should be allowed to dissolve slowly (about 10 minutes) and swallowing should be minimized. Not more than 5 lozenges in 6 hours or more than 20 lozenges per day should be used.

C. Initial and Updated Risk Assessment: N/A

D. Basis for Approvability or Not-Approval Recommendation

Inadequate. The Division of Biopharmaceutics has recommended new dissolution acceptance criteria. The Division of Bioequivalence has considered the bioequivalence study data unacceptable and has recommended a CR-Major letter. Hence, the application remains inadequate.

Chemistry Review of Amendment dated 05/02/2017

The applicant responded to the complete response letter by submitting an amendment dated 05/02/2017. In addition, the applicant provided updated stability data (36 M) for the drug product. In this amendment review, the applicant's responses are assessed and all pertinent drug substance and drug product sections are updated.

2.3. S DRUG SUBSTANCE: Adequate

S.1 No Change; Adequate per Review #1

S.2 No Change; Adequate per Review #1

S.3 No Change; Adequate per Review #1

S.4 No Change; Adequate per Review #1a

Drug substance specification: Nicotine Polacrilex

Most recent drug substance specification (*01/23/2017*)

(b) (4)

[redacted]

Retest: 12 months

S.5 No Change; Adequate per Review #1

S.6 No Change; Adequate per Review #1

S.7 No Change; Adequate per Review #1a

2.3. P DRUG PRODUCT: Inadequate

P.1 No Change; Adequate per Review #1a

P.2 No Change; Adequate per Review #1a

P.3 Adequate per Review #2

Reviewer's Assessment: Adequate

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Endorsement Block:

Chemistry Review #2
Chemist Name/Date: Chandrasekar Manoharan/ 06/19/2017
Chemistry Branch Chief Name/Date: Suhas Patankar/ 06/21/2017
Project Manager Name/Date: Adrienne Belton

Chemistry Review #1
Chemist Name/Date: Chandrasekar Manoharan/11/24/2016; 12/19/2016; 12/21/2016; 02/08/2017; 02/17/2017; 02/22/2017
Chemistry Branch Chief Name/Date: Suhas Patankar/ 12/11/2016; 12/21/2016; 02/16/2017; 02/17/2017; 2/23/2017
Project Manager Name/Date: Adrienne Belton

Chandrasekar Manoharan

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Date: 7/07/2017 12:37:28PM
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Suhas Patankar

Digitally signed by Suhas Patankar
Date: 7/11/2017 09:38:50AM
GUID: 508da70600028a4abf9ab8b19093cd0d

A. Check List

Solid IR/Oral Sol. RPN < 60 or Injection/Ophthalmic Q1/Q2 = RLD – 2 Tier	☒
First Generic – 3 Tier	☐
Other Criteria under "Exceptions List" for Table 1 of SOP – 3 Tier	☐

B. Approvability: – ***No, Minor Deficiency***

ANDA 207868

Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg, Mint

PLD Acquisitions LLC, DBA Avema Pharma Solutions

Chandrasekar Manoharan
Division of Immediate Release Products II
Office of Lifecycle Drug Products

Table of Contents

Chemistry Review Data Sheet

1. **ANDA:** 207868

2. **REVIEW #:** 1a

3. **REVIEW DATE:** 11/24/2016; 02/08/2017

4. **REVIEWER:** Chandrasekar Manoharan

5. **PREVIOUS DOCUMENTS:**

Previous Document(s)	Document Date
N/A	

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
New ANDA (Original) - 1	06/19/2014
Quality Response to Information Request	09/17/2015
Resubmission to RTR*	12/02/2015
Quality/Response to information request†	01/23/2017
Correspondence@	01/26/2017

*** ANDA was RTR on 09/29/2015.**
† Information request #1, dated 12/21/2016.
@ Submission only has verification statement in regards to 81 FR 69580.

7. **NAME & ADDRESS OF APPLICANT:**

Name:	PLD Acquisitions LLC, DBA Avema Pharma Solutions
Address:	10400 29th Terrace, Miami, FL 33172 USA
Representative:	Mehul Govani mgovani@pldevelopments.com
Telephone:	(b) (4)

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: None

Non-Proprietary Name (USAN): Nicotine Polacrilex Mini Lozenge

9. LEGAL BASIS FOR SUBMISSION:

The legal basis for submission of this ANDA is the reference listed drug (RLD), Nicorette® (Nicotine Polacrilex) lozenges 2 mg and 4 mg, the subject NDA 022360 (approval: May 18, 2009) held by Glaxosmithkline Consumer Healthcare as listed in the Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. As shown below, the RLD has two patents listed in the Orange Book and both patents claim the drug product. There is no unexpired exclusivity for this product in the Orange Book database. The applicant has provided Paragraph IV Certification.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N022360	001	8501164	Jun 14, 2029		Y		
N022360	001	8940772	Apr 30, 2029		Y		

10. PHARMACOL. CATEGORY: Smoking cessation adjunct

11. DOSAGE FORM: Lozenge, Mini

12. STRENGTH/POTENCY: 2 mg and 4 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:

☐ Rx ☒ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed ☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed ☒ Not a NANO product

15c. PRECEDENT:

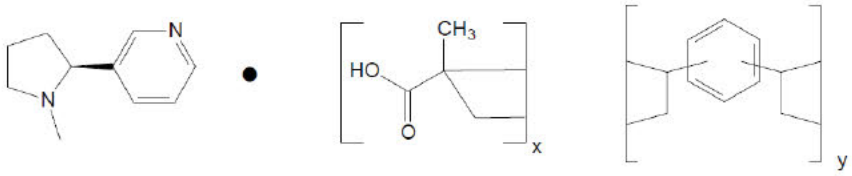
☐ The review of this ANDA establishes a precedent – TL concurrence

☒ Not a Precedent

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2-Propenoic acid, 2-methyl-, polymer with diethenylbenzene, compound with 3-[(2S)-1-methyl-2-pyrrolidinyl] pyridine.

Structural Formula:



Nicotine Polacrilex

Molecular Formula: $C_{10}H_{14}N_2 (C_4H_6O_2)_x (C_{10}H_{10})_y$

Molecular Weight: 162.23 + 86x +130y

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s):

DMF #	Type	HOLDER	ITEM REFERENCED	STATUS [1]	DATE REVIEW COMPLETED	Reviewer
(b) (4)	II	(b) (4)	Nicotine Polacrilex, 15%, USP	Adequate	06/22/2016	Jayani R Perera Note: Review noted NAI.
	III		(b) (4)	N/A		
	III			N/A		
	III			N/A		

[1] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 22360	Nicotine Polacrilex Mini Lozenge, 2 mg and 4 mg, Mint (Nicorette®)

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Methods Validation	N/A		
Labeling	Adequate	09/07/2016	Marshall Florence
Bioequivalence	Inadequate*	02/02/2017	Yi Zhang
Biopharmaceutics	Inadequate	01/11/2017	An-Chi Lu
Toxicology/Clinical	N/A		
EA	Categorical exclusion		
Radiopharmaceutical	N/A		
Samples Requested	Yes		

* A consult was initiated with Division of Clinical Review on 11/18/2016 by Yi Zhang. Consult was completed on 01/27/2017.

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. FACILITY INFORMATION

Overall Recommendation: Approve as of 02/17/2017			
Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
[redacted]	[redacted]	[redacted] (b) (4)	Approve 12/29/2015
			Status
			Approve 01/07/2016

Chemistry Review for ANDA 207868

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable, CR Minor.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

I Drug Substance

Nicotine Polacrilex is an official USP drug substance. Nicotine Polacrilex 15% is a white to off-white free flowing powder. (b) (4) (b) (4) Due to the resinate characteristics of the drug substance, a defined molecular mass does not exist. Nicotine Polacrilex is practically insoluble in water and insoluble to slightly soluble in most common organic solvents. However, Nicotine in its base form is miscible in water and nonpolar solvents. Nicotine Polacrilex 15% does not exhibit polymorphism and isomerism. Nicotine Polacrilex is likely to be slightly hygroscopic. Nicotine has a pKa of 8.5.

Drug substance for this ANDA application is manufactured by (b) (4) (b) (4).

II Drug Product

Nicotine Polacrilex mini lozenge (2 mg and 4 mg) is a white, uncoated, oval shaped lozenge indicated for reducing withdrawal symptoms, including nicotine craving, associated with quitting smoking. This is an OTC drug product and a monograph is not established in USP. The 2 mg and 4 mg lozenges are top engraved with 129 and 131, respectively, and the bottom is plain. Each lozenge contains Nicotine Polacrilex equivalent to 2 mg or 4 mg of Nicotine. The inactive ingredients include: mannitol, sodium stearyl fumarate, sodium bicarbonate, calcium polycarbophil, (b) (4) flavor, sodium alginate, maltodextrin, aspartame, xanthan gum, and talc.

(b) (4)

[redacted]

Maximum Daily Dose (MDD): 80 mg

	Identification Threshold (IT)	Qualification Threshold (QT)
Drug Substance	0.10%	0.15%
Drug Product	0.2%	0.25%

B. Description of How the Drug Product is Intended to be Used

Nicotine Polacrilex mini lozenges are designed to dissolve slowly in the mouth. The lozenge should not be swallowed or chewed. The lozenge should be placed in the mouth and occasionally moved from side to side. The lozenge should be allowed to dissolve slowly (about 10 minutes) and swallowing should be minimized. Not more than 5 lozenges in 6 hours or more than 20 lozenges per day should be used.

C. Initial and Updated Risk Assessment

Initial risk assessment was performed by Suhas Patankar.

(b) (4)

[redacted]

(b) (4)

*** However, the API has Low Solubility.**
Risk assessment updated by Chandrasekar Manoharan.

D. Basis for Approvability or Not-Approval Recommendation

The application is not approvable due to Minor deficiencies related to CMC.

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	N/A
Non-Proprietary Name of Drug Product	Nicotine Polacrilex Mini Lozenges, Mint
Non-Proprietary Name of Drug Substance	Nicotine Polacrilex 15% USP
Company Name	PLD Acquisitions LLC
Dosage Form	Lozenge
Strength(s)	2 mg and 4 mg
Route of Administration	Oral
Proposed Indication(s)	Reducing withdrawal symptoms, including nicotine craving, associated with quitting smoking.

2.3.S DRUG SUBSTANCE [Nicotine Polacrilex 15% USP]

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Information Provided: Refer to Item 16 above.

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

Information Provided:

Physical Description: Nicotine Polacrilex 15% is a white to off-white free flowing powder.

Solubility: The Nicotine Polacrilex is practically insoluble in water and insoluble to slightly soluble in most common organic solvents. However, Nicotine in its base form is miscible in water and nonpolar solvents.

pKa: Nicotine pKa is 8.5.

Polymorphism: Nicotine Polacrilex 15% does not exhibit polymorphism.

Isomerism: Nicotine is the only component of concern with regards to isomerism of Nicotine Polacrilex. (b) (4)

(b) (4)

(b) (4)

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ADMINISTRATIVE

Endorsement Block

Chemist Name/Date: Chandrasekar Manoharan/11/24/2016; 12/19/2016; 12/21/2016; 02/08/2017; 02/17/2017; 02/22/2017
Chemistry Branch Chief Name/Date: Suhas Patankar/ 12/11/2016; 12/21/2016; 02/16/2017; 02/17/2017; 2/23/2017
Project Manager Name/Date:

TYPE OF LETTER: Minor Deficiency; CR letter

Suhas Patankar

Digitally signed by Suhas Patankar
Date: 2/23/2017 02:01:50PM
GUID: 508da70600028a4abf9ab8b19093cd0d

Chandrasekar Manoharan

Digitally signed by Chandrasekar Manoharan
Date: 2/23/2017 11:09:51AM
GUID: 567431f7006e1e99507d87ad28722781

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207868

BIOEQUIVALENCE REVIEW(s)

BIOPHARMACEUTICS

Product Background:

ANDA: 207868-ORIG-1-AMEND-21 (Resubmission after CR)

Drug Product Name / Strength: Nicotine Polacrilex Mini Lozenges/ 2 mg and 4 mg

Route of Administration: Oral

Applicant Name: PLD Acquisitions LLC, D/B/A Avema Pharma Solutions

Review Recommendation: Adequate

Approved Dissolution Method:

Parameter	Value
Medium	pH7.4 phosphate buffer, USP
Volume	900 mL
Temperature	37 ± 0.5 °C
Apparatus	Apparatus 1 (Basket)
Rotational Speed	100 rpm
Time Point	30, 60, 90, 120 and 180 minutes
Sample Volume	1.5 mL

Approved Dissolution Acceptance Criteria for nicotine polacrilex mini lozenges, 2 & 4 mg:

Time, min	Acceptance Range, %
30 min	(b) (4) %
60 min	%
180 min	NLT (b) (4) %

Introduction:

The original ANDA, submitted on 12/2/2015, and associated amendments, were CR'd on 2/24/2017, 7/14/2017, and 10/25/2018. The original submission and subsequent amendments were reviewed by Dr. An-Chi Lu (2/17/2017, 2/26/2017) and Dr. Tien Mien Chen (10/16/2018).

This review is an assessment of the Applicant's response to the Biopharmaceutics CR comments in the action letter dated 10/25/2018.

List of Submissions reviewed:

Application 207868 - Sequence 0020 - 0020 (21) 11/09/2018 ORIG-1 /Multiple Categories/Subcategories

Highlight of Key Outstanding Issues from the Last Review Cycle:

The following Biopharmaceutics deficiency comments were included in the CR letter dated 10/25/2018:

Your newly proposed dissolution acceptance criteria are not acceptable from the Division of Biopharmaceutics perspective due to:

a. Incomplete dissolution profile data submitted.

b. According to the IVIVC guidance, without an established IVIVC study, the proposed dissolution acceptance criteria would be set with a range for the mean +/- 12.5% (from the mean).
https://www.fda.gov/downloads/drugs/guidances/ucm070239.pdf

In the future filing of this Application, submit complete dissolution profile data (raw, mean +/- SD; n=12/lot, and mean profile/lot), with the proposed dissolution acceptance criteria for both the 4 and 2 mg strengths including the complete lot information (lot No. and date, site, size. of the lot manufactured). Include in your submission, rationale and justification supporting your newly proposed dissolution acceptance criteria to the Agency for review; you may also revert to the previous acceptance criteria agreed to between FDA and your firm.

Applicant's Response:

The Applicant provided rationale, based on results from three bioequivalence studies that were conducted with one pilot batch and two bio batches with differing dissolution profiles, for an acceptance range of (b) (4) % at 30 and 60 min. The Applicant's new proposed dissolution acceptance criteria are:

Time in minutes	Proposed Acceptance Criteria (b) (4) %) Release
30	Between (b) (4) %
60	Between %
180	Not less tha (b) (4) %

Details of the Applicant's response can be found at \\cdsesub1\evsprod\anda207868\0020\m1\us\1-2-cover-letters\cover-letter-0020-11092018.pdf.

The tabular summary of the dissolution and bioequivalence data submitted by the Applicant are:

Studies		Results			Dissolution Mean (Apparatus I)		
Study No.	Lot No.	Parameter	Ratio	90% CI	30 min	60 min	180 min
AJ-1401	BM033298	AUC_{0-t} AUC_{0-inf} C_{max}	97.33 97.24 93.70	90.39 – 104.81 89.76 - 105.34 85.31 – 102.91	34	62	99
AJ-1403	BM033299	AUC_{0-t} AUC_{0-inf} C_{max}	92.18 92.23 100.03	84.80 – 100.20 84.66 – 100.47 93.95 – 106.50	29	49	99
11879301	CM097374	AUC_{0-t} AUC_{0-inf} C_{max}	92.82 94.02 90.85	88.56 – 97.28 89.54 – 98.73 85.98 – 96.00	23	44	99

Reviewer's Assessment:

The Applicant's rationale for the proposed (b) (4)% dissolution acceptance range at 30 and 60 min is acceptable.

Concise Description of Outstanding Issues: None.

Conclusion and Review Recommendation:

The Division of Biopharmaceutics finds the Applicant's response to the CR comments acceptable; ANDA 207868 is therefore ADEQUATE and recommended for approval.

Biopharmaceutics Reviewer:
Okpo Eradiri.
Branch Chief, Division of Biopharmaceutics II
ONDP/OPQ

Okponanabofa Eradiri

Digitally signed by Okponanabofa Eradiri
Date: 1/25/2019 01:33:45PM
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DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	207868	
Drug Product Name	Nicotine Polacrilex Mini Lozenges	
Strength(s)	EQ 2 mg Base and EQ 4 mg Base*	
Applicant Name	PLD Acquisitions LLC, D/B/A Avema Pharma Solutions	
Applicant Address	10400 NW 29th Terrace Miami, FL 33172 USA	
Applicant's Point of Contact	Mehul Govani mgovani@pldevelopments.com	
Contact's Telephone Number	(b) (4)	
Contact's Fax Number	(516) 272-8203	
Original Submission Date(s)	12/02/2015 (Resubmission/After Refuse to Receive) *[06/19/2014 (Subject to a refuse to receive)]***	
Submission Date(s) of Amendment(s) Under Review	04/30/2018 (Supp. Document #17) Resubmission/After Action-Complete; Quality/Quality Information; Bioequivalence/Other. 09/17/2018 (Supp. Document #18) Bioequivalence/Response to Information Request.	
Primary Assessor	Yi Zhang, Ph.D.	
Secondary Assessor	Li Gong, Ph.D.	
Study Number (s)	AJ-1403	AJ-1401
Study Type (s)	Pivotal Fasting Study (Original)	Pilot Fasting Study
Strength (s)	1 x 4 mg	1 x 4 mg
Clinical Site	Phase One Solutions, Inc.	
Clinical Site Address	1405 NW 167th Street Miami Gardens, FL 33169 USA Phone: (305) 624-9191	
Analytical Site	(b) (4)	
Analytical Site Address		
Study Number (s)	11879301	
Study Type (s)	Pivotal Fasting Study (***Current***)	
Strength (s)	1 x 4 mg	
Clinical Site	Novum Pharmaceutical Research Services	
Clinical Site Address	3760 Pecos McLeod	

	Las Vegas, NV 89121 USA Tel: 702-435-3739 Fax: 702-435-7249
Analytical Site	(b) (4)
Analytical Site Address	

OSIS status	**Backlog, Year 1 and Year 2 ANDAs** ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent)	**Post October 1, 2014 ANDAs** ☐ Pending ☒ Complete ☐ For Cause Inspection ☐ N/A (Waiver/Deem Bioequivalent)
Waiver/Deem Bioequivalent	☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A	
QC Dissolution	☐ Pending ☒ Adequate ☐ Inadequate	
Formulation	☒ Adequate ☐ Inadequate	
Will Response to CR Result in a Reformulation?	☐ Possibly ☒ No ☐ N/A	
Deficiency Classification	☐ Major (Deficiencies to be communicated by CR) ☐ Minor ☒ N/A (Review is Adequate)	
Overall Review Result	☒ Adequate ☐ Inadequate	
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: *Recommended Jan2011and revised Sep 2018*[1] RLD Number: NDA 022360 ☐ N/A	
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO	

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1, 2, 3, 8 & 17, 18	Pivotal BE Study	4 mg	ADEQUATE
3	Pilot BE Study	4 mg	ADEQUATE
1, 2, 3, 8 & 17, 18	Deem BE/Waiver	2 mg	ADEQUATE

[1] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240974.pdf

Note:
* Each Lozenge containing Nicotine Polacrilex equivalent to Nicotine Base 2 mg and 4 mg, respectively. Throughout the current review the 2 mg and 4 mg strength refer to EQ amount of the Nicotine Base.

**This application was originally filed on 06/19/2014 as ANDA 207868. On 09/29/2015, a refuse to receive letter was issued due to several reasons including but not limited to incomplete information[2]. The firm responded to the deficiencies in the filing review, and resubmitted the current application on 12/02/2015 with the same ANDA number.

[2] DARRTS ANDA 207868: COR-ANDAFILE-03(Refuse to Receive); BENSON, JASON A; Submit/Final Date: 09/29/2015.

Review of an Amendment

I. Executive Summary

This is a review of bioequivalence (BE) portion of the firm's post-Complete Response (CR) response dated 04/30/2018 (Supporting document #17)[3] in response to the Agency's CR Letter dated 07/14/2017[4].

Per the original BE review[5], BE amendment review[6], and subsequent post-CR meeting request responses[7,8], the firm's pivotal (#AJ-1403) and pilot (#AJ-1401) BE studies are NOT acceptable due to the violation of the reserve sample regulations as require by 21 CFR 320.38 and 320.63 at the clinical site, Phase One Solutions, Inc. The retained samples of the investigational products used for the original BE studies have been destroyed. Hence, the authenticity of the test and reference drug products cannot be confirmed due to the lack of reserve samples. Thus, the firm was asked to repeat the pivotal fasting BE study using unexpired batches of the test and reference products.

In the current amendment dated 04/30/2018, the firm submitted a new pivotal *in vivo* BE study (#11879301) conducted on the new test bio-batch (#CM097374/RD039-24), comparing it to the new/unexpired corresponding RLD batch (#15376). The new pivotal BE study was also designed as a single-dose, two-way crossover study in healthy male and female subjects (smokers). Due to the subject recruitment of "current smokers", in addition to the BE results based on the original/uncorrected plasma nicotine data submitted, the Division of Bioequivalence III (DBIII) sent a BE Information Request (IR) on 09/13/2018, and the firm re-conducted pharmacokinetic (PK) and statistical analyses using baseline-corrected nicotine data in response to the said IR on 09/17/2018. The reviewer's verified results of this BE study are summarized in the tables below.

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[3] DARRTS, ANDA 207868, Resubmission/After Action- Complete; Quality/Quality Information; Bioequivalence/Other (Supp. Document #17); Submit/Final Date: 04/30/2018.

[4] GDRP/Panorama, ANDA 207868: COR-ANDAACTION (Complete Response; BENSON, JASON A); Submitted/Final Date: 07/14/2017.

[5] GDRP/Panorama, ANDA 207868 (ANDA-207868-ORIG-1-RESUB-3): Bioequivalence Discipline Review (Bioequivalence Primary Review: A207868N000DB_N12022015.docx); Last Update: 02/18/2017. http://panorama.fda.gov/task/view?ID=566154ac0141beee6e16a23c11cb43fa.

[6] GDRP/Panorama, ANDA 207868 (ANDA-207868-ORIG-1-AMEND-11): Bioequivalence Discipline Review (Bioequivalence Primary Review: A207868N000DB_NA05022017.docx); Last Update: 06/13/2017. http://panorama.fda.gov/task/view?ID=590cc9b8005b538a64f58ba9363ebbca.

[7] GDRP/Panorama for ANDA 207868 (ANDA-207868-GI-1-MEETING-12): Post-CR Meeting Request (Written Response: A207868N000DB-Response01-PostCRMR07282017.docx); Date: 09/29/2017. http://panorama.fda.gov/project/view?ID=597f83a2003f9fd70833fc2f96fd3f1c.

[8] GDRP/Panorama for ANDA 207868 (ANDA-207868-GI-1-MEETING-12; FDA Correspondence - Project for ANDA 207868): Post-CR Meeting Request/Amendment (Written Response: A207868N000DB-Response01-PostCRMRAmend10192017.docx); Date: 01/19/2018. http://panorama.fda.gov/project/view?ID=5a37e28700096049a910fb2d6b60ed0e.

Summary of Statistical Analysis - Reviewer Calculated

Nicotine Polacrilex Mini Lozenges 4 mg Dose (1 × 4 mg), N=40 (Male & Female; Completed) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Pivotal Bioequivalence Study (Study No. 11879301)					
Baseline Corrected Nicotine (n=40)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	46.36	49.95	0.93	88.56	97.27
AUC∞ (ng·hr/mL)	49.19	52.75	0.93	88.75	97.95
Cmax (ng/mL)	11.83	13.02	0.91	85.98	96.00

The 90% CIs of the test/reference ratios for LnCmax, LnAUC0-t and LnAUC∞ fall within the acceptance range of 80.00-125.00% for baseline-corrected nicotine in this pivotal BE study (Please see *Section V.1.1.1* of this review for details). Therefore, the firm's new pivotal BE study (#11879301) is **adequate**.

In addition, in the current amendment, the firm also submitted new comparative dissolution data from corresponding new 4 mg bio-batch of test (#CM097374/RD039-24) and RLD (#15376) products using both original USP Apparatus I (Basket) and USP Apparatus III (reciprocating cylinders; current FDA-recommended method). Based on the original and new dissolution data submitted, the dissolution testing is considered **acceptable** with respect to supporting the waiver request for the 2 mg strength of the test product. The test formulations remain **adequate**.

Therefore, the DBIII grants the waiver request of *in vivo* BE study requirement for the lower strength, EQ 2 mg Base, based on criteria set forth in 21 CFR § 320.22 (d) (2).

Office of Study Integrity and Surveillance (OSIS)

As per the memorandums provided by the Division of Generic Drug Bioequivalence Evaluation (DGDBE), for both clinical site (Novum Pharmaceutical Research Services)[9] and analytical site [redacted (b) (4)][10], OSIS recommends accepting data without on-site inspection for both sites due to the recent inspection outcome of "No Action Indicated (NAI)". In addition, the study submitted in the current ANDA does not indicate

[9] GDRP/Panorama, ANDA-207868-ORIG-1-AMEND-17, Clinical PK/PD Sites: Decline to Inspect_A207868_NovumLasVegas_Clin.pdf, added by Nicola fenty-Stewart on 6/6/2018 (http://panorama.fda.gov/task/view?ID=5aeb2b9800742e373ba0baeabcd2af84).

[redacted (b) (4)]

any conduct issues and no data integrity deficiencies were identified by the reviewer. Thus, the OSIS inspection status for the current ANDA is **complete** (Please see *Section F* for details).

As a result, the application is **adequate** with no deficiencies.

II. Table of Contents

III. Background Information

1. On 12/02/2015, the firm, PLD Acquisitions LLC, originally submitted ANDA 207868 containing a pivotal fasting BE study (#AJ-1403) comparing a test product, Nicotine Polacrilex Mini Lozenges, EQ 4 mg base, to the corresponding reference product, GlaxoSmithKline Consumer Healthcare's Nicorette® (nicotine polacrilex) Mini Lozenge, EQ 4 mg base [NDA 022360, approved on 05/18/2009; Over-the-Counter (OTC)]. The application also contains a waiver request for the EQ 2 mg base strength. The pivotal BE study was designed as randomized, single-dose, two-way crossover study in healthy male and female subjects. The determination of BE was based on the 90% confidence interval (CI) of plasma nicotine data. The results are summarized in the tables below (calculated by the firm).

Nicotine Polacrilex Mini Lozenges Dose (1 × 4 mg), N=26 (Male=20 and Female=6; Completed) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study (Study No. AJ1403)					
Nicotine					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	34.7	37.9	91.56	84.50	99.21
AUC∞ (ng·hr/mL)	37.8	41.1	91.92	84.66	99.81
Cmax (ng/mL)	8.30	8.42	98.60	92.33	105.30
Baseline Corrected Nicotine					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	32.3	35.0	92.18	84.80	100.20
AUC∞ (ng·hr/mL)	35.1	38.0	92.23	84.66	100.47
Cmax (ng/mL)	7.87	7.87	100.03	93.95	106.50

Per the original BE review, the firm's pivotal BE study was adequate. The formulations of the test product were also considered adequate as per the firm's ECD response (Supp. Document #8; 10/26/2016), and a safety consult response from the Division of Clinical Review (DCR) dated 01/30/2017 for the evaluation of safety concern and clinical significance due to the (b) (4) of three excipients, Sodium Stearyl Fumarate, Maltodextrin, and Talc (b) (4) respectively).

In addition to the pivotal study, the firm also conducted a three-way crossover pilot fasting study (#AJ-1401), with two investigational test formulations against the RLD product. However, the firm did not provide the detailed formulations and other related information for this pilot study (Please see Section 4.5.1 of the original BE review

for details). The firm was asked to submit all related eCTD-formatted BE data summary tables and detailed information of adverse events (AEs).

Also, for the clinical site, as per the review of Clinical Establishment Inspection Report (EIR), although clinical site was closed for the business in 2015, clinical study records from this site were audited for [redacted] (b) (4) during the OSIS inspection, and an FDA Form-483 was issued with four inspectional findings. The inspection was completed on 02/10/2017 with an outcome classified as "*Voluntary Action Indicated (VAI)*". Based on the EIR review and BE evaluation, the OSIS finding #1 was considered systemically objectionable. The firm was requested to address this inspectional finding #1 for its impact on the *in vivo* BE studies of the current application (please see Section 4.4 of the original BE review for details).

The BE deficiencies were communicated to the firm in the Agency's CR Letter dated 02/24/2017.

2. In the subsequent BE amendment dated 05/02/2017 (Supporting document #11), the firm addressed the above deficiency by providing additional information/data for the pilot fasting study (# AJ-1401) as requested. Based on the information/data submitted, the firm's pilot fasting study was considered adequate (complete).

   However, for the clinical site, based on the information provided in this amendment, the retained samples of the investigational products had been destroyed. The clinical site, Phase One Solutions, Inc., did not retain reserve samples appropriately as require by 21 CFR 320.38 and 320.63. Hence, the authenticity of the test and reference drug products used in the pivotal (AJ-1403) and pilot (AJ-1401) BE studies cannot be confirmed due to lack of reserve samples. Consequently the original BE studies are NOT acceptable since the reliability of data is impaired by the violation of the reserve sample regulations. Thus, the following BE deficiency was communicated to the firm in a second CR Letter dated 07/14/2017:

   Deficiency Related to the OSIS Inspection

   As per 21 CFR 320.38 and 320.63, "The applicant of an abbreviated application or a supplemental application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act, or, if bioequivalence testing was performed under contract, the contract research organization shall retain reserve samples of any test article and reference standard used in conducting an in vivo or in vitro bioequivalence study required for approval of the abbreviated application or supplemental application. The applicant or contract research organization shall retain the reserve samples in accordance with, and for the period specified in, 320.38 and shall release the reserve samples to FDA upon request in accordance with 320.38". In the absence of reserve samples at the study site or an independent third party, the

authenticity of test and reference drug products used in studies cannot be ensured.

Based upon the information you provided in the current post-complete response (CR) amendment (dated 05/02/2017), the clinical site, Phase One Solutions, Inc., did not retain reserve samples properly of the investigational products used in the related bioequivalence (BE) studies for the current ANDA as require by 21 CFR 320.38 and 320.63, as you stated that "During the week of 02/20/17 we were informed by Phase One over the phone that ***the retain samples which were stored at the temporary location were destroyed****"; and that you were "not informed about this and you were not provided with a certificate of destruction." Therefore, the authenticity of the test and reference drug products used in your pivotal (Study No. AJ-1403) and pilot (Study No. AJ-1401) BE studies cannot be confirmed due to lack of reserve samples. As a result, the in vivo BE study data from the current studies, #AJ-1403 and #AJ-1401, are* ***not*** *acceptable since the reliability of data has been impaired by the violation of reserve sample regulations.*

3. On 07/28/2017, the firm submitted a post-CR meeting request to the Office of Generic Drugs (OGD) to seek Agency's reconsideration of the above deficiency identified in the CR letter regarding the violation of reserve sample regulations. With DBIII's re-evaluation, a written response was granted on 09/29/2017 to respond to the firm's meeting request briefly as below:

   You failed to meet the regulatory requirements for the CRO to reserve samples [21 CFR 320.38 and 320.63] for in vivo BE studies; Please be advised to repeat your pivotal fasting BE study using unexpired batches of the test and reference products.

   Also, as requested by the Office of Generic Drug Policy (OGDP), additional deficiencies/details were communicated to the firm dated 10/12/2017 (as a supplemental letter to the above mentioned Post-CR MR written response) as follows:

   For PLD site/in-house samples (As requested by the OGDP): You did not provide
   - *(1) SOPs for in-house sample retention and storage;*
   - *(2) Complete on-site inventory records for both test and reference to allow for reconciliation and accountability of the drug products.*

   For CRO site (POS): You did not provide
   - *(1) Drug inventory or accountability of both test and reference;*
   - *(2) Record of transferring reserved samples from the CRO site to the temporarily stored facility;*
   - *(3) Record for the disposal/destruction of reserved samples, such as numbers of unit of drugs being destroyed.*

4. In the subsequent Amendment to Post-CR Meeting Request dated 10/19/2017, the firm responded to the deficiencies related to PLD site (in-house sample retention & storage), and provided (1) "*RLD and test usage documentation*" demonstrating the same batches of test and reference products were reserved at the PLD site; and (2) "*SOPs and quality policies*" indicating the in-house samples were stored at well-controlled conditions. However, the firm still did not provide complete documentation requested for the CRO site. Moreover, the retained samples and the submitted SOPs at PLD site (i.e. manufacturing site) were not considered a portion of the samples tested for the BE studies because the *in vivo* BE studies were conducted at the CRO site. And the chain of custody was also broken at the CRO site due to the lack of complete documentation mentioned above.

   Furthermore, an OB-OGDP internal meeting was held on 12/11/2017 to discuss the issue of sample retention for the current ANDA 207868 (meeting minutes[11]). The following BE deficiency was communicated to the firm as a conclusion dated 01/25/2018[12].

   > *As we previously communicated to you in our Complete Response (CR) Letter dated 07/14/2017 and our Post-CR Meeting Request Written Response dated 09/29/2017, your in vivo pivotal (Study No. AJ-1403) and pilot (Study No. AJ-1401) BE studies were both conducted at the CRO clinical site. To deter possible bias and fraud in the studies and to assure that the reserved samples be a portion of the samples used in the BE studies, the storage conditions well-controlled, and the chain of custody unbroken, as per 21 CFR 320.38 and 320.63, the reserve samples should be retained and stored at a study site, or at an independent third party site. However, you failed to meet the regulatory requirements for the CRO to retain such samples for your current application, ANDA 207868, and the reserved samples have been destroyed at the CRO site. Therefore, the authenticity of the test and reference drug products used in your BE studies cannot be assured.*
   >
   > *Please be advised to repeat your pivotal fasting BE study using unexpired batches of the test and reference products. Please refer to draft guidance on Nicotine Polacrilex Lozenge for details (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240974.pdf; Recommended Jan 2011). Please note that sufficient quantities of the drug products used in the study should be retained as per FDA Guidance for Industry: Handling and Retention of BA*

[11] Meeting Minutes: GDRP/Panorama, FDA Correspondence - Project; Final Date 01/19/2018; http://panorama.fda.gov/task/view?ID=5a37e28700096069a6c2bbddb80c2ea2.

[12] GDRP/Panorama for ANDA 207868 (FDA Correspondence - Project for ANDA 207868): Post-CR Meeting Request/Amendment (A207868N000DPM-DBResponse-PostCRMRAmend10192017.pdf); Final Date: 01/25/2018. http://panorama.fda.gov/project/view?ID=5a37e28700096049a910fb2d6b60ed0e.

and BE Testing Samples (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf; May 2004).

5. In the current amendment dated 04/30/2018 (DARRTS Supporting document #17), the firm responded to the above BE deficiency and conducted a new pivotal *in vivo* BE study (#11879301).

IV. Submission Summary

A. Drug Product Information, PK/PD Information, and Relevant DB History

The PK/PD information and relevant DB history have not been updated since the original and post-CR amendment BE reviews below were conducted. [13, 14]

Please refer to GDRP/Panorama for ANDA 207868:

- ANDA-207868-ORIG-1-RESUB-3: Bioequivalence Discipline Review (Original) (A207868N000DB_N12022015.docx; Yi Zhang); Date Uploaded: 02/18/2017. [15]
- ANDA-207868-ORIG-1-AMEND-11: Bioequivalence Discipline Review (Post-CR Amendment) (A207868N000DB_NA05022017.docx; Yi Zhang); Date Uploaded: 06/13/2017.[16]

Please note that the drug product-specific BE guidance (PSG) for a similar drug product, Nicorette® (Nicotine Polacrilex) Oral Troche/Lozenge by GlaxoSmithKline Consumer Healthcare [NDA 021330, approved on 10/31/2002; Over the Counter (OTC)][17] (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM533399.pdf; *Recommended Dec. 2016 and revised Sep 2018*) is currently published as of the current BE assessment. The PSG revision changed waiver requirements for other flavors to in line with the current OGD policy and practice, permitting applicants to submit the test products with different flavors in a single ANDA (rather than separate submissions), as follows:

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[13] Electronic Orange Book (Updated Through 07/2018): https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=022360, last assessed: 09/10/2018.

[14] Labeling and clinical pharmacology (online database): for Nicorette®, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=991704ed-781a-489b-8b56-0b558e8fc385 (Updated: 05/22/2018); last assessed 09/10/2018.

[15] GDRP/Panorama, ANDA 207868 (ANDA-207868-ORIG-1-RESUB-3): Bioequivalence Discipline Review (Bioequivalence Primary Review: A207868N000DB_N12022015.docx); Last Update: 02/18/2017. http://panorama.fda.gov/task/view?ID=566154ac0141beee6e16a23c11cb43fa.

[16] GDRP/Panorama, ANDA 207868 (ANDA-207868-ORIG-1-AMEND-11): Bioequivalence Discipline Review (Bioequivalence Primary Review: A207868N000DB_NA05022017.docx); Last Update: 06/13/2017. http://panorama.fda.gov/task/view?ID=590cc9b8005b538a64f58ba9363ebbca.

[17] Electronic Orange Book (Updated Through 07/2018): https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021330#, last assessed: 09/20/2018.

Remove "Please refer to the Mirtazapine Tablet Guidance for additional information regarding waivers of in-vivo testing." and "Lozenges with alternate flavors cannot be filed in the same ANDA as the mint flavored lozenge. For each flavor, a separate submission (ANDA) should be submitted." from the section of Waiver request of in vivo testing. Also, make minor edits to the waiver eligibility criteria for Lozenges with alternate flavors.

The revision of the PSG would not have any impact on the current application, since a BE study was conducted.

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	-
Steady-state	No	-
In vitro dissolution	Yes	1
Waiver requests	Yes	1
BCS Waivers	No	-
Vasoconstrictor Studies	No	-
Clinical Endpoints	No	-
Failed Studies	No	-
Adverse Event Individual Case Safety Report	No	-
Amendments	Yes	1

C. Review of Amendment Submissions

Deficiency Related to the Office of Study Integrity and Surveillance (OSIS) Inspection

As per 21 CFR 320.38 and 320.63, "The applicant of an abbreviated application or a supplemental application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act, or, if bioequivalence testing was performed under contract, the contract research organization shall retain reserve samples of any test article and reference standard used in conducting an in vivo or in vitro bioequivalence study required for approval of the abbreviated application or supplemental application. The applicant or contract research organization shall retain the reserve samples in accordance with, and for the period specified in, 320.38 and shall release the reserve samples to FDA upon request in accordance with 320.38". In the absence of reserve samples at the study site or an independent third party, the authenticity of test and reference drug products used in studies cannot be ensured.

Based upon the information you provided in the current post-complete response (CR) amendment (dated 05/02/2017), the clinical site, Phase One Solutions, Inc., did not retain reserve samples properly of the investigational products used in the related bioequivalence (BE) studies for the current ANDA as require by 21 CFR 320.38 and 320.63, as you stated that "During the week of 02/20/17 we were informed by Phase One over the phone that ***the retain samples which were stored at the temporary location were destroyed****"; and that you were "not informed about this and you were not provided with a certificate of destruction." Therefore, the authenticity of the test and reference drug products used in your pivotal (Study No. AJ-1403) and pilot (Study No. AJ-1401) BE studies cannot be confirmed due to lack of reserve samples. As a result, the in vivo BE study data from the current studies, #AJ-1403 and #AJ-1401, are* ***not*** *acceptable since the reliability of data has been impaired by the violation of reserve sample regulations.*

Firm's Response to BE Deficiency:

PLD Acquisitions LLC D/B/A Avema Pharma Solutions repeated the bioequivalence study using unexpired batches of test and reference product and the test product meets the bioequivalence requirements. New batch of the test product was manufactured for repeating this pivotal fasting BE study. The study number is 11879301/Protocol No. PLDA000218.

All documents pertaining to the bioequivalence study have been provided in Module 5 of this submission and the summaries are provided in Module 2.

Reviewer's Comments on Firm's Response to BE Deficiency:

- The firm's response to the BE deficiency mentioned above is adequate. Please see sections below for the detailed review of newly submitted pivotal BE study (Study No. 11879301).

D. Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Analytical Report P18012_EBG, Appendix II, Page 46
Analyte	Nicotine
Internal standard (IS)	Nicotine-d4
Method description	(b) (4) [redacted]

Limit of quantitation	0.200 ng/mL
Average recovery of drug (%)	QC A: 100.7%, QC B: 100.5%, QC C: 100.1%
Average recovery of IS (%)	96.2%
Standard curve concentrations (units/mL)	0.200 to 15.0 ng/mL
QC concentrations (units/mL)	LLOQ: 0.200 ng/mL, QC A: 0.600 ng/mL, QC B: 4.50 ng/mL, QC C: 12.0 ng/mL, QC ULOQ: 15.0 ng/mL
QC Intraday precision range (%)	2.9% to 9.0%
QC Intraday accuracy range (%)	100.7% to 114.0%
QC Interday precision range (%)	3.5% to 9.6% (43.1%[1])
QC Interday accuracy range (%)	100.0% to 107.0% (116.0%[1])
Bench-top stability (hrs)	23.7 hours at RT°
Stock stability (days)	27 days, 23 days and 21 days at concentrations of 1.00 mg/mL, 100 ng/mL and 20.0 ng/mL, respectively, when stored at -20±10°C in methanol. 491 days and 21 days at concentrations of 100 mcg/mL and 4.00 mcg/mL, respectively, when stored at -20±10°C in acetonitrile for Nicotine-d4
Processed stability (hrs)	83.7 hours at RT°
Freeze-thaw stability (cycles)	5 cycles -20±10°C
Long-term storage stability (days)	49 days at -20±10°C
Dilution integrity	24.0 ng/mL diluted 2 fold and 4 fold 30.0 ng/mL diluted 5 fold and 10 fold
Selectivity	Selectivity cannot be demonstrated for Nicotine due to exogenous levels. However, least 90% of the donors were free of significant interference at the internal standard retention time

Note: [1]In run 09VAL458, one QC LLOQ had a concentration of 0.753 ng/mL. This run was thoroughly reviewed under investigation event EID2018-08 and the results showed that this anomalous value appears to be a processing issue for this specific sample. The run showed no other discrepancies. If the concentration is excluded from the statistics presented in Table 8 of the validation report, the %Difference at the QC LLOQ level is 7.0% with a %CV of 9.6%.

SOP for bioanalytical method validation submitted?	☒ Yes ☐ No
Is the same anticoagulant used in the pre-method validation study and BE sample analysis? **If not, was cross validation study conducted?**	☒ Yes ☐ No

Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☒ Yes ☐ No
Was the % recovery consistent across QC concentrations?	☒ Yes ☐ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☒ Yes ☐ No

Comments on the Pre-Study Method Validation:

- A sensitive and selective liquid chromatographic tandem mass spectrometric (LC-MS/MS) method was developed and validated for the quantitative analysis of nicotine in human plasma. Nicotine-D_4 was used as the internal standard.

- The firm used Dipotassium Ethylenediaminetetraacetic Acid (K_2EDTA) as an anticoagulant in the pre-study bioanalytical method validation. The same anticoagulant K_2EDTA was used in fasting BE study sample processing.

- The firm submitted the long term storage stability (LTSS) data for nicotine as 49 days at -20°C±10°C (in K_2EDTA human plasma), which exceed the maximum storage period of study samples (28 days at -20°C±10°C) for the fasting BE study.

- The average percent recovery values were consistent across the testing QC concentrations for nicotine (100.1-100.7%; %CV: 1.6%-2.9%). The average percent recovery for the internal standard, nicotine-D_4, was 96.2% (%CV: 1.4%).

- Thus, the pre-study method validation for nicotine is **adequate**.

E. In Vivo Studies

Summary of all in vivo Bioequivalence Studies (By Firm)
For Nicotine (uncorrected data)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects [No. (M/F)] Type Age: mean (Range)	Mean Parameters (±SD) (% CV)						Study Report Location
					C_{max} (mcg/mL)	T_{max} (min)*	AUC_{0-t} (mcg.min/mL)	$AUC_{0-\infty}$ (mcg min/mL)^	$t_{½}$ (min)^	λ_z (1/min)^	
Study No. 11879301 Protocol No. PLDA000218	A Study to Evaluate the Relative Bioavailability of a Test Formulation of Nicotine Polacrilex Lozenges, EQ 4 mg base (PLD Acquisitions, LLC) Compared to Nicorette® (nicotine polacrilex) Lozenges, EQ 4 mg base (GlaxoSmithKline) in Healthy Adult Subjects under Fasted Conditions	Open-Label, Single-Dose, Randomized, Two-Treatment, Two-Period, Two-Sequence, Crossover Study (Fasted)	**Test product A** Nicotine Polacrilex 4 mg Mini Lozenge PLD Acquisitions, LLC Manufacture Date: 08/01/17 Route: Oral Dose: 1 x 4 mg nicotine polacrilex mini lozenge [Lot No.: RD039-24 (CM097374)]	33 qualifying (29M/4F) Healthy subjects 42.5 ± 14.2 (19 – 71)	12.7482 ± 4.4608 (34.9919)	90.0000 (40.0000 – 120.0000)	3209.2740 ± 1690.4208 (52.6730)	3572.2281 ± 2229.7295 (62.4185)	193.2269 ± 46.6530 (24.1442)	0.0038 ± 0.0009 (23.4913	5.3.1.2: study-report-body (Page 35,36 of 65)
			Reference product B Nicorette®, Nicotine Polacrilex 4 mg Mini Lozenge Distributed By: GSK Consumer Healthcare Expiration Date: 02/2019 Route: Oral Dose: 1 x 4 mg nicotine polacrilex mini lozenge [Lot No.: 15376]		13.8445 ± 3.8814 (28.0359)	75.0000 (20.0000 – 150.000)	3440.4525 ± 1625.1927 (47.2378)	3817.8454 ± 2188.9240 (57.3340)	186.0684 ± 53.5686 (28.7897)	0.0040 ± 0.0009 (23.6022)	

For Baseline-Corrected Nicotine

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: Mean (Range)	Mean Parameters ± SD (% CV)						Study Report Location
					Cmax (ng/mL)	Tmax (min)	AUC0-t (min·ng/mL)	AUC0-∞ (min·ng/mL)	T1/2 (min)	Kel (min^{-1})	
Study No. 11879301 Protocol No. PLDA000218	A Study to Evaluate the Relative Bioavailability of a Test Formulation of Nicotine Polacrilex Lozenges, EQ 4 mg base (PLD Acquisitions, LLC) Compared to Nicorette® (nicotine polacrilex) Lozenges, EQ 4 mg base (GlaxoSmithKline) in Healthy Adult Subjects under Fasted Conditions	Open-Label, Single-Dose, Randomized, Two-Treatment, Two-Period, Two-Sequence, Crossover Study (Fasted)	**Test product A** Nicotine Polacrilex 4 mg Mini Lozenge PLD Acquisitions, LLC Manufacture Date: 08/01/17 Route: Oral Dose: 1 x 4 mg nicotine polacrilex mini lozenge [Lot No.: RD039-24]	40 eligible (36M/4F) Healthy subjects 42.7 ± 14.4 (19 - 71)	12.5768 ± 4.4156 (35.1090)	90.0000 (40.0000 – 120.0000)	3073.5014 ± 1555.8071 (50.6200)	3385.7548 ± 1950.1900 (57.5999)	165.3666 ± 47.2001 (28.5427)	0.0046 ± 0.0015 (32.2703)	5.3.1.2: study-report-body Pg 8, 13, 16
			Reference product B Nicorette®, Nicotine Polacrilex 4 mg Mini Lozenge Distributed By: GSK Consumer Healthcare Expiration Date: 02/2019 Route: Oral Dose: 1 x 4 mg nicotine polacrilex mini lozenge [Lot No.: 15376]		13.5275 ± 3.8373 (28.3662)	75.0000 (20.0000 – 150.000)	3252.1142 ± 1491.5043 (45.8626)	3543.7591 ± 1890.9669 (53.3605)	157.3003 ± 49.5046 (31.4714)	0.0048 ± 0.0015 (31.6203)	

F. OSIS Status (if applicable)

Reviewer's Comments for OSIS Inspection:

For the clinical site [Novum Pharmaceutical Research Services (3760 Pecos McLeod, Las Vegas, NV 89121, USA)], as per the memorandum provided by the Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) dated 05/22/2018[18] , "*OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI)*". Thus, OSIS recommends accepting data without on-site inspection for the current ANDA 207868.

Similarly, for the analytical site (b) (4) (b) (4) as per the memorandum provided by DGDBE within OSIS dated (b) (4)[9], "*OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI)*". Thus, OSIS recommends accepting data without on-site inspection for the current ANDA 207868.

Also, based on evaluation of the submitted data, the OSIS inspection of the clinical and analytical sites for the current ANDA 207868 is not necessary. The studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiency was identified by the reviewer.

Thus, the overall OSIS inspectional status for the current ANDA is **COMPLETE**.

[18] GDRP/Panorama, ANDA-207868-ORIG-1-AMEND-17, Clinical PK/PD Sites: Decline to Inspect_A207868_NovumLasVegas_Clin.pdf, added by Nicola fenty-Stewart on 6/6/2018 (http://panorama.fda.gov/task/view?ID=5aeb2b9800742e373ba0baeabcd2af84)

(b) (4)

V. APPENDIX

1.1 Individual Study Reviews

1.1.1 Single-dose Fasting Bioequivalence Study

1.1.1.1 Study Design

1.1.1.1.1 Study Information

Study Number	Study No. 11879301/Protocol No. PLDA000218
Study Title	A Study to Evaluate the Relative Bioavailability of a Test Formulation of Nicotine Polacrilex Lozenges, EQ 4 mg base (PLD Acquisitions, LLC) Compared to Nicorette® (nicotine polacrilex) Lozenges, EQ 4 mg base (GlaxoSmithKline) in Healthy Adult Subjects under Fasted Conditions
Clinical Site (Name & Address)	Novum Pharmaceutical Research Services 3760 Pecos McLeod Las Vegas, NV 89121 United States of America (USA) Tel: 702-435-3739 Fax: 702-435-7249
Principal Clinical Investigator	Darin B. Brimhall, D.O., FACP, CPI DBrimhall@novumprs.com
Dosing Dates	Period 1: 02/28/2018 Period 2: 03/07/2018
Analytical Site (Name & Address)	(b) (4)
Principal Analytical Investigator	
Analysis Dates	
Sample Storage : **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range (e.g., -20°C to -80°C)**	a) 28 days from first day of sample collection to last day of sample analysis b) -20±10°C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	49 days at -20±10°C

1.1.1.1.2 Product (Bio-batch) Information

Product	Test	RLD
Treatment ID	T	R
Product Name	Nicotine Polacrilex 4 mg mini lozenge	Nicorette® 4 mg mini lozenge
Manufacturer	PLD Acquisitions LLC D/B/A Avema Pharma Solutions	GlaxoSmithKline, Inc.
Batch/Lot No.	CM097374 (RD039-24)	15376
Manufacture Date	08/01/2017	
Expiration Date		02/2019
Strength	4.0 mg	4.0 mg
Dosage Form	Lozenge	Lozenge
Bio-Batch Size	(b) (4)	
Production Batch Size		
Potency (Assay)	4.0 mg	4.0 mg
Content Uniformity (expressed as mean, % CV or per USP)	100.9, 0.8%,	
Dose Administered	1 x 4 mg Nicotine Polacrilex Lozenge	1 x 4 mg Nicotine Polacrilex Lozenge
Route of Administration	Oral	Oral

Are the test and reference products expired at the time of study? If Yes, please comment.	☐ Yes ☒ No
Is same bio-batch used in the dissolution and all BE studies? If No, please comment.	☒ Yes ☐ No
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? If No, please comment.	☒ Yes ☐ No
Is difference of the potency values for the Test and RLD within 5%? If No, please comment.	☒ Yes ☐ No

1.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 42 Dosed: 42 (P I), 40 (P II) Completed: 40 Samples Analyzed: 40 Statistically Analyzed: 33 (original) 40 (baseline-corrected)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization	☒ Yes ☐ No Please see Appendix 16.1.7 for the subject randomization schedule and codes.
Blood Sampling Times	A total of twenty (20) blood samples will be collected during each period. Blood samples (6 mL) were collected in appropriately labeled blood collection tubes containing K_2EDTA as the anticoagulant within 90 minutes prior to dosing and at 10, 20, 30, 40, 50 minutes and 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0 and 12.0 hours after study drug administration in each study period.
IRB Approval	☒ Yes Date: 02/13/2018 ☐ No
Informed Consent	☒ Yes Date: 02/15/2018 ☐ No
Length of Fasting	N/A
Length of Confinement	Subjects were housed at least 36 hours before dosing and remained confined until at least 12 hours after dosing in each study period. At the scheduled dosing time, the clinical staff administered the lozenge in the subject's mouth (buccal cavity), above a rear molar tooth, between the upper cheek and gum.
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☒ Yes ☐ No ☐ N/A
Safety Monitoring	☒ Yes ☐ No

Comments on Study Design: Adequate

- As requested in the previous Agency's CR Letter dated 07/14/2017, the firm conducted a new pivotal *in vivo* BE study (Study# 11879301) on the 4 mg bio-strength, comparing the new test product (#CM097374/RD039-24) to the new/unexpired RLD product (#15376).

- The new pivotal study was designed as an open label, balanced, randomized, two-way crossover, BE study in healthy smokers, male and non-pregnant female, under

fasting condition (Per the subject inclusion criteria: current cigarette smoker who has smoked cigarettes daily for at least 1 year; Please also see *Section V.1.1.1.4*).

- A total of 42 subjects were enrolled, and all 42 subjects dosed in period I. 40 subjects were dosed in period II and 40 subjects completed both periods of the study. 2 Subjects (b) (6)) were discontinued before P2 (not because of an adverse event). For the original/uncorrected data, 7 subjects (b) (6) (b) (6)) were excluded from statistical analysis (due to the measurable pre-dose concentrations in at least one period that were greater than 5% of the measured Cmax value for that specific study period), and final PK analysis was carried out on the 33 subjects (statistical analysis is not appropriate since the pre-dose nicotine concentrations were due to the subject recruitment of consistent smoker). As requested in BE IR (dated 09/13/2018), the firm re-conducted statistical analysis using baseline-corrected nicotine concentrations, and final results were based on 40 subjects. (Please see *Section V.1.1.1.4* for details)

- Per the study protocol (Protocol # PLDA000218 (Revision 0); Date: 02/08/2018), in order to minimize the potential of any nicotine related adverse events all subjects will be current cigarette users who smoke regularly for at least 1 year before initial dosing. For 36 hours prior to each dosing and for 12 hours after dosing, subjects will not be allowed to use any tobacco- or other nicotine-containing products. At the scheduled dosing time, the clinical staff will administer the lozenge in the subject's mouth (buccal cavity), above a rear molar tooth, between the upper cheek and gum. The lozenge will be moved from one side of the mouth to the other side of the mouth every two (2) minutes (with the aid of their tongue, while keeping their mouth closed). The lozenge should be left between the cheek and gum and moved from side to side, as noted above, until it has disintegrated. If this procedure is followed, the study drug is expected to dissolve over an approximate 20-30 minute period. The subject will be instructed to minimize swallowing, to not swallow the lozenge, and to let the lozenge dissolve without splitting, chewing, or biting. No water will be given to the subject to aid in dissolving the study drug. The time complete dissolution is observed will be recorded.

- Per RLD labeling, Tmax for nicotine is about 1 hour after oral administration of lozenge, and the elimination half-life is approximately 2 hours. Therefore, the current sampling time up to 12 hours is adequate to cover the absorption, distribution and elimination phases, and continue for more than five times of the plasma half-life.

- Thus, the study design is **acceptable**.

1.1.1.2 Clinical Results

1.1.1.2.1 Demographic Profile of Subjects

Study No. 11879301/ Protocol No. PLDA000218			
		Treatment Groups	
		Test A N = 40	Reference B N = 40
Age (years)	Mean ± SD	42.7 ± 14.4	42.7 ± 14.4
	Range	19 - 71	19 - 71
Age Groups	< 18	0 (0.0%)	0 (0.0%)
	18 – 40	17 (42.5%)	17 (42.5%)
	41 – 64	22 (55.0%)	22 (55.0%)
	65 – 75	1 (2.5%)	1 (2.5%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	Male	36 (90.0%)	36 (90.0%)
	Female	4 (10.0%)	4 (10.0%)
Race	Asian	0 (0.0%)	0 (0.0%)
	Black	22 (55.0%)	22 (55.0%)
	Caucasian	11 (27.5%)	11 (27.5%)
	Hispanic	4 (10.0%)	4 (10.0%)
	Other	3 (7.5%)	3 (7.5%)
BMI (kg/m^2)	Mean ± SD	25.4 ± 2.7	25.4 ± 2.7
	Range	19.2 - 29.8	19.2 - 29.8
Other Factors			
Weight (lbs)	Mean ± SD	168.7 ± 23.9	168.7 ± 23.9
	Range	101 - 222	101 - 222
Tobacco Users*	Yes	40 (100.0%)	40 (100.0%)
	No	0 (0.0%)	0 (0.0%)

* Defined as current tobacco user (having used tobacco- or nicotine-containing products within 30 days before initial dosing)

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

1.1.1.2.2 Dropout Information

Study No. 11879301/ Protocol No. PLDA000218				
Subject No/ Treatment	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**

	(b) (6)	(b) (6) Date: 03/05/2018; Time: 15:39 Period I: Test A	Period II, Before Dosing	No	N/A
		Withdrawal by Subject Date: 03/05/2018; Time: 14:07 Period I: Test A	Period II, Before Dosing	No	N/A

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

1.1.1.2.3 Study Adverse Events

Reported Incidence by Treatment Groups Fasted Bioequivalence Study Study No. 11879301/ Protocol No. PLDA000218		
Body System/Adverse Event	**Test A (%)**	**Reference B (%)**
Gastrointestinal disorders		
Nausea	1 (2.4%)	2 (5.0%)
General disorders and administration site conditions		
Application site pain	1 (2.4%)	0 (0.0%)
Feeling hot	0 (0.0%)	1 (2.5%)
Feeling jittery	4 (9.5%)	4 (10.0%)
Investigations		
Blood pressure increased	0 (0.0%)	1 (2.5%)
Heart rate increased	0 (0.0%)	1 (2.5%)
Metabolism and nutrition disorders		
Decreased appetite	1 (2.4%)	0 (0.0%)
Nervous system disorders		
Dizziness	2 (4.8%)	1 (2.5%)
Somnolence	0 (0.0%)	1 (2.5%)
Respiratory, thoracic and mediastinal disorders		
Cough	1 (2.4%)	1 (2.5%)
Oropharyngeal pain	1 (2.4%)	0 (0.0%)
Rhinorrhoea	0 (0.0%)	1 (2.5%)
TOTAL# (%)	10 (23.8%)	11 (27.5%)

= Number of subjects reporting AE
% = (Number of subjects reporting AE / number of subjects dosed with respective study drug) x 100
Total # = Number of subjects reporting at least one AE

Total % = (Number of subjects reporting at least one AE / number of subjects dosed with respective study drug) x 100
Test product = 42 subjects dosed.
Reference product = 40 subjects dosed.

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	Test/ Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
N/A	-	-	-	-	-

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☐ No ☒ N/A
If yes, does the time of emesis exceed two times the median Tmax value (IR products) or the labeled dosing interval (MR products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

1.1.1.2.4 Protocol Deviations

Study No. 11879301/ Protocol No. PLDA000218		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Carbon Monoxide Assessment Performed Out of Window: Period 2	(b) (6)	
Consumption or Use of A Restricted Item: Period 1		
Other: Mouth Check Performed Out of Window: Period 1		

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results: Adequate

Dropouts:

- There were a total of 42 healthy, adult subjects enrolled and dosed in this study and 40 subjects completed both periods of the study. 2 Subjects (b) (6) were discontinued before P2 not because of an AE as below, which is considered acceptable.
  - Subject (b) (6) positive for substance abuse during P2 check-in and was discontinued from the study owing to this non-compliance.
  - Subject (b) (6): Withdrew consent before P2 check-in.

Adverse Events:

- Subjects were monitored throughout the fasting study for any adverse experiences. There were no deaths, SAE or significant adverse events reported in this study.

- A total of 25 AEs were reported by 16 of the 42 subjects who participated in this study. Of reported AEs, 11 occurred after administration of Test A and 14 occurred after administration of Reference B. All 25 events were considered "mild" in intensity, which were all recovered/resolved spontaneously by study completion.

- There were 3 nausea events reported but no emesis/vomiting occurred.

Protocol Deviations:

- The sampling time point deviations are summarized in Appendix 16.2.5[20]. The actual time of sample collection was used in the pharmacokinetic analysis of plasma concentration data from the concerned subjects. Therefore, no impact is foreseen on the outcome of the study.

- As per clinical study protocol[21], "*For subjects whose lozenge is not dissolved within 30 minutes….the study staff will check the subjects' mouth to confirm that the drug is yet to be dissolved.*" Subject (b) (6) had his mouth checked at 0905 (29 minutes after dosing), resulting in a 1 minute deviation from the protocol specified mouth assessment. Early mouth check has no effect on absorption of lozenge.

[20] ANDA 207868, View EDR: Appendix 16.2.5 "Blood Draw Time Deviation Table" in Module 5.3.1.2; Received Date: 04/30/2018; \\cdsesub1\evsprod\anda207868\0016\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\11879301\compliance-and-or-drug-concentration.pdf.

[21] ANDA 2078688, View EDR: Appendix 16.1.1 "Protocol or Amendment" in Module 5.3.1.2; Received Date: 04/30/2018; \\cdsesub1\evsprod\anda207868\0016\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\11879301\protocol-or-amendment.pdf.

- Subject [redacted] reported taking a vitamin containing garlic and vitamin B approximately 75 hours before Period II dosing and Subject 3030 took a single dose of Dayquil (15 mL) to relieve cough approximately 64 hours before dosing in Period II. Both of these concomitant medications were expected to be completely metabolized and eliminated before Period II dosing. Therefore, no impact was expected on the study outcome.

- Per study protocol 6.4.4, "*Within 2 hours before dosing and at 2, 6, and 10 hours (± 30 minutes) after dosing, the subjects will be required to perform a breath carbon monoxide test using a validated system.*" Prior to Period II dosing, multiple subjects ([redacted] had their individual carbon monoxide (CO) breath test performed slightly outside of the scheduled pre-dose time, from a minimum of 1 minute to a maximum of 14 minutes. All subjects tested within "non-smoker" limits and the deviation of up to 14 minutes did not compromise the continuation of any subjects in the study, did not have any effect on the integrity of the study.

- Therefore, the listed protocol deviations did not have any significant impact on the outcome of the study.

Thus, the firm's handling of "Dropouts/Adverse Events/Protocol Deviations" is **adequate**.

1.1.1.3 Bioanalytical Results

1.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
[redacted] (b) (4)		Coding of Study Samples, Calibration Standards and Quality Control Samples, Selection of Repeats and Data Reporting
		Preparation of Standards, Quality Control Samples and Their Acceptance Criteria for Analytical Runs
		Incurred Sample Reanalysis

All necessary SOPs submitted?	☒ Yes ☐ No

1.1.1.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. 11879301 Nicotine									
Parameter	**Standard Curve Samples**								
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**
Concentration (ng/mL)	0.200	0.400	1.00	1.50	3.00	6.00	9.00	13.5	15.0
Inter day Precision (%CV)	3.4	4.0	2.6	2.3	2.8	2.5	1.3	1.2	1.1
Inter day Accuracy (%Bias)	3.0	-0.5	-0.4	-0.7	-2.0	0.7	-0.8	0.7	0.0
Linearity	0.9988 to 0.9998								
Linearity Range (ng/mL)	0.200 to 15.0								
Sensitivity/LOQ (ng/mL)	0.200								

Bioequivalence Study No. 11879301 Nicotine	
Parameter	**Quality Control Samples**

	QC A	MQC	QC B	QC C
Concentration (ng/mL)	0.600	2.00	4.50	12.0
Inter day Precision (CV %)	3.1	2.2	2.6	2.0
Inter day Accuracy (%Bias)	-2.3	-1.5	0.9	-1.7

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

1.1.1.3.3 Reanalysis of Study Samples

Bioequivalence Study No. 11879301 Nicotine Additional information in Bioanalytical Report Page 12, 24,39								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays[2]**		**Actual number**		**% of total assays[2]**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic [1]	0	0	0.0	0.0	0	0	0.0	0.0
AAR	54	63	3.4	3.9	54	63	3.4	3.9
BAR	2	3	0.1	0.2	2	3	0.1	0.2
IA	2	9	0.1	0.6	2	9	0.1	0.6
IISR	8	5	0.5	0.3	8	5	0.5	0.3

Investigation	0	3	0.0	0.2	0	0	0.0	0.0
PP	22	27	1.4	1.7	0	0	0.0	0.0
Total	88	110	5.5	6.9	66	80	4.1	5.0

Total number of samples analyzed = 1599

AAR – Sample Concentration Above Acceptance Range
BAR – Sample Concentration Below Quantitative Limit
IA - Incomplete Analysis
ISR – Inconsistent Internal Standard Response
PP –Positive Pre-Dose

Note: When a sample was repeated more than once, only the first repeat code assigned was included in the calculation in order to adequately represent the total number of samples analyzed.

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0".
[2] The % of total assays is calculated by dividing the actual number by the total number of samples analyzed.

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No
If no, is recalculation of PK parameters necessary?	☐ Yes ☒ No ☐ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☒ No ☐ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☒ Yes ☐ No ☐ N/A

Comments on Bioanalytical Results: Adequate

- Along with approximate 20% representative chromatograms (from 9 subjects), the firm also submitted complete (100%) numerical raw data in run sequence order (i.e. Run log) in the instrument printout format from all analytical runs of the new pivotal BE study as Appendix V and VI to the Bioanalytical Report [Study Report No: P18012_EBG; Date: 04/16/2018] in Module 5.3.1.4 (\\cdsesub1\evsprod\anda207868\0016\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\11879301\bioanalytical-report-and-method-validation.pdf).

- All data being reported for this study are from acceptable runs as per the firm's run acceptance criteria. As documented in Table 1 of the Bioanalytical submitted by the firm, total 20 analytical runs (including 2 runs for incurred sample reanalysis and 4 runs for individual/batch repeats) were carried out for the analyte of nicotine, and only one rejected run, Run#10EBG (Subjects [redacted] (b) (6) was identified due to the reason of "*Not injected due to interference (Run was stopped due to interference. Investigation showed that all blank and STD A samples had unacceptable interference. Run injection was not completed)*", and accordingly these 3 subject samples was re-assayed in the subsequent run.

- According to above Summary Table of "*Reanalysis of Study Samples*" and the Bioanalytical Report, in the current BE study, of 1599 study samples analyzed and reported (from 40 subjects), a total of 198 samples [88 samples from the test treatment (5.5%) and 110 samples from the reference treatment (6.9%)] were reanalyzed for nicotine. Please see comments below for details.

    - Repeat Code AAR (Sample Concentration above Acceptance Range): During the BE study, there were 117 samples [54 samples from the test treatment and 63 samples from the reference treatment] reanalyzed for nicotine due to the reason of "*Sample concentration above Acceptance Range (Code AAR)*". Based on the raw data submitted, the reviewer verified the original values of these samples were all higher than the ULOQ of 15 ng/mL, and these samples were diluted and repeated in singlet in the subsequent repeat runs, and the obtained reassayed value after dilution was within the calibration curve range. Also, the reviewer verified that the final reassayed values after dilution and correction with the dilution factor was greater than 85% of the ULOQ ((b) (4) (b) (4)). Therefore, as per the firm's re-assay SOP (b) (4) the reviewer agrees that the reanalysis of these samples meet the pre-established acceptance criteria and confirmed the reassay values were used in the final pharmacokinetic and statistical analyses.

    - Repeat Code BAR (Sample Concentration below Acceptance Range): During the BE study, there were 5 samples [2 samples from the test treatment and 3 samples from the reference treatment] reanalyzed for nicotine due to the reason of "*Sample concentration below Acceptance Range (Code BAR)*", which was pre-defined in the firm's re-assay SOP (b) (4) as "*When the LLOQ standard (STD B) is rejected or lost, any sample, whose concentration falls below STD C, including samples that are reported BQL, will be coded BAR*", which can be considered as below truncated calibration curve. Based on the raw data submitted for the original run (Run#02EBG, analyzed on 03/14/2018) of these samples (from Subject (b) (6)), the reviewer verified that the lowest CC sample (P18012_EBG STD B 1; 0.305 ng/ml) was rejected due to the %Accuracy fail (152.5%), and therefore excluded from the regression calculation as per firm's re-assay SOP. Thus, the reviewer agrees that the reanalysis of these samples are acceptable.

    - Repeat Code IISR (Inconsistent Internal Standard Response): There were 13 samples [8 samples from the test treatment and 5 samples from the reference treatment] reanalyzed for nicotine due to the reason of "*Inconsistent Internal Standard Response (Code IISR)*", which was defined in the firm's re-assay SOP ((b) (4) as "*study sample for which the internal standard peak response is above or below f 3 SD of the internal standard mean response, is coded IISR. In addition, any study samples for which an IS area of less than*

50% or greater than 180% of the IS mean will be coded IISR". Based on the raw data submitted, the reviewer verified the firm followed the aforementioned criteria for the reassay. The peak areas of internal standard (ISTD Peak Area Count) of these samples in the original runs were beyond the criteria, and sample repeats are acceptable. Therefore, the reassayed values were used in the final pharmacokinetic and statistical analyses.

- Repeat Code IA (Incomplete Analysis): There were 3 samples reanalyzed for nicotine due to the reason of "*Incomplete Analysis (Code IA)*" as specified in the firm's re-assay SOP Section 6.2.1. Based on the raw numerical data, the reviewer verified that no responses were detected for both nicotine (analyte) and internal standard of these samples in the original run. Therefore, the current reviewer considers the reanalysis of these samples acceptable and the reassay values were used as final reported value in the pharmacokinetic and statistical analyses.

- Repeat Code PP (Positive Pre-dose): 49 samples [22 sample from the test treatment and 27 samples from the reference treatment] were reanalyzed for nicotine due to the reason "*Positive predose (Code PP)*", as per Section 6.3.1 of the firm's re-assay SOP as non-analytical reasons. Based on the raw data submitted, the reviewer verified that the initial area counts/values in the original runs for these pre-dose samples were higher than LLOQ (0.200 g/ml). Moreover, the measurable pre-dose nicotine concentrations in 7 subjects (Subject No (b) (6)) were greater than 5% of the respective measured Cmax values, and therefore "*these 7 subjects were excluded from statistical analysis*" according to the study report. However, as evaluated by the reviewer, the positive pre-dose levels was due to the subject recruitment of "*current smokers*" as specified in "*Inclusion Criteria*" of firm's clinical study protocol (Protocol# PLDA000218; Date: 02/08/2018) "*Subject is a current smoker and has smoked regularly for at least 1 year before initial dosing*". Thus, from BE stand point, the pharmacokinetic and statistical analyses should be based on the data of baseline-corrected nicotine concentrations (the measured nicotine concentration at each time point should be corrected by subtracting the contribution from the corresponding pre-dose level) which had been requested in the BE IR dated 09/13/2018, in addition to the current statistical results with non-correct data. However, based on the current submission, all the original values of these samples were used as final reported values in the pharmacokinetic and statistical analyses, therefore, reviewer deemed that the reassay of these pre-dose samples would have no impact on the study outcomes.

- In addition, there were 3 samples [from the reference treatment] reanalyzed for nicotine due to the reason of "*Investigation*". As documented in the study

report, during the data review of study, an unexpected low concentration result was observed for sample [(b) (6)] 0.833h*1, which is unexpected when compared to the time points before and after in the same subject. The run in which this sample was analyzed (run #12EBG) was thoroughly reviewed and no other discrepancy was observed. Since no analytical reason was found to justify the anomalous low value, it was repeated in triplicate in run #15EBG (one replicate using aliquot 1 and two replicates using aliquot 2) along with the samples [(b) (6)] 0.667h*1 and [(b) (6)] 1h*1 for investigation purposes, as per SOP #GP17.6. Four values (original value and three re-assay values) of these three samples are listed as below. These four values are used in the final reporting. For all samples, all three replicates re-assays confirmed each other and the original value. Therefore, the reviewer deemed that the reassay of these investigational samples would have no impact on the study outcomes since the original values were used as final reported values in the pharmacokinetic and statistical analyses.

Sample Name		Run ID	Run Sequence Number	Corrected Conc ng/mL	Repeat Code	Sample Status	Reported Conc ng/mL
P18012_EBG 423010002685 [(b) (6)]	1 P1 0.667h PLM-1	12	138	9.30	2	Accepted	9.30
P18012_EBG 423010002685	1 P1 0.667h PLM-1	15	74	9.23			
P18012_EBG 423010002685	1 P1 0.667h PLM-1	15	117	9.43			
P18012_EBG 423010002685	1 P1 0.667h PLM-1	15	158	9.62			
P18012_EBG 423010002686	1 P1 0.833h PLM-1	12	109	6.43	2	Accepted	6.43
P18012_EBG 423010002686	1 P1 0.833h PLM-1	15	36	6.59			
P18012_EBG 423010002686	1 P1 0.833h PLM-1	15	91	6.62			
P18012_EBG 423010002686	1 P1 0.833h PLM-1	15	155	6.76			
P18012_EBG 423010002687	1 P1 1h PLM-1	12	117	12.2	2	Accepted	12.2
P18012_EBG 423010002687	1 P1 1h PLM-1	15	32	12.2			
P18012_EBG 423010002687	1 P1 1h PLM-1	15	103	12.7			
P18012_EBG 423010002687	1 P1 1h PLM-1	15	147	12.3			

- To confirm the reproducibility of bioanalytical method during study sample analysis, in this study, a total of 160 samples out of 1599 samples (10.0% of the total samples analyzed) were reanalyzed in its incurred samples reproducibility (ISR) testing. ISR testing was performed as per SOP [(b) (4)] (Incurred Sample Reanalysis). Of 157 ISR samples considered (3 samples were excluded due to IISR and AAR), 156 samples (99.4%) were acceptable and meeting the acceptance criteria of no more than ± 20% difference when compared to the original analysis values. The firm's selection for ISR samples was as per the current FDA Guidance (Guidance for Industry: Bioanalytical Method Validation; recommended September 2013)[22]. The firm's ISR analysis is acceptable and the method is reproducible.

[22] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf

- As a result, the firm's during study assay validation is considered **complete** (adequate).

1.1.1.4 Pharmacokinetic Results

1.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters - Reviewer Calculated

Fasting Bioequivalence Study No.										
		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng·hr/mL	51.225	50.62	21.71	135.33	54.204	45.85	27.06	127.05	0.95
AUCI	ng·hr/mL	55.582	58.52	22.61	170.04	58.424	53.68	28.33	171.68	0.95
CMAX	ng/mL	12.577	35.11	4.53	24.10	13.528	28.37	6.71	22.42	0.93
TMAX	hr	1.500	.	0.67	2.00	1.250	.	0.33	2.50	1.20
KE	hr-1	0.274	31.84	0.14	0.56	0.295	33.18	0.12	0.53	0.93
THALF	hr	2.749	28.28	1.23	4.81	2.589	32.46	1.30	5.96	1.06

* Tmax values are presented as median, range

1.1.1.4.2 Geometric Means and 90% Confidence Intervals - Firm Calculated

Nicotine Polacrilex Mini Lozenges 4 mg Dose (1 × 4 mg), N=40 (Male & Female; Completed) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals							
Pivotal Bioequivalence Study (Study No. 11879301)							
Nicotine (N=33*)							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio %**	**90% C.I.**	
AUC0-t (ng·min/mL)	2922	33	3191	33	91.58	87.00	96.39
AUC∞ (ng·min/mL)	3167	33	3450	33	91.79	87.14	96.69
Cmax (ng/mL)	12.13	33	13.52	33	89.69	84.82	94.84
Baseline Corrected Nicotine (N=40)							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio %**	**90% C.I.**	
AUC0-t (ng·min/mL)	2781	40	2997	40	92.82	88.56	97.28
AUC∞ (ng·min/mL)	3017	39**	3209	39**	94.02	89.54	98.73
Cmax (ng/mL)	11.83	40	13.02	40	90.85	85.98	96.00

Note: * 7 subjects (Subject No (b) (6)) were excluded from statistical analysis for non-corrected data due to pre-dose nicotine concentrations greater than 5% of the respective measured Cmax values.

** As confirmed by the reviewer, Subject No (b) (6) was not included in the calculation of AUCinf due to the non-linearity of the elimination phase during P2 (Reference).

1.1.1.4.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Nicotine Polacrilex Mini Lozenges 4 mg Dose (1 × 4 mg), N=40 (Male & Female; Completed) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Pivotal Bioequivalence Study (Study No. 11879301)					
Baseline Corrected Nicotine (N=40)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	46.36	49.95	0.93	88.56	97.27
AUC∞ (ng·hr/mL)	49.19	52.75	0.93	88.75	97.95
Cmax (ng/mL)	11.83	13.02	0.91	85.98	96.00

1.1.1.4.4 Additional Information for the Study

Root Mean Square Error	AUCt: 0.1242 AUCi: 0.1306 Cmax: 0.1461
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).**	☐ Yes ☒ No
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed).**	☐ Yes ☒ No
Are there first measurable drug concentration as Cmax? **If yes, please comment.**	☐ Yes ☒ No
Are there Cmax at the first time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Ratio of AUC0-t/AUC∞[23]				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	40	0.94	0.80	1.00

[23] See individual test to reference ratios of PK Parameters in SAS Output

Reference	40	0.95	0.74	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	AUC Ratio was slightly less than 0.8 for reference product. The current sampling time up to 12 hours is adequate to cover the absorption, distribution and elimination phases, and continue for more than five times of the plasma half-life.			

Comments on PK results: Adequate

- Per the recommendations in the current BE draft guidance, for Nicotine Polacrilex Mini Lozenges, only one fasting BE study is recommended on the biostrength of Eq. 4 mg base in general population (healthy males and nonpregnant females), and bioequivalence should be established based on 90% CI of nicotine.

- As submitted in the current post-CR amendment, the new pivotal *in vivo* BE study (Study# 11879301) was conducted in the normal healthy smokers [Per firm's subject "*Inclusion Criteria*" in clinical study protocol (Protocol# PLDA000218; Date: 02/08/2018) and report, "*Subject is a current smoker and has smoked regularly for at least 1 year before initial dosing*"). The firm's original PK and statistical analysis (submission date 04/30/2018) was only conducted on the original/uncorrected nicotine concentrations. However, based on the raw data submitted and study report, positive pre-dose nicotine concentrations were observed for at least one period in 29 subjects, which accounts for 72.5% of total 40 subjects who completed the study. Also, the measurable pre-dose nicotine concentrations in 7 subjects (Subject No (b) (6)) were greater than 5% of the respective measured Cmax values, and "*these 7 subjects were excluded from statistical analysis*". Therefore, considering the subject recruitment of "*current smokers*" and predominant measurable pre-dose nicotine concentrations observed, in the BE IR dated 09/13/2018, the firm was asked re-conduct the PK and statistical analysis using the data of baseline-corrected nicotine concentrations (the measured nicotine concentration at each time point should be corrected by subtracting the contribution from the corresponding pre-dose level), and resubmit the study outcomes (Please see Section I for details).

- In the IR response dated 09/17/2018, the firm re-conducted baseline-corrected concentration analyses, and as reported in study report amendment (Study# 11879301; Date: 09/14/2018), "*all post-dose blood samples were baseline corrected for each subject (per period) by subtracting the pre-dose value (0-hour sample). Baseline correction was specific to each subject and period. If, after baseline correction, any plasma concentration was a negative value then the calculated concentration was set to zero (0.00) for pharmacokinetic analysis*".

- The 90% CIs for the T/R ratio of least squares geometric means of $LnAUC_{0-t}$, $LnAUC_{0-\infty}$ and LnC_{max} for both nicotine and baseline-corrected nicotine reported by

the firm are all within acceptable BE limits of 80.00-125.00%. To confirm the firm's results, the reviewer re-conducted statistical analysis with baseline-corrected nicotine data submitted by the firm using DB's standard SAS program (TwoWay_PLASMA_CALCKE.SAS). The reviewer calculated 90% CIs for $LnAUC_{0-t}$ and LnC_{max} are in good agreement with the firm's calculation (please note that the firm's PK analysis using "minute" for sampling time point instead of usually "hour" and final results of AUC were expressed as "ng·min/mL"). The slightly difference in $LnAUC_{0-\infty}$ results is more likely due to the exclusion of Subject# (b) (6) in firm's calculation due to the non-linearity of the elimination phase during P2. Both the reviewer's and the firm's calculations are within acceptable BE limits of 80.00-125.00%, and therefore meet the BE criteria.

- The median Tmax and range of the test products were still considered comparable to those of the reference products for nicotine under the current study conditions.

	Tmax/Test (h)	Tmax/Reference (h)	T/R Ratio
Rotigotine	1.500 (0.67 - 2.00)	1.250 (0.33 - 2.50)	1.20

- In addition, there was only one subject (Subject (b) (6) P2/Reference) identified in the current fasting study with AUC0-t/AUC∞ ratio <0.8 (Ratio of AUC0-t/AUC∞=0.74), which is due to the non-linearity of elimination phase.

- The firm's *in vivo* fasting BE study is **adequate** (complete).

1.1.1.5 Overall Comment

Was the fasting bioequivalence study acceptable? Acceptable.

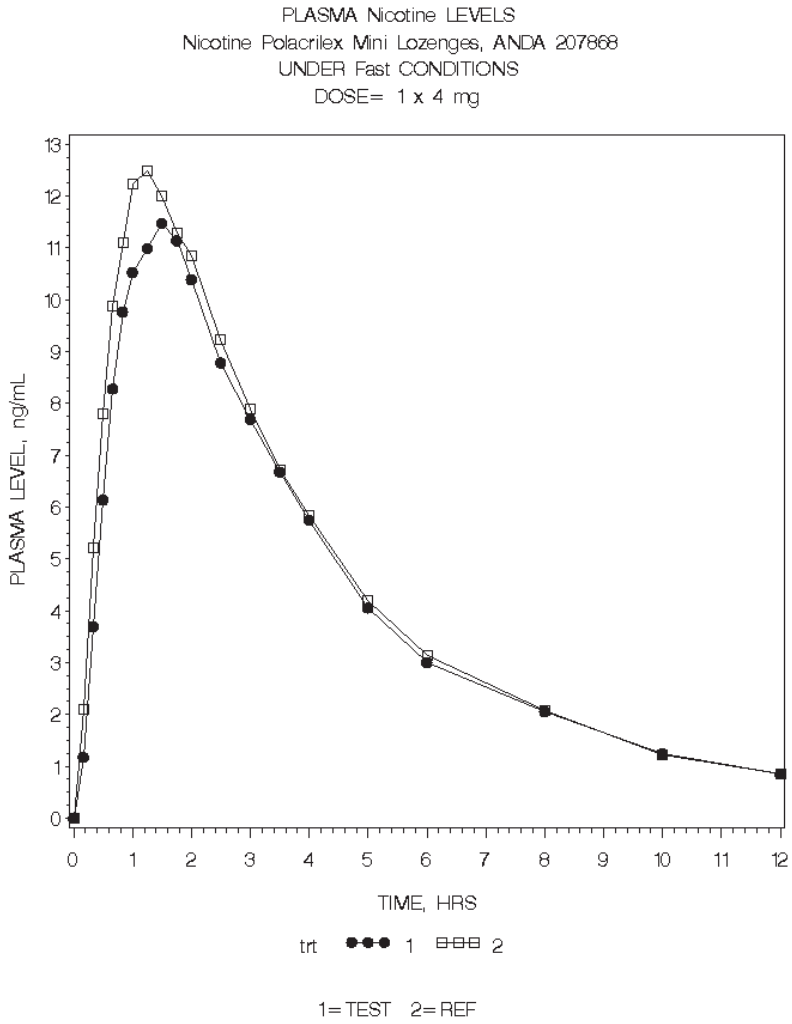
Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

(By reviewer)

	Test (n=40)		Reference (n=40)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.17	1.17	82.08	2.10	66.73	0.56
0.33	3.70	52.65	5.22	49.49	0.71
0.50	6.14	41.94	7.81	36.30	0.79
0.67	8.28	39.25	9.88	29.75	0.84
0.83	9.77	33.86	11.10	29.63	0.88
1.00	10.53	33.67	12.23	28.94	0.86
1.25	10.99	34.66	12.48	30.83	0.88
1.50	11.48	37.57	11.99	33.79	0.96
1.75	11.14	39.95	11.28	36.55	0.99
2.00	10.39	40.33	10.84	38.60	0.96
2.50	8.79	41.22	9.23	40.73	0.95
3.00	7.70	47.02	7.90	44.87	0.97
3.50	6.68	52.93	6.72	44.73	0.99
4.00	5.75	56.44	5.83	51.03	0.99
5.00	4.06	64.10	4.19	59.52	0.97
6.00	3.01	71.74	3.14	67.47	0.96
8.00	2.06	90.92	2.06	82.28	1.00
10.00	1.24	102.49	1.23	105.58	1.01
12.00	0.85	124.09	0.86	119.00	0.99

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

(By reviewer)



1.2 Formulation Data

The formulation data for the test product do not change in the current amendment. The test product formulations remain **adequate** (Please refer to the original BE for details[24]).

[24] GDRP/Panorama, ANDA 207868 (ANDA-207868-ORIG-1-RESUB-3): Bioequivalence Discipline Review (Bioequivalence Primary Review: A207868N000DB_N12022015.docx); Last Update: 02/18/2017. http://panorama fda.gov/task/view?ID=566154ac0141beee6e16a23c11cb43fa.

1.3 Dissolution Testing (Applicable only if there are waiver requests)

1.3.1 Dissolution Data

Dissolution method with USP Apparatus I (Basket):

Summary of In Vitro Dissolution Study – *4mg Strength (Bio-strength)*

Dissolution Conditions	**Apparatus:**	Apparatus 1 (Basket)
	Speed of Rotation:	100 rpm
	Medium:	pH7.4 phosphate buffer, USP
	Volume:	900mL
	Temperature:	37 ± 0.5 °C
Firm's Proposed Specifications	NLT (b) (4) and NMT (b) (4) of Nicotine LC dissolved in 30 min NLT and NMT of Nicotine LC dissolved in 60 min NLT of Nicotine dissolved in 180 minutes	
Dissolution Testing Site (Name, Address)	PLD Acquisitions, LLC D/B/A Avema Pharma Solutions, 10400 NW 29th Terrace, Miami, FL 33172, USA.	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 30	60	180	Study Report Location
QCRD020, P19	01/30/18	Test : CM097374 (Manufacturing date: 08/01/2017)	4 mg Lozenge	12	Mean (%)	23	44	99	Notebook# QCRD020, Page 19
					Range	(b) (4)			
					%CV	4.2	9.0	1.6	
QCRD020, P22	02/01/18	Reference: 15376 (Expiration date: 02/2019)	4 mg Lozenge	12	Mean (%)	34	58	103	Notebook# QCRD020, Page 22
					Range	(b) (4)			
					%CV	4.3	4.9	1.4	

Summary of In Vitro Dissolution Study – *4mg Strength* *(Bio-strength)* (from original submission)

Dissolution Conditions	**Apparatus:**	Apparatus 1 (Basket)
	Speed of Rotation:	100 rpm
	Medium:	pH7.4 phosphate buffer, USP
	Volume:	900mL
	Temperature:	37 ± 0.5 °C
Firm's Proposed Specifications	NLT (b) (4) and NMT (b) (4) of Nicotine LC dissolved in 30min NLT and NMT of Nicotine LC dissolved in 60min NLT of Nicotine LC dissolved in 90min NLT of Nicotine LC dissolved in 120min NLT ((b) (4) of Nicotine LC dissolved in 180minutes	
Dissolution Testing Site (Name, Address)	PLD Acquisitions, LLC D/B/A Avema Pharma Solutions, 10400 NW 29th Terrace, Miami, FL 33172, USA.	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**					**Study Report Location**
						30	**60**	**90**	**120**	**180**	
QC-309 Page- 166	06/06/14	Test: BM033299 (Manufacturing date:02/11/14)	4.0mg Lozenge	12	Mean (%)	31	55	76	91	99	Test results form PS003381 located in the corresponding finished product folder
					Range (%)	(b) (4)					
					%RSD	5.3	7.8	7.6	6.0	2.7	
QC-313 Page-107	11/25/13	Reference: 14347 (Expiration date: 07/2015)	4.0mg Lozenge	12	Mean (%)	27	46	63	80	103	Test results form PS003381 located in the corresponding finished product folder
					Range (%)	(b) (4)					
					%RSD	4.9	3.9	3.6	5.2	1.0	

Summary of In Vitro Dissolution Study – *2mg Strength* (from original submission)

Dissolution Conditions	**Apparatus:**	Apparatus 1 (Basket)
	Speed of Rotation:	100 rpm
	Medium:	pH7.4 phosphate buffer, USP
	Volume:	900mL
	Temperature:	37 ± 0.5 °C
Firm's Proposed Specifications		NLT (b) (4) and NMT (b) (4) of Nicotine LC dissolved in 30min NLT and NMT of Nicotine LC dissolved in 60min NLT of Nicotin dissolved in 90min NLT of Nicotine LC dissolved in 120min NLT (b) (4) f Nicotine LC dissolved in 180minutes
Dissolution Testing Site (Name, Address)		PLD Acquisitions, LLC D/B/A Avema Pharma Solutions, 10400 NW 29th Terrace, Miami, FL 33172, USA.

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**					**Study Report Location**
						30	**60**	**90**	**120**	**180**	
QC-294 Page- 101	06/05/14	Test: BM033296 (Manufacture Date: 02/06/14)	2.0mg Lozenge	12	Mean (%)	35	62	85	98	101	Lab Notebook QC-294 Page- 101
					Range (%)	(b) (4)					
					%RSD	3.4	4.0	4.7	2.4	1.1	
QC-394 Page-118	09/10/15	Reference: 14848 (Expiration date: 01/2017)	2.0mg Lozenge	12	Mean (%)	31	54	74	95	103	Lab Notebook QC-394 Page-118
					Range (%)	(b) (4)					
					%RSD	4.5	4.2	4.3	3.2	1.5	

FDA-recommended dissolution method with USP Apparatus III (reciprocating cylinders):

Summary of In Vitro Dissolution Study – *4mg Strength* *(Bio-strength)*

Time (minutes)	Lot No. CM097374 (repeat slow formulation)	Nicorette Lot No. 15376 (unexpired reference product)
15	(b) (4)	(b) (4)
30		
45		
60		

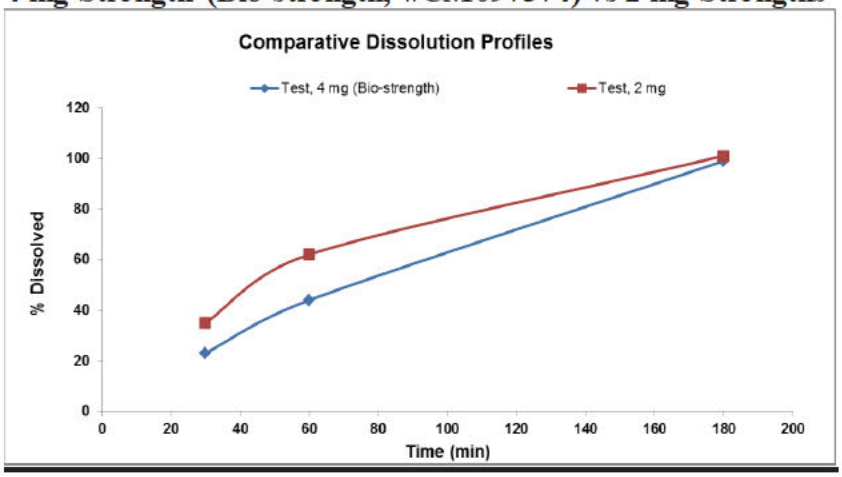
Summary of In Vitro Dissolution Study – *2mg Strength*

Not provided (see comments below)

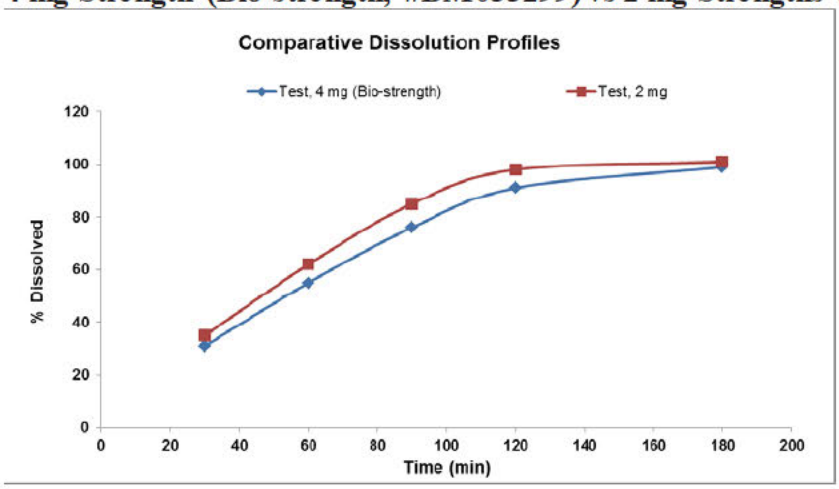
1.3.2 Dissolution Profiles (By Reviewer)

Dissolution method with USP Apparatus I (Basket):

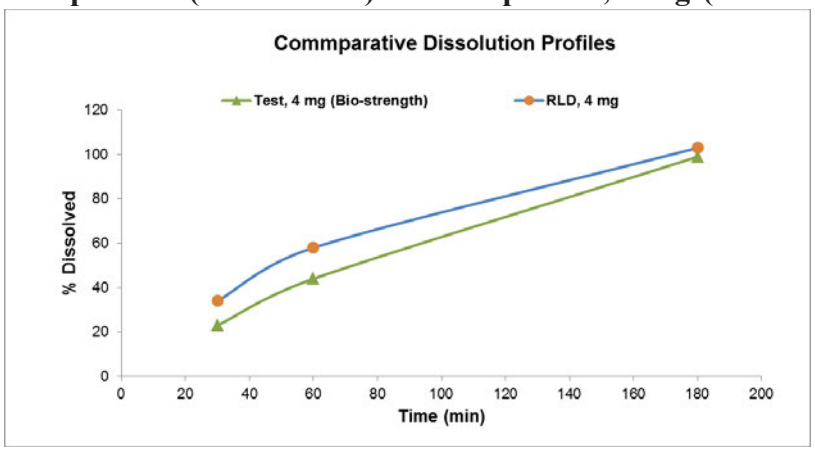
4 mg Strength (Bio-strength, #CM097374) vs 2 mg Strengths



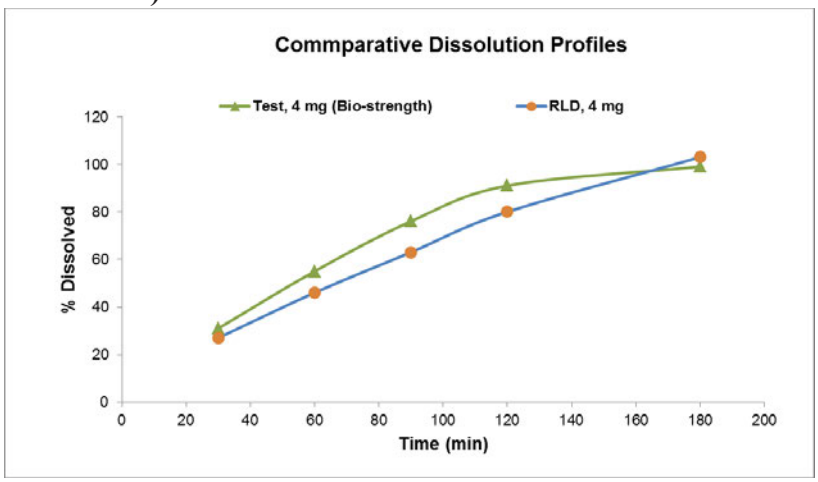
4 mg Strength (Bio-strength, #BM033299) vs 2 mg Strengths (original submission)



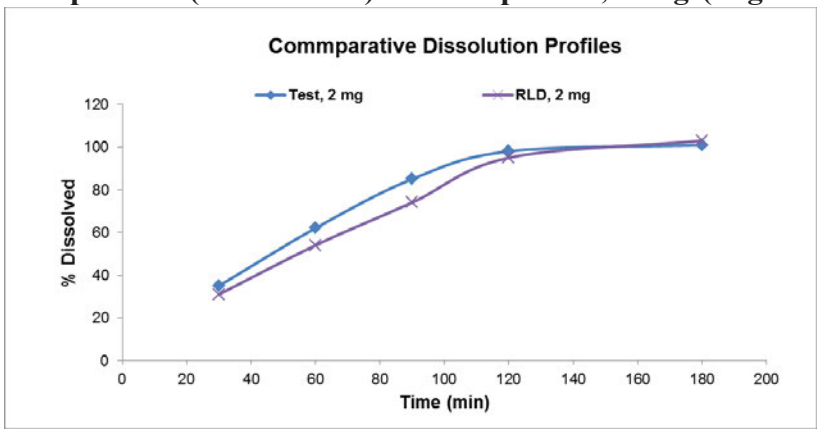
Test product (#CM097374) vs. RLD product, 4 mg (Bio-strength)



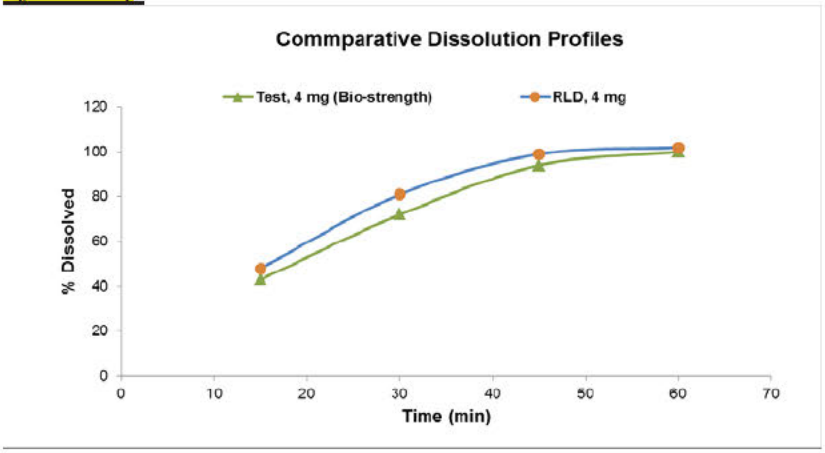
Test product (#BM033299) vs. RLD product, 4 mg (Bio-strength) (original submission)



Test product (#BM033296) vs. RLD product, 2 mg (original submission)



FDA-recommended dissolution method with USP Apparatus III (reciprocating cylinders):



1.3.3 F2 Metric

F2 metric calculated?	☒ Yes ☐ No
If no, reason why F2 not calculated	N/A

F2 Metric, biostudy strength (4 mg) compared to other strengths of test product (By Reviewer):

F2 metric, Test product, Biostudy strength compared to other strength(s)		
Dissolution Method: FDA-recommended method (USP Apparatus I)		
Biostudy Strength	**Other Strength**	**F2 metric for TEST**
4 mg (Batch# CM097374)	2 mg (Batch# BM033296; from original submission)	45.01*
4 mg (Batch# BM033299; from original submission)	2 mg (Batch# BM033296; from original submission)	57.58

Note: f2 value were calculated based on new dissolution data on 4 mg and original dissolution data on 2 mg, which was included for information only since only 2 time points in 4 mg data with drug release <85%.

F2 Metric Test vs RLD (all strengths)	
Dissolution Method: FDA-recommended method (USP Apparatus I)	
4 mg (Batch# CM097374)	48.77*
4 mg (Batch# BM033299)	52.21(based on original submission)
2 mg (Batch# BM033296)	56.79 (based on original submission)
Dissolution Method: FDA-recommended method (USP Apparatus III)	

4 mg (Batch# CM097374)	58.75
2 mg	Data not provided

Note: the firm reported f2 value=51.5, which was based on a dissolution data below. However, the mean value for test product at 60 min time point was mistakenly reported as "47%" as verified by the reviewer based on the raw data also shown below.

Table 2 shows the mean and range for dissolution for both the test product, Nicotine Polacrilex 4 mg Lot No. CM097374 and the reference product, Nicorette 4 mg Lot No. 15376.

Time (minutes)	Nicotine Polacrilex 4 mg Lot No. CM097374			Nicorette 4 mg Lot No. 15376		
30		(b) (4)			(b) (4)	
60						
180						

Nicotine 4 mg Mini Lozenge (Test), Lot CM097374

Time (min)	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Vessel 7	Vessel 8	Vessel 9	Vessel 10	Vessel 11	Vessel 12	Mean	%rsd	Min	Max
30												(b) (4)	23	4.2		(b) (4)
60													44	9.0		
18													99	1.6		

Reviewer's Comments on Dissolution Testing:

- The review of *in vitro* dissolution testing was conducted separately by the biopharmaceutics quality reviewer at the Office of Pharmaceutical Quality (OPQ), which was completed recently on 07/30/2018[25]. In the current BE review, the dissolution data were evaluated for the consideration of waiver request only for the lower strength (EQ 2 mg Base) of test products.

- There is no USP method for Nicotine Polacrilex Mini Lozenges, but there is an FDA-recommended method posted on the FDA External Dissolution Database as follows[26]. (*Note*: The dissolution method and specifications for this product has not yet been posted on the FDA internal dissolution database[27]):

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Nicotine Polacrilex	Lozenge (Mini)	III (Reciprocating Cylinder)	20 dpm	Phosphate Buffer, pH 7.4	250	15, 30, 45, 60 and 90	03/09/2017

[25] ANDA 207868 (ANDA-207868-ORIG-1- AMEND-17): Biopharmaceutics Quality Review (ANDA 207868-BIOPHARMACEUTIC REVIEW- RESPONSE to IR.06-04-18.docx); Last Update: 07/30/2018 http://panorama.fda.gov/task/view?ID=5ae9cdb50060798ce53624c3f7189044.

[26] FDA External Dissolution Database: http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm; Search Term: Nicotine Polacrilex (updated date: 03/09/2017); last accessed: 09/13/2018.

[27] OGD Internal Dissolution Database; Search Term: Nicotine Polacrilex; last accessed: 09/13/2018.

- As indicated in the table above, the FDA-recommended dissolution method was revised on 03/09/2017 from the original USP Apparatus I (Basket) to the current USP Apparatus III (reciprocating cylinders). To reflect this change, in the current amendment[28], the firm submitted dissolution data using both Apparatus III and I conducted on the new batches of test and RLD products.

- The firm only submitted individual unit data for dissolution testing with Apparatus I, but not for Apparatus III.

- For dissolution testing with Apparatus I, the dissolution method was same as used in the original dissolution testing, except for the less sampling time points (30, 60, 180 min of current vs 30, 60, 90, 120, 180 min of original; Please see tables above), and the firm only submitted testing data/results on the new batches of 4 mg bio-strength of test (Batch# CM097374) and RLD (Batch# 15376) products. The summary table of 2 mg strength (Test Batch# BM033296) with Apparatus I method above was obtained from original submission (no new dissolution testing was conducted for the lower 2 mg strength of test or reference product in the current amendment).

- For dissolution testing with Apparatus III (current FDA-recommended method), the firm only submitted testing data/results from 4 mg bio-strength of test (Batch# CM097374) and RLD (Batch# 15376) products, but no testing data were provided for the lower 2 mg strength on both the test and RLD products.

- Based on the dissolution data submitted with Apparatus I (original FDA-recommended method), the dissolution profiles of the test product between the bio-strength of 4 mg and lower 2 mg strength are considered comparable for the release of nicotine with calculated similarity factor (f2) values above 50 (original data), or closed to 50 (new data due to the incomplete profile of limit sampling time points) (Please see figures of dissolution profiles and f2 values above calculated by the reviewer). For dissolution testing with Apparatus III, no comparison could be performed for dissolution profile between the two test strength due to no data submitted for lower 2 mg strength. However, the test products showed comparable dissolution profiles as the RLD products on the corresponding strength with similarity factor f2 values above (or very closed to) 50 for all test conditions.

- Therefore, at the time of this review, based on the evaluation of dissolution testing/data in the original BE review, and also, in the current submission, the new and original dissolution data, including the comparable dissolution profiles between 4 mg and 2 mg strengths (with Apparatus I) and also between test and reference

[28] ANDA 207868, View EDR: "BE SummaryTables" in Module 2.7.1 (\\cdsesub1\evsprod\anda207868\0016\m2\27-clin-sum\summary-of-biopharm-pdf.pdf); "Quality Information Amendment" in Module 1.11.1 (\\cdsesub1\evsprod\anda207868\0016\m1\us\1-11-information-amendment\1-11-1-quality-information-amendment\quality-information-amendment.pdf); Received Date: 04/30/2018.

products (with Apparatus I and III), the dissolution data are **adequate** with respect to supporting the waiver request for the 2 mg strength of the test product.

G. Comments for Other OGD Disciplines

Discipline	Comment
N/A	--

H. Pending Consults (Clinical, Statistical, Science Staff, Chemistry etc.)

Discipline	Comment
N/A	--

I. Information Request (IR) Response

The DBIII's IR to the Firm Dated 09/13/2018:

The deficiency below represents bioequivalence (BE) Information Request (IR) identified during the full ANDA review and the current ANDA review cycle will remain open. The following comments should be communicated to the firm via a Division of Bioequivalence III (DBIII)'s IR.

1. In the current amendment dated 04/30/2018, your submitted a new pivotal *in vivo* bioequivalence (BE) study (#11879301) conducted on the new test (#CM097374/RD039-24) and reference (#15376) bio-batches. As per the "*Inclusion Criteria*" in your clinical study protocol (Protocol# PLDA000218; Date: 02/08/2018) and report (Study# 11879301; Date: 04/24/2018) "*Subject is a current smoker and has smoked regularly for at least 1 year before initial dosing*", and positive pre-dose nicotine concentrations were observed for at least one period in 29 subjects, which accounts for 72.5% of total 40 subjects who completed the study. Also, based on the raw data submitted and your study report, the measurable pre-dose nicotine concentrations in 7 subjects (Subject No (b) (6) and (b) (6)) were greater than 5% of the respective measured Cmax values, and therefore "*these 7 subjects were excluded from statistical analysis*". Therefore, considering your subject recruitment of "*current smoker*" and predominant measurable pre-dose nicotine concentrations observed, please re-conduct your pharmacokinetic (PK) and statistical analyses using the data of **baseline-corrected** nicotine concentrations (the measured nicotine concentration at each time point should be corrected by subtracting the contribution from the corresponding pre-dose level), and resubmit the study outcomes, including BE Summary Table 2 and 3, and corresponding part of your study report and statistical report.

Please also submit related SAS transport (.xpt) datasets for plasma concentration and PK parameters in the following format:

Plasma Concentration Data

SUB	SEQ	PER	GRP	TRT	C1	C2…	Cn	T1	T2…	Tn	KE_FIRST	KE_LAST

Definition Table for SAS Transport Dataset of Individual Plasma Concentration Data

Variable Name	Variable Label	Type	Notes
SUB	Subject Identification Number	Char/Num	Unique subject identifier (b) (6), …)
PER	Period	Numeric	Period identifier
SEQ	Sequence	Numeric	Sequence identifier (1=RT; 2=TR)
TRT	Treatment	Numeric	Treatment group (1=Test; 2=Reference)
GRP	Group Identification Number	Numeric	Dosing group identifier if subjects are dosed in more than one group
C1	Concentration Time 1	Numeric	Concentration at the first time point*
C2	Concentration Time 2	Numeric	Concentration at the second time point*
Cn	Concentration Time n	Numeric	Concentration at the nth time point*
T1	Time Point 1	Numeric	First **Actual** Sampling Time (e.g., 0 hour)
T2	Time Point 2	Numeric	Second **Actual** Sampling Time (e.g., 0.167 hour)
Tn	Nth Time Point	Numeric	Nth **Actual** Sampling Time (e.g., 12 hours)
KE_FIRST	First time point for KE calculation	Numeric	First time point of the elimination segment (of the concentration-time curve) selected for calculating KE**
KE_LAST	Last time point for KE calculation	Numeric	Last time point of the elimination segment (of the concentration-time curve selected for calculating KE**

NOTE:
*, C1, C2, …, Cn should be baseline-corrected nicotine concentrations.
**, KE_FIRST and KE_LAST should be given as the sequential numbers of the time points, and NOT the time values themselves. For example:
KE_FIRST = 10 which means the 10th time point, not "10 hours"
KE_LAST = 24 which means the 24th time point, not "24 hours"

PK Parameter Data

SUB	SEQ	PER	GRP	TRT	Tmax	Cmax	AUCt	AUCi	Ke	Thalf

Definition Table for SAS Transport Dataset of Individual PK Parameter Data

Variable Name	Variable Label	Type	Notes
SUB	Subject Identification Number	Char/Num	Unique subject identifier

PER	Period	Numeric	Period identifier
SEQ	Sequence	Numeric	Sequence identifier (1=RT; 2=TR)
TRT	Treatment	Numeric	Treatment group (1=Test; 2=Reference)
GRP	Group Identification Number	Numeric	Dosing group identifier if subjects are dosed in more than one group
AUCt	Area Under the Curve from zero hour (0) to the last time point with measurable concentration (t)	Numeric	Area under the curve from time 0 to t
AUCi	Area Under the Curve from zero hour (0) to infinity	Numeric	Area under the curve from time 0 to infinity
Cmax	Cmax	Numeric	Maximum concentration
Tmax	Tmax	Numeric	Time at maximum concentration
Thalf	Half-life	Numeric	Half-life calculated from the terminal phase of the elimination
Ke	Ke	Numeric	Elimination rate constant

2. Based on your current submission, Table 14.2.1 "*Concentration Values for Individual Subjects*" in your study report (Study# 11879301; Date: 04/24/2018) is incomplete, which only include concentrations of sampling time point until 120 min. Please resubmit a complete table including data from all sampling time points.

Firm's Response Dated 09/17/2018:

Response to BE Comment #1:
Additional pharmacokinetic and statistical analyses were performed using the baseline-corrected nicotine concentrations (the measured nicotine concentration at each time point was corrected by subtracting the contribution from the corresponding pre-dose level) and a Statistical Amendment for Study #11879301 has been provided in Module 5.3.1.2 to present the analyses and results. Data from all 40 subjects who completed both periods of the study were included in the Pharmacokinetic and Statistical analyses of baseline-corrected nicotine in this Statistical Amendment. Conclusions of bioequivalence based on the analysis of baseline-corrected nicotine concentrations are comparable to the baseline-uncorrected analysis, in which the test formulation of Nicotine Polacrilex 4 mg Mini Lozenge (PLD Acquisitions, LLC) was demonstrated to be bioequivalent to the reference formulation of Nicorette®, Nicotine Polacrilex 4 mg Mini Lozenge (Distributed by GlaxoSmithKline Consumer Healthcare, L.P.) under fasted conditions. BE Summary Table 2 and Table 3, which include baseline-corrected nicotine results, have also been provided.

The SAS transport datasets containing randomization data, plasma nicotine concentration data, and pharmacokinetic parameters are provided in the requested format. Plasma nicotine concentration data and pharmacokinetic parameters are provided for both baseline-corrected and baseline-uncorrected data.

Response to BE Comment #2:
Complete Table 14.2.1 (Concentration Values for Individual Subjects (ng/mL): Nicotine - Test A) and Table 14.2.2 (Concentration Values for Individual Subjects (ng/mL): Nicotine - Reference B), dated l7APR20l8 including data from all sampling time points, are provided since the tables included in the initially submitted clinical study report (Study# I1879301; Pages 57-62) were incomplete.

Reviewer's Comment:

The review of firm's responses has been included in the current BE review (Please see Section V.1.1 for details).

J. Additional Attachments

SAS Output

Study	Analyte	SAS Data	SAS Stat	SAS Output/Table
New Pivotal BE Study #11879301	Nicotine	207868_Fast_Datasets_Nicotine.doc	207868_Fast_stat_NicotineACTUAL.doc	207868_Fast_table_NicotineACTUAL.doc

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	207868
APPLICANT:	PLD Acquisitions LLC, D/B/A Avema Pharma Solutions
DRUG PRODUCT:	Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base

The Division of Bioequivalence III (DBIII) has completed its review of your submission acknowledged on the cover sheet and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

K. Outcome Page

ANDA: 207868

Completed Assignment for 207868 ID: 36565

Reviewer:	Zhang, Yi	**Date Completed:**
Verifier:		**Date Verified:**
Division:	Division of Bioequivalence	
Description:	Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base; PLD Acquisitions LLC, D/B/A; Post-CR, BE	

Productivity:
Items:

36565	4/30/2018	BIO	ANDA Amendment [1]	1	1
36565	4/30/2018	Parallel	Study Amendment [1]	1	1
36565	4/30/2018	Parallel	Fasting Study (Full template) [1]	1	1
36565	4/30/2018	Parallel	Dissolution-Based Waiver (IR) (For all waiver strengths) [0.25]	0.25	0.25
				Total:	3.25

QUALITY ASSESSMENT

BIOPHARMACEUTICS

Product Background:

NDA/ANDA: ANDA 207868

Drug Product Name / Strength: Nicotine Polacrilex Mini Lozenges/ 2 mg and 4 mg

Route of Administration: oral

Applicant Name: PLD Acquisitions LLC, D/B/A Avema Pharma Solutions

Review Summary: Inadequate

The proposed drug product, Nicotine Polacrilex Mini Lozenges/ 2 mg and 4 mg is the generic version of reference product, Nicorette® 2mg and 4mg (approved on 5/18/2009), indicated to reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking. The composition of the proposed drug product is shown in Table 1.

Table 1: Nicotine Polacrilex Mini Lozenge drug product composition and function of excipients

Ingredient	4.0 mg Dose	2.0 mg Dose	Function
	mg/unit	mg/unit	
Nicotine Polacrilex 15%		(b) (4)	Active
Mannitol			(b) (4)
Sodium Bicarbonate			
Sodium Stearyl Fumarate			
Maltodextrin			
(b) (4)			
Calcium Polycarbophil			
Xanthan Gum			
Aspartame			
Sodium Alginate			
Talc			
Totals			

The Applicant followed the dissolution method recommended by FDA as shown below:

Parameter	Value
Medium	pH7.4 phosphate buffer, USP
Volume	900 mL
Temperature	37 ± 0.5 °C
Apparatus	Apparatus 1 (Basket)
Rotational Speed	100 rpm
Time Point	30, 60, 90, 120 and 180 minutes
Sample Volume	1.5 mL

The dissolution method is acceptable. The dissolution acceptance criteria are not adequate and an IR will be sent to request the applicant to revise the acceptance criteria.

List Submissions being reviewed (table):

Application 207868 - Sequence 0000 - 0000 (1) 06/19/2014 ORIG-1 /Multiple Categories/Subcategories

Application 207868 - Sequence 0010 - 0010 (11) 05/02/2017 ORIG-1 /Multiple Categories/Subcategories

Highlight Key Outstanding Issues from Last Cycle:

A. Submit the complete dissolution data (i.e. all raw data, range, mean, %CV, dates of testing) for the following:

1. The generic batch# BP033725 (4 mg).

2. Those for the generic 2 mg strength (three exhibit batches)

B. We have the following comments regarding the dissolution acceptance criteria:

a) For extended release products the establishment of at least three specification time-points covering the initial, middle, and terminal phases of the complete dissolution profile data must be set. The acceptance criteria ranges must be based on the overall dissolution data generated at these times.

b) In general, the selection of the dissolution acceptance criteria ranges is based on mean target value (b) (4)% and NLT (b) (4)% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model.

c) The dissolution acceptance criteria should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with dissolution profiles outside those that were tested clinically.

Concise Description Outstanding Issues Remaining:

The Applicant's proposed specification is too liberal. Based on the dissolution data submitted, this reviewer proposes a specification of the following:

Time in minutes	% Release
30	Between (b) (4) %
60	Between (b) (4) %
180	Not less than (b) (4) %

The Applicant will be asked to acknowledge the acceptance of the recommended specification and provide revised specifications table.

BCS Designation

Reviewer's Assessment: The Applicant stated nicotine is Class I in BCS classification.

Solubility: Soluble in water and non-polar solvents

Permeability: Not provided

Dissolution: Please see below:

Dissolution Method and Acceptance Criteria

The Applicant used the dissolution method as per the FDA recommended method as described below:

Parameter	Value
Medium	pH7.4 phosphate buffer, USP
Volume	900 mL
Temperature	37 ± 0.5 °C
Apparatus	Apparatus 1 (Basket)
Rotational Speed	100 rpm
Time Point	30, 60, 90, 120 and 180 minutes
Sample Volume	1.5 mL

The mean comparative dissolution data and profile of Nicotine Polacrilex Mini Lozenge 4 mg (Lot no. : BM033299, Manufacturing date: 02/11/14)) vs. Reference Listed Drug- Nicorette® (Nicotine Polacrilex) Mini Lozenge 4 mg (Lot no. 14347 (Expiration date: 07/2015) are shown in Table 2 and Figure 1.

Both Batch #s. BM033299 and BP033725 were listed as the "Test Batches" under Product Information in Biopharm Summary Section of the submission, however, only batch BP033725 was listed as the clinical batch used in the in vivo BE study (AJ1403). Therefore, it does not appear that batch BM033299 is the biobatch.

Reviewer's note:

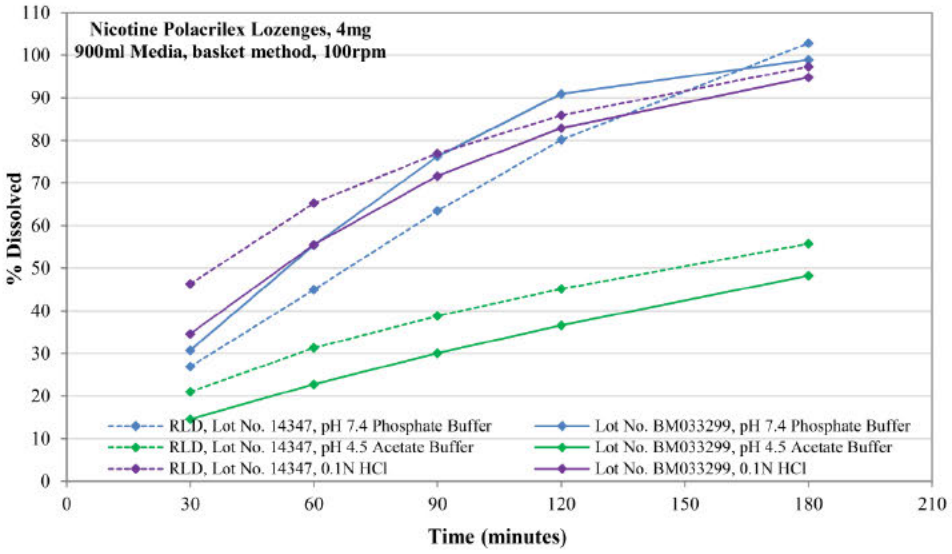
It was found that BM033299 and BP033725 are referring to the same batch that was used in the in vivo BE study. BM033299 is the Batch No. and BP033725 is the Lot No.

Table 2: Mean Comparative Dissolution Data of Nicotine Polacrilex Mini Lozenge 4 mg biobatch (Lot no. : BM033299, Manufacturing date: 02/11/14)) vs. Reference Listed Drug- Nicorette® (Nicotine Polacrilex) Mini Lozenge 4 mg biobatch (Lot no. 14347 (Expiration date: 07/2015) in Proposed Dissolution Media (pH 7.4 Phosphate Buffer)

Dissolution Conditions	**Apparatus:**	Apparatus 1 (Basket)
	Speed of Rotation:	100 rpm
	Medium:	pH7.4 phosphate buffer, USP
	Volume:	900mL
	Temperature:	37 ± 0.5 °C
Firm's Proposed Specifications	NLT (b) (4)% and NMT (b) (4)% of Nicotine LC dissolved in 30min NLT % and NMT % of Nicotine LC dissolved in 60min NLT % of Nicotine LC dissolved in 90min NLT % of Nicotine LC dissolved in 120min NLT % ((b) (4) %) of Nicotine LC dissolved in 180minutes	
Dissolution Testing Site (Name, Address)	PLD Acquisitions, LLC D/B/A Avema Pharma Solutions, 10400 NW 29th Terrace, Miami, FL 33172, USA.	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)** 30	60	90	120	180	**Study Report Location**
QC-309 Page- 166	06/06/14	Test: BM033299 (Manufacturing date:02/11/14)	4.0mg Lozenge	12	Mean (%)	31	55	76	91	99	Test results form PS003381 located in the corresponding finished product folder
					Range (%)	(b) (4)					
					%RSD	5.3	7.8	7.6	6.0	2.7	
QC-313 Page-107	11/25/13	Reference: 14347 (Expiration date: 07/2015)	4.0mg Lozenge	12	Mean (%)	27	46	63	80	103	Test results form PS003381 located in the corresponding finished product folder
					Range (%)	(b) (4)					
					%RSD	4.9	3.9	3.6	5.2	1.0	

Figure 1: Mean Comparative Dissolution Data of Nicotine Polacrilex Mini Lozenge 4 mg biobatch (Lot no. : BM033299, Manufacturing date: 02/11/14)) vs. Reference Listed Drug- Nicorette® (Nicotine Polacrilex) Mini Lozenge 4 mg biobatch (Lot no. 14347 (Expiration date: 07/2015) in Three Different Media (pH 7.4 Phosphate Buffer, pH 4.5 Acetate Buffer, 0.1N HCl)



An Information Request (IR) was sent to the applicant on 2/24/2017 as follows:

Submit the complete dissolution data [i.e. all raw data, range, mean, coefficient of variation (%CV), dates of testing] for the following.
a. The generic batch# BP033725 (4 mg)
b. Those for the generic 2 mg strength (three exhibit batches)

The applicant requested clarification via email on 3/9/2017 regarding the requirement of submitting three exhibit batches. The Agency replied with the following:*If the dissolution testing was conducted prior to June 20, 2014 or even the release of the OGD guidance in December, 2013, you are not obliged to submit the dissolution data from three exhibit batches per guidance recommended. Therefore, please provide your rationale and the needed data (i.e., dissolution data of the 2 mg strength from three exhibit batches if it was conducted after June 20, 2014, or dissolution data from one batch of the 2 mg strength if it was conducted before June 20, 2014).*

Since BM033299 and BP033725 are referring to the same batch (biobatch), the applicant submitted additional dissolution data of one exhibit batch of 4 mg and two batches of 2 mg. The mean comparative dissolution data of Nicotine Polacrilex Mini Lozenge 4 mg biobatch (Lot no. : BM033298, Manufacturing date: 02/10/14)) vs. Reference Listed Drug- Nicorette® (Nicotine Polacrilex) Mini Lozenge 4 mg biobatch (Lot no. 14347 (Expiration date: 07/2015) are shown in Table 3. The mean comparative dissolution of two batches of Nicotine Polacrilex Mini Lozenge 2 mg vs. RLD 2 mg is shown in Table 4 and Table 5.

Table 3: Mean comparative dissolution data of Nicotine Polacrilex Mini Lozenge 4 mg biobatch (Lot no. : BM033298, Manufacturing date: 02/10/14)) vs. Reference Listed Drug- Nicorette® (Nicotine Polacrilex) Mini Lozenge 4 mg biobatch (Lot no. 14347 (Expiration date: 07/2015)

Dissolution Conditions	**Apparatus:**	Apparatus 1 (Basket)
	Speed of Rotation:	100 rpm
	Medium:	pH7.4 phosphate buffer, USP
	Volume:	900mL
	Temperature:	37 ± 0.5 °C
Firm's Proposed Specifications	NLT (b) (4)% and NMT (b) (4)% of Nicotine LC dissolved in 30min NLT % and NMT % of Nicotine LC dissolved in 60min NLT % of Nicotine LC dissolved in 90min NLT % of Nicotine LC dissolved in 120min NLT % ((b) (4)%) of Nicotine LC dissolved in 180minutes	
Dissolution Testing Site (Name, Address)	PLD Acquisitions, LLC D/B/A Avema Pharma Solutions, 10400 NW 29th Terrace, Miami, FL 33172, USA.	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**					**Study Report Location**
						30	**60**	**90**	**120**	**180**	
QC340, P10	2/18/14	Test 1: BM033298 (Manufacturing date: 02/10/14)	4.0mg Lozenge	6	Mean (%)	34	62	83	96	99	Notebook# QC340, Page-10
					Range	(b) (4)					
					%CV	3.42	4.91	2.85	1.44	1.62	
QC313, P107	11/25/13	Reference: 14347 (Expiration date: 07/2015)	4.0mg Lozenge	12	Mean (%)	27	46	63	80	103	Notebook# QC313 Page-107
					Range	(b) (4)					
					%CV	4.87	3.91	3.65	5.17	0.98	

Table 4: Mean comparative dissolution data of Nicotine Polacrilex Mini Lozenge 2 mg (Lot no. : BM033258, Manufacturing date: 02/05/14)) vs. Reference Listed Drug- Nicorette® (Nicotine Polacrilex) Mini Lozenge 2 mg (Lot no. 14848 (Expiration date: 01/2017)

Dissolution Conditions	**Apparatus:**	Apparatus 1 (Basket)
	Speed of Rotation:	100 rpm
	Medium:	pH 7.4 phosphate buffer, USP
	Volume:	900mL
	Temperature:	37 ± 0.5 °C
Firm's Proposed Specifications	NLT (b) (4)% and NMT (b) (4)% of Nicotine LC dissolved in 30min NLT % and NMT % of Nicotine LC dissolved in 60min NLT % of Nicotine LC dissolved in 90min NLT % of Nicotine LC dissolved in 120min NLT % ((b) (4)%) of Nicotine LC dissolved in 180minutes	
Dissolution Testing Site (Name, Address)	PLD Acquisitions, LLC D/B/A Avema Pharma Solutions, 10400 NW 29th Terrace, Miami, FL 33172, USA.	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**					**Study Report Location**
						30	**60**	**90**	**120**	**180**	
QC340, P5	2/12/14	Test: BM033258 (Manufacture Date: 02/05/14)	2.0mg Lozenge	6	Mean (%)	38	64	87	99	100	Notebook# QC340, Page-5
					Range	(b) (4)					
					%CV	6.48	4.20	2.91	1.18	0.75	
QC394, P118	09/9/15	Reference: 14848 (Expiration date: 01/2017)	2.0mg Lozenge	12	Mean (%)	31	54	74	95	103	Notebook# QC394, Page-118
					Range	(b) (4)					
					%CV	4.50	4.23	4.32	3.24	1.46	

Table 5: Mean comparative dissolution data of Nicotine Polacrilex Mini Lozenge 2 mg (Lot no. : BM033296, Manufacturing date: 02/0614)) vs. Reference Listed Drug- Nicorette® (Nicotine Polacrilex) Mini Lozenge 2 mg (Lot no. 14848 (Expiration date: 01/2017)

Dissolution Conditions	**Apparatus:**	Apparatus 1 (Basket)
	Speed of Rotation:	100 rpm
	Medium:	pH 7.4 phosphate buffer, USP
	Volume:	900mL
	Temperature:	37 ± 0.5 °C
Firm's Proposed Specifications	NLT (b)(4)% and NMT (b)(4)% of Nicotine LC dissolved in 30min NLT % and NMT % of Nicotine LC dissolved in 60min NLT % of Nicotine LC dissolved in 90min NLT % of Nicotine LC dissolved in 120min NLT % (b)(4)%) of Nicotine LC dissolved in 180minutes	
Dissolution Testing Site (Name, Address)	PLD Acquisitions, LLC D/B/A Avema Pharma Solutions, 10400 NW 29th Terrace, Miami, FL 33172, USA.	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)** 30	60	90	120	180	**Study Report Location**
QC-294 Page- 101	06/05/14	Test 2: BM033296 (Manufacture Date: 02/06/14)	2.0mg Lozenge	12	Mean (%)	35	62	85	98	101	Lab Notebook QC-294 Page- 101
					Range	(b)(4)					
					%CV	3.4	4.0	4.7	2.4	1.1	
QC-394 Page-118	09/10/15	Reference: 14848 (Expiration date: 01/2017)	2.0mg Lozenge	12	Mean (%)	31	54	74	95	103	Lab Notebook QC-394 Page-118
					Range	(b)(4)					
					%CV	4.5	4.2	4.3	3.2	1.5	

Dissolution Acceptance Criterion

The Applicant's original proposed dissolution acceptance criteria for both 2 mg and 4 mg were as follows:

NLT (b)(4)% and NMT (b)(4)% of Nicotine LC dissolved in 30 minutes
NLT % and NMT % of Nicotine LC dissolved in 60 minutes
NLT % of Nicotine LC dissolved in 90 minutes
NLT % of Nicotine LC dissolved in 120 minutes
NLT % (b)(4)%) of Nicotine LC dissolved in 180 minute

As a response to the IR, the applicant revised the acceptance criteria based on the FDA's recommendation and summary data from dissolution data generated on stability at 24 months and 36 months as follows:

Table 6: Summary of all Dissolution Data Generated on Stability (thru 24 months)

Time Point	Mean	Min	Max	Proposed Specification
30	33	(b)(4)		NLT (b)(4)% - NMT (b)(4)%
60	59			
90	81			---
120	94			---
180	99			NLT (b)(4)%

Table 7: Summary of all Dissolution Data Generated on Stability (thru 36 months)

Time Point	Mean	Min	Max	Proposed Specification
30	36	(b) (4)		NLT (b) (4) - NMT (b) (4)%
60	64			(b) (4)%
90	85			---
120	95			---
180	100			NLT (b) (4)%

All the submitted dissolution data of the 2 mg and 4 mg show that the test drug products release meet the proposed acceptance criteria. The applicant noted that for 36 month stability data, 60 minute individuals result lies outside the proposed limits of (b) (4)%, but is still acceptable for level 2 which is (b) (4)

The applicant referred to the Guidance "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations" under Setting Dissolution Specifications Without an IVIVC, and stated that in the absence of an In Vitro/In Vivo Correlation that, "In certain cases, reasonable deviations from the ± 10 % range can be accepted provided that the range at any time point does not exceed 25%. Specifications greater than 25% may be acceptable based on evidence that lots (side batches) with mean dissolution profiles that are allowed by the upper and lower limit of the specifications are bioequivalent."

The applicant stated that the two test formulations of 4 mg Nicotine Polacrilex lozenges (BM033298 & BM033299) with different dissolution profiles were shown to be bioequivalent to the RLD as well as to each other, as shown in Table 8, Table 9, and Table 10.

Table 8: Summary of Results for Statistical Tests on Nicotine for the Fasting Study, Study AJ-1401 (Fast Formulation - Lot No. BM033298)

Parameter	Test[1]	Reference[1]	Ratio[2]	CV%[3]	90% CI[4]
AUC_{0-t}	33.8	34.8	97.33	11.9	90.39 – 104.81
AUC_{0-inf}	36.7	37.8	97.24	12.9	89.76 – 105.34
C_{max}	7.94	8.36	93.70	15.1	85.31 – 102.91
T_{max}	1.36	1.56	87.33	-	-
λ_z	0.2261	0.2305	98.08	-	-
$t_{1/2}$	3.16	3.19	99.04	-	-

Table 9: Summary of Results for Statistical Tests on Nicotine for the Fasting Study, Study AJ-1401 (Slow Formulation - Lot No. BM033299)

Parameter	Test[1]	Reference[1]	Ratio[2]	CV%[3]	90% CI[4]
AUC_{0-t}	34.5	34.8	99.33	11.9	92.24 – 106.96
AUC_{0-inf}	37.4	37.8	98.87	12.9	91.27 – 107.10
C_{max}	8.30	8.47	97.95	15.1	89.18 – 107.58
T_{max}	1.66	1.56	106.05	-	-
λ_z	0.2446	0.2305	106.10	-	-
$t_{1/2}$	3.02	3.19	94.65	-	-

Table 10: Summary of Results for Statistical Tests on Nicotine for the Fasting Study, Study AJ-1401 (Fast Formulation – Lot No. BM033298 vs Slow Formulation - Lot No. BM033299)

Parameter	Test 1[1]	Test 2[1]	Ratio[2]	CV%[3]	90% CI[4]
AUC_{0-t}	33.8	34.5	97.99	11.9	91.00 – 105.52
AUC_{0-inf}	36.7	37.4	98.35	12.9	90.79 – 106.54
C_{max}	7.94	8.30	95.67	15.1	87.10 – 105.07
T_{max}	1.36	1.66	82.35	-	-
λ_z	0.2261	0.2446	92.44	-	-
$t_{1/2}$	3.16	3.02	104.64	-	-

Reviewer's comments:

The applicant's proposed dissolution specification is too liberal. The applicant's submitted data to support the proposed wide specification range is limited. It is not clear as to how Lot No. BM033299 is defined as "slow formulation" and Lot No. BM033298 is as "fast formulation" since the formulation/composition of these two clinical batches could not be located nor the study report of No. AJ-1401 in the ANDA. . Therefore, based on the dissolution data submitted for the two clinical batches (Lot No. BM033298 and Lot No. BM033299), this reviewer recommends the following dissolution acceptance criteria (mean (b) (4) %):

At 30 minutes: (b) (4) %

At 60 minutes: %

At 180 minutes: NLT (b) (4) %

Analytical Method Validation

Parameters	Acceptance Criteria	Results
Specificity	(b) (4)	
System Precision		

	(b) (4)
Linearity	
Accuracy	
Method Precision	
Intermediate Precision {Ruggedness}	

	(b) (4)
Robustness	
Solution Stability	
Filter	

Reviewer's Assessment:

- **The applicant used the FDA-recommended method for dissolution testing of the drug product. There is no USP dissolution method for nicotine.**

- **The applicant submitted acceptable dissolution analytical method validation including specificity, system precision, linearity, accuracy, method precision, intermediate precision (ruggedness), robustness, solution stability, and filter study. Linearity was validated with concentrations ranging from (b) (4), which is (b) (4)% of the lower expected % Nicotine Label claim dissolved at 30 minutes ((b) (4)%) for Nicotine Polacrilex Mini 2 mg to 1 (b) (4)% of the expected % Nicotine Label Claim dissolved at 1 80 minutes ((b) (4)%) for Nicotine Polacrilex Mini 4 mg**

- **The Applicant provided the complete dissolution data with 12 units for each strength (i.e. all raw data, range, mean, %CV, dates of testing) with two exhibit batches for each strength in the submission. Both Lot No. BM033298 and Lot No. BM033299 are biobatches (both batches were used in Study No. AJ1401, and Batch No. BM033299 was used in AJ1403).**

- **The applicant's proposed dissolution specification is shown below:**

30 minutes: (b) (4)%

60 minutes: (b) (4)%

180 minutes: NLT (b) (4)%

The proposed specification is too liberal. Based on the dissolution data submitted for the two clinical batches (Lot No. BM033298 and Lot No. BM033299), this reviewer recommends the following dissolution acceptance criteria ((b) (4)%):

At 30 minutes: (b) (4)%

At 60 minutes: (b) (4)%

At 180 minutes: NLT (b) (4)%*Application of dissolution/IVIVC in QbD*

Reviewer's Assessment: n/a

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: n/a

In-Vitro Soft-food Interaction Study

Reviewer's Assessment: n/a

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment: n/a

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

Reviewer's Assessment: n/a

In-Vitro Dissolution Testing for Abuse-deterrent Products

Reviewer's Assessment: n/a

In-Vitro BE Evaluation for Pulmonary Products

Reviewer's Assessment: n/a

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: n/a

Bridging of Formulations

Reviewer's Assessment: The final formulation was used in the BE study as well as in vitro dissolution tests.

Biowaiver Request

Reviewer's Assessment: The Applicant requested for a waiver of evidence of in vivo bioavailability or bioequivalence for the lower strength, Nicotine Polacrilex 2 mg by stating that Nicotine Polacrilex 4mg and 2mg mini lozenge formulations are proportionally similar in their active and inactive ingredients. The biowaiver request for the generic 2 mg lozenge is to be assessed by the BE reviewer in OGD. Note, no complete dissolution profile data of generic 2 mg lozenge (three exhibit batches) were submitted for review.

R Regional Information

Comparability Protocols

Reviewer's Assessment: n/a

Post-Approval Commitments

Reviewer's Assessment: n/a

Lifecycle Management Considerations

Reviewer's Assessment: n/a

List of Deficiencies:

Your proposed acceptance criteria are too liberal. The following acceptance criteria are recommended based on the dissolution data submitted:

Time in minutes	% Release
30	Between (b) (4) %
60	Between (b) (4) %
180	Not less than (b) (4) %

We request that you acknowledge your acceptance of the recommended dissolution acceptance criteria. Implement the recommended dissolution acceptance criteria for the proposed drug product, and provide the revised specifications table with the updated acceptance criterion for the dissolution test.

Primary Biopharmaceutics Reviewer Name and Date:

An-Chi (Angela) Lu, Pharm.D.

Biopharmaceutics Reviewer

ONDP/Division of Biopharmaceutics

June 6th, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I concur. ***06/06/17***

Tien-Mien Chen, Ph.D.
Acting Biopharm. Lead
DB/ONDP/OPQ

An-Chi Lu

Digitally signed by An-Chi Lu
Date: 6/26/2017 02:43:55PM
GUID: 508da73f0002b8f58e8154431f048ac2

Tien Mien Chen

Digitally signed by Tien Mien Chen
Date: 6/26/2017 04:01:08PM
GUID: 508da7240002a26723d38018ce005126

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	207868	
Drug Product Name	Nicotine Polacrilex Mini Lozenges	
Strength(s)	EQ 2 mg Base and EQ 4 mg Base*	
Applicant Name	PLD Acquisitions LLC, D/B/A Avema Pharma Solutions	
Applicant Address	10400 NW 29th Terrace Miami, FL 33172 USA	
Applicant's Point of Contact	Mehul Govani	
Contact's Telephone Number	(b) (6)	
Contact's Fax Number	(516) 272-8203	
Contact's Email Address	mgovani@pldevelopments.com	
Original Submission Date(s)	12/02/2015 (Resubmission/After Refuse to Receive) *[06/19/2014 (Subject to a refuse to receive)]***	
Submission Date(s) of Amendment(s) Under Review	09/17/2015 (Supp. Document #2) Quality/Response To Information Request; 12/02/2015 (Supp. Document #3) Quality/Manufacture Information; User Fee/Coversheet; Resubmission/After Refuse to Receive; Labeling/Container-Carton Draft; 10/26/2016 (Supp. Document #8) Response to ECD/Bioequivalence; 02/13/2017 Establishment Inspection Report (EIR) for Clinical Site (Phase One Solutions, Inc)[1]; 05/02/2017 (Supp. Document #11), Bioequivalence/Other; Quality/Quality Information; Resubmission/After Action- Complete.	
Reviewer	Yi Zhang, Ph.D.	
Secondary Reviewer	Li Gong, Ph.D.	
Tertiary Reviewer	April C. Braddy, Ph.D.	
Study Number (s)	AJ-1403	AJ-1401
Study Type (s)	Pivotal Fasting Study	Pilot Fasting Study
Strength (s)	1 x 4 mg	1 x 4 mg
Clinical Site	Phase One Solutions, Inc.	
Clinical Site Address	1405 NW 167th Street Miami Gardens, FL 33169 USA Phone: (305) 624-9191	
Analytical Site	(b) (4)	
Analytical Site Address		

(b) (4)

	(b) (4)		
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**	**Post October 1, 2014 ANDAs** ☐ **Pending** ☒ **Inadequate** ☐ **For Cause Inspection** ☐ **N/A (Waiver/Deem Bioequivalent)**	
Waiver/Deem Bioequivalent	☐ **Granted** ☐ **Tentatively granted** ☒ **Not granted** ☐ **N/A**		
QC Dissolution	☒ **Pending** ☐ **Adequate** ☐ **Inadequate**		
Formulation	☒ **Adequate** ☐ **Inadequate**		
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☒ **No** ☐ **N/A**		
Deficiency Classification	☒ **Major (Deficiencies to be communicated by CR)** ☐ **Minor** ☐ **N/A (Review is Adequate)**		
OVERALL REVIEW RESULT	☐ **Adequate** ☒ **Inadequate** *(due to inadequate OSIS/clinical site)*		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**		
Communication	☐ **ECD** ☐ **IR** ☒ **Not Applicable** *(Deficiencies to be communicated by CR)*		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 2, 3 & 8	**Pivotal Fasting**	**4 mg**	**Inadequate**
3	**Pilot Fasting**	**4 mg**	**Inadequate**
1, 2, 3 & 8	**Waiver**	**2 mg**	**Inadequate**

Note:
* Each Lozenge containing Nicotine Polacrilex equivalent to Nicotine Base 2 mg and 4 mg, respectively. Throughout the current review the 2 mg and 4 mg strength refer to EQ amount of the Nicotine Base.

**This application was originally filed on 06/19/2014 as ANDA 207868. On 09/29/2015, a refuse to receive letter was issued due to several reasons including but not limited to incomplete information[2]. The firm responded to the deficiencies in the filing review, and resubmitted the current application on 12/02/2015 with the same ANDA number.

[2] DARRTS ANDA 207868: COR-ANDAFILE-03(Refuse to Receive); BENSON, JASON A; Submit/Final Date: 09/29/2015.

Review of a Post-CR Amendment

I. Executive Summary

This is a review of bioequivalence (BE) portion of the firm's post-Complete Response (CR) response dated 05/02/2017 (Supporting document #11)[3] in response to the Agency's CR Letter dated 02/24/2017[4].

On 12/02/2015, the firm, PLD Acquisitions LLC, originally submitted an ANDA containing a pivotal fasting bioequivalence (BE) study (#AJ-1403) comparing a test product, Nicotine Polacrilex Mini Lozenges, 4 mg, to the corresponding reference product, GlaxoSmithKline Consumer Healthcare's Nicorette® Mini Lozenge, 4 mg [NDA 022360, approved on 05/18/2009; Over the Counter (OTC)][5]. The application also contains a waiver request for the 2 mg strength.

As per the original BE review[6] and the related Safety/Efficacy Consult to the Division of Clinical Review (DCR; Dated 11/18/2016)[7], the firm's pivotal fasting BE studies on the strength of 4 mg (Study No. AJ-1403) was considered adequate (complete). In addition, the formulations of the test products were adequate, and the dissolution data were also adequate with respect to supporting waiver request of the lower strength, 2 mg.

In addition to the pivotal study, as reported in the pharmaceutical development report (Report# D00068; Date: 06/17/2014; Module 3.2.P.2), the firm also conducted a three-way crossover pilot fasting study (Study No. AJ-1401), with two investigational test formulations against the RLD product, to investigate the influence of drug release profiles. However, the firm did not provide the detailed formulations and other related information for this pilot study in its original submission. The deficiencies regarding to the non-submission of eCTD-formatted BE data summary tables and detailed information of adverse events (AEs) were communicate to the firm in the above mentioned Agency's CR Letter dated 02/24/2017.

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[3] DARRTS, ANDA 207868, Bioequivalence/Other; Quality/Quality Information; Resubmission/After Action- Complete (Supp. Document #11); Submit/Final Date: 05/02/2017.

[4] GDRP/Panorama, ANDA 207868: ANDA-207868-ORIG-1-AMEND-11 (Complete Response; BENSON, JASON A); Submitted/Final Date: 02/24/2017.

[5] Electronic Orange Book (Updated Through 03/2017): http://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=022360#; Search Term: NDA 022360; last accessed on 05/18/2017.

[6] GDRP/Panorama, ANDA 207868 (ANDA-207868-ORIG-1-RESUB-3): Bioequivalence Discipline Review (Bioequivalence Primary Review: A207868N000DB_N12022015.docx); Last Update: 02/18/2017. http://panorama.fda.gov/task/view?ID=566154ac0141beee6e16a23c11cb43fa.

[7] GDRP/Panorama for ANDA-207868-ORIG-1-RESUB-3: Bioequivalence ECD/IR and Consults//Send Consult Request (A207868N000DB_C11032016.docx); Date uploaded: 11/18/2016; (http://panorama fda.gov/task/view?ID=581b8881004658643ab857434fe8f650).

On 05/02/2017, the firm submitted its responses to the above BE deficiencies, and provided additional information/data for the pilot fasting study (Study No. AJ-1401) as requested. Based on the information/data firm submitted in the current amendment, the firm's pilot fasting study (Study No. AJ-1401) is now considered adequate (complete).

Office of Study Integrity and Surveillance (OSIS) Inspection:
This ANDA is a GDUFA CY4 application. As per the original BE review[6], OSIS inspection status for the analytical site remains "**complete**", as recommended by the Division of Generic Drug Bioequivalence Evaluation (DGDBE) at the OSIS (memorandum dated 01/20/2016) for the current ANDA 207868.

For the clinical site, as per the review of Clinical Establishment Inspection Report (EIR) and the evaluation in the original BE review, the firm was requested to address the inspectional finding #1 for its impact on all related *in vivo* BE studies of the current application, and provide information regarding the availability of the retention samples, specifically, investigational product, Nicotine Polacrilex Mini Lozenges 4 mg manufactured by PLD Acquisitions LLC, and reference product, Nicorette® Mini Lozenge 4 mg, used in the current BE studies (Agency's CR Letter dated 02/24/2017).

However, based on the information the firm provided in the current amendment, the retained samples of the investigational products have been destroyed. The clinical site, Phase One Solutions, Inc., did not retain reserve samples appropriately as require by 21 CFR 320.38 and 320.63. Hence, the authenticity of the test and reference drug products used in the pivotal (AJ-1403) and pilot (AJ-1401) BE studies cannot be confirmed due to lack of reserve samples. Consequently the current BE studies are NOT acceptable since the reliability of data is impaired by the **violation of the reserve sample regulations** (please see *Section IV.C Reviewer's Comments to Deficiency #3* for the details).

As a result, the BE portion of the application is **inadequate** with a deficiency per comments above.

II. Table of Contents

III. Background Information

1. On 12/02/2015, the firm originally submitted a pivotal fasting BE study (#AJ-1403) comparing its test products, PLD Acquisitions LLC, D/B/A Avema Pharma Solutions's Nicotine Polacrilex Mini Lozenges, 4 mg, to the corresponding reference product, GlaxoSmithKline Consumer Healthcare's Nicorette® Mini Lozenge, 4 mg [NDA 022360, approved on 05/18/2009; Over the Counter (OTC)]. The application also contains a waiver request for the 2 mg strength. The fasting BE study on the strength of 4 mg was designed as open label, balanced, randomized, single-dose, two-way, crossover study in healthy male and female subjects. The determination of BE was based on the 90% confidence interval (CI) of plasma nicotine data. The results are summarized in the tables below (calculated by the firm).

Nicotine Polacrilex Mini Lozenges Dose (1 × 4 mg), N=26 (Male=20 and Female=6; Completed) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study (Study No. AJ1403)					
Nicotine					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	34.7	37.9	91.56	84.50	99.21
AUC∞ (ng·hr/mL)	37.8	41.1	91.92	84.66	99.81
Cmax (ng/mL)	8.30	8.42	98.60	92.33	105.30

Nicotine Polacrilex Mini Lozenges Dose (1 × 4 mg), N=26 (Male=20 and Female=6; Completed) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study (Study No. AJ1403)					
Baseline Corrected Nicotine					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	32.3	35.0	92.18	84.80	100.20
AUC∞ (ng·hr/mL)	35.1	38.0	92.23	84.66	100.47
Cmax (ng/mL)	7.87	7.87	100.03	93.95	106.50

The 90% CIs of the test/reference ratios for LnC_{max}, $LnAUC_{0-t}$, and $LnAUC_{0-\infty}$ fall within the acceptance range of 80.00-125.00% for both nicotine and baseline-corrected nicotine in the fasting study (Please see *Section 4.1.1.4* of the original BE review for details). The firm's fasting BE study is adequate.

Based on the data submitted in the original submission, the formulation for the 2 mg strength of the test product is proportionally similar to that of the 4 mg strength of the test product which underwent bioequivalence testing. However, the maximum daily intake (MDI) of the inactive ingredients of Sodium Stearyl Fumarate, Maltodextrin, and Talc (125.0, 175.0 and 50.0 respectively), based on the unit amounts in the test formulations, exceed the daily intake levels of these inactive ingredients listed in the FDA's Inactive Ingredient Guide for the same route of administration (troche/lozenge, buccal or sublingual). The deficiency was communicated to the firm via a Division of Bioequivalence III (DBIII)'s Easily Correctable Deficiencies (ECD) request dated 09/12/2016.

2. Based on the firm's ECD response (Supp. Document #8; 10/26/2016), in which, the firm's justification was not considered adequate, a DBIII's safety/efficacy consult was issued to the Division of Clinical Review (DCR) dated 11/18/2016 for the evaluation of safety concern and clinical significance due to the (b) (4) amounts of these three excipients. As per the DCR's consult response dated 01/30/2017, "*from clinical and nonclinical perspectives, that the levels of sodium stearyl fumarate, maltodextrin and talc in the proposed generic nicotine lozenge drug product are acceptable*". Thus, the formulations of the test product were considered **adequate**.

3. In addition to the pivotal study, the firm also conducted a three-way crossover pilot fasting study (#AJ-1401), with two investigational test formulations against the RLD product, to investigate the influence of drug release profiles. However, the firm did not provide the detailed formulations and other related information for this pilot study (Please see *Section 4.5.1* of the original BE review for details). The firm was asked to submit all related eCTD-formatted BE data summary tables and detailed information of adverse events (AEs).

4. Also, for the clinical site, as per the review of Clinical Establishment Inspection Report (EIR), although clinical site was closed for the business in 2015, clinical study records from this site were audited for (b) (4) during the OSIS inspection, and an FDA Form-483 was issued with four inspectional findings. The inspection was completed on 02/10/2017 with an outcome classified as "Voluntary Action Indicated (VAI)". Based on the EIR review and BE reviewer's evaluation, the OSIS finding #1 was considered systemically objectionable. The firm was requested to address this inspectional finding #1 for its impact on the in vivo BE study of the current application, and provide information regarding the availability of the retention samples, specifically, investigational product, Nicotine Polacrilex Mini Lozenges 4 mg manufactured by PLD Acquisitions LLC, and reference product, Nicorette® Mini Lozenge 4 mg, used in the pivotal fasting study [(#AJ-1403); please see *Section 4.4* of the original BE review for details].

The BE deficiencies were communicated to the firm in the Agency's CR Letter dated 02/24/2017.

5. In the current post-CR amendment dated 05/02/2017 (Supporting document #11), the firm responded to the above BE deficiencies in Agency's CR Letter dated 02/24/2017.

IV. Submission Summary

A. Drug Product Information, PK/PD Information, and Relevant DB History

The PK/PD information and relevant DB history have not been revised since the original BE review below was conducted. [8, 9]

Please refer to GDRP/Panorama for ANDA 207868 (ANDA-207868-ORIG-1-RESUB-3): Bioequivalence Discipline Review (A207868N000DB_N12022015.docx; Yi Zhang), 02/18/2017.[6]
http://panorama.fda.gov/task/view?ID=566154ac0141beee6e16a23c11cb43fa.

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1 pilot
Single-dose fed	No	-
Steady-state	No	-
In vitro dissolution	No	-
Waiver requests	Yes	1
BCS Waivers	No	-
Vasoconstrictor Studies	No	-
Clinical Endpoints	No	-
Failed Studies	No	-
Adverse Event Individual Case Safety Report	No	-
Amendments	Yes	1

[8] Electronic Orange Book (Updated Through 02/2017): https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020356, last assessed: 05/30/2017.

[9] Labeling and clinical pharmacology (online database): for SULAR® (nisoldipine) ER Tablets, http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=bcdeafac-f4ef-4dda-bdb7-1f819c33bb76; last assessed 05/30/2017.

C. Review of Amendment Submissions

Deficiency #1:

As stated in your pharmaceutical development report (Report No.: D000684 Version 1; in Module 3, Section 3.2.P.2, Date: 06/17/2014), you conducted a three-way crossover in vivo pilot fasting bioequivalence (BE) study (Study No. AJ-1401) with two investigational test formulations, one fast release formulation and another slow release formulation, against the reference-listed drug (RLD) product. However, you did not provide the detailed formulation and batch information on these two investigational test lots. Per the current Guidance for Industry: Submission of Summary Bioequivalence Data for ANDAs (issued May 2011; see the link below for details: http://www.fda.gov/downloads/Drugs/GuidancesComplianceRegulatoryInformation/Guidances/UCM134846.pdf), please submit complete 16 eCTD-formatted data summary tables for the said pilot BE study (Study No. AJ-1401) conducted using the table templates shown at the following link: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf.

Firm's Response to Deficiency #1:

As stated in the pharmaceutical development report (Report No.: D000684 Version 1; in Module 3, Section 3.2.P.2, Date: 06/17/2014), we conducted a three-way crossover *in vivo* pilot fasting bioequivalence (BE) study (Study No. AJ-1401) with the following two investigational test formulations against the RLD product.

1. Fast formulation (Batch No. BM033298/BP033711)
2. Slow formulation (Batch No. BM033299/BP033725)

Based on the dissolution and clinical data from the study results of this pilot bioequivalence study, the slow formulation was selected and a 2-way crossover fasted pivotal BE study (AJ-1403) was conducted against the RLD product which was submitted in the original ANDA.

The completed 16 eCTD-formatted data summary tables for pilot BE study AJ-1401 has been provided in **Section 2.7.1** and **Section 2.7.4** using the table templates from the link above. These tables include the **formulation** and **batch information** on these two investigational test lots. Both PDF and MS Word files for these documents have been provided in this submission. In addition, the executed batch record for the fast formulation has been provided in **Module 3.2.R.P.**

Reviewer's Comments on Firm's Response to Deficiency #1:

- To respond to the BE deficiency #1 with respect to the pilot fasting BE study (Study No. AJ-1401), the reviewer verified that, in the current post-CR amendment dated

05/22/2017, the firm provided completed 16 eCTD-formatted data summary tables in Module 2.7.1 and 2.7.4, including the detailed formulations and batch information for the two investigational test lots, fast release formulation (Batch No. BM033298/BP033711) and slow release formulation (Batch No. BM033299/BP033725).

- Based on formulation data and batch information provided, the same RLD Lot# 14347 was used in this pilot study (Study No. AJ-1401) and the pivotal fasting BE study (Study No. AJ-1403). For the test product, the slow release formulation of investigational Lot# BM033299/BP033725 used for this pilot study (Study No. AJ-1401) was exactly same as that used in the pivotal BE testing (Study No. AJ-1403), which is the final ANDA formulation (i.e. bio-batch). Please see tables of investigational formulations below for the details:

Product	Test 1	Test 2	Reference
Treatment ID	A	B	C
Product Name	Nicotine Polacrilex 4 mg mini lozenge	Nicotine Polacrilex 4 mg mini lozenge	Nicorette® 4 mg mini lozenge
Manufacturer	PLD Acquisitions LLC D/B/A Avema Pharma Solutions	PLD Acquisitions LLC D/B/A Avema Pharma Solutions	GlaxoSmithKline, Inc.
Batch/Lot No.	BM033298/BP033711	BM033299/BP033725	14347
Manufacture Date	02/10/2014	02/11/2014	N/A
Expiration Date	N/A	N/A	07/15
Strength	4.0 mg	4.0 mg	4.0 mg
Dosage Form	Lozenge	Lozenge	Lozenge
Bio-batch Size	(b) (4)		N/A
Production Batch Size			N/A
Potency	4.0 mg	4.0 mg	4.0 mg
Content Uniformity (mean, %CV)	98.8%, 1.1%	98.0%, 1.3%	100.3%, 1.6%
Dose Administered	1 x 4 mg	1 x 4 mg	1 x 4 mg
Route of Administration	Oral	Oral	Oral

Slow Formulation: Nicotine Polacrilex 2 mg mini lozenge, BM033296
Nicotine Polacrilex 4 mg mini lozenge, BM033299

Ingredient	Amount (mg) / Lozenge		Amount (%) / lozenge	
	Strength 1 (4.0mg)	Strength 2 (2.0mg)	Strength 1 (4.0mg)	Strength 2 (2.0mg)
Cores				
Nicotine Polacrilex 15%				
Mannitol				
Sodium Bicarbonate				
Sodium Stearyl Fumarate				
Maltodextrin				
Calcium Polycarbophil				
Xanthan Gum				
Aspartame				
Sodium Alginate				
Talc				
Total	**250.00**	**250.00**	**100.00**	**100.0**

Fast Formulation: Nicotine Polacrilex 2 mg mini lozenge, BM033258
Nicotine Polacrilex 4 mg mini lozenge, BM033298

Ingredient	Amount (mg) / Lozenge		Amount (%) / lozenge	
	Strength 1 (4.0mg)	Strength 2 (2.0mg)	Strength 1 (4.0mg)	Strength 2 (2.0mg)
Cores				
Nicotine Polacrilex 15%				
Mannitol				
Sodium Bicarbonate				
Sodium Stearyl Fumarate				
Maltodextrin				
Calcium Polycarbophil				
Xanthan Gum				
Aspartame				
Sodium Alginate				
Talc				
Total				**100.0**

- Therefore, the firm's response to BE deficiency #1 is **adequate**.

Deficiency #2:

In addition to BE Summary Table 8 "Incidence of Adverse Events in Individual Studies" requested above, please provide the details of all adverse events (AEs) observed in your pilot BE study (Study No. AJ-1401), including the severity/intensity of the AEs (i.e., mild, moderate, severe, serious etc.), onset and resolution times. Please use the following summary guide table in response to this deficiency:

Subject #	Test/ Reference	Period	Adverse Reaction(AE)	AE Severity/Intensity (e.g. mild, moderate, severe, etc.)	Time and Date of dosing	Time and Date of AE	Duration Between Dosing and Start of AE (hours)	Time and Date of Resolution	Additional Comments

Firm's Response to Deficiency #2:

The details of all adverse events (AEs) observed in the pilot BE study AJ-1401 has been provided in Section 2.7.4 using the format stated in the comment above.

Reviewer's Comments on Firm's Response to Deficiency #2:

- To respond to the BE deficiency #2, in the current post-CR amendment, the firm provided the details of all adverse events (AEs) observed in the pilot BE study as follows:

Incidence of Adverse Events in Individual Studies

Body System/ Adverse Event	Reported Incidence by Treatment Group Fasted Bioequivalence Study Study No. AJ-1401		
	Test 1 N=15	Test 2 N=15	Reference N=15
Gastrointestinal Disorders			
Bitter Taste	1 (6.67%)	1 (6.67%)	1 (6.67%)
Burning Sensation (in the mouth)	0 (0.0%)	0 (0.0%)	1 (6.67%)
Heartburn	1 (6.67%)	1 (6.67%)*	0 (0.0%)

Hiccups	5 (33.33%)	5 (33.33%)	5 (33.33%)
Throat Itching	0 (0.0%)	1 (6.67%)	0 (0.0%)
Total	7 (46.67%)	8 (53.33%)	7 (46.67%)

1. N% = Number of subjects reporting AE / number of subjects dosed with respective study drug (x 100).
2. Total N% = Number of subjects that reported at least one AE/number of subjects dosed with respective study drug (x 100).

* Reported by the same subject twice in the same period; counted only once.
Test 1: Nicotine Polacrilex Mini Lozenge, 4 mg BM033298/BP033711
Test 2: Nicotine Polacrilex Mini Lozenge, 4 mg BM033299/BP033725
Reference Product: Nicorette® Mini Lozenge, 4 mg (distributed by GlaxoSmithKline)

Adverse Event Listings: Study No. AJ-1401

Test 1: Fast Formulation (Nicotine Polacrilex 4 mg Mini Lozenge, BM033298, Packaging Lot No. BP033711)
Test 2: Slow Formulation (Nicotine Polacrilex 4 mg Mini Lozenge, BM033299, Packaging Lot No. BP033725)
Reference: Nicorette® 4 mg Mini Lozenge

Subject #	Test/ Reference	Period	Adverse Reaction (AE)	AE Severity/Intensity (e.g. mild, moderate, severe, etc.)	Time and Date of dosing	Time and Date of AE	Duration Between Dosing and Start of AE (hours)	Time and Date of Resolution	Additional Comments
(b) (6)	Reference	2	Hiccups	Mild	24-Mar-14 08:04	24-Mar-14 (08:05)	00:01	24-Mar-14 ~(08:15)	N/A
	Test 1	3	Hiccups	Mild	26-Mar-14 08:04	26-Mar-14 (8:05)	00:01	26-Mar-14 (08:11)	N/A
	Test 1	3	Hiccups	Mild	26-Mar-14 08:06	26-Mar-14 (08:09)	00:03	26-Mar-14 (08:16)	N/A
	Test 2	2	Hiccups	Mild	24-Mar-14 08:10	24-Mar-14 (08:12)	00:02	24-Mar-14 (08:19)	N/A
	Reference	3	Hiccups	Mild	26-Mar-14 08:10	26-Mar-14 (08:12)	00:02	26-Mar-14 (08:15)	N/A
	Test 1	2	Hiccups	Mild	24-Mar-14 08:12	24-Mar-14 (08:13)	00:01	24-Mar-14 (08:24)	N/A
	Test 1	2	Hiccups	Mild	24-Mar-14 08:12	24-Mar-14 (08:24)	00:12	24-Mar-14 (08:28)	N/A
	Test 2	3	Heartburn	Mild	26-Mar-14 08:12	26-Mar-14 (08:13)	00:01	26-Mar-14 (08:22)	N/A
	Test 2	3	Heartburn	Mild	26-Mar-14 08:12	26-Mar-14 ~(09:00)	00:48	26-Mar-14 (10:30)	N/A
	Test 2	1	Hiccups	Mild	22-Mar-14 08:14	22-Mar-14 (08:10)	00:00	22-Mar-14 (08:23)	AE reported before dosing
	Reference	2	Hiccups	Mild	24-Mar-14 08:14	24-Mar-14 (08:15)	0:01	24-Mar-14 (08:20)	N/A

Subject #	Test/ Reference	Period	Adverse Reaction (AE)	AE Severity/Intensity (e.g. mild, moderate, severe, etc.)	Time and Date of dosing	Time and Date of AE	Duration Between Dosing and Start of AE (hours)	Time and Date of Resolution	Additional Comments
(b) (6)	Test 1	3	Hiccups	Mild	26-Mar-14 08:14	26-Mar-14 (08:18)	0:04	26-Mar-14 (08:27)	N/A
	Test 2	2	Hiccups	Mild	24-Mar-14 08:16	24-Mar-14 (08:18)	0:02	24-Mar-14 (08:26)	N/A
	Test 2	2	Hiccups	Mild	24-Mar-14 08:18	24-Mar-14 (08:20)	0:02	24-Mar-14 (08:25)	N/A
	Reference	3	Hiccups	Mild	26-Mar-14 08:18	26-Mar-14 (08:22)	0:04	26-Mar-14 (08:25)	N/A
	Reference	1	Hiccups	Mild	22-Mar-14 08:22	22-Mar-14 (08:25)	0:03	22-Mar-14 (08:26)	N/A
	Test 1	2	Hiccups	Mild	24-Mar-14 08:22	24-Mar-14 (08:26)	0:04	24-Mar-14 (08:32)	N/A
	Test 2	3	Hiccups	Mild	26-Mar-14 08:22	26-Mar-14 (08:29)	0:07	26-Mar-14 (08:36)	N/A
	Test 1	1	Bitter Taste	Mild	22-Mar-14 08:28	22-Mar-14 (08:28)	0:00	22-Mar-14 ~(08:38)	N/A
	Test 2	2	Bitter Taste	Mild	24-Mar-14 08:28	24-Mar-14 (08:28)	0:00	24-Mar-14 ~(08:45)	N/A
	Test 2	2	Throat Itching	Mild	24-Mar-14 08:28	24-Mar-14 (08:30)	0:02	24-Mar-14 ~(08:45)	N/A
	Reference	3	Bitter Taste	Mild	26-Mar-14 08:28	26-Mar-14 (08:30)	0:02	26-Mar-14 (08:42)	N/A
	Reference	3	Burning Sensation (in the Mouth)	Mild	26-Mar-14 08:28	26-Mar-14 (08:30)	0:02	26-Mar-14 (08:42)	N/A

- Based on information/data provided, during this pilot fasting study (Study No. AJ-1401), 7 AEs were observed in test treatment group/fast release formulation (Batch No. BM033298/BP033711), 8 AEs were observed in test treatment group/slow release formulation (Batch No. BM033299/BP033725), and 7 AEs in reference treatment group. The AE profiles observed during this study were comparable for the test and reference products. All AEs reported were considered mild in intensity and all were resolved by the end of the study.

- In addition, as per the original BE review, based on the PK results, the 90% confidence intervals of Cmax, AUC0-t and AUCinf are all within the acceptable BE limits of 80.00-125.00% for both test formulations. The median Tmax of the test products were comparable to that of the reference product for both test formulations. Therefore, both the fast and slow release formulations of the pilot clinical batches were found to be bioequivalent to the RLD.

- As a result, the pilot fasting study (Study No. AJ-1401) is now considered **adequate**.

Deficiency #3:

Deficiency Related to the Office of Study Integrity and Surveillance (OSIS) Inspection

During November 22 to 25, 2016, the FDA Office of Study Integrity and Surveillance (OSIS)'s Division of Bioequivalence and GLP Compliance (DBGLPC) conducted (audited) a surveillance inspection for the clinical site, Phase One Solutions, Inc. (1405 NW 167th Street, Miami Gardens, FL 33169, USA). During the OSIS inspection, clinical study records from this site were audited for the studies from another application. This clinical site is the same as used for the in vivo BE study in the current application. FDA Form-483 was issued to this clinical site following the inspection. For considering the impact of similar study conducted and site practices by the same facility on the BE study of the current ANDA, DBIII reviewed the OSIS inspection reports and found that the following objectionable finding by the OSIS at the above mentioned clinical site could potentially compromise the integrity of the study of the current ANDA as well:

> *Observation #1*
> *Samples of the test article, reference standard used in a bioequivalence study were not retained.*

Please address the above specific finding identified by the OSIS with respect to its impact on all related in vivo BE studies in the current ANDA, providing information and any necessary supporting documents (if applicable) in your response regarding whether the study samples of the investigational products, specifically, Nicotine Polacrilex Mini Lozenges 4 mg manufactured by PLD Acquisitions LLC, and the reference product, Nicorette® Mini Lozenge 4 mg, used in your in vivo BE study, were retained and thus can be released to the FDA upon request.

Firm's Response to Deficiency #3:

In compliance with 21 CFR 320.63, PLD Acquisitions LLC d/b/a Avema Pharma Solutions provided investigational samples of Nicotine Polacrilex 4 mg lozenges (lot BP#033725, February 2016 expiry) to Phase One Solutions, Inc. for the conduct of bioequivalence (BE) study AJ-1403 on May 1, 2014. Additionally, PLD provided Phase One Solutions with the RLD Nicorette mini lozenge (GSK lot# 14347, July 2015 expiry). Phase One confirmed in their letter of receipt that 12 bottles of each would be designated for retention, with the remaining 2 bottles to be used for dosing in the BE study. Thus, a total of 14 bottles of investigational product were provided for each of the brand and PLD product.

Moreover, Phase One Solutions was under contractual agreement with PLD regarding study AJ-1403 to select and maintain retention samples on behalf of PLD. This agreement is provided.

On November 5, 2015, PLD reached out to Phase One regarding the status on the retain samples and we were informed that Phase one had to close their facilities because of an issue related to an acquisition. They informed us that our retain samples had been transported to a new temperature controlled secured locked facility since they were going to reopen the company at a new location. The address where the retain samples were

temporarily stored was 8700 NW 77ct, Medley, Florida 33166. This site was a vendor chosen by Phase One solutions.

PLD reached out again on 02/17/17 when we received the complete response letter from our Regulatory Project Manager. During the week of 02/20/17 we were informed by Phase One over the phone that the retain samples which were stored at the temporary location were destroyed. PLD was not informed about this and we were not provided with a certificate of destruction.

PLD recognizes that these unfortunate circumstances prohibit full compliance with the retention sample requirements, and remains committed through its continuous quality improvement efforts to ensure that there will be no recurrence of such nonconformities. In the absence of the planned retention samples, PLD offers that it continues to maintain the samples of the same lot BP#033725 from which the BE study was conducted. These samples remain securely stored in the PLD facility located at 10400 NW 29th terrace, Miami, FL 33172. These samples may be released to FDA upon request.

In addition, we have also submitted samples of Nicotine Polacrilex lozenges 2 mg and 4 mg in the proposed container closure system to our RPM in January 2017. This was a request in the Information request we received in December 2016.

Reviewer's Comments on Firm's Response to Deficiency #3:

- To respond to the BE deficiency with respect to the OSIS inspectional finding (Observation #1) related to study sample retention for the clinical site [Phase One Solutions, Inc. (1405 NW 167th Street, Miami Gardens, FL 33169, USA)], the firm stated that "*During the week of 02/20/17 we were informed by Phase One over the phone that* ***the retain samples which were stored at the temporary location were destroyed****. PLD was not informed about this and we were not provided with a certificate of destruction.*" As a solution, the firm agree to "*offer that it* ***continues to maintain*** *the samples of the same lot BP#033725 from which the BE study was conducted*", and "*these samples may be released to FDA upon request*".

- As per 21 CFR 320.38 and 320.63, a proper number of samples from the BE study, including samples of both test article and reference standard, should be retained at the study site, or at independent third parties, which should be available for releasing to FDA upon request. In the absence of reserve samples at the study site or an independent third party, the authenticity of test and reference drug products used in studies cannot be ensured. However, as the firm indicated above, the retained samples of the investigational products used in the current *in vivo* BE studies, specifically, Nicotine Polacrilex Mini Lozenges 4 mg manufactured by PLD Acquisitions LLC and the reference product, Nicorette® Mini Lozenge 4 mg, have been destroyed. The clinical site, Phase One Solutions, Inc., did not retain

reserve samples appropriately of the investigational products used in the related BE studies in the current ANDA as require by 21 CFR 320.38 and 320.63.

- Hence, the authenticity of the test and reference drug products used in the pivotal (AJ-1403) and pilot (AJ-1401) BE studies cannot be confirmed due to lack of reserve samples. As a result, the *in vivo* BE study data from the current studies, #AJ-1403 and #AJ-1401, are **NOT** considered acceptable since the reliability of data is impaired by the violation of the reserve sample regulations.

D. Comments for Other OGD Disciplines

Discipline	Comment
N/A	--

E. Pending Consults (Clinical, Statistical, Science Staff, Chemistry etc.)

Discipline	Comment
N/A	--

F. Review of the Office of Study Integrity and Surveillance (OSIS) Inspection Reports

This ANDA is a GDUFA CY4 submission, the OSIS inspection status for the current ANDA is COMPLETE (but the clinical site is **inadequate)**. Please see *Section IV.C, Reviewer's Comments to Deficiency #3* for the details.

G. Additional Attachments

1. The completed 16 eCTD-formatted data summary tables for pilot BE study #AJ-1401 provided in the current amendment dated 05/02/2017.


M2.7.1_summary-bio pharm.doc


M2.7.4_summary-clin -safety.doc

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 207868

APPLICANT: PLD Acquisitions LLC, D/B/A Avema Pharma Solutions

DRUG PRODUCT: Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base

[The following deficiency should be communicated to the firm via a CR letter.]

The Division of Bioequivalence III (DBIII) has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

Deficiency Related to the Office of Study Integrity and Surveillance (OSIS) Inspection

As per 21 CFR 320.38 and 320.63, "*The applicant of an abbreviated application or a supplemental application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act, or, if bioequivalence testing was performed under contract, the contract research organization shall retain reserve samples of any test article and reference standard used in conducting an in vivo or in vitro bioequivalence study required for approval of the abbreviated application or supplemental application. The applicant or contract research organization shall retain the reserve samples in accordance with, and for the period specified in, 320.38 and shall release the reserve samples to FDA upon request in accordance with 320.38"*. In the absence of reserve samples at the study site or an independent third party, the authenticity of test and reference drug products used in studies cannot be ensured.

Based upon the information you provided in the current post-complete response (CR) amendment (dated 05/02/2017), the clinical site, Phase One Solutions, Inc., did not retain reserve samples properly of the investigational products used in the related bioequivalence (BE) studies for the current ANDA as require by 21 CFR 320.38 and 320.63, as you stated that "*During the week of 02/20/17 we were informed by Phase One over the phone that* ***the retain samples which were stored at the temporary location were destroyed****";* and that you were "*not informed about this and you were not provided with a certificate of destruction.*" Therefore, the authenticity of the test and reference drug products used in your pivotal (Study No. AJ-1403) and pilot (Study No. AJ-1401) BE studies cannot be confirmed due to lack of reserve samples. As a result, the *in vivo* BE study data from the current studies, #AJ-1403 and #AJ-1401, are **not** acceptable since the reliability of data has been impaired by the violation of reserve sample regulations.

Please note that the bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

H. Outcome Page

ANDA: 207868

Completed Assignment for 207868 ID: 31153

Reviewer: Zhang, Yi **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base; PLD Acquisitions LLC, D/B/A Avema Pharma Solutions; Post-CR

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
31153	5/2/2017	BIO	ANDA Amendment [1]	1	1
31153	5/2/2017	Parallel	Study Amendment [1]	1	1
31153	5/25/2017	BIOQUALITY	Quality Assessment [1-5]	4.5	4.5
				Total:	6.5

QUALITY ASSESSMENT

BIOPHARMACEUTICS

Product Background:

NDA/ANDA: ANDA 207868

Drug Product Name / Strength: Nicotine Polacrilex Mini Lozenges/ 2 mg and 4 mg

Route of Administration: oral

Applicant Name: PLD Acquisitions LLC, D/B/A Avema Pharma Solutions

Review Summary:

The proposed drug product, Nicotine Polacrilex Mini Lozenges/ 2 mg and 4 mg is the generic version of reference product, Nicorette® 2mg and 4mg (approved on 5/18/2009), indicated to reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking. The composition of the proposed drug product is shown in Table 1.

Table 1: Nicotine Polacrilex Mini Lozenge drug product composition and function of excipients

Ingredient	4.0 mg Dose	2.0 mg Dose	Function
	mg/unit	mg/unit	
Nicotine Polacrilex 15%		(b) (4)	Active
Mannitol			(b) (4)
Sodium Bicarbonate			
Sodium Stearyl Fumarate			
Maltodextrin			
(b) (4)			
Calcium Polycarbophil			
Xanthan Gum			
Aspartame			
Sodium Alginate			
Talc			
Totals			

The Applicant followed the dissolution method recommended by FDA as shown below:

Parameter	Value
Medium	pH7.4 phosphate buffer, USP
Volume	900 mL
Temperature	37 ± 0.5 °C
Apparatus	Apparatus 1 (Basket)
Rotational Speed	100 rpm
Time Point	30, 60, 90, 120 and 180 minutes
Sample Volume	1.5 mL

The dissolution method is acceptable.

List Submissions being reviewed (table):

Application 207868 - Sequence 0000 - 0000 (1) 06/19/2014 ORIG-1 /Multiple Categories/Subcategories

Highlight Key Outstanding Issues from Last Cycle: N/A. This is the first cycle of review from biopharmaceutics perspective.

Concise Description Outstanding Issues Remaining:

A. Submit the complete dissolution data (i.e. all raw data, range, mean, %CV, dates of testing) for the following:

1. The generic batch# BP033725 (4 mg).

2. Those for the generic 2 mg strength (three exhibit batches)

B. We have the following comments regarding the dissolution acceptance criteria:

a) For extended release products the establishment of at least three specification time-points covering the initial, middle, and terminal phases of the complete dissolution profile data must be set. The acceptance criteria ranges must be based on the overall dissolution data generated at these times.

b) In general, the selection of the dissolution acceptance criteria ranges is based on mean target value (b) (4) % and NLT (b) (4) % for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model.

c) The dissolution acceptance criteria should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with dissolution profiles outside those that were tested clinically.

BCS Designation

Reviewer's Assessment: The Applicant stated nicotine is Class I in BCS classification.

Solubility: Soluble in water and non-polar solvents

Permeability: Not provided

Dissolution: Please see below:

Dissolution Method and Acceptance Criteria

The Applicant used the dissolution method as per the FDA recommended method as described below:

Parameter	Value
Medium	pH7.4 phosphate buffer, USP
Volume	900 mL
Temperature	37 ± 0.5 °C
Apparatus	Apparatus 1 (Basket)
Rotational Speed	100 rpm
Time Point	30, 60, 90, 120 and 180 minutes
Sample Volume	1.5 mL

The mean comparative dissolution data and profile of Nicotine Polacrilex Mini Lozenge 4 mg (Lot no. : BM033299, Manufacturing date: 02/11/14)) vs. Reference Listed Drug- Nicorette® (Nicotine Polacrilex) Mini Lozenge 4 mg (Lot no. 14347 (Expiration date: 07/2015) are shown in Table 2 and Figure 1.

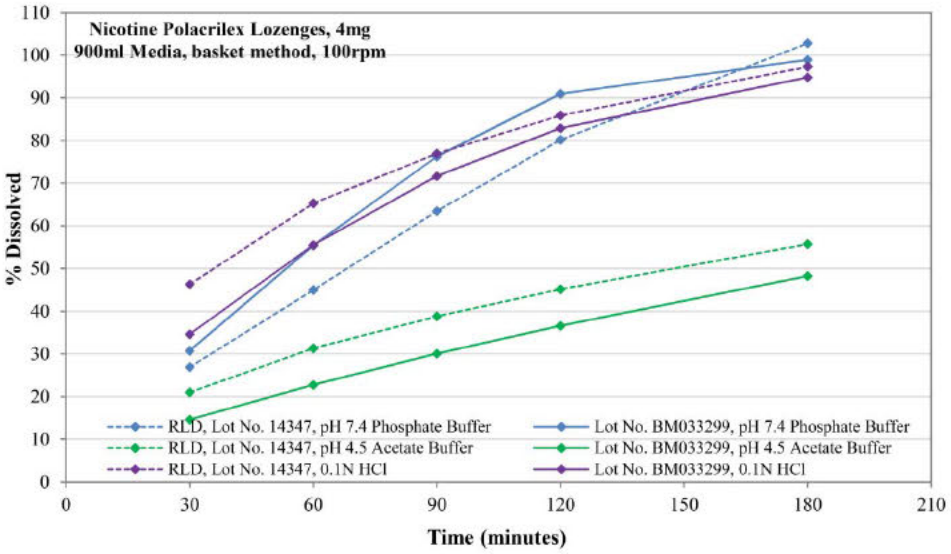
Both Batch #s. BM033299 and BP033725 were listed as the "Test Batches" under Product Information in Biopharm Summary Section of the submission, however, only batch BP033725 was listed as the clinical batch used in the in vivo BE study (AJ1403). Therefore, it does not appear that batch BM033299 is the biobatch.

Table 2: Mean Comparative Dissolution Data of Nicotine Polacrilex Mini Lozenge 4 mg (Lot no. : BM033299, Manufacturing date: 02/11/14)) vs. Reference Listed Drug- Nicorette® (Nicotine Polacrilex) Mini Lozenge 4 mg (Lot no. 14347 (Expiration date: 07/2015) in Proposed Dissolution Media (pH 7.4 Phosphate Buffer)

Dissolution Conditions	**Apparatus:**	Apparatus 1 (Basket)
	Speed of Rotation:	100 rpm
	Medium:	pH7.4 phosphate buffer, USP
	Volume:	900mL
	Temperature:	37 ± 0.5 °C
Firm's Proposed Specifications	NLT (b)(4)% and NMT (b)(4)% of Nicotine LC dissolved in 30min NLT (b)(4)% and NMT (b)(4)% of Nicotine LC dissolved in 60min NLT [redacted]% of Nicotine LC dissolved in 90min NLT [redacted]% of Nicotine LC dissolved in 120min NLT [redacted]% (b)(4)%) of Nicotine LC dissolved in 180minutes	
Dissolution Testing Site (Name, Address)	PLD Acquisitions, LLC D/B/A Avema Pharma Solutions, 10400 NW 29th Terrace, Miami, FL 33172, USA.	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**					**Study Report Location**
						30	**60**	**90**	**120**	**180**	
QC-309 Page- 166	06/06/14	Test: BM033299 (Manufacturing date:02/11/14)	4.0mg Lozenge	12	Mean (%)	31	55	76	91	99	Test results form PS003381 located in the corresponding finished product folder
					Range (%)	[redacted] (b) (4)					
					%RSD	5.3	7.8	7.6	6.0	2.7	
QC-313 Page-107	11/25/13	Reference: 14347 (Expiration date: 07/2015)	4.0mg Lozenge	12	Mean (%)	27	46	63	80	103	Test results form PS003381 located in the corresponding finished product folder
					Range (%)	[redacted] (b) (4)					
					%RSD	4.9	3.9	3.6	5.2	1.0	

Figure 1: Mean Comparative Dissolution Data of Nicotine Polacrilex Mini Lozenge 4 mg (Lot no. : BM033299, Manufacturing date: 02/11/14)) vs. Reference Listed Drug- Nicorette® (Nicotine Polacrilex) Mini Lozenge 4 mg (Lot no. 14347 (Expiration date: 07/2015) in Three Different Media (pH 7.4 Phosphate Buffer, pH 4.5 Acetate Buffer, 0.1N HCl)



Dissolution Acceptance Criterion

The Applicant's proposed dissolution acceptance criteria for both 2 mg and 4 mg are as follows:
NLT (b) (4)% and NMT (b) (4)% of Nicotine LC dissolved in 30 minutes
NLT [redacted]% and NMT [redacted]% of Nicotine LC dissolved in 60 minutes
NLT [redacted]% of Nicotine LC dissolved in 90 minutes
NLT [redacted]% of Nicotine LC dissolved in 120 minutes
NLT [redacted]% ([redacted] (b) (4)%) of Nicotine LC dissolved in 180 minute

Figure 1 shows that the test drug products release meet the proposed acceptance criteria.

Analytical Method Validation

Parameters	Acceptance Criteria	Results
Specificity	(b) (4)	
System Precision		
Linearity		
Accuracy		
Method		

Precision	(b) (4)
Intermediate Precision {Ruggedness}	
Robustness	
Solution Stability	

Filter	(b) (4)

Reviewer's Assessment:

- **The applicant used the FDA-recommended method for dissolution testing of the drug product. There is no USP dissolution method for nicotine.**

- **The applicant submitted acceptable dissolution analytical method validation including specificity, system precision, linearity, accuracy, method precision, intermediate precision (ruggesdness), robustness, solution stability, and filter study. Linearity was validated with concentrations ranging from (b) (4), which is (b) (4)% of the lower expected % Nicotine Label claim dissolved at 30 minutes (b) (4)) for Nicotine Polacrilex Mini 2 mg to 1 (b) (4)% of the expected % Nicotine Label Claim dissolved at 1 80 minutes ((b) (4)%) for Nicotine Polacrilex Mini 4 mg**

- **The Applicant did not provide the complete dissolution data with 12 units for each strength (i.e. all raw data, range, mean, %CV, dates of testing) in the submission.**

- **Both Batch #s. BM033299 and BP033725 were listed as the "Test Batches" under Product Information in Biopharm Summary Section of the submission, however, only batch BP033725 was listed as the clinical batch used in the in vivo BE study (AJ1403). Therefore, it does not appear that batch BM033299 is a biobatch. The Applicant will be requested to provide the complete dissolution profile data of the biobatch BP033725.**

In addition, the complete dissolution data on the proposed generic 2 mg lozenge (3 exhibit batches) were not submitted.

- **The appropriateness of the applicant's proposed dissolution specification will be decided upon the dissolution raw data of 4 mg and 2 mg is submitted.**

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: n/a

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: n/a

In-Vitro Soft-food Interaction Study

Reviewer's Assessment: n/a

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment: n/a

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

Reviewer's Assessment: n/a

In-Vitro Dissolution Testing for Abuse-deterrent Products

Reviewer's Assessment: n/a

In-Vitro BE Evaluation for Pulmonary Products

Reviewer's Assessment: n/a

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: n/a

Bridging of Formulations

Reviewer's Assessment: The final formulation was used in the BE study as well as in vitro dissolution tests.

Biowaiver Request

Reviewer's Assessment: The Applicant requested for a waiver of evidence of in vivo bioavailability or bioequivalence for the lower strength, Nicotine Polacrilex 2 mg by stating that Nicotine Polacrilex 4mg and 2mg mini lozenge formulations are proportionally similar in their active and inactive ingredients. The biowaiver request for the generic 2 mg lozenge is to be assessed by the BE reviewer in OGD. Note, no complete dissolution profile data of generic 2 mg lozenge (three exhibit batches) were submitted for review.

R Regional Information

Comparability Protocols

Reviewer's Assessment: n/a

Post-Approval Commitments

Reviewer's Assessment: n/a

Lifecycle Management Considerations

Reviewer's Assessment: n/a

List of Deficiencies:

A. Submit the complete dissolution data (i.e. all raw data, range, mean, %CV, dates of testing) for the following:

1. The generic batch# BP033725 (4 mg).

2. Those for the generic 2 mg strength (three exhibit batches)

B. We have the following comments regarding the dissolution acceptance criteria:

a) For extended release products the establishment of at least three specification time-points covering the initial, middle, and terminal phases of the complete dissolution profile data must be set. The acceptance criteria ranges must be based on the overall dissolution data generated at these times.

b) In general, the selection of the dissolution acceptance criteria ranges is based on mean target value (b) (4)% and NLT (b) (4)% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model.

c) The dissolution acceptance criteria should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with dissolution profiles outside those that were tested clinically.

Primary Biopharmaceutics Reviewer Name and Date:

An-Chi (Angela) Lu, Pharm.D.

Biopharmaceutics Reviewer

ONDP/Division of Biopharmaceutics

December 14th, 2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I concur. 01/10/17

Tien-Mien Chen, Ph.D.
Acting Biopharm. Lead

DB/ONDP/OPQ

An-Chi Lu

Digitally signed by An-Chi Lu
Date: 2/17/2017 01:34:43PM
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DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	207868	
Drug Product Name	Nicotine Polacrilex Mini Lozenges	
Strength(s)	EQ 2 mg Base and EQ 4 mg Base*	
Applicant Name	PLD Acquisitions LLC, D/B/A Avema Pharma Solutions	
Applicant Address	10400 NW 29th Terrace Miami, FL 33172 USA	
Applicant's Point of Contact	Mehul Govani	
Contact's Telephone Number	(b) (4)	
Contact's Fax Number	(516) 272-8203	
Contact's Email Address	mgovani@pldevelopments.com	
Original Submission Date(s)	12/02/2015 (Resubmission/After Refuse to Receive) *[06/19/2014 (Subject to a refuse to receive)]***	
Submission Date(s) of Amendment(s) Under Review	09/17/2015 (Supp. Document #2) Quality/Response To Information Request; 12/02/2015 (Supp. Document #3) Quality/Manufacture Information; User Fee/Coversheet; Resubmission/After Refuse to Receive; Labeling/Container-Carton Draft; 10/26/2016 (Supp. Document #8) Response to ECD/Bioequivalence	
Reviewer	Yi Zhang, Ph.D.	
Secondary Reviewer	Li Gong, Ph.D.	
Tertiary Reviewer	April C. Braddy, Ph.D.	
Study Number (s)	AJ-1403	AJ-1401
Study Type (s)	Pivotal Fasting Study	Pilot Fasting Study
Strength (s)	1 x 4 mg	1 x 4 mg
Clinical Site	Phase One Solutions, Inc.	
Clinical Site Address	1405 NW 167th Street Miami Gardens, FL 33169 USA Phone: (305) 624-9191	
Analytical Site	(b) (4)	
Analytical Site Address		
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver/Deem**	**Post October 1, 2014 ANDAs** ☒ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☐ **Complete**

	Bioequivalent)		
Waiver/Deem Bioequivalent	☒ **Granted** ☐ **Tentatively granted** ☐ **Not granted** ☐ **N/A**		
QC Dissolution	☐ **Pending** ☐ **Adequate** ☒ **Inadequate*** **		
Formulation	☒ **Adequate** ☐ **Inadequate**		
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☒ **No** ☐ **N/A**		
Deficiency Classification	☐ **Major (Deficiencies to be communicated by CR)** ☒ **Minor** ☐ **N/A (Review is Adequate)**		
OVERALL REVIEW RESULT	☐ **Adequate** ☒ **Inadequate**		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**		
Communication	☐ **ECD** ☐ **IR** ☒ **Not Applicable** *(Deficiencies to be communicated by CR as per RPM)*		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 2, 3 & 8	**Pivotal Fasting**	**4 mg**	**Adequate**
3	**Pilot Fasting**	**4 mg**	**Inadequate**
1, 2, 3 & 8	**Waiver**	**2 mg**	**Adequate**

Note:
* Each Lozenge containing Nicotine Polacrilex equivalent to Nicotine Base 2 mg and 4 mg, respectively. Throughout the current review the 2 mg and 4 mg strength refer to EQ amount of the Nicotine Base.

**This application was originally filed on 06/19/2014 as ANDA 207868. On 09/29/2015, a refuse to receive letter was issued due to several reasons including but not limited to incomplete information[1]. The firm responded to the deficiencies in the filing review, and resubmitted the current application on 12/02/2015 with the same ANDA number.

***The dissolution review was completed recently by the Division of Biopharmaceutics at the Office of New Drug Products (ONDP) in the Office of Pharmaceutical Quality (OPQ) on 01/11/2017 with inadequate outcome. The current BE review was updated accordingly. However, the deficiencies identified in the dissolution review do not impact the waiver request consideration for the BE portion.

[1] DARRTS ANDA 207868: COR-ANDAFILE-03(Refuse to Receive); BENSON, JASON A; Submit/Final Date: 09/29/2015.

1 EXECUTIVE SUMMARY

This ANDA is a GDUFA CY4 submission.

This application contains the results of a pivotal fasting bioequivalence (BE) study (#AJ-1403) comparing a test product, PLD Acquisitions LLC, D/B/A Avema Pharma Solutions's Nicotine Polacrilex Mini Lozenges, 4 mg, to the corresponding reference product, GlaxoSmithKline Consumer Healthcare's Nicorette® Mini Lozenge, 4 mg [NDA 022360, approved on 05/18/2009; Over the Counter (OTC)][2]. The application also contains a waiver request for the 2 mg strength. The BE study was designed as an open label, randomized, single-dose, two-way, crossover study in healthy male and female subjects. The plasma concentration of nicotine was measured. The determination of BE was based on the 90% confidence interval (CI) of plasma nicotine data. The results are summarized in the tables below (calculated by the firm).

Nicotine Polacrilex Mini Lozenges Dose (1 × 4 mg), N=26 (Male=20 and Female=6; Completed) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study (Study No. AJ1403)					
Nicotine					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	34.7	37.9	91.56	84.50	99.21
AUC∞ (ng·hr/mL)	37.8	41.1	91.92	84.66	99.81
Cmax (ng/mL)	8.30	8.42	98.60	92.33	105.30

Nicotine Polacrilex Mini Lozenges Dose (1 × 4 mg), N=26 (Male=20 and Female=6; Completed) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study (Study No. AJ1403)					
Baseline Corrected Nicotine					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	32.3	35.0	92.18	84.80	100.20
AUC∞ (ng·hr/mL)	35.1	38.0	92.23	84.66	100.47
Cmax (ng/mL)	7.87	7.87	100.03	93.95	106.50

The 90% CIs of the test/reference ratios for LnC_{max}, $LnAUC_{0-t}$, and $LnAUC_{0-\infty}$ fall within the acceptance range of 80.00-125.00% for both nicotine and baseline-corrected nicotine in the fasting study (Please see *Section 4.1.1.4* of this review for details). The firm's fasting BE study is **adequate**.

[2] Electronic Orange Book (Updated Through 06/2016): http://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=022360#; Search Term: NDA 022360; last accessed on 08/17/2016.

The review of *in vitro* dissolution testing was conducted separately by the biopharmaceutics quality reviewer at the Office of New Drug Products (ONDP) in the Office of Pharmaceutical Quality (OPQ), which was completed recently on 01/11/2017 with deficiencies identified related to the incomplete submission of dissolution raw data and unacceptable dissolution criteria. However, in the current BE review, the dissolution data were evaluated only for the waiver request consideration. Based on the comparative dissolution data submitted using the acceptable FDA-recommended method, the dissolution testing is considered **acceptable** with respect to supporting the waiver request for the 2 mg strength of the test product.

The formulation for the 2 mg strength of the test product is proportionally similar to that of the 4 mg strength of the test product which underwent bioequivalence testing. However, the maximum daily intake (MDI) of the inactive ingredients of Sodium Stearyl Fumarate, Maltodextrin, and Talc ((b) (4) respectively) based on the unit amounts in the test formulations exceed the daily intake levels of these inactive ingredient listed in the FDA's Inactive Ingredient Guide for the same route of administration (troche/lozenge, buccal or sublingual). The firm was asked to provide its justifications if the amounts of Sodium Stearyl Fumarate, Maltodextrin, and Talc present in the test formulation would significantly compromise the safety and efficacy of the test drug products. The deficiency was communicated to the firm via a Division of Bioequivalence III (DBIII)'s Easily Correctable Deficiencies request dated 09/12/2016 (ECD; please see *Section 4.6.1* of current review for details).

On 10/26/2016, the firm submitted its responses to the DBIII's ECD request (Supp. Document #8), in which, the firm's justification was considered incorrect (Please see Reviewer's Notes in *Section 4.6.1* for details). In addition, the firm also provided supportive documents, including a summary of "*Nonclinical Information Amendment*" along with clinical/research literatures and reports in Module 1.11.2. Therefore, the DBIII requested a safety/efficacy consult to the Division of Clinical Review (DCR) dated 11/18/2016 in seeking the expert opinion/comments for the evaluation of the firm's responses with respect to the safety concern and clinical significance due to the (b) (4) amounts of these three excipients. As per the DCR's consult response dated 01/30/2017, "*from clinical and nonclinical perspectives, that the levels of sodium stearyl fumarate, maltodextrin and talc in the proposed generic nicotine lozenge drug product are acceptable*". Thus, the formulations of the test product are now considered **adequate**.

Therefore, the DBIII grants the waiver request of *in vivo* BE study requirement for the lower strength, EQ 2 mg Base, based on criteria set forth in 21 CFR § 320.22 (d) (2).

In addition to the pivotal study, as reported in the pharmaceutical development report (Report# D000684 Version 1; Date: 06/17/2014; Module 3, Section 3.2.P.2 in GlobalSubmit Review), the firm also conducted a 3-way crossover pilot fasting study (#AJ-1401), with two investigational test formulations against the RLD product, to investigate the influence of drug release profiles. However, the firm did not provide the detailed formulations and other related information for this pilot study (Please see *Section*

4.5.1 for details). The firm will be asked to submit all related eCTD-formatted BE data summary tables and detailed information of adverse events (AEs).

Office of Study Integrity and Surveillance (OSIS) Inspection:

This ANDA is a GDUFA CY4 application. The overall OSIS inspection status for the current ANDA, therefore, is "To Be Determined by OSIS". In addition, for the analytical site, as per the memorandum dated 01/20/2016, the Division of Generic Drug Bioequivalence Evaluation (DGDBE) at the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection at the analytical site for the current ANDA 207868. The OSIS review for the clinical site will be conducted separately at a later date. (Please see *Section 4.4* of this review for details). Also, based on evaluation of the submitted data, the OSIS inspection of the clinical and analytical sites for the current ANDA 207868 is not necessary. The studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiency was identified by the reviewer.

As a result, the application is **inadequate** with a deficiency.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information[2]

Test Product	Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base
Reference Product	Nicorette® (nicotine polacrilex; OTC) mini Lozenges, EQ 2 mg Base and EQ 4 mg Base (4 mg is RLD strength)
RLD Manufacturer	GlaxoSmithKline Consumer Healthcare
NDA No.	022360
RLD Approval Date	05/18/2009
Indication	Used to reduce withdrawal symptoms, including nicotine craving associated with quitting smoking.

3.2 PK/PD Information[3]

Bioavailability	The oral bioavailability of nicotine is about 25 to 30%
Food Effect	Labeling does not make any statements about the effect of food on absorption or administration.
Tmax	Approximately one hour (1 h) for nicotine polacrilex lozenge
Metabolism	Extensively metabolized to several less active metabolites. Continine is the major metabolite, and is formed by two-step process, via CYP450 enzyme (CYP2A6) and aldehyde oxidase.
Excretion	Nicotine and its metabolites are excreted almost exclusively in the urine.
Half-life	Approximately 2 hours
Dosage and Administration	• if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you. • before using this product, read the enclosed User's Guide for complete directions and other important information • begin using the lozenge on your quit day • if you smoke your first cigarette more than 30 minutes after waking up, use 2mg nicotine lozenge • if you smoke your first cigarette within 30 minutes of waking up, use 4mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

• nicotine lozenge is a medicine and must be used a certain way to get the best results
• place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 - 30 minutes). Minimize swallowing. Do not chew or swallow lozenge.
• you may feel a warm or tingling sensation
• occasionally move the lozenge from one side of your mouth to the

[3] Labeling and clinical pharmacology (online database), https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=991704ed-781a-489b-8b56-0b558e8fc385 (Updated: 06/07/2016); Search Term: Nicorette®; last accessed on 08/17/16.

	other until completely dissolved (about 20 - 30 minutes) • do not eat or drink 15 minutes before using or while the lozenge is in your mouth • to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks • do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects • do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day. • it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.
Maximum Daily Dose	80 mg (maximal 20 lozenges per day for 4 mg strength) 40 mg (maximal 20 lozenges per day for 2 mg strength)
Drug Specific Issues	**If you are pregnant or breast-feeding, only us e this medicine on the advice of your health care provider.** Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known. **Do not use (Mint)** •if you are allergic to soya **Ask a doctor before us e if you have** •a sodium-restricted diet •heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate. •high blood pressure not controlled with medication. Nicotine can increase your blood pressure. •stomach ulcer or diabetes **Ask a doctor or pharmacist before us e if you are** •using a non-nicotine stop smoking drug •taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted. **Stop us e and ask a doctor if** •mouth problems occur •persistent indigestion or severe sore throat occurs •irregular heartbeat or palpitations occur •you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat •you have symptoms of an allergic reaction (such as difficulty breathing or rash) **Keep out of reach of children and pets.**

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	1, fasting

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	Eq. 4 mg base
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	N/A

Analytes to measure (in plasma/serum/blood):	Nicotine in plasma	
Bioequivalence based on:	90% CI of Nicotine	
Waiver request of in-vivo testing:	Eq. 2 mg based on (i) acceptable bioequivalence study on the Eq. 4 mg base strength, (ii) acceptable in-vitro dissolution testing on all strengths, and (iii) proportional similarity of the formulation across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in-vivo testing. Lozenges with alternate flavors cannot be filed in the same ANDA as the mint flavored lozenge. For each flavor, a separate submission (ANDA) should be submitted. Lozenges with an alternate flavor may be eligible for a waiver of the bioequivalence study requirements based on (1) an acceptable bioequivalence study on the 4 mg strength of the mint lozenge, (2) acceptable dissolution testing for the nicotine polacrilex lozenge with additional flavor vs. the RLD, (3) proportional similarity in the formulations of the nicotine polacrilex lozenge with additional flavor and nicotine polacrilex lozenge with mint flavor, and (4) the additional flavor (the inactives) has been approved for the same route of administration.	
Source of most recent recommendations or provide the link to the current draft guidance:	Bioequivalence Recommendations for Specific Products: Draft Guidance on Nicotine Polacrilex Lozenge; linked to NDA 022360. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240974.pdf Recommended Jan 2011.	
Summary of OGD or DB History	Pending ANDAs (Being Reviewed)[4]	ANDA-207868 (current): PLD Acquisitions LLC, D/B/A Avema Pharma Solutions ANDA-208875: Watson Laboratories Inc ANDA-209206: Watson Laboratories Inc
	Approved ANDAs	According to the Electronic Orange Book, there is only one ANDA currently approved for this particular drug product on the market:[5] ANDA 203690, PERRIGO R&D CO, Approved on 10/09/2012.

[4] DARRTS. Search term "Nicotine Polacrilex" under ANDA; last accessed: 08/17/2016.
[5] Electronic Orange Book (Updated Through 06/2016); Search term: Nicotine Polacrilex; http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm?resetfields=1; last assessed: 08/18/2016.

	Previously Reviewed ANDAs	ANDA 203690
	Protocols	There is one protocol (02-065 from L. Perrigo) submitted to OGD for Nicotine Polacrilex/Lozenge in the OGD protocols tracking system.[6]
	Controls	There are several controlled correspondence documents submitted for Nicotine Polacrilex/Lozenge available in CONTROLS Document Tracking.[7]

Ctl No	Description	Doc Date	From
09-0554	Requesting dissolution guidance for this product.	10/15/2009 (Closed 2/20/2010)	Perrigo
14-0459	Chemistry Guidance/Recommendation Nicotine Polacrilex Lozenge, 2mg/4 mg - Switch from natural nicotine to synthetic nicotine in the manufacture	5/20/2014 (Open)	Perrigo R&D Company

3.4 Pre-Study Bioanalytical Method Validation

Information Requested	Data			
Bioanalytical method validation report location	AP14_005_02			
Analytes	Nicotine			
Internal standard (IS)	Nicotine-D_4			
Method description	Solid phase extraction procedure			
Limit of quantitation	LLOQ 0.2000 ng/mL			
Average recovery of drug (%)	105.1%			
Average recovery of IS (%)	88.9%			
Standard curve concentrations	0.2000, 0.4000, 1.000, 2.000, 5.000, 10.00, 20.00 and 25.00			
QC concentrations (ng/mL)	LLOQ LQC MQC-2	0.2000 ng/mL 0.5000 ng/mL 2.500 ng/mL	MQC-2 HQC	12.50 ng/mL 18.75 ng/mL
QC Intra-day precision range (%CV)	LLOQ LQC MQC-2	3.0 to 6.2% 1.8 to 4.4% 0.9 to 3.1%	MQC-2 HQC	0.8 to 2.1% 0.5 to 2.8%

[6] Division of Bioequivalence Protocols Tracking: http://fdswv04385/seltrack/Protocols.asp; search term: Nicotine Polacrilex; last accessed: 08/18/2016.

[7] Internal Control Correspondence Database: http://cdsogd1/controls/; Search term: Nicotine Polacrilex; last accessed: 08/18/2016.

QC Intra-day accuracy range (%Bias)	LLOQ -0.4 to 6.0% LQC 1.0 to 2.6% MQC- 0.2 to 1.6%	MQC- -0.6 to 2.2% 2 -1.2 to 1.9% HQC
QC Inter-day precision range (%CV)	1.8 to 5.5%	
QC Inter-day accuracy range	0.2 to 1.9%	
Bench-top stability (hrs)	Analyte stability in human plasma: 24 hours at room temperature with and without metabolites.	
Stock stability (hours/days)	6 hours at room temperature and 15 days at -20°C ± 10°C for nicotine stock solution, internal standard stock solution, nicotine intermediate stock solution and internal standard	
Processed stability (hrs)	• Autosampler stability 28 hours at room temperature • Processed sample stability 72 hours at room temperature	
Freeze-thaw stability (cycles)	3 cycles (frozen at -20°C ± 10°C, thawed at room temperature)	
Long-term stability (days)	• 83 days at -20°C ± 10°C in K_2EDTA human plasma • 77 days at -20°C ± 10°C in K_2EDTA human plasma with metabolites	
Dilution integrity	• DI-LTS samples (83 days at -20°C ± 10°C), assayed using a 10- fold dilution • DI-FT samples (3 cycles, frozen at -20°C ± 10°C, thawed at room temperature), assayed using a 10-fold dilution • DI-SBM samples (24 hours at room temperature), assayed using a 10-fold dilution	
Selectivity	There were interfering peaks in the blank plasma samples at the retention times of nicotine and the internal standard as seen in the chromatograms due to Environmental Tobacco Smoke (ETS) which is generated from side-stream smoke and mainstream smoke exhaled by smokers. As a consequence, nicotine from ETS is commonly found in measurable concentrations in air, surface and dust samples and it is very	

SOPs submitted	Yes
Does the duration of the each of the LTSS stability parameters support the sample preparation and assay dates	Yes

Comments on the Pre-Study Method Validation:

- A sensitive and selective liquid chromatographic tandem mass spectrometric (LC-MS/MS) method was developed and validated for the quantitative analysis of nicotine in human plasma. Nicotine-D_4 was used as the internal standard.

- The firm used Dipotassium Ethylenediaminetetraacetic Acid (K_2EDTA) as an anticoagulant in the pre-study bioanalytical method validation. The same anticoagulant K_2EDTA was used in fasting BE study sample processing.

- The firm submitted the long term storage stability (LTSS) data for nicotine as 83 days at -20°C±10°C (in K_2EDTA human plasma) and 77 days at -20°C±10°C (in K_2EDTA human plasma with metabolites), which exceed the maximum storage period of study samples (14 days at -20°C±10°C) for the fasting BE study.

- The average percent recovery values were consistent across all the QC concentrations for nicotine and overall CV% was 5.2% (Imprecision within each concentration level and across the concentration range must not exceed 15%). The average percent recovery for the internal standard, nicotine-D_4, was 88.9%.

- Thus, the pre-study method validation for nicotine is **adequate**.

3.5 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Summary of Bioavailability Study for Nicotine Polacrilex Mini Lozenges, 4 mg (Fasting Study: AJ-1403)

For Nicotine

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (%CV)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (hr*ng/mL)	AUC∞ (hr*ng/mL)	T½ (hr)	Kel (hr-1)	
AJ1403	Nicotine Polacrilex 4 mg Mini Lozenge/Oral versus Nicorette® 4 mg Mini Lozenge/Oral (RLD) in a Randomized, Open-Label, Single-Dose, Two-Way Crossover Study in Healthy Smokers	Open-label, randomized, single-dose, two-treatment, two-period crossover	Nicotine Polacrilex 4 mg Mini Lozenge Lot Number: BP033725 Nicorette® 4 mg Mini Lozenge Lot Number:	26 completing (19M/7F) Healthy subjects Age: 45.6 (20-65)	8.74 (34.8%) 8.86 (35.1%)	1.38 (0.883 - 2.67) 1.25 (0.500 - 6.00)	38.0 (49.7%) 41.0 (43.3%)	41.6 (52.6%) 44.9 (46.7%)	3.20 (41.0%) 2.93 (23.0%)	0.2358 (22.7%) 0.2480 (21.9%)	Appendix 16.2.6 page 399

For Baseline-Corrected Nicotine

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (%CV)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (hr*ng/mL)	AUC∞ (hr*ng/mL)	T½ (hr)	Kel (hr-1)	
AJ1403	Nicotine Polacrilex 4 mg Mini Lozenge/Oral versus Nicorette® 4 mg Mini Lozenge/Oral (RLD) in a Randomized, Open-Label, Single-Dose, Two-Way Crossover Study in Healthy Smokers	Open-label, randomized, single-dose, two-treatment, two-period crossover	Nicotine Polacrilex 4 mg Mini Lozenge Lot Number: BP033725	26 completing (19M/7F) Healthy subjects Age: 45.6 (20-65)	8.27 (33.5%)	1.38 (0.883 - 2.67)	35.2 (48.3%)	38.5 (51.4%)	3.20 (41.0%)	0.2359 (22.7%)	Appendix 16.2.6 page 483
			Nicorette® 4 mg Mini Lozenge Lot Number:		8.24 (33.9%)	1.25 (0.500 - 6.00)	37.4 (40.0%)	41.0 (43.5%)	2.93 (22.9%)	0.2482 (21.9%)	

Table 2. Reanalysis of Study Samples

Study No. AJ-1403 Nicotine								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Low internal standard	1.00	1.00	0.09	0.09	1.00	1.00	0.09	0.09
Investigational repeat	1.00	1.00	0.09	0.09	1.00	1.00	0.09	0.09
Total	2.00	2.00	1.19	1.19	2.00	2.00	1.19	1.19

Total Assay: 1059 samples

Table 3. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Sample Analysis (Chromatographic)
		Sample Reanalysis and Reporting Criteria

Is there any other particular concern that should be investigated further?	No

Comments from the Reviewer:

- The SOPs for sample re-analysis were provided and effective during the sample re-analysis of the fasting study (Study No. AJ-1403).

- Along with analytical raw data, approximately 20% of representative chromatograms from Subject # (b) (6) were provided in the Bioanalytical Report (Project No. AJ-1403, Report Date: 06/03/2014) in module 5.3.1.4.

- The firm also provided complete (100%) raw numerical data for all the subjects from all analytical runs (#01 to #18) of the fasting BE study in module 5.3.1.4 (Please see Sections 4.1.1.3 for details).

Fasting Study (No. AJ-1403)

According to above Summary Table of Reanalysis of Study Samples and the Bioanalytical Report, in the fasting BE study, a total of 4 out of 1059 study samples [2 samples from the test treatment (1.19%) and 2 samples from the reference treatment (1.19%)] were reanalyzed for nicotine. Please see attachment below the Bioanal tical Report for details.

Table 4 Summary of Repeat Analysis Data for Nicotine in Human Plasma

Subject	Period	Time	Original Conc. ng/mL	Original Curve Number	Reason for Reassay	Reassay Conc. ng/mL	Reassay Curve Number	Reported Conc. ng/mL	Reason for Reported Conc.
(b) (6)	1	2h	5.493	6	1	5.537	15	5.537	1
	2	0.083h	0.9680	6	1	1.005	15	1.005	1
	2	6h	7.834	9	2	7.845, 7.873	18, 18	7.845	2
	2	3h	3.102	9	2	3.244, 3.211	18, 18	3.211	2

Reasons For Reassay:
1). LIS - Low Internal Standard
2). INVR - Investigation Required

Reasons For Reported Conc.:
1). Repeat Value Reported
2). Median of Selections Reported

- Low Internal Standard: As reported in the Summary Table of Reanalysis and the Bioanalytical Report, a total of 2 samples [1 sample from the test treatment (0.09%) and 1 sample from the reference treatment (0.09%)] were reanalyzed for nicotine due to the

reason of "*Sample(s) with High, Low or No Internal Standard*", which was pre-defined in Section 3.4 of the firm's re-assay SOP ([redacted](b) (4) as "*Study samples whose IS response is less than 50% of the minimum or greater than 150% of the maximum IS response of the passing standards and quality control samples within the batch run are considered anomalous and must be flagged for repeat analysis. These samples will be repeated in single*". Based on the raw data submitted, the reviewer verified the firm followed the aforementioned criteria for the reassay. The peak areas of internal standard (ISTD Area) of these two samples ([redacted](b) (6) P1 2.0 h and [redacted](b) (6) P2 0.083 h) in the original run (Run #06) were far below the criteria (<50% of mean IS response), and sample repeats are acceptable. Therefore, the reassayed values were used in the final pharmacokinetic and statistical analyses.

- Investigational Repeat: there were also 2 samples [1 sample from the test treatment (0.09%) and 1 sample from the reference treatment (0.09%)] reanalyzed for nicotine in this fasting study due to the reason of "*Investigational Repeat*". However, no detailed reasons were reported, and this repeat reason was not defined in firm's re-assay SOP (No. [redacted](b) (4)). Therefore, from the bioequivalence standpoint, the reviewer considers these two sample reassays ([redacted](b) (6) P2 6.0 h and [redacted](b) (6) P2 3.0 h) as "PK repeats". However, based on the raw data submitted and the reviewer's calculation (the reviewer confirmed the original and reassay concentrations reported in above Table 4 "*Summary of Repeat Analysis*"), the original value for these two sample were 7.834 ng/ml and 3.102 ng/ml, whereas the duplicate reassay values were 7.845/7.873 ng/ml and 3.244/3.211 ng/ml, respectively, and the differences were less than 5%, which is considered acceptable. Thus, although the reviewer considers these two sample reassays as 'PK repeats', however, the reassay of these samples should not have any impact on the study outcome based on the closeness of the original and reassay values for these two samples, and also the consistency of duplicate reassay values (difference <5%).

- In addition to the individual reassayed samples as mentioned above, as documented in the Bioanalytical Report (Project No. AJ-1403, Report Date: 06/03/2014), for nicotine, there was one rejected run, Run#12 ([redacted](b) (6)), was identified due to the reason of all 3 Control Blank samples and both STD0 samples had responses at the retention time of nicotine between STD1 and STD3, and therefore failed to meet the acceptance criteria. These subject samples were repeated in subsequent Run#15.

- Overall, the firm's study sample reanalyses are **adequate**.

3.6 Waiver Request(s) For Immediate Release Dosage Forms

Strengths for which waivers are requested, if applicable	2 mg
Waiver regulation cited?	21 CFR § 320.22 (d) (2)
Strengths considered for 21 CFR 320.24 (b)(6)	N/A
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	The review of in vitro dissolution testing was completed recently with deficiencies. However, the dissolution data are considered acceptable with respect to supporting the waiver request for the 2 mg strength of the test product.
Waivers granted?	**WAIVER GRANTED**
If not then why?	N/A

3.7 Deficiency Comments

Please refer to the deficiency comment specified in the letter attached.

3.8 Comments for Other OGD Disciplines

Discipline	Comment
N/A	N/A

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4. Study Information

Study Number	AJ-1403
Study Title	Nicotine Polacrilex 4 mg Mini Lozenge/Oral versus Nicorette® 4 mg Mini Lozenge/Oral (RLD) in a Randomized, Open-Label, Single-Dose, Two-Way Crossover Study in Healthy Smokers Under Fasted Conditions
Study Type	*In Vivo* BE
Clinical Site (Name & Address)	Phase One Solutions, Inc. 1405 NW 167th Street Miami Gardens, FL 33169 USA Phone: (305) 624-9191
Principal Investigator	Lawrence A. Galitz, MD lawrencegalitz@phase1solutions.com
Dosing Dates	**Period 1:** 14-May-2014 **Period 2:** 19-May-2014
Analytical Site (Name & Address)	(b) (4) [redacted]
Analysis Dates	
Analytical Director	
Storage Period of Biostudy Samples (a) Duration (No. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g.,-20°C to -80°C)	(a) Fourteen (14) days from the first sample collected on 14-May-2014 to the last sample extracted on 28-May-2014. (b) -20°C±10°C
Long-Term Storage Stability Coverage (no. days @ temp °C)	83 days at -20°C±10°C in K_2EDTA human plasma

Table 5. Product information

Product	Test	Reference
Treatment ID	T (A)	R (B)
Product Name	Nicotine Polacrilex 4.0 mg mini lozenge	Nicorette® 4.0 mg mini lozenge
Manufacturer	PLD Acquisitions, LLC D/B/A Avema Pharma Solutions	GSK
Batch/Lot No.	BM033299 / BP033725	14347
Manufacture Date	02/11/14	
Expiration Date	N/A	07/15
Strength	4.0 mg	4.0 mg
Dosage Form	Lozenge	Lozenge
Bio-Batch Size	(b) (4)	
Production Batch Size		
Potency (Assay)	98.8%*	98.1%†
Content Uniformity (AV)	98.0%, 1.3%	100.3%, 1.6%
Dose Administered	1 x 4 mg	1 x 4 mg
Route of Administration	Oral	Oral

*Obtained from the Certificate of Analysis (COA) of the test product (Batch# BP033725), located in Module 5, Section 3.2.P.5.4 Batch Analysis.
† Obtained from the COA of the reference product (Batch #14347), located in Module 5, Section 2.7.1.

Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	N/A

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	**Enrolled:** 29 **Dosed:** 29 **Completed:** 26 **Samples Analyzed:** 27 **Data Analyzed:** 26
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	5 days
Randomization Scheme (Sequence of T and R)	**Yes** Please see Appendix 16.1.7 for the subject randomization schedule and codes.

Blood Sampling Times	A total of twenty (20) blood samples will be collected during each period. Blood samples (6 mL) were collected in appropriately labeled blood collection tubes containing K_2EDTA as the anticoagulant within 90 minutes prior to dosing and at 5, 10, 15, 30, 40 and 50 minutes and 1.0, 1.25, 1.5, 1.75, 2.0, 2.33, 2.67, 3.0, 4.0, 6.0, 8.0, 10.0 and 12.0 hours after study drug administration in each study period.
Anticoagulant used	K_2EDTA
Blood Sample Processing & Storage (include storage temperature)	Blood samples were collected from an indwelling catheter or by direct venipuncture. Any deviation from the scheduled time of post-dose collection was documented as a sampling time deviation. A summary of these deviations is provided in Appendix 16.2.2. The total volume of blood collected from each subject who completed the study was not expected to exceed 280 mL. Immediately after collection, the filled blood collection tubes were gently inverted at least 8 times to insure that the anticoagulant was thoroughly mixed with the blood and then placed on an ice water bath. The blood samples were centrifuged at 4°C for 10 minutes at 3000 RPM within 30 minutes after collection. Plasma was harvested from the centrifuged samples and transferred, split into equally sized samples, into appropriately labeled polypropylene screw top transfer tubes. The harvested plasma samples were transferred, within 90 minutes of collection, to a -20°C (± 10 °C) freezer, where they were frozen in the upright position until they were shipped to the bioanalytical facility. Split samples were kept separate, so that there were two complete sets of samples. One set of frozen samples was transferred to the bioanalytical facility for analysis following collection of the final PK sample in the study. Samples were carefully packed in a polystyrene shipping container with a sufficient amount of dry ice to insure that they would remain frozen for 72 hours. Only upon verification of receipt of the first set was the second set of frozen samples shipped to the bioanalytical facility.

Comments on Study Design:

- The study (#AJ-1403) was designed as an open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative oral bioequivalence study of the Test and Reference formulations of Nicotine Polacrilex mini lozenge 4 mg in normal healthy smokers, male and non-pregnant female, under fasting condition (Per the subject inclusion criteria: current cigarette smoker who has smoked cigarettes daily for at least 1 year; Please see *Section 4.1.1.4* for details).

- Per the study protocol, within 30 days of qualifying screening examinations, the subjects will report to SITE's dormitory facility approximately 14 hrs or earlier prior to study drug administration. All subjects will be required to fast at least 10 hrs prior to dose and must abstain from smoking during their confinement. The assigned study drug will be placed in the subject's mouth by SITE staff and subject will be instructed to allow lozenge to completely dissolve slowly over approximately 20-30 minutes. The subject will be asked not to chew or swallow the lozenge and move the lozenge around the mouth while it dissolves. No water will be administered in conjunction with lozenge. The subject will be asked to minimize swallowing as the lozenge dissolves. The time the lozenge has completely dissolved will be noted by the SITE staff for each subject. After dosing, no

food will be allowed until 4 hrs post-dose. No water may be consumed for 1 hr pre-dose through 1 hr post-dose. Drinking water will be *ad libitum* at all other times.

- A total of 29 volunteers were enrolled and all 29 volunteers dosed in both period I. 26 subjects were dosed in period II and 26 subjects completed the study. Final PK analysis was carried out on the 26 subjects.

- Per RLD labeling, Tmax for nicotine is about 1 hour after oral administration of lozenge, and the elimination half-life is approximately 2 hours. Therefore, the current sampling time up to 12 hours is adequate to cover the absorption, distribution and elimination phases, and continue for more than five times of the plasma half-life.

- The firm's fasting study design is **acceptable**.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. AJ-1403			
		Treatment Groups	
		Test Product N = 26	Reference Product N = 26
Age (years)	Mean ± SD	46.0 ± 13.8	46.0 ± 13.8
	Range	20 - 65	20 - 65
Age Groups	< 18	0 (0.0%)	0 (0.0%)
	18 – 40	6 (23.1%)	6 (23.1%)
	41 – 64	18 (69.2%)	18 (69.2%)
	65 – 75	2 (7.7%)	2 (7.7%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	Male	20 (76.9%)	20 (76.9%)
	Female	6 (23.1%)	6 (23.1%)
Race	Asian	0 (0.0%)	0 (0.0%)
	Black	0 (0.0%)	0 (0.0%)
	Caucasian	1 (3.8%)	1 (3.8%)
	Hispanic	25 (96.2%)	25 (96.2%)

	Other	0 (0.0%)	0 (0.0%)
Other Factors	N/A	N/A	N/A

Table 8. Dropout Information, Fasting Bioequivalence Study

Study No. AJ-1403				
Subject No/ Treatment	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Withdrew Consent	P2, prior to dosing	No	No
	Emesis/Withdrew Consent/Medical grounds per the Principal Investigator	P1, prior to 40 minute PK sample	No	No
	Vomiting, time thought to be insufficient for complete absorption of drug; subject number not assigned	P1, 17 minutes after dosing	No	No

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System/ Adverse Event	**Reported Incidence by Treatment Group**	
	Fasted Bioequivalence Study Study No. AJ-1403	
	Test	**Reference**
Gastrointestinal Disorders		
Nausea	1 (3.4%)	1 (3.4%)
Vomit	1 (3.4%)	1 (3.4%)
Total	2 (6.8%)	2 (6.8%)

Subjects Experiencing Emesis (Include in eCTD)

Subject Number*	**Test/Reference**	**Period**	**Duration Between Dosing and Emesis (hrs)**
(b) (6)	R	P1	40 min
	T	P1	17 min

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.

Yes. As submitted in the Clinical Study Report (Project No. AJ-1403, Version: Final, Report Date: 06/12/2014 01), a total of 4 adverse events (2 following Test, 2 following Reference) were reported by 2 of the subjects who participated in this study. All adverse events were considered mild and all were resolved. However, there is still not enough information to make a comparison only based on sparse occurrence of AEs in the different disease categories related to the fasting study due to the nature of relatively small number of study subjects; consequently, these AEs are not significant and/or should not have significant impact on the outcome of the fasting study.

Are there any serious adverse events or death? If so, are they reported to the OGD Safety Committee?

No deaths, serious adverse events, or significant adverse events reported or occurred for any subjects over the course of the fasting study.

Are there any other safety concerns based on the adverse event profile?

No

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Study No. AJ-1403		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Laboratory Assessment Deviations – blood samples collected late	(b) (6)	

Comments:

Dropouts:

- In the fasting study (Study No. AJ-1403), a total of 29 healthy, adult subjects were enrolled and 26 subjects completed both the periods of the study. Subject (b) (6) withdrew consent prior to Period 2. Subject (b) (6) was withdrawn from the study for medical reasons (nausea and vomiting) by the Principal Investigator prior to completion of Period 1. Subject (b) (6) (screen#) vomited 17 minutes after dosing was initiated; the residence time of the lozenge in the oral cavity was thought to be insufficient for complete absorption of drug and for that reason a subject number was not assigned and blood samples were not collected. All these three subjects were never replaced with any substitute or were included in further analysis. Pharmacokinetic analysis was performed on data obtained from 26 subjects who completed the study.

Adverse Events:

- The subjects were monitored throughout the fasting study for any adverse experiences. There were no deaths, SAEs, or other significant AEs reported in the study.

- A total of 4 adverse events (2 following Test, 2 following Reference) were reported by 2 of the subjects who participated in this study. All adverse events were considered mild and all were resolved. The most frequent adverse events reported for the Test product were nausea and vomiting, reported by 2 and 2 subjects respectively.

- Two emesis events occurred shortly after dosing (1 of which was not assigned a subject number) and were dropped from the study by the Principal Investigator (please see dropout subject for details), and therefore have no impact on the study outcome.

Protocol Deviations:

- As submitted in Appendix 16.2.2 and Section 10.2 of the fasting study report, details of the protocol deviations that occurred over the course of the study were also appended in Table 10 above. There were no early draws reported, however, there were some late draws during the study. Most of blood sampling time deviations in the study occurred less than 5% of the nominal time points (except for S(b) (6) 50min, S(b) (6) 1.75h, S(b) (6) 30min, S(b) (6) 1.0h, S(b) (6) 1.0h, S(b) (6) 50min, S(b) (6) 1.25h, S(b) (6) 5min, S(b) (6) 50min for P1, S(b) (6) 5min for P2, S(b) (6) 30min, S(b) (6) 10min, S(b) (6) 30min, S(b) (6) 40min, S(b) (6) 5min and 40min, S(b) (6) 5min, S(b) (6) 5min and 10min, S(b) (6) 10min, S(b) (6) 30min and 1.0h, S(b) (6) 5min, 30min and 40min). The detailed information of all deviations between the scheduled and actual times of sample collection is presented in the table below. However, the blood sample collection time point deviations should not have any impact on the outcome of the study since the actual blood sample collection times were utilized for the pharmacokinetic and statistical analysis.

Subject Number	Period	Drug	Time Point	Deviation	Time Late MM:SS
(b) (6)	2	A	1.75Hr	Blood sample collected late	0:02:44
	1	A	40min	Blood sample collected late	0:02:21
	2	B	5min	Blood sample collected late	0:01:23
	1	A	50min	Blood sample collected late	0:01:30
	2	B	5min	Blood sample collected late	0:01:53
	2	B	50min	Blood sample collected late	0:01:35
	2	A	5min	Blood sample collected late	0:06:11
	2	A	10min	Blood sample collected late	0:02:12
	2	A	40min	Blood sample collected late	0:01:10
	2	A	3.0Hr	Blood sample collected late	0:01:29
	2	A	4.0Hr	Blood sample collected late	0:02:10
	1	A	1.75Hr	Blood sample collected late	0:04:40
	2	B	10min	Blood sample collected late	0:01:02
	2	B	1.75Hr	Blood sample collected late	0:02:01
	2	A	1.0Hr	Blood sample collected late	0:01:02
	1	B	50min	Blood sample collected late	0:01:20
	1	B	1.0Hr	Blood sample collected late	0:04:20
	2	A	30 min.	Blood sample collected late	0:02:00
	2	A	1.75Hr	Blood sample collected late	0:03:05
	2	A	8.0Hr	Blood sample collected late	0:03:01
	1	A	40min	Blood sample collected late	0:04:00
	1	A	1.75Hr	Blood sample collected late	0:02:45
	1	A	10.0Hr	Blood sample collected late	0:06:00
	2	B	15min	Blood sample collected late	0:05:01
	2	B	30min	Blood sample collected late	0:03:02
	2	B	4.0Hr	Blood sample collected late	0:01:38

Subject Number	Period	Drug	Time Point	Deviation	Time Late MM:SS
(b) (6)	2	A	1.75Hr	Blood sample collected late	0:02:44
	1	A	40min	Blood sample collected late	0:02:21
	2	B	5min	Blood sample collected late	0:01:23
	1	A	50min	Blood sample collected late	0:01:30
	2	B	5min	Blood sample collected late	0:01:53
	2	B	50min	Blood sample collected late	0:01:35
	2	A	5min	Blood sample collected late	0:06:11
	2	A	10min	Blood sample collected late	0:02:12
	2	A	40min	Blood sample collected late	0:01:10
	2	A	3.0Hr	Blood sample collected late	0:01:29
	2	A	4.0Hr	Blood sample collected late	0:02:10
	1	A	1.75Hr	Blood sample collected late	0:04:40
	2	B	10min	Blood sample collected late	0:01:02
	2	B	1.75Hr	Blood sample collected late	0:02:01
	2	A	1.0Hr	Blood sample collected late	0:01:02
	1	B	50min	Blood sample collected late	0:01:20
	1	B	1.0Hr	Blood sample collected late	0:04:20
	2	A	30 min.	Blood sample collected late	0:02:00
	2	A	1.75Hr	Blood sample collected late	0:03:05
	2	A	8.0Hr	Blood sample collected late	0:03:01
	1	A	40min	Blood sample collected late	0:04:00
	1	A	1.75Hr	Blood sample collected late	0:02:45
	1	A	10.0Hr	Blood sample collected late	0:06:00
	2	B	15min	Blood sample collected late	0:05:01
	2	B	30min	Blood sample collected late	0:03:02
	2	B	4.0Hr	Blood sample collected late	0:01:38

- There was no other protocol deviation recorded during the study. Therefore, the listed protocol deviations did not have any significant impact on the outcome of the study.

Thus, the overall "Dropouts/Adverse Events/Protocol Deviations" did not compromise the integrity of the study and the firm's handling of these matters is **acceptable**.

4.1.1.3 Bioanalytical Results

Table 11. Sample Analysis Calibration and Quality Control

Bioequivalence Study No. AJ-1403 Analyte Name: Nicotine								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.2000	0.4000	1.000	2.000	5.000	10.00	20.00	25.00
Inter day Precision (%CV)	5.7	4.2	2.8	1.7	1.7	2.0	1.8	2.1
Inter day Accuracy (%Bias)	-0.4	-0.1	1.7	0.6	0.4	-0.6	-0.8	-0.9
Linearity	"r^2" values: 0.996004 to 0.999667							

Linearity Range (ng/mL)	0.2000 to 25.00 ng/mL
Sensitivity/LLOQ (ng/mL)	LLOQ 0.2000 ng/mL

Bioequivalence Study No. AJ-1403 Analyte Name: Nicotine				
Parameter	**Quality Control Samples**			
Concentration (ng/mL)	LQC 0.5000	MQC-1 2.500	MQC-2 12.50	HQC 18.75
Inter day Precision (%CV)	9.7	2.3	1.9	2.2
Inter day Accuracy (%Bias)	2.5	1.1	-0.2	-0.6

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Are there any concerns related to sample analysis (including reanalysis, run rejection, etc.)?	No

Were 20% of chromatograms included?	Yes.
Did the firm provide 100% numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log) in the instrument printout format?	Yes.

Table 12. SOP's Dealing with Sample Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Sample Analysis (Chromatographic)
		Sample Reanalysis and Reporting Criteria
		Incurred Sample Reanalysis

Comments:

- The firm submitted representative original chromatograms for approximate 20% of total study samples (Subject # (b) (6)) for the fasting study (Study No. AJ-1403) in the Bioanalytical Report (Project No. AJ-1403, Report Date: 06/03/2014) in module 5.3.1.4.

- The firm also provided complete (100%) raw numerical data for all the subjects from all analytical runs (Run#01 to #18) of the fasting BE study as an attachment "*Study AJ-1403 Raw data*" in module 5.3.1.4.

- All data being reported for this study are from acceptable runs as per the firm's run acceptance criteria predefined in Section 8 of firm's SOP "*Sample Analysis*

(Chromatographic)". As documented in the Bioanalytical Report submitted by the firm, total 18 analytical runs (including 2 runs for incurred sample reanalysis and 2 runs for individual/batch repeats) were carried out for the analyte of nicotine, and only one rejected run, Run#12 (Subjects (b) (6)), was identified due to "All 3 Control Blank samples and both STD0 samples failed to meet acceptance criteria", and accordingly these two subject samples was re-assayed in the subsequent run.

- To confirm the reproducibility of bioanalytical method during study sample analysis, in this study, for nicotine, the firm used 121 samples out of 1059 (11.3% of the total samples analyzed) in its incurred samples reproducibility (ISR) testing. ISR testing was performed as per SOP C(b) (4) (Reanalysis of Incurred Bioanalytical Samples; effective date: (b) (4)). Of 121 ISR samples considered, 120 samples (99.2%) met the acceptance criteria: at least ⅔ of reanalyzed samples must have a relative difference for the repeat values of within ± 20%. The firm's selection for ISR samples was as per the current FDA Guidance (Guidance for Industry: Bioanalytical Method Validation; recommended September 2013)[8]. The firm's ISR analysis is acceptable and the method is reproducible.

- As a result, the firm's during study assay validation is considered **complete** (adequate).

4.1.1.4 Pharmacokinetic Results

Is there a Tmax difference between T and R	Yes. T/R = 1.104 for Nicotine. Acceptable, please see the comments below.
Are any CIs marginal?	No
Were the subjects dosed in groups?	No
Is the study design replicate and/or reference-scaled?	No
Is sampling time adequate?	Yes. Per RLD labeling, Tmax for nicotine is about 1 hour after oral administration of lozenge, and the elimination half-life is approximately 2 hours. In the current study, half-life for nicotine is approximately 3.20 hours for the test and 2.93 hours for the reference products. Blood samples were collected up to 12 hours after drug administration, and the sampling times are adequate to cover the absorption, distribution and elimination phases, and continue for more than four to five times of the plasma half-life.

Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE Studies for Nicotine for Fasting Study (No. AJ-1403)

Nicotine Polacrilex Mini Lozenges **Dose (1 × 4 mg), N=26 (Male=20 and Female=6; Completed)** **Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals** **Fasting Bioequivalence Study (Study No. AJ1403)**

[8] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf

Nicotine					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	34.7	37.9	91.56	84.50	99.21
AUC∞ (ng·hr/mL)	37.8	41.1	91.92	84.66	99.81
Cmax (ng/mL)	8.30	8.42	98.60	92.33	105.30

Nicotine Polacrilex Mini Lozenges Dose (1 × 4 mg), N=26 (Male=20 and Female=6; Completed) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study (Study No. AJ1403)					
Baseline Corrected Nicotine					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	32.3	35.0	92.18	84.80	100.20
AUC∞ (ng·hr/mL)	35.1	38.0	92.23	84.66	100.47
Cmax (ng/mL)	7.87	7.87	100.03	93.95	106.50

Overall Comment:

- Per the recommendations in the currently BE draft guidance, for Nicotine Polacrilex Mini Lozenges, only one fasting BE study is recommended on the biostrength of Eq. 4 mg base in general population (healthy males and nonpregnant females), and bioequivalence should be established based on 90% CI of nicotine. The agency does not recommend correcting the data for baseline. However, since the current BE study was conducted in the normal healthy smokers (Per firm's subject inclusion criteria: current cigarette smoker who has smoked cigarettes daily for at least 1 year, please see Section 4.1.1.1 for details), and "*positive pre-dose nicotine levels were observed in at least one period in all subjects except Subject* (b) (6) *(i.e. 50 subject-period cases)*" as reported by the firm, therefore, pharmacokinetic and statistical analyses were conducted using the data of both original/uncorrected and baseline-corrected nicotine concentrations (the measured nicotine concentration was corrected by subtracting the contribution from the pre-dose level), which are considered acceptable.

- The 90% CIs for the T/R ratio of least squares geometric means of $LnAUC_{0-t}$, $LnAUC_{0-\infty}$ and LnC_{max} for both nicotine and baseline-corrected nicotine reported by the firm are all within acceptable BE limits of 80.00-125.00%, and therefore meet the BE criteria.

- The ratio of median Tmax values for test (1.38 hours) vs. reference (1.25 hours) products is 1.104 for nicotine, with individual Tmax values ranging from 0.883 to 2.67 hours for the test product and from 0.500 to 6.00 hours for the reference product. Therefore, the median Tmax difference between the test and reference products is acceptable.

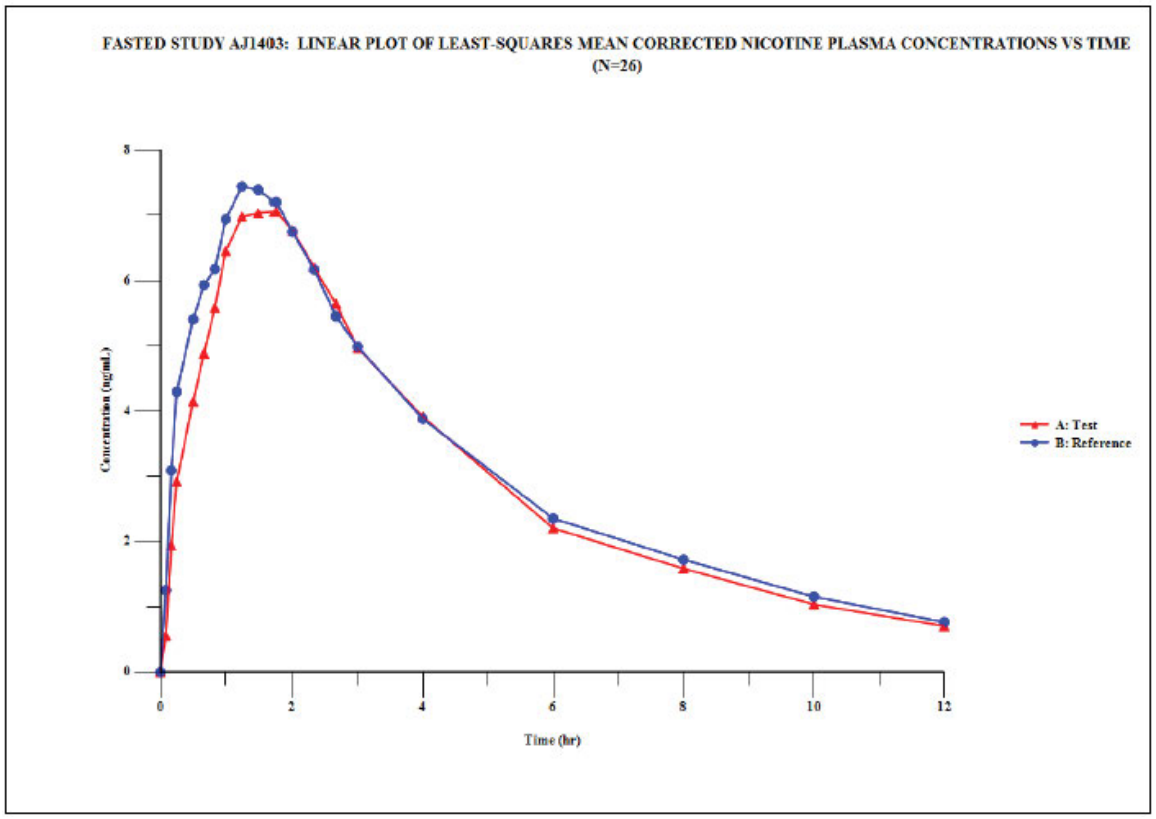
- The firm's *in vivo* fasting BE study is **adequate** (complete) as per comments above.

Table 13. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (Firm-Submitted Data in Firm's Format)

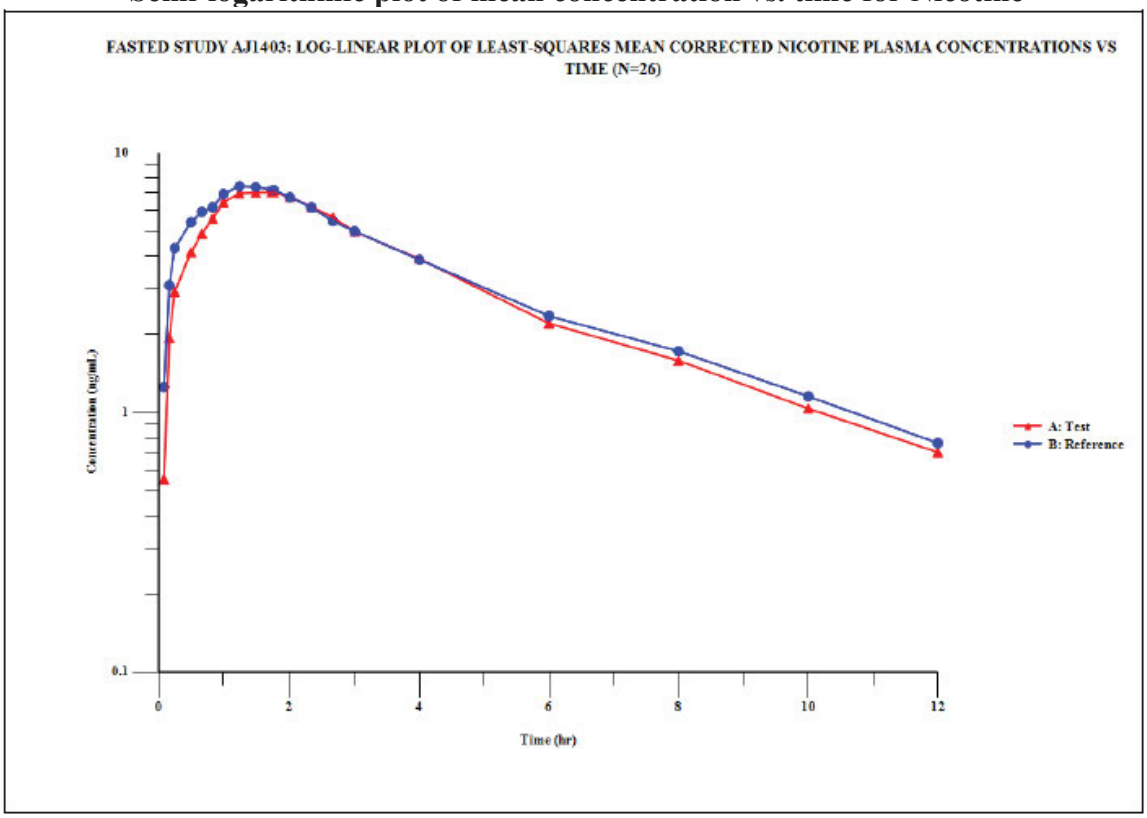
Collection (Hour)	Least-Squares Means (ng/mL)		P-Value*
	Test	Reference	
0.000	0.0000	0.0000	-
0.083	0.5537	1.2528	0.0383
0.167	1.9416	3.0899	0.0014
0.250	2.9182	4.2948	<0.0001
0.500	4.1436	5.4054	0.0002
0.667	4.8839	5.9314	0.0127
0.833	5.5815	6.1720	0.1522
1.000	6.4497	6.9361	0.3201
1.250	6.9759	7.4414	0.3023
1.500	7.0332	7.3876	0.1931
1.750	7.0569	7.1991	0.6268
2.000	6.7653	6.7457	0.9485
2.330	6.1972	6.1650	0.8995
2.670	5.6417	5.4525	0.4054
3.000	4.9692	4.9854	0.9374
4.000	3.9088	3.8789	0.8629
6.000	2.2034	2.3529	0.5662
8.000	1.5846	1.7223	0.5676
10.00	1.0359	1.1543	0.3710
12.00	0.7025	0.7628	0.4824

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (Firm-Submitted Plot)

Linear plot of mean concentration vs. time for Nicotine



Semi-logarithmic plot of mean concentration vs. time for Nicotine



4.2 Formulation Data

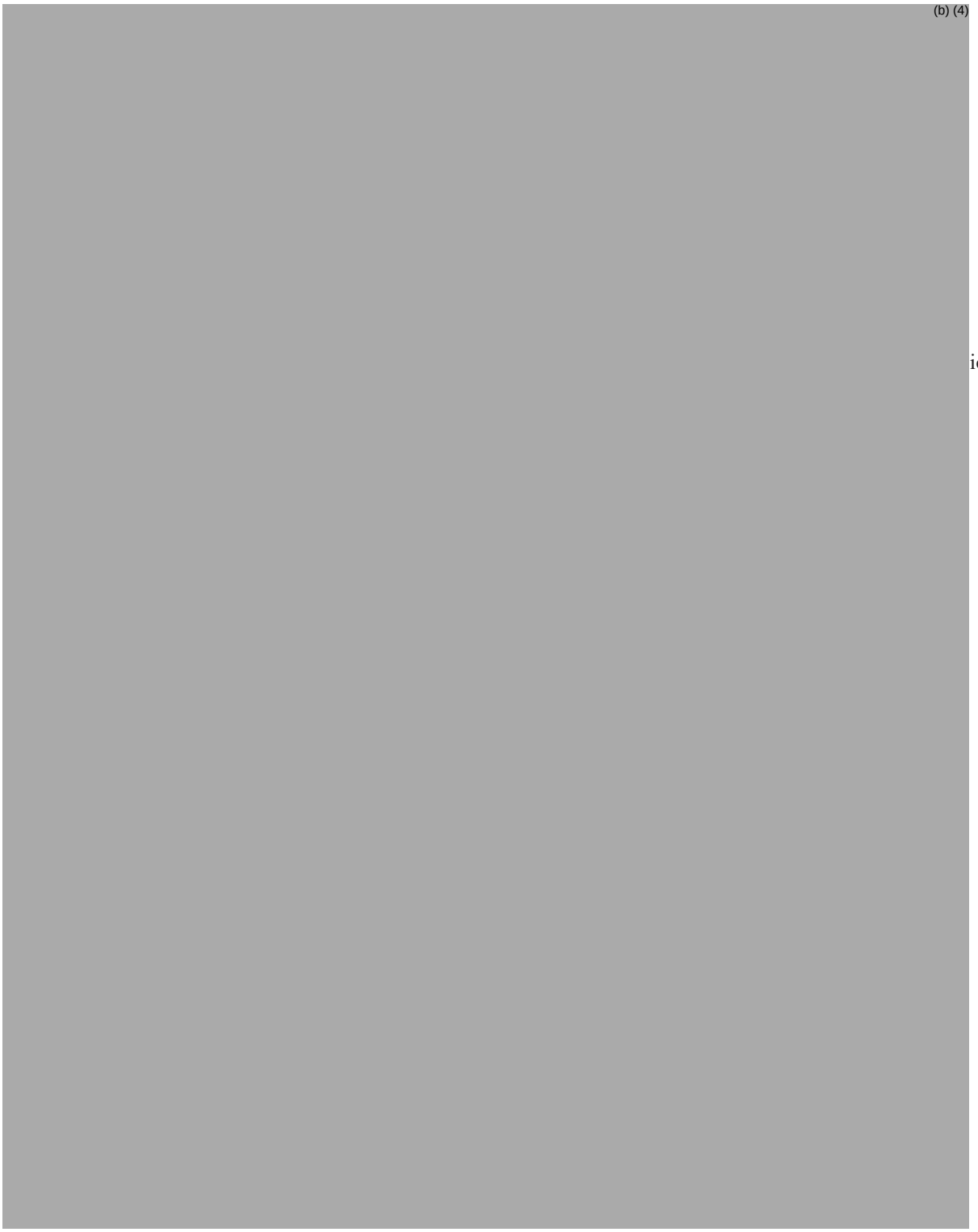
Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg (Bio-strength)

Components	4 mg		2 mg		Pharmaceutical Function
	mg per unit	% w/w	mg per unit	% w/w	
Nicotine Polacrilex 15%			(b) (4)	(b) (4)	Active
Mannitol					(b) (4)
Sodium Bicarbonate					
Sodium Stearyl Fumarate					
Maltodextrin					
(b) (4)					
Calcium Polycarbophil					
Xanthan Gum					
Aspartame					
Sodium Alginate					
Talc					
Total Weight				100.00	N/A

Reviewer's comments:

(b) (4)

(b) (4)



icotine

[9] GDRP/Panorama for ANDA-207868-ORIG-1-RESUB-3, Parent: Filing Review (A207868N000DFR_CHK.docx; Beena Mathew); Date uploaded: 01/11/2016.


(b) (4)

[11] FDA IIG database: http://intranetapps.test fda.gov/scripts/iig/; last accessed: 12/1/2015.

(b) (4)

Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD) within IIG (per unit) limits?	No
If no, are they all above/within IIG (per day) limits?	Within
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	YES
Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	YES

Reviewer's Additional Comments on Formulation:

- The formulation for the lower strength of the test product, Nicotine Polacrilex Mini Lozenges, 2 mg, is proportionally similar to that of the 4 mg strength of the test product, which underwent bioequivalence testing.

- The amount of elemental iron consumed is below FDA limit for elemental iron of 5 mg per day [21 CFR 73.1200 (c)].

- (b) (4)

  The firm provided justificatons/supportive documents, including a summary of "*Nonclinical Information Amendment*" along with clinical/research literatures and reports in Module 1.11.2 in its ECD response, which was not considered adequate (Please see Reviewer's Notes in *Section 4.5.2* for details). Therefore, a safety/efficacy consult was requested to the Division of Clinical Review (DCR) dated 11/18/2016 in seeking the expert opinion/comments for the evaluation of the firm's responses with respect to the safety concern and clinical significance due to the (b) (4) amounts of these three excipients. As per the DCR's consult response dated 01/30/2017, "*from clinical and nonclinical perspectives, that the levels of sodium stearyl fumarate, maltodextrin and talc in the proposed generic nicotine lozenge drug product are acceptable*". (Please see *Section 4.6* for details)

- Thus, the test product formulations are now considered **adequate**.

4.3 Dissolution Data

Dissolution Review Path	As of the date of 08/23/2016, the *in vitro* dissolution testing has not yet been reviewed. The review of *in vitro* dissolution testing will be conducted separately by ONDP (Assessment of the Biopharmaceutics under the Quality Review) at a later time. *Notes:* The dissolution review was completed recently on 01/11/2017, the related part in the current review has been updated to 01/31/2017.

Table 24. Summary of In vitro Dissolution Studies – 4 mg strength

Dissolution Conditions			**Apparatus:**	Apparatus 1 (Basket)								
			Speed of Rotation:	100 rpm								
			Medium:	pH7.4 phosphate buffer, USP								
			Volume:	900mL								
			Temperature:	37 ± 0.5 °C								
Firm's Proposed Specifications			NLT (b) (4) and NMT (b) (4) of Nicotine LC dissolved in 30min NLT and NMT of Nicotine LC dissolved in 60min NLT of Nicotine LC dissolved in 90min NLT of Nicotine LC dissolved in 120min NLT ((b) (4) of Nicotine LC dissolved in 180minutes									
Dissolution Testing Site (Name, Address)			PLD Acquisitions, LLC D/B/A Avema Pharma Solutions, 10400 NW 29th Terrace, Miami, FL 33172, USA.									
Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**					**Study Report Location**
						30	**60**	**90**	**120**	**180**	
QC-309 Page- 166	06/06/14	Test: BM033299 (Manufacturing date:02/11/14)	4.0mg Lozenge	12	Mean (%)	31	55	76	91	99	Test results form PS003381 located in the corresponding finished product folder
					Range (%)	(b) (4)					
					%RSD	5.3	7.8	7.6	6.0	2.7	
QC-313	11/25/13	Reference: 14347	4.0mg	12	Mean (%)	27	46	63	80	103	Test results form

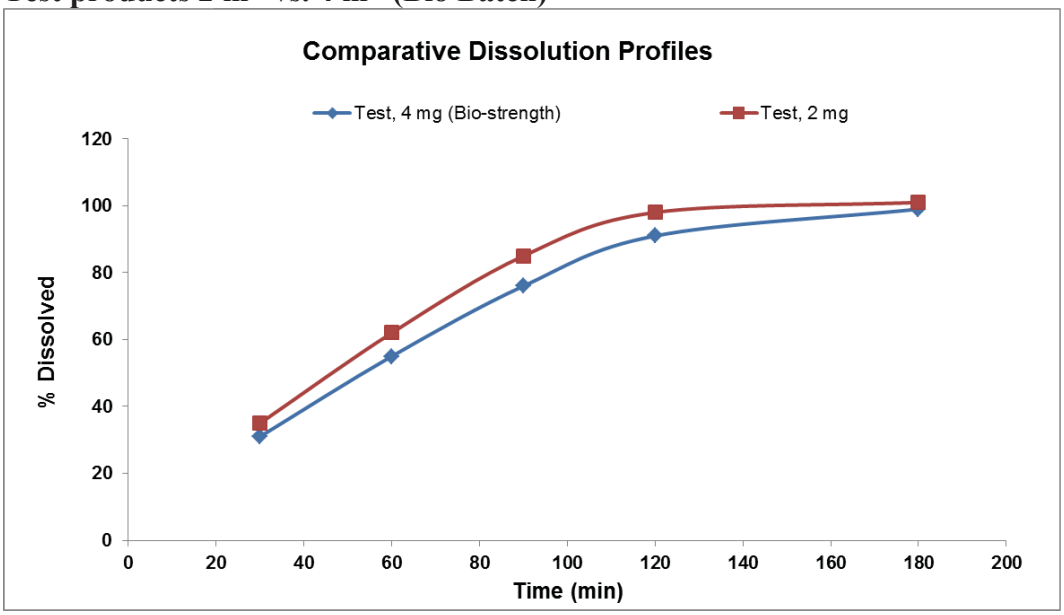
Page-107		(Expiration date: 07/2015)	Lozenge		Range (%)	[redacted] (b) (4)					PS003381 located in the corresponding finished product folder
					%RSD	4.9	3.9	3.6	5.2	1.0	

Summary of In vitro Dissolution Studies – 2mg strength

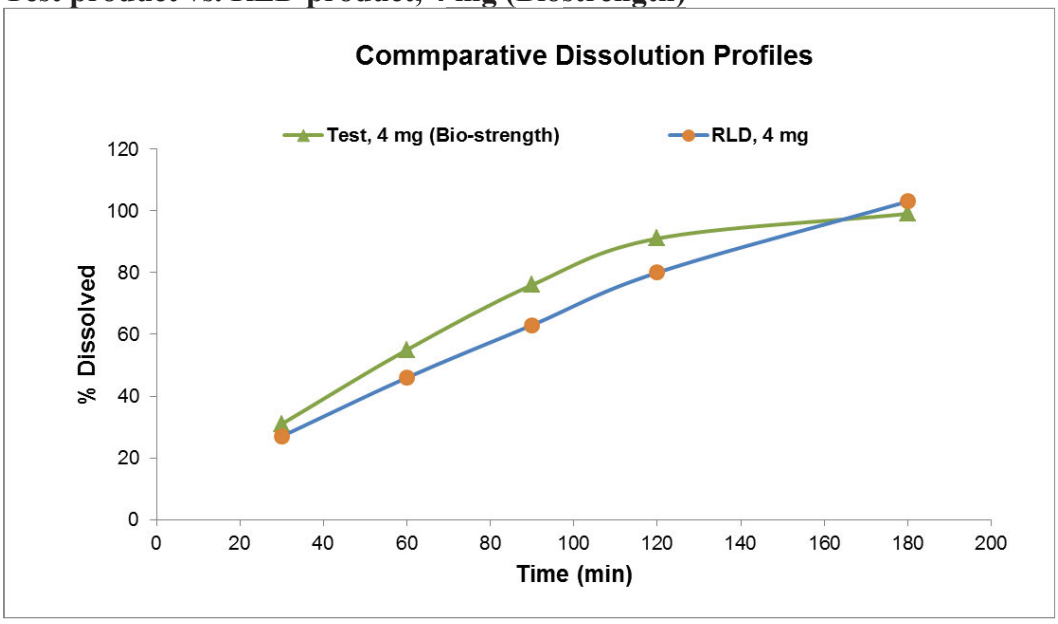
Dissolution Conditions		**Apparatus:**	Apparatus 1 (Basket)								
		Speed of Rotation:	100 rpm								
		Medium:	pH7.4 phosphate buffer, USP								
		Volume:	900mL								
		Temperature:	37 ± 0.5 °C								
Firm's Proposed Specifications		NLT [redacted] (b) (4) and NMT [redacted] (b) (4) of Nicotine LC dissolved in 30min NLT [redacted] and NMT [redacted] of Nicotine LC dissolved in 60min NLT [redacted] of Nicotine LC dissolved in 90min NLT [redacted] of Nicotine LC dissolved in 120min NLT [redacted] of Nicotine LC dissolved in 180minutes									
Dissolution Testing Site (Name, Address)		PLD Acquisitions, LLC D/B/A Avema Pharma Solutions, 10400 NW 29th Terrace, Miami, FL 33172, USA.									
Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**					**Study Report Location**
						30	**60**	**90**	**120**	**180**	
QC-294 Page- 101	06/05/14	Test: BM033296 (Manufacture Date: 02/06/14)	2.0mg Lozenge	12	Mean (%)	35	62	85	98	101	Lab Notebook QC-294 Page- 101
					Range (%)	[redacted] (b) (4)					
					%RSD	3.4	4.0	4.7	2.4	1.1	
QC-394 Page-118	09/10/15	Reference: 14848 (Expiration date: 01/2017)	2.0mg Lozenge	12	Mean (%)	31	54	74	95	103	Lab Notebook QC-394 Page-118
					Range (%)	[redacted] (b) (4)					
					%RSD	4.5	4.2	4.3	3.2	1.5	

Comparative Dissolution Profile for Nicotine Polacrilex Mini Lozenges with FDA-recommended method (By reviewer):

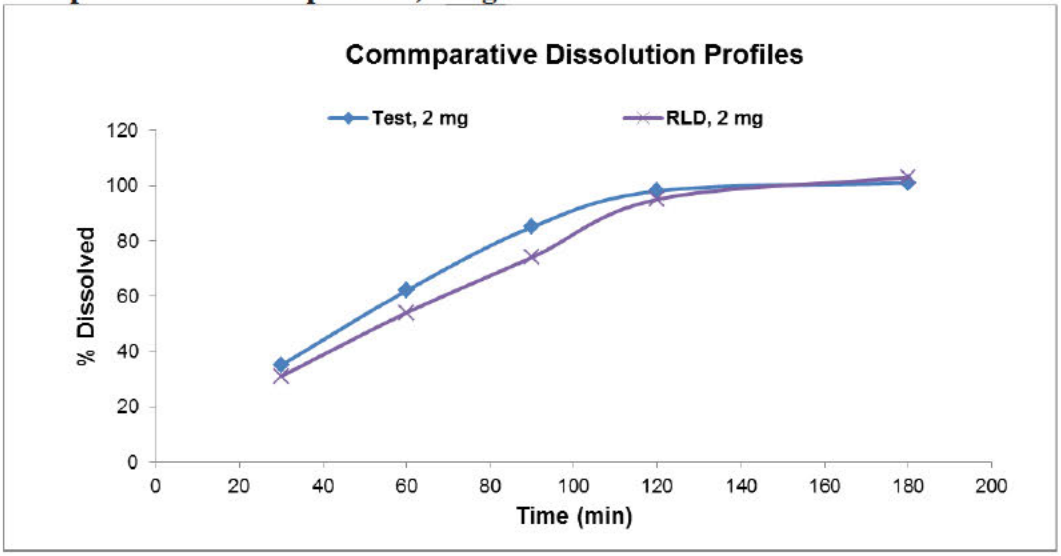
Test products 2 m vs. 4 m (Bio Batch)



Test product vs. RLD product, 4 mg (Biostrength)



Test product vs. RLD product, 2 mg



F2 metric, biostudy strengths compared to other strength(s)		
Dissolution Method: FDA-recommended method		
Biostudy Strength	**Other Strength**	**F2 metric between two test strengths**
4 mg (Bio-Lot# 2008026)	2 mg (Lot# 2007901)	57.58

F2 Metric Test vs RLD (all strengths)	
Dissolution Method: FDA-recommended method	
4 mg	52.21
2 mg	56.79

Please comment on whether dissolution data are adequate to support waiver requests.	Inadequate. Please see comments below

Overall Comment:

- The review of *in vitro* dissolution testing was conducted separately by the biopharmaceutics quality reviewer at the Office of New Drug Products (ONDP) in the Office of Pharmaceutical Quality (OPQ), which was completed recently on 01/11/2017 (http://panorama.fda.gov/task/view?ID=566154ad0141c025b3ecfb8c1188bb79).

- There is no USP method for Nicotine Polacrilex Mini Lozenges, but there is an FDA-recommended method posted on the FDA External Dissolution Database as follows[12]

[12] FDA External Dissolution Database: http://www.accessdata fda.gov/scripts/cder/dissolution/index.cfm; Search Term: Nicotine Polacrilex (updated date: 12/23/2010); last accessed: 08/22/2016.

(*Note*: The dissolution method and specifications for this product has not yet been posted on the FDA internal dissolution database[13]):

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Nicotine Polacrilex	Lozenge (Mini)	I (Basket)	100	Phosphate Buffer, pH 7.4	900	30, 60, 90, 120 and 180	12/23/2010

- The firm conducted dissolution testing using the FDA-recommended method at the time points of 30, 60, 90, 120 and 180 min. The test products showed comparable dissolution profiles as the RLD products on the corresponding strength with similarity factor f2 values above 50 (Please see dissolution profiles and f2 values above for details). The *in vitro* dissolution testing and *in vivo* BE studies on the biostrength were conducted on the same Test (#BM033299) and RLD (#14347) lots.

- The reviewer verified that the summary dissolution data in the tables are in agreement with the individual unit data submitted by the firm. The variability of the dissolution data are less than 10% for all the dissolution sampling time points of both test and reference products.

- Based on the firm-provided *in vitro* dissolution summary data tables, the *in vitro* dissolution testing using FDA method was performed within 4 months since manufacture date of the test products. The reference products used in the dissolution test were before the RLD expiration date.

- As per the separate dissolution review, the firm's dissolution method was acceptable; however, deficiencies were identified related to the incomplete submission of dissolution raw data and unacceptable dissolution criteria/specifications. Please refer to the original dissolution review for details (http://panorama.fda.gov/task/view?ID=566154ad0141c025b3ecfb8c1188bb79).

- In the current BE review, the dissolution data were evaluated for the waiver request consideration only. Based on the comparative dissolution data submitted using FDA-recommended method, the dissolution profiles of the test products are considered comparable between the bio-strength, 4 mg, and the lower strength, 2 mg, with calculated similarity factor f2 values above 50 (Please see Figures and f2 values above for the dissolution profiles between the two test strengths). Please note that sampling time points of 30, 60, 90 and 120 min were used for calculation of f2 value between the test strengths.

- Therefore, at the time of this review, the dissolution data are **adequate** with respect to supporting the waiver request for the 2 mg strength of the test product.

[13] OGD Internal Dissolution Database; Search Term: Nicotine Polacrilex; last accessed: 08/22/2016.

4.4 The Office of Study Integrity and Surveillance (OSIS) Inspection

Reviewer's Comments for OSIS Inspection:

Based on OSIS site search "OSI: Site Search" [14], no OSIS inspection was requested at either clinical site (Phase One Solutions, Inc.) or analytical site ([(b) (4)]) under the current ANDA.

For the analytical site [[(b) (4)], [(b) (4)])], as per the memorandum provided by the Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) dated 01/20/2016[15], "*OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI)*". Thus, OSIS recommends accepting data without on-site inspection for the current ANDA 207868.

For the clinical site, no review or memorandum is currently available or provided by the DGDBE/OSIS in the GDRP/Panorama as of dated 08/23/2016 (original) and 01/31/2017 (update). The review of OSIS for the clinical site will be conducted separately at a later date.

In addition, based on evaluation of the submitted data, the OSIS inspection of the clinical and analytical sites for the current ANDA 207868 is not necessary. The studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiency was identified by the reviewer.

Overall, since this ANDA is a GDUFA CY4 submission, the OSIS inspection status for the current ANDA is "**To Be Determined by OSIS"**.

[14] OSI Site Search: http://fdswv04385/bioprod/Bioequivalence_Project_Managment/Interface/ASPTest/DSI/index.asp, last assessed date: 08/23/2016.

[(b) (4)]

4.5 Attachments

4.5.1 Additional Studies (If applicable)

Are there any additional studies? (e.g. pilot, failed) **If yes, please provide the location of report (complete/summary).**	☒ Yes ☐ No Pilot fasting BE study (#AJ-1401)
Number of Subjects	15
Are the test formulations in the pilot/failed studies and pivotal studies similar[16]?	☒ Yes ☐ No ☐ N/A No detailed formulation was provided
What was the objective of pilot/failed study?	Investigate the influence of drug release profiles against the innovator product. One fast release formulation and one slow release formulation was compared for the purpose of pivotal study.
Please comment on reason(s) of failure.	N/A. BE criteria was passed
Any serious adverse events or deaths reported?	☐ Yes ☐ No ☒ N/A Information not provided

Table 7: Summary of Results for Statistical Tests on Nicotine for the Fasting Study (Fast Formulation)

Parameter	Test[1]	Reference[1]	Ratio[2]	CV%[3]	90% CI[4]
AUC_{0-t}	33.8	34.8	97.33	11.9	90.39 – 104.81
AUC_{0-inf}	36.7	37.8	97.24	12.9	89.76 – 105.34
C_{max}	7.94	8.36	93.70	15.1	85.31 – 102.91
T_{max}	1.36	1.56	87.33	-	-
λ_z	0.2261	0.2305	98.08	-	-
$t_{1/2}$	3.16	3.19	99.04	-	-

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; CV%, coefficient of variation

1. Results are presented as least-squares geometric means for AUC and Cmax and arithmetic means for other parameters.
2. Ratio calculated as Test least-squares mean divided by the Reference least-squares mean expressed as a percentage. None of the comparisons were detected as statistically significant by ANOVA (α=0.05).
3. Estimated intra-subject CV%=100*SQRT(e^{MSE}-1), where MSE is the mean square error term from the ANOVA.
4. CI on the ratio expressed as a percentage.

Table 8: Summary of Results for Statistical Tests on Nicotine for the Fasting Study (Slow Formulation)

Parameter	Test[1]	Reference[1]	Ratio[2]	CV%[3]	90% CI[4]
AUC_{0-t}	34.5	34.8	99.33	11.9	92.24 – 106.96
AUC_{0-inf}	37.4	37.8	98.87	12.9	91.27 – 107.10
C_{max}	8.30	8.47	97.95	15.1	89.18 – 107.58
T_{max}	1.66	1.56	106.05	-	-
λ_z	0.2446	0.2305	106.10	-	-
$t_{1/2}$	3.02	3.19	94.65	-	-

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; CV%, coefficient of variation

1. Results are presented as least-squares geometric means for AUC and Cmax and arithmetic means for other parameters.
2. Ratio calculated as Test least-squares mean divided by the Reference least-squares mean expressed as a percentage. None of the comparisons were detected as statistically significant by ANOVA (α=0.05).
3. Estimated intra-subject CV%=100*SQRT(e^{MSE}-1), where MSE is the mean square error term from the ANOVA.
4. CI on the ratio expressed as a percentage.

[16] Submission of Summary Bioequivalence Data for Abbreviated New Drug Applications

Figure 3: Nicotine Plasma Profile of the Proposed Product vs the RLD for the Fasted Study

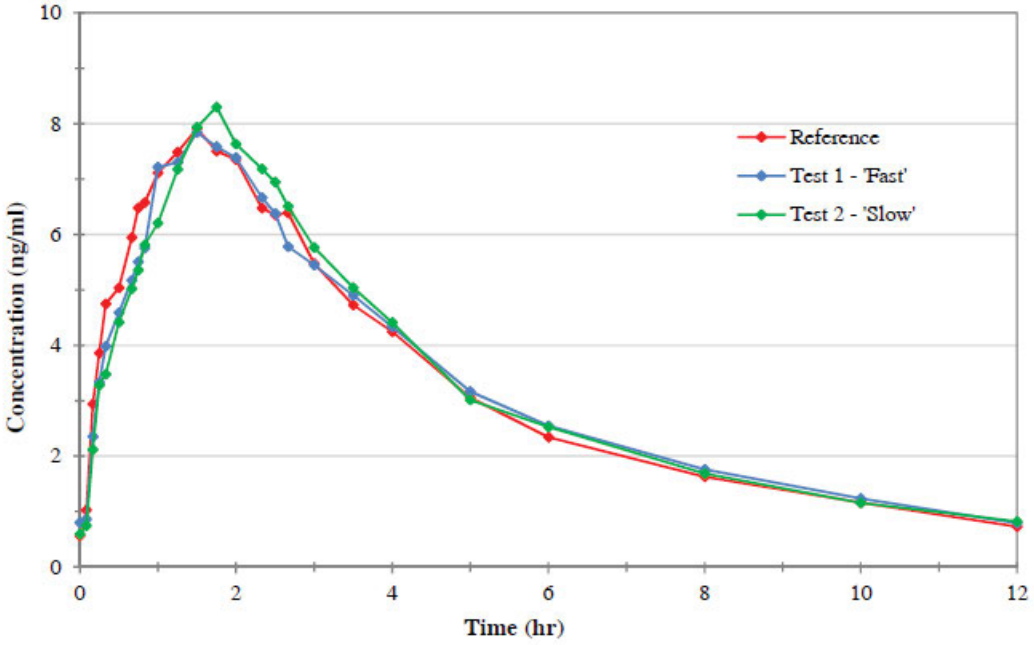
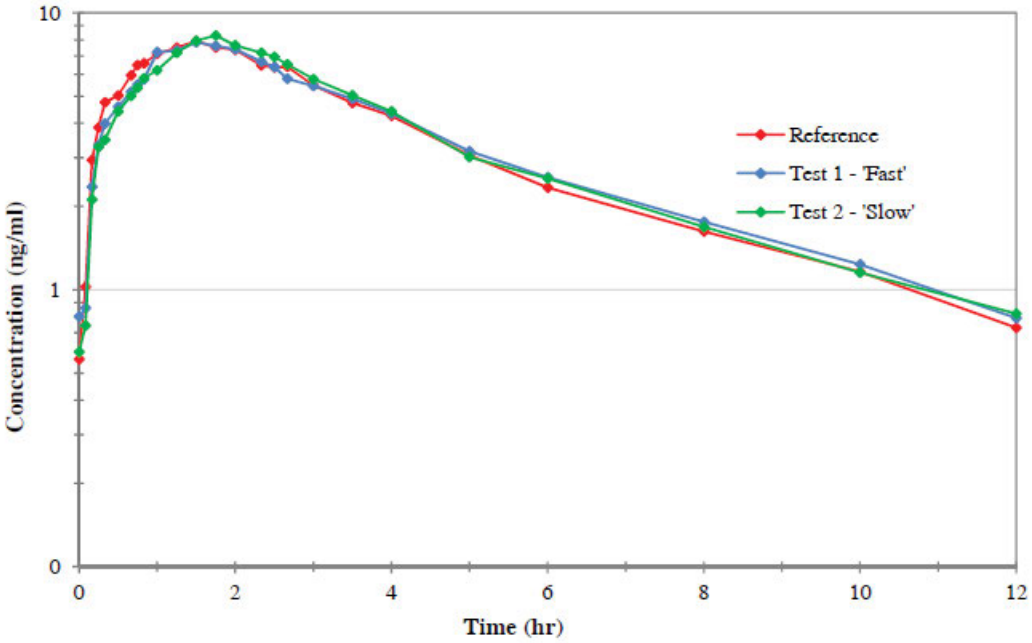


Figure 4: Log Linear Nicotine Plasma Profile of the Proposed Product vs the RLD for the Fasted Study



Reviewer's comments on pilot study

- As per Section 4.2 of the pharmaceutical development report (Report No.: D000684 Version 1; Date: 06/17/2014, Module 3, Section 3.2.P.2, GlobalSubmit Review), the firm stated "*from the product and process understanding gained throughout pharmaceutical development, two (2) separate pilot clinical batches, one (1) fast release formulation and one (1) slow release formulation, were manufactured*", and in order to "*investigate the influence of drug release profiles against the innovator product*", a 3-way crossover, 15

patient fasted study was conducted (study# AJ-1401). However, the detailed formulations and batch information were not provided for the test product of the said pilot fasting study.

- Based on the PK results in the tables above, the 90% confidence intervals of C_{max}, AUC_{0-t} and AUC_{inf} are all within the acceptable BE limits of 80.00-125.00% for both test formulations. Therefore, both the fast and slow release formulations of the pilot clinical batches were found to be bioequivalent to the RLD.

- In addition, the median Tmax of the test products were considered comparable to that of the reference product for both test formulations, in this pilot fasting study (The range of Tmax were not provided).

	Tmax/Test (h)	**Tmax/Reference (h)**	**T/R Ratio**
Fast release formulation	1.36	1.56	0.873
Slow release formulation	1.66	1.56	1.061

- Therefore, as the firm stated that "*from the clinical data generated from the pilot bioequivalence study, the slow release formulation was selected*" for the pivotal study (study# AJ-1403).

- However, in addition to the information summarized above, no other information was provided for this pilot fasting study in the current submission. As per the Agency's current practice, the firm will be asked to provide the all BE data/information for this pilot study using the data summary tables for BE submissions (Table 1 to Table 16 if applicable) found at the following link: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf. The firm will also be asked to refer to the FDA's guidance "*Submission of Summary Bioequivalence Data for ANDAs* (http://www.fda.gov/downloads/Drugs/.../Guidances/UCM134846.pdf; May 2011)" for details.

- In addition, the firm will be asked to provide the details of all adverse events (AEs) observed in this pilot fasting study, including the severity/intensity of the AEs (i.e., mild, moderate, severe, serious etc.), onset and resolution times.

4.5.2 Easily Correctable Deficiency (ECD) Request

The DBIII's ECD Request to the Firm Dated 09/12/2016 (Reference# 10140263):

ANDA No.	207868
Drug Product Name	Nicotine Polacrilex Mini Lozenges
Strength(s)	EQ 2 mg Base and EQ 4 mg Base
Applicant Name	PLD Acquisitions LLC, D/B/A Avema Pharma Solutions
Applicant Address	10400 NW 29th Terrace Miami, FL 33172 USA
Applicant's Point of Contact	Mehul Govani
Contact's Telephone Number	(b) (4)
Contact's Fax Number	(516) 272-8203
Contact's Email Address	mgovani@pldevelopments.com
Original Submission Date(s)	12/02/2015 (Resubmission/After Refuse to Receive) *[06/19/2014 (Subject to a refuse to receive)]*
Submission Date(s) of Amendment(s) Under Review	09/17/2015 (Supp. Document #2) Quality/Response To Information Request 12/02/2015 (Supp. Document #3) Quality/Manufacture Information; User Fee/Coversheet; Resubmission/After Refuse to Receive; Labeling/Container-Carton Draft
Reviewer	Yi Zhang, Ph.D.
Study Number (s)	AJ-1403
Study Type (s)	Fasting
Strength (s)	1 x 4 mg
Clinical Site	Phase One Solutions, Inc.
Clinical Site Address	1405 NW 167th Street Miami Gardens, FL 33169 USA
Analytical Site	(b) (4)
Analytical Site Address	
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)** **Post October 1, 2014 ANDAs** ☒ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☐ **Complete**
OVERALL REVIEW RESULT	**INADEQUATE**
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**
COMMUNICATION	☒ **ECD** ☐ **IR**

	☐ NOT APPLICABLE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 2 & 3	**Fasting**	**4 mg**	**INADEQUATE**
1, 2 & 3	**Waiver**	**2 mg**	**INADEQUATE**

The deficiency below represents *EASILY CORRECTABLE DEFICIENCY* identified during the full ANDA review and the current ANDA review cycle will remain open. The following comment/deficiency with respect to the inactive ingredients in the formulation exceeding the IIG limits should be communicated to the firm via a Division of Bioequivalence III (DBIII)'s ECD request.

1. You stated in the Section of "*Description and Composition of the Drug Product*" in Module 2.3 of "*Quality Overall Summary*" and Module 3.2.P of "*Drug Product*" in the current submission dated 12/02/2015, that "*all excipients fall below IIG or other applicable limits for oral route of administration*", as shown in the table below:

Table 2 Nicotine Polacrilex Mini 4.0 mg and 2.0 mg Lozenge IIG or other applicable limits

Ingredient	Nicotine Polacrilex Mini 4.0 mg Lozenges (mg/unit)	Nicotine Polacrilex Mini 2.0 mg Lozenges (mg/unit)	IIG Levels (Oral Products) or other applicable limits (mg)
Mannitol			(b) (4)
Sodium Bicarbonate			
Sodium Stearyl Fumarate			
Maltodextrin			
(b) (4)			
Calcium Polycarbophil			
Xanthan Gum			
Aspartame			
Sodium Alginate			
Talc			
			(b) (4)

However, as per the approved reference listed drug (RLD) labeling for Nicorette® (nicotine polacrilex) Mini Lozenges, the patient should be advised to "*place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 - 30 minutes). Minimize swallowing. Do not chew or swallow lozenge*". Therefore, the maximum daily intake (MDI) of each excipient present in the test product formulation should be calculated based on the same route of administration (e.g. troche/lozenge, buccal or sublingual).

The MDI levels of the respective Sodium Stearyl Fumarate, Maltodextrin, and Talc present in your test formulation were (b) (4), respectively, and they exceed the maximum amounts listed in the FDA's Inactive Ingredient Guide (IIG) based on the maximum daily dose (MDD) of 20 lozenges for Nicotine Polacrilex Mini Lozenges intended for the above said route of administration. Therefore, please provide your justification along with supportive data that the amounts of Sodium Stearyl Fumarate, Maltodextrin, and Talc present in your test formulation would not significantly compromise the safety and/or efficacy of your test drug product.

Firm's Email Inquiry dated 09/13/2016
Hello Linda,

We have some questions regarding Easily correctable deficiency Bioequivalence reference# 10140263.

The deficiency talks about 3 inactive ingredients (Sodium sterayl fumarate, maltodextrin and talc) exceeding the Maximum daily intake (MDI). Based on the FDA guidance "ANDA submissions- Refuse to receive standards".

(b) (4)

Please let us know if the above explanation satisfies your concerns.

Thanks,
Mehul

Mehul Govani, Regulatory Affairs Manager
PL Developments | http://www.PLDevelopments.com
w|516-986-1700 (b) (4)
email| mgovani@pldevelopments.com
609-2 Cantiague Rock Road | Westbury, NY | 11590

Reviewer's Note:

- The BE review team prepared a DBIII's Response to firm's email inquiry. However, as per the current regulatory practice as suggested by the DBIII upper management and the RPM that "*We will not process or review a partial response. Facsimile or e-mail responses will not be accepted*", the firm was asked to respond to the best of their ability to the ECD request directly[17].

Firm's Response to the DBIII's ECD Request Dated 10/26/2016 (Supp. Document #8):

Response to Question 1:

As per the FDA guidance ANDA submissions- Refuse to receive standards and as per the confirmation from FDA-Substance Registration System team, it is our understanding that the potency described in the IID database corresponds to "per dosage unit" and not the "maximum daily intake".

Based on the FDA guidance ANDA submissions- Refuse to receive standards, "Applicants can justify inactive ingredient levels by reference to the IID, which is a listing of inactive ingredients and their maximum levels of use (per dosage unit or percent composition), arranged by either route of administration or dosage form."

It is also our understanding that maximum daily intake (MDI) is calculated using the following formula:

$$MDI = \frac{MDD}{A} \times P$$

Where,
MDD: Highest recommended daily dose of the drug identified in the approved drug labeling.
P: Potency of the inactive ingredient per dosage unit.
MDD/A is the maximum number of dosage units that could be consumed per day.

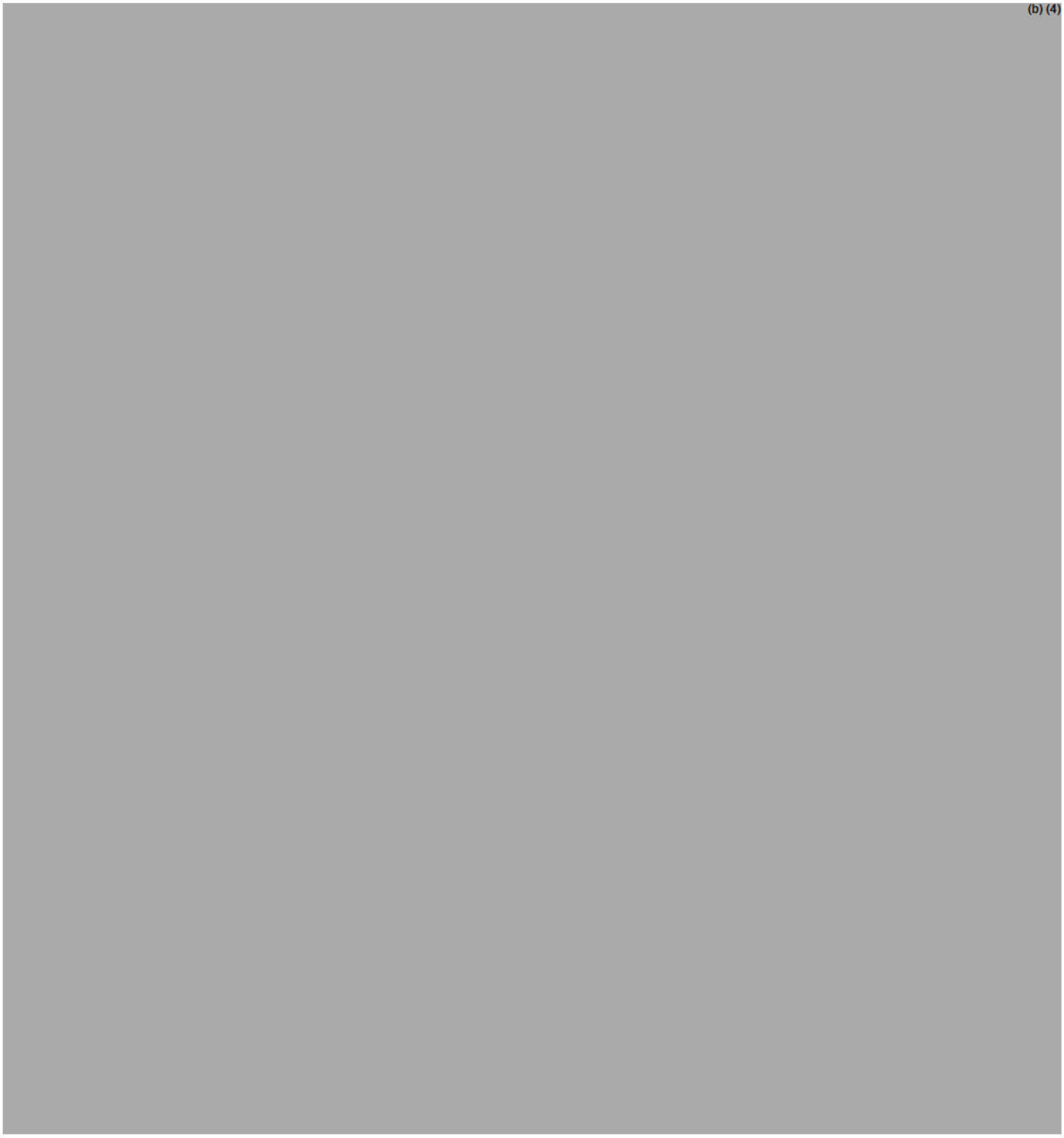
The reference source for the formula above is the "Inactive Ingredient Database - FDA

[17] GDRP/Panorama for ANDA-207868-ORIG-1-RESUB-3, ECD extension (http://panorama fda.gov/task/view?ID=580656590001fbe9e5cb8bec83e888097&activeTab=list-task-documents; Linda Park) Date uploaded: 10/18/2016.

Update" presentation by **Robert Iser**.

If we were to calculate MDI based on this formula then the calculations would be as mentioned below.

MDI calculations:



(b) (4)

Reviewer's Note:

- Based on the maximum daily dose (MDD) of 20 lozenges/per day for Nicotine Polacrilex Mini Lozenges, the firm's proposed maximum daily intake (MDI) amounts for three of the inactive ingredients, Sodium Stearyl Fumarate, Maltodextrin, and Talc ((b) (4) (b) (4)), in the test product formulations, as calculated by the BE reviewer, exceed the maximum daily intake levels of the same inactive ingredients in previously FDA-approved drug products intended for the same route of administration (i.e. troche/lozenge, buccal or sublingual).

- Based on the administration route of the lozenges, the justification of IID levels should use troche/lozenge, buccal or sublingual routes, since these dosage forms are all dissolved in the mouth, other than passing through down to the digestive track. Therefore, the firm's justification using other orally administered dosage forms (e.g., oral routes via digestive track) for the lozenge is not acceptable unless appropriate supportive data/safety information are provided. Thus, the usage of the oral route of administration for the calculation of reference/approved MDI as IIG limit justification is not acceptable.

- The firm's calculation of MDI in its test product is consistent with reviewer's calculation. However, the calculation method to determine the maximal MDI from reference/approved drug products is incorrect. As the formula firm described above, "P (Potency of the inactive ingredient per dosage unit)" and "MDD/A (maximum number of dosage units that could be consumed per day)" firm used were from different drug products, i.e., in firm's calculation, "P" ((b) (4) (b) (4)) was chosen from IID database of other approved drug product, however, (b) (4) is the maximum units/lozenges per day for the current test product, which is not acceptable.

- In the current response dated 10/26/2016, the firm also provided supportive documents, including a summary of "*Nonclinical Information Amendment*" along with clinical/research literatures and reports in Module 1.11.2, and claimed that "*the amounts of Sodium Stearyl Fumarate, Maltodextrin, and Talc present in our test formulation would not significantly compromise the safety and/or efficacy of our test drug product.*" The DBIII is seeking expert opinion/comments from the Division of Clinical Review (DCR) for the evaluation of the firm's current responses to the safety concern and clinical significance due to the (b) (4) amounts of these three excipients. The BE review outcome will be pending for DCR's consult review.

4.6 Consult Reviews

The DBIII's Safety/Efficacy Consult to the Division of Clinical Review (DCR) Dated 11/18/2016:

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Daiva Shetty, M.D., Acting Director, Division of Clinical Review Office of Bioequivalence Office of Generic drugs			FROM: Yi Zhang, Ph.D., Reviewer, DBIII/Team 36 Through Nilufer Tampal, Ph.D. Acting Director, Division of Bioequivalence III (DBIII) Office of Bioequivalence Office of Generic Drugs	
DATE November 18, 2016	IND NO. N/A	ANDA NO. 207868	TYPE OF DOCUMENT Consult	DATE OF DOCUMENT December 2, 2015 (Original) October 26, 2016 (ECD response)
NAME OF DRUG Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base		PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG Smoking Cessation Therapeutic Agent	DESIRED COMPLETION DATE 01/06/2016 (TAD of the ANDA: 02/20/2017)
NAME OF FIRM: PLD Acquisitions LLC, D/B/A Avema Pharma Solutions				
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): Original ANDA
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			☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE	

☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

Introduction:

On June 19, 2014, the firm, PLD Acquisitions LLC, D/B/A Avema Pharma Solutions, submitted an abbreviated new drug application (ANDA) for Nicotine Polacrilex Mini Lozenges, 2mg and 4 mg. The application was refused to received (RTR) due to incomplete information and was subsequently accepted for filing on December 2, 2015. As per the current product specific guidance[18], the original submission contained the results of an *in vivo* fasting bioequivalence (BE) study (Study No. AJ1403) comparing it's test product, Nicotine Polacrilex Mini Lozenges, 4 mg, to the corresponding reference product, GlaxoSmithKline Consumer Healthcare's Nicorette® Mini Lozenge, 4 mg [NDA 022360, approved on 05/18/2009; Over the Counter (OTC)][19], along with a waiver request for the 2 mg strength. Upon the initial BE review, the only deficiency identified during the full ANDA review (***Attachment 1***) by the Division of Bioequivalence III (DBIII) was related to the proposed maximum daily intake (MDI) amounts of the following three inactive ingredients: Sodium Stearyl Fumarate, Maltodextrin, and Talc, in the test formulation. The individual amounts for all three of the inactive ingredients exceeded the inactive ingredients limits (IIG) limits for the troche/lozenge, buccal or sublingual route of administration. Please see information below for details.

Issue Details:

As per the RLD labeling for Nicorette®, the directions state "*Do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day*"[20] for both strengths of the drug product. Therefore, based on the MDD (20 lozenges/per day), the amounts of the three inactive ingredients in test products are as follows:

Inactive ingredient(s)	Unit amount (mg per unit) in 2 mg or 4 mg strength test products	Proposed MDI (mg) based on MDD for Nicotine Polacrilex Lozenges (× 20 units)	Maximum level (mg) listed in the FDA IIG database for Approved Drug Products with the same route of administration	Ref. No/Note
Sodium Stearyl Fumarate	(b) (4)			
Maltodextrin(1)				
Talc				

(b) (4)

Based on the data currently available to the Agency for the same route of administration (i.e. troche/lozenge, buccal or sublingual), the proposed amounts for these three inactive ingredients, Sodium Stearyl Fumarate, Maltodextrin and Talc, in the test formulations, appeared to potentially exceed the maximum daily intake levels (Please see Section 4.2 of BE review for details (***Attachment 1***). Thus, a deficiency was communicated to the firm via an ECD request dated 09/12/2016. The firm

[18] FDA Product-Specific Recommendations for Generic Drug Development, http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240974.pdf; Recommended Jan 2011. Last accessed: 11/14/2016.

[19] Electronic Orange Book (Updated Through 06/2016): http://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=022360#; Search Term: NDA 022360.

[20] Labeling and clinical pharmacology (online database), https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=991704ed-781a-489b-8b56-0b558e8fc385 (Updated: 06/07/2016); Search Term: Nicorette®.

was asked to provide its justification along with supportive data that the amounts of Sodium Stearyl Fumarate, Maltodextrin, and Talc present in the test formulation would not significantly compromise the safety and/or efficacy of the test drug product (***Attachment 2***).

On 09/13/2016, the firm submitted an email inquiry to the DBIII regarding the issued ECD request (***Attachment 3***). In preparing a response to the firm's inquiry, the BE review team informally consulted the Pharm/Tox team in the Division of Clinical Review (DCR) (***Attachment 4***). However, this information was not communicated to the applicant, due to the recommendations put forth by DBIII management and Regulatory Project Manager (RPM) in OGD that "*We will not process or review a partial response. Facsimile or e-mail responses will not be accepted*"[21].

On 10/26/2016, the firm submitted a complete response to the above deficiency comment made by DBIII (***Attachment 5***). However, the firm's justification is based on the usage of the oral route of administration (e.g., oral routes via digestive track) for calculation of the MDI and IIG limits. In addition, the firm incorrectly calculated the maximal MDI from approved drug products based on the equation provided in its response. Also, the firm provided supportive documents, including a summary of "*Nonclinical Information Amendment*" along with additional clinical/research literatures and reports in Module 1.11.2 (***Attachment 6 and 7***), and claimed that *"the amounts of Sodium Stearyl Fumarate, Maltodextrin, and Talc present in our test formulation would not significantly compromise the safety and/or efficacy of our test drug product."*

Consult Request:

DBIII seeks your expert opinion/advice for the evaluation of the safety and toxicity and overall acceptability of the firm's formulations of Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg based on the route of administration for the excipients: Sodium Stearyl Fumarate, Maltodextrin and Talc. Please comment on the following question:

Is there any safety concern and/or clinical significance on the proposed MDI levels of Sodium Stearyl Fumarate (b) (4) (b) (4), Maltodextrin (b) (4) and Talc (b) (4)), based on the MDD of this drug (up to 20 lozenges per day), by the troche/lozenge, buccal or sublingual route(s) of administration used in the test formulation for the Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg?

Attachments:

1) ***Attachment 1***: DBIII BE review document can be found at:
http://panorama fda.gov/task/view?ID=566154ac0141beee6e16a23c11cb43fa

A207868N000DB_N1 2022015.docx

2) ***Attachment 2***: DBIII ECD request (Date: 09/12/2016):
http://panorama fda.gov/task/view?ID=57d75f910141f3c9ad5691ff7370fbb6

A207868N000DB_ECD 08312016.docx

3) ***Attachment 3***: The firm's email inquiry to ECD request (Reference#10140263; Date: 09/13/2016)
http://panorama fda.gov/issue/view?ID=57d8498d014bbe515990013d8297e7d3

[21] GDRP/Panorama for ANDA-207868-ORIG-1-RESUB-3, ECD extension (http://panorama fda.gov/task/view?ID=58065659001fbe9e5cb8bec83e888097&activeTab=list-task-documents; Linda Park) Date uploaded: 10/18/2016.

Firm's Email Inquiry.docx

4) ***Attachment 4***: E-mail communication between DBIII and DCR (Not to be released under FOIA)

RE MDI limit of IIGs for Nicotine Polacrilex

5) ***Attachment 5***: The firm's response to ECD request (Supp. Document #8; Date: 10/26/2016):
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-2-cover-letters\cover-letter-0007-10262016.pdf

cover-letter-0007-10262016.pdf

6) ***Attachment 6***: Summary Report of "*Nonclinical Information Amendment*" provided in the current response:
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\1112-safety-amendment.pdf

1112-safety-amendment.pdf

7) ***Attachment 7***: Several clinical/research literatures/reports and other supportive documents were provided in Module 1.11.2:
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\bergfeld-2012cir.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\fda-scogs-61.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\freers-2012.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\hajiar-1992-epa-talc.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\kibbe-2012.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\moreton-2012.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\nicorettepi20160609.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\robert-iser-2013.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\spectrum-msds.pdf

Thank you for your consideration. Please address comments/questions to Nilufer.Tampal@fda hhs.gov

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

Consult Response from the Division of Clinical Review (DCR) Dated 01/30/2017:

Division of Clinical Review Consultation

Nicotine Polacrilex Mini Lozenges, 2 mg Base and 4 mg Base

Drug Product:	Nicotine Polacrilex Mini Lozenges. EQ 2 mg Base and EQ 4 mg Base
ANDA:	207868
ANDA Sponsor:	PLD Acquisitions LLC, D/B/A Avema Pharma Solutions
Reference Listed Drug (RLD) **NDA, Approval Date** **RLD Sponsor:**	Nicorette® Mini Lozenge 4 mg, 2 mg strength NDA 022360, Approved 5/18/2009 GlaxoSmithkline Consumer Healthcare
Pharmacology-Toxicology Primary Reviewer:	Mi Young Yang, PhD Pharmacologist Division of Clinical Review (DCR) Office of Generic Drugs (OGD)
Pharmacology-Toxicology Secondary Reviewer:	Robert Dorsam, PhD Pharmacology/Toxicology Team Leader DCR, OGD
Medical Officer Primary Reviewer:	Shahreen Hussain-Malik , MD Medical Officer DCR, OGD
Medical Officer Secondary Reviewer:	Nancy Snow, DO Acting Team Leader DCR, OGD
Tertiary Reviewer	Daiva Shetty, MD Deputy Director DCR, OGD
To:	Yi Zhang, PhD Reviewer Division of Bioequivalence III (DB III)/Team 36
Reason for Consult:	Is there any safety concern and/or clinical significance on the proposed MDI levels of Sodium Stearyl Fumarate (b) (4) Maltodextrin (b) (4) and Talc (b) (4) based on the MDD of this drug (up to 20 lozenges per day), by the troche/lozenge, buccal or sublingual route(s) of administration used in the test formulation for the Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg.
Date of Submission:	12/2/2015
Date of Consult:	11/18/2016
Date Assigned:	12/5/2016
Date of Completion:	1/27/2017
Conclusion:	DCR concludes from clinical and nonclinical perspectives, that the levels of sodium stearyl fumarate, maltodextrin and talc in the proposed generic nicotine lozenge drug product are acceptable.

1. Executive Summary:

This review addresses a consult from DBIII requesting DCR to assess the safety and acceptability of the levels of three excipients, sodium stearyl fumarate, maltodextrin and talc, in the proposed generic nicotine lozenges drug product.

PLD Acquisitions LLC, D/B/A/ Avema Pharma Solutions, submitted an ANDA on 6/19/2014 for a generic Nicotine Polacrilex Mini Lozenges drug product, 2mg and 4 mg. The reference listed drug (RLD) is Nicorette® Mini Lozenge 2 mg and 4 mg, NDA 022360, approved on 5/18/2009. Nicotine Lozenges are indicated for the reduction of withdrawal symptoms, including nicotine craving, associated with quitting smoking. The maximum daily dose (MDD) is 20 lozenges. The proposed generic drug product contains three excipients not found in the RLD, sodium stearyl fumarate, maltodextrin and talc. The maximum daily intake (MDI) levels of each excipient in the proposed generic drug product are (b) (4) for sodium stearyl fumarate, (b) (4) for maltodextrin and (b) (4) for talc.

DCR reviewed the safety and acceptability of the three excipients in question from both clinical and Pharmacology/Toxicology perspectives, and considered not only systemic absorption of the excipient, but also local effects on the oral mucosa. From a clinical perspective, the proposed MDIs of the three excipients were compared to their MDIs in FDA-approved drug products with a similar clinical context of use. Clinical safety information available from the literature for each excipient was also considered in the current evaluation. From a Pharmacology/Toxicology perspective, DCR reviewed the safety of each excipient, with an emphasis on their genetic toxicity, chronic oral toxicity, and local toxicity using relevant animal studies.

From both a clinical and nonclinical perspective, DCR concludes that the levels of sodium stearyl fumarate, maltodextrin and talc in the proposed generic nicotine lozenge drug product are acceptable and would not pose an increased risk for adverse events when the generic drug product is taken in place of the RLD.

2. Recommendation:

DCR concludes that the proposed levels of sodium stearyl fumarate (b) (4) maltodextrin (b) (4) and talc (b) (4) in the generic nicotine lozenge drug product are acceptable.

3. **The following comments/deficiencies and/or recommendations should be conveyed to the ANDA applicant:**

Not applicable. There is nothing to be conveyed to the sponsor.

DBIII Reviewer's Comments on DCR Consult Response:

- Although the firm's proposed maximum daily intake (MDI) amounts for Sodium Stearyl Fumarate (b) (4), Maltodextrin (b) (4) and Talc (b) (4) based on the maximum daily dose (MDD) of this drug product (up to 20 lozenges per day), in the test product formulations, exceed the MDI levels of the same inactive ingredients in previously FDA-approved drug products intended for the same route of administration (i.e. troche/lozenge, buccal or sublingual); However, as per the DCR's consult response dated 01/30/2017, from clinical and nonclinical perspectives, considering their local and systemic safety attributes in Pharmacology/Toxicology, the levels of these three

excipients in the proposed generic nicotine lozenge drug product do not pose a toxicity concern. Therefore, the proposed formulations of the test products with these three excipients are considered acceptable (Please see DCR's consult response and ***Section 4.2*** of the current BE review for the details).

Consult Response
20170130_A207868_D

- The related part of the current BE review has been updated as per the recommendation of the DCR consult response.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:	207868
APPLICANT:	PLD Acquisitions LLC, D/B/A Avema Pharma Solutions
DRUG PRODUCT:	Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base

[The following deficiencies/comments should be communicated to the firm via a CR letter]

The Division of Bioequivalence III (DBIII) has completed its review and has identified the following deficiencies:

1. As stated in your pharmaceutical development report (Report No.: D000684 Version 1; in Module 3, Section 3.2.P.2, GlobalSubmit Review; Date: 06/17/2014), you conducted a three-way crossover *in vivo* pilot fasting bioequivalence (BE) study (Study No. AJ-1401) with two investigational test formulations, one fast release formulation and another slow release formulation, against the reference-listed drug (RLD) product. However, you did not provide the detailed formulation and batch information on these two investigational test lots. Per the current Guidance for Industry: Submission of Summary Bioequivalence Data for ANDAs (issued May 2011; see the link below for details: http://www.fda.gov/downloads/Drugs/GuidancesComplianceRegulatoryInformation/Guidances/UCM134846.pdf), please submit complete 16 eCTD-formatted data summary tables for the said pilot BE study (Study No. AJ-1401) conducted using the table templates shown at the following link: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf.

2. In addition to BE Summary Table 8 "*Incidence of Adverse Events in Individual Studies*" requested above, please provide the details of all adverse events (AEs) observed in your pilot BE study (Study No. AJ-1401), including the severity/intensity of the AEs (i.e., mild, moderate, severe, serious etc.), onset and resolution times. Please use the following summary guide table in response to this deficiency:

Subject #	Test/ Reference	Period	Adverse Reaction (AE)	AE Severity/Intensity (e.g. mild, moderate, severe, etc.)	Time and Date of dosing	Time and Date of AE	Duration Between Dosing and Start of AE (hours)	Time and Date of Resolution	Additional Comments

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.7 Outcome Page

ANDA: 207868 Original BE Review

Completed Assignment for 207868 ID: 28725

Reviewer: Zhang, Yi **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base; PLD Acquisitions LLC, D/B/A Avema Pharma Solutions

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
28725	12/2/2015	BIO	ANDA Original [1]	1	1
28725	12/2/2015	Parallel	Dissolution-Based Waiver (IR) (For all waiver strengths) [0.25]	0.25	0.25
28725	12/2/2015	Parallel	Fasting Study (Abbreviated Template) (No extra credit for additional analytes) [0.75]	0.75	0.75
28725	8/23/2016	BIOQUALITY	Quality Assessment [1-5]	5	5
				Total:	7

ANDA: 207868, DCR Consult and Consult Response Review (REF# 11137918)

Completed Assignment for 207868 ID: 30138

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Score	Subtotal
30138	1/30/2017	BIO	Consult Review (For Consults to Other Office) [1]	1	1
30138	1/30/2017	Parallel	Review of the Consult Response and Formal Consult [1]	1	1
30138	2/2/2017	BIOQUALITY	Quality Assessment [1-5]	4	4
				Total:	6

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	207868	
Drug Product Name	Nicotine Polacrilex Mini Lozenges	
Strength(s)	EQ 2 mg Base and EQ 4 mg Base*	
Applicant Name	PLD Acquisitions LLC, D/B/A Avema Pharma Solutions	
Applicant Address	10400 NW 29th Terrace Miami, FL 33172 USA	
Applicant's Point of Contact	Mehul Govani	
Contact's Telephone Number	(b) (6)	
Contact's Fax Number	(516) 272-8203	
Contact's Email Address	mgovani@pldevelopments.com	
Original Submission Date(s)	12/02/2015 (Resubmission/After Refuse to Receive) *[06/19/2014 (Subject to a refuse to receive)]***	
Submission Date(s) of Amendment(s) Under Review	09/17/2015 (Supp. Document #2) Quality/Response To Information Request; 12/02/2015 (Supp. Document #3) Quality/Manufacture Information; User Fee/Coversheet; Resubmission/After Refuse to Receive; Labeling/Container-Carton Draft; 10/26/2016 (Supp. Document #8) Response to ECD/Bioequivalence 02/13/2017 Establishment Inspection Report (EIR) for Clinical Site (Phase One Solutions, Inc)[1]	
Reviewer	Yi Zhang, Ph.D.	
Secondary Reviewer	Li Gong, Ph.D.	
Tertiary Reviewer	April C. Braddy, Ph.D.	
Study Number (s)	AJ-1403	AJ-1401
Study Type (s)	Pivotal Fasting Study	Pilot Fasting Study
Strength (s)	1 x 4 mg	1 x 4 mg
Clinical Site	Phase One Solutions, Inc.	
Clinical Site Address	1405 NW 167th Street Miami Gardens, FL 33169 USA Phone: (305) 624-9191	
Analytical Site	(b) (4)	
Analytical Site Address		

(b) (4)

OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☒ **Complete (Inadequate)**
Waiver/Deem Bioequivalent	☒ **Granted** ☐ **Tentatively granted** ☐ **Not granted** ☐ **N/A**	
QC Dissolution	☐ **Pending** ☐ **Adequate** ☒ **Inadequate*****	
Formulation	☒ **Adequate** ☐ **Inadequate**	
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☒ **No** ☐ **N/A**	
Deficiency Classification	☐ **Major (Deficiencies to be communicated by CR)** ☒ **Minor** ☐ **N/A (Review is Adequate)**	
OVERALL REVIEW RESULT	☐ **Adequate** ☒ **Inadequate**	
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**	
Communication	☐ **ECD** ☐ **IR** ☒ **Not Applicable** *(Deficiencies to be communicated by CR as per RPM)*	

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 2, 3 & 8	**Pivotal Fasting**	**4 mg**	**Adequate**
3	**Pilot Fasting**	**4 mg**	**Inadequate**
1, 2, 3 & 8	**Waiver**	**2 mg**	**Adequate**

Note:
* Each Lozenge containing Nicotine Polacrilex equivalent to Nicotine Base 2 mg and 4 mg, respectively. Throughout the current review the 2 mg and 4 mg strength refer to EQ amount of the Nicotine Base.

**This application was originally filed on 06/19/2014 as ANDA 207868. On 09/29/2015, a refuse to receive letter was issued due to several reasons including but not limited to incomplete information[2]. The firm responded to the deficiencies in the filing review, and resubmitted the current application on 12/02/2015 with the same ANDA number.

***The dissolution review was completed recently by the Division of Biopharmaceutics at the Office of New Drug Products (ONDP) in the Office of Pharmaceutical Quality (OPQ) on 01/11/2017 with inadequate outcome. The current BE review was updated accordingly. However, the deficiencies identified in the dissolution review do not impact the waiver request consideration for the BE portion.

[2] DARRTS ANDA 207868: COR-ANDAFILE-03(Refuse to Receive); BENSON, JASON A; Submit/Final Date: 09/29/2015.

1 EXECUTIVE SUMMARY

This ANDA is a GDUFA CY4 submission.

This application contains the results of a pivotal fasting bioequivalence (BE) study (#AJ-1403) comparing a test product, PLD Acquisitions LLC, D/B/A Avema Pharma Solutions's Nicotine Polacrilex Mini Lozenges, 4 mg, to the corresponding reference product, GlaxoSmithKline Consumer Healthcare's Nicorette® Mini Lozenge, 4 mg [NDA 022360, approved on 05/18/2009; Over the Counter (OTC)][3]. The application also contains a waiver request for the 2 mg strength. The BE study was designed as an open label, randomized, single-dose, two-way, crossover study in healthy male and female subjects. The plasma concentration of nicotine was measured. The determination of BE was based on the 90% confidence interval (CI) of plasma nicotine data. The results are summarized in the tables below (calculated by the firm).

Nicotine Polacrilex Mini Lozenges Dose (1 × 4 mg), N=26 (Male=20 and Female=6; Completed) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study (Study No. AJ1403)					
Nicotine					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	34.7	37.9	91.56	84.50	99.21
AUC∞ (ng·hr/mL)	37.8	41.1	91.92	84.66	99.81
Cmax (ng/mL)	8.30	8.42	98.60	92.33	105.30

Nicotine Polacrilex Mini Lozenges Dose (1 × 4 mg), N=26 (Male=20 and Female=6; Completed) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study (Study No. AJ1403)					
Baseline Corrected Nicotine					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	32.3	35.0	92.18	84.80	100.20
AUC∞ (ng·hr/mL)	35.1	38.0	92.23	84.66	100.47
Cmax (ng/mL)	7.87	7.87	100.03	93.95	106.50

The 90% CIs of the test/reference ratios for LnC_{max}, $LnAUC_{0-t}$, and $LnAUC_{0-\infty}$ fall within the acceptance range of 80.00-125.00% for both nicotine and baseline-corrected nicotine in the fasting study (Please see *Section 4.1.1.4* of this review for details). The firm's fasting BE study is **adequate**.

[3] Electronic Orange Book (Updated Through 06/2016): http://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=022360#; Search Term: NDA 022360; last accessed on 08/17/2016.

The review of *in vitro* dissolution testing was conducted separately by the biopharmaceutics quality reviewer with deficiencies identified. However, in the current BE review, the dissolution data were evaluated only for the waiver request consideration. Based on the comparative dissolution data submitted using the acceptable FDA-recommended method, the dissolution testing is considered **acceptable** with respect to supporting the waiver request for the 2 mg strength of the test product.

The formulation for the 2 mg strength of the test product is proportionally similar to that of the 4 mg strength of the test product which underwent bioequivalence testing. However, the maximum daily intake (MDI) of the inactive ingredients of Sodium Stearyl Fumarate, Maltodextrin, and Talc (125.0, 175.0 and 50.0 respectively), based on the unit amounts in the test formulations, exceed the daily intake levels of these inactive ingredients listed in the FDA's Inactive Ingredient Guide for the same route of administration (troche/lozenge, buccal or sublingual). The deficiency was communicated to the firm via a Division of Bioequivalence III (DBIII)'s Easily Correctable Deficiencies (ECD) request dated 09/12/2016 (please see *Section 4.6.1* of current review for details).

Based on the firm's ECD response (Supp. Document #8; 10/26/2016), in which, the firm's justification was not considered adequate (Please see *Section 4.6.1* for details), a DBIII's safety/efficacy consult was issued to the Division of Clinical Review (DCR) dated 11/18/2016 for the evaluation of safety concern and clinical significance due to the (b) (4) amounts of these three excipients. As per the DCR's consult response dated 01/30/2017, "*from clinical and nonclinical perspectives, that the levels of sodium stearyl fumarate, maltodextrin and talc in the proposed generic nicotine lozenge drug product are acceptable*" (Please see *Section 4.6* for details). Thus, the formulations of the test product are now considered **adequate**.

Therefore, the DBIII grants the waiver request of *in vivo* BE study requirement for the lower strength, EQ 2 mg Base, based on criteria set forth in 21 CFR § 320.22 (d) (2).

In addition to the pivotal study, as reported in the pharmaceutical development report (Report# D00068; Date: 06/17/2014; Module 3.2.P.2), the firm also conducted a 3-way crossover pilot fasting study (#AJ-1401), with two investigational test formulations against the RLD product, to investigate the influence of drug release profiles. However, the firm did not provide the detailed formulations and other related information for this pilot study (Please see *Section 4.5.1* for details). The firm will be asked to submit all related eCTD-formatted BE data summary tables and detailed information of adverse events (AEs).

Office of Study Integrity and Surveillance (OSIS) Inspection:

This ANDA is a GDUFA CY4 application. For the analytical site, as per the memorandum dated 01/20/2016, the Division of Generic Drug Bioequivalence Evaluation (DGDBE) at the OSIS recommends accepting data without on-site inspection at the analytical site for the current ANDA 207868.

The OSIS review for the clinical site was updated on 02/13/2017. As per the review of Clinical Establishment Inspection Report (EIR), although clinical site was closed for the business in 2015, clinical study records from this site were audited for (b) (4) (b) (4) during the OSIS inspection, and an FDA Form-483 was issued with four inspectional findings. The inspection was completed on 02/10/2017 with an outcome classified as "Voluntary Action Indicated (VAI)". Based on the EIR review and BE reviewer's evaluation, the OSIS findings #2-#4 would not likely affect the outcome of the current BE study, however, OSIS finding #1 was considered systemically objectionable. The firm will be requested to address this inspectional finding #1 for its impact on the *in vivo* BE study of the current application, ANDA 207868, and provide information regarding the availability of the retention samples, specifically, investigational product, Nicotine Polacrilex Mini Lozenges 4 mg manufactured by PLD Acquisitions LLC, and reference product, Nicorette® Mini Lozenge 4 mg, used in the pivotal fasting study [(#AJ-1403); Please see *Section 4.4* of this review for details].

As a result, the application is **inadequate** with deficiencies.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information[2]

Test Product	Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base
Reference Product	Nicorette® (nicotine polacrilex; OTC) mini Lozenges, EQ 2 mg Base and EQ 4 mg Base (4 mg is RLD strength)
RLD Manufacturer	GlaxoSmithKline Consumer Healthcare
NDA No.	022360
RLD Approval Date	05/18/2009
Indication	Used to reduce withdrawal symptoms, including nicotine craving associated with quitting smoking.

3.2 PK/PD Information[4]

Bioavailability	The oral bioavailability of nicotine is about 25 to 30%
Food Effect	Labeling does not make any statements about the effect of food on absorption or administration.
Tmax	Approximately one hour (1 h) for nicotine polacrilex lozenge
Metabolism	Extensively metabolized to several less active metabolites. Continine is the major metabolite, and is formed by two-step process, via CYP450 enzyme (CYP2A6) and aldehyde oxidase.
Excretion	Nicotine and its metabolites are excreted almost exclusively in the urine.
Half-life	Approximately 2 hours
Dosage and Administration	• if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you. • before using this product, read the enclosed User's Guide for complete directions and other important information • begin using the lozenge on your quit day • if you smoke your first cigarette more than 30 minutes after waking up, use 2mg nicotine lozenge • if you smoke your first cigarette within 30 minutes of waking up, use 4mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

• nicotine lozenge is a medicine and must be used a certain way to get the best results
• place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 - 30 minutes). Minimize swallowing. Do not chew or swallow lozenge.
• you may feel a warm or tingling sensation
• occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 - 30 minutes)

[4] Labeling and clinical pharmacology (online database), https://dailymed nlm nih.gov/dailymed/drugInfo.cfm?setid=991704ed-781a-489b-8b56-0b558e8fc385 (Updated: 06/07/2016); Search Term: Nicorette®; last accessed on 02/02/2017.

	• do not eat or drink 15 minutes before using or while the lozenge is in your mouth • to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks • do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects • do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day. • it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.
Maximum Daily Dose	80 mg (maximal 20 lozenges per day for 4 mg strength) 40 mg (maximal 20 lozenges per day for 2 mg strength)
Drug Specific Issues	**If you are pregnant or breast-feeding, only us e this medicine on the advice of your health care provider.** Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known. **Do not use (Mint)** •if you are allergic to soya **Ask a doctor before us e if you have** •a sodium-restricted diet •heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate. •high blood pressure not controlled with medication. Nicotine can increase your blood pressure. •stomach ulcer or diabetes **Ask a doctor or pharmacist before us e if you are** •using a non-nicotine stop smoking drug •taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted. **Stop us e and ask a doctor if** •mouth problems occur •persistent indigestion or severe sore throat occurs •irregular heartbeat or palpitations occur •you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat •you have symptoms of an allergic reaction (such as difficulty breathing or rash) **Keep out of reach of children and pets.**

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	1, fasting

1.	**Type of study:**	Fasting

	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	Eq. 4 mg base
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	N/A

Analytes to measure (in plasma/serum/blood):	Nicotine in plasma
Bioequivalence based on:	90% CI of Nicotine
Waiver request of in-vivo testing:	Eq. 2 mg based on (i) acceptable bioequivalence study on the Eq. 4 mg base strength, (ii) acceptable in-vitro dissolution testing on all strengths, and (iii) proportional similarity of the formulation across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in-vivo testing. Lozenges with alternate flavors cannot be filed in the same ANDA as the mint flavored lozenge. For each flavor, a separate submission (ANDA) should be submitted. Lozenges with an alternate flavor may be eligible for a waiver of the bioequivalence study requirements based on (1) an acceptable bioequivalence study on the 4 mg strength of the mint lozenge, (2) acceptable dissolution testing for the nicotine polacrilex lozenge with additional flavor vs. the RLD, (3) proportional similarity in the formulations of the nicotine polacrilex lozenge with additional flavor and nicotine polacrilex lozenge with mint flavor, and (4) the additional flavor (the inactives) has been approved for the same route of administration.
Source of most recent recommendations or provide the link to the current draft guidance:	Bioequivalence Recommendations for Specific Products: Draft Guidance on Nicotine Polacrilex Lozenge; linked to NDA 022360. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240974.pdf Recommended Jan 2011.
Summary of OGD or DB History	Pending ANDAs[5]

ANDA-207868 (current)	PLD Acquisitions LLC, D/B/A Avema Pharma Solutions
ANDA-208875	Watson Laboratories Inc
ANDA-209206	Watson Laboratories Inc
ANDA-209519	Watson Laboratories Inc
ANDA-209520	Watson Laboratories Inc

[5] DARRTS. Search term "Nicotine Polacrilex" under ANDA; last accessed: 02/07/2017.

<table>
<tr><td rowspan="4"></td><td>Approved ANDAs</td><td>According to the Electronic Orange Book, there is only one ANDA currently approved for this particular drug product on the market:[6]

ANDA 203690, PERRIGO R&D CO, Approved on 10/09/2012.</td></tr>
<tr><td>Previously Reviewed ANDAs</td><td>ANDA 203690</td></tr>
<tr><td>Protocols</td><td>There is one protocol (02-065 from L. Perrigo) submitted to OGD for Nicotine Polacrilex/Lozenge in the OGD protocols tracking system.[7]</td></tr>
<tr><td>Controls</td><td>There are several controlled correspondence documents submitted for Nicotine Polacrilex/Lozenge available in CONTROLS Document Tracking.[8]
<table>
<tr><th>Ctl No</th><th>Description</th><th>Doc Date</th><th>From</th></tr>
<tr><td>09-0554</td><td>Requesting dissolution guidance for this product.</td><td>10/15/2009 (Closed 2/20/2010)</td><td>Perrigo</td></tr>
<tr><td>14-0459</td><td>Chemistry Guidance/Recommendation Nicotine Polacrilex Lozenge, 2mg/4 mg - Switch from natural nicotine to synthetic nicotine in the manufacture</td><td>5/20/2014 (Open)</td><td>Perrigo R&D Company</td></tr>
</table></td></tr>
</table>

3.4 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	AP14_005_02
Analytes	Nicotine
Internal standard (IS)	Nicotine-D_4
Method description	Solid phase extraction procedure
Limit of quantitation	LLOQ 0.2000 ng/mL
Average recovery of drug (%)	105.1%
Average recovery of IS (%)	88.9%
Standard curve concentrations	0.2000, 0.4000, 1.000, 2.000, 5.000, 10.00, 20.00 and 25.00

[6] Electronic Orange Book (Updated Through 06/2016); Search term: Nicotine Polacrilex; http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm?resetfields=1; last assessed: 02/02/2017.
[7] Division of Bioequivalence Protocols Tracking: http://fdswv04385/seltrack/Protocols.asp; search term: Nicotine Polacrilex; last accessed: 02/02/2017.
[8] Internal Control Correspondence Database: http://cdsogd1/controls/; Search term: Nicotine Polacrilex; last accessed: 02/02/2017.

QC concentrations (ng/mL)	LLOQ 0.2000 ng/mL LQC 0.5000 ng/mL MQC-2 2.500 ng/mL	MQC-2 12.50 ng/mL HQC 18.75 ng/mL
QC Intra-day precision range (%CV)	LLOQ 3.0 to 6.2% LQC 1.8 to 4.4% MQC-2 0.9 to 3.1%	MQC-2 0.8 to 2.1% HQC 0.5 to 2.8%
QC Intra-day accuracy range (%Bias)	LLOQ -0.4 to 6.0% LQC 1.0 to 2.6% MQC-2 0.2 to 1.6%	MQC-2 -0.6 to 2.2% HQC -1.2 to 1.9%
QC Inter-day precision range (%CV)	1.8 to 5.5%	
QC Inter-day accuracy range	0.2 to 1.9%	
Bench-top stability (hrs)	Analyte stability in human plasma: 24 hours at room temperature with and without metabolites.	
Stock stability (hours/days)	6 hours at room temperature and 15 days at -20ºC ± 10ºC for nicotine stock solution, internal standard stock solution, nicotine intermediate stock solution and internal standard	
Processed stability (hrs)	• Autosampler stability 28 hours at room temperature • Processed sample stability 72 hours at room temperature	
Freeze-thaw stability (cycles)	3 cycles (frozen at -20ºC ± 10ºC, thawed at room temperature)	
Long-term stability (days)	• 83 days at -20ºC ± 10ºC in K_2EDTA human plasma • 77 days at -20ºC ± 10ºC in K_2EDTA human plasma with metabolites	
Dilution integrity	• DI-LTS samples (83 days at -20ºC ± 10ºC), assayed using a 10- fold dilution • DI-FT samples (3 cycles, frozen at -20ºC ± 10ºC, thawed at room temperature), assayed using a 10-fold dilution • DI-SBM samples (24 hours at room temperature), assayed using a 10-fold dilution	
Selectivity	There were interfering peaks in the blank plasma samples at the retention times of nicotine and the internal standard as seen in the chromatograms due to Environmental Tobacco Smoke (ETS) which is generated from side-stream smoke and mainstream smoke exhaled by smokers. As a consequence, nicotine from ETS is commonly found in measurable concentrations in air, surface and dust samples and it is very	

SOPs submitted	Yes
Does the duration of the each of the LTSS stability parameters support the sample preparation and assay dates	Yes

Comments on the Pre-Study Method Validation:

- A sensitive and selective liquid chromatographic tandem mass spectrometric (LC-MS/MS) method was developed and validated for the quantitative analysis of nicotine in human plasma. Nicotine-D_4 was used as the internal standard.

- The firm used Dipotassium Ethylenediaminetetraacetic Acid (K_2EDTA) as an anticoagulant in the pre-study bioanalytical method validation. The same anticoagulant K_2EDTA was used in fasting BE study sample processing.

- The firm submitted the long term storage stability (LTSS) data for nicotine as 83 days at -20°C±10°C (in K_2EDTA human plasma) and 77 days at -20ºC±10ºC (in K_2EDTA human plasma with metabolites), which exceed the maximum storage period of study samples (14 days at -20°C±10°C) for the fasting BE study.

- The average percent recovery values were consistent across all the QC concentrations for nicotine and overall CV% was 5.2% (Imprecision within each concentration level and across the concentration range must not exceed 15%). The average percent recovery for the internal standard, nicotine-D_4, was 88.9%.

- Thus, the pre-study method validation for nicotine is **adequate**.

3.5 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Summary of Bioavailability Study for Nicotine Polacrilex Mini Lozenges, 4 mg (Fasting Study: AJ-1403)

For Nicotine

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (%CV)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (hr*ng/mL)	AUC∞ (hr*ng/mL)	T½ (hr)	Kel (hr-1)	
AJ1403	Nicotine Polacrilex 4 mg Mini Lozenge/Oral versus Nicorette® 4 mg Mini Lozenge/Oral (RLD) in a Randomized, Open-Label, Single-Dose, Two-Way Crossover Study in Healthy Smokers	Open-label, randomized, single-dose, two-treatment, two-period crossover	Nicotine Polacrilex 4 mg Mini Lozenge Lot Number: BP033725 Nicorette® 4 mg Mini Lozenge Lot Number:	26 completing (19M/7F) Healthy subjects Age: 45.6 (20-65)	8.74 (34.8%) 8.86 (35.1%)	1.38 (0.883 - 2.67) 1.25 (0.500 - 6.00)	38.0 (49.7%) 41.0 (43.3%)	41.6 (52.6%) 44.9 (46.7%)	3.20 (41.0%) 2.93 (23.0%)	0.2358 (22.7%) 0.2480 (21.9%)	Appendix 16.2.6 page 399

For Baseline-Corrected Nicotine

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (%CV)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (hr*ng/mL)	AUC∞ (hr*ng/mL)	T½ (hr)	Kel (hr-1)	
AJ1403	Nicotine Polacrilex 4 mg Mini Lozenge/Oral versus Nicorette® 4 mg Mini Lozenge/Oral (RLD) in a Randomized, Open-Label, Single-Dose, Two-Way Crossover Study in Healthy Smokers	Open-label, randomized, single-dose, two-treatment, two-period crossover	Nicotine Polacrilex 4 mg Mini Lozenge Lot Number: BP033725 Nicorette® 4 mg Mini Lozenge Lot Number:	26 completing (19M/7F) Healthy subjects Age: 45.6 (20-65)	8.27 (33.5%) 8.24 (33.9%)	1.38 (0.883 - 2.67) 1.25 (0.500 - 6.00)	35.2 (48.3%) 37.4 (40.0%)	38.5 (51.4%) 41.0 (43.5%)	3.20 (41.0%) 2.93 (22.9%)	0.2359 (22.7%) 0.2482 (21.9%)	Appendix 16.2.6 page 483

Table 2. Reanalysis of Study Samples

Study No.
AJ-1403
Nicotine

Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Low internal standard	1.00	1.00	0.09	0.09	1.00	1.00	0.09	0.09
Investigational repeat	1.00	1.00	0.09	0.09	1.00	1.00	0.09	0.09
Total	2.00	2.00	1.19	1.19	2.00	2.00	1.19	1.19

Total Assay: 1059 samples

Table 3. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
[redacted] (b) (4)		Sample Analysis (Chromatographic)
		Sample Reanalysis and Reporting Criteria

Is there any other particular concern that should be investigated further?	No

Comments from the Reviewer:

- The SOPs for sample re-analysis were provided and effective during the sample re-analysis of the fasting study (Study No. AJ-1403).

- Along with analytical raw data, approximately 20% of representative chromatograms from Subject # [redacted] (b) (6) were provided in the Bioanalytical Report (Project No. AJ-1403, Report Date: 06/03/2014) in module 5.3.1.4.

- The firm also provided complete (100%) raw numerical data for all the subjects from all analytical runs (#01 to #18) of the fasting BE study in module 5.3.1.4 (Please see Sections 4.1.1.3 for details).

Fasting Study (No. AJ-1403)

According to above Summary Table of Reanalysis of Study Samples and the Bioanalytical Report, in the fasting BE study, a total of 4 out of 1059 study samples [2 samples from the test treatment (1.19%) and 2 samples from the reference treatment (1.19%)] were reanalyzed for nicotine. Please see attachment below the Bioanalytical Report for details.

Table 4 Summary of Repeat Analysis Data for Nicotine in Human Plasma

Subject	Period	Time	Original Conc. ng/mL	Original Curve Number	Reason for Reassay	Reassay Conc. ng/mL	Reassay Curve Number	Reported Conc. ng/mL	Reason for Reported Conc.
[redacted] (b) (6)	1	2h	5.493	6	1	5.537	15	5.537	1
	2	0.083h	0.9680	6	1	1.005	15	1.005	1
	2	6h	7.834	9	2	7.845, 7.873	18, 18	7.845	2
	2	3h	3.102	9	2	3.244, 3.211	18, 18	3.211	2

Reasons For Reassay:
1). LIS - Low Internal Standard
2). INVR - Investigation Required

Reasons For Reported Conc.:
1). Repeat Value Reported
2). Median of Selections Reported

- Low Internal Standard: As reported in the Summary Table of Reanalysis and the Bioanalytical Report, a total of 2 samples [1 sample from the test treatment (0.09%) and 1 sample from the reference treatment (0.09%)] were reanalyzed for nicotine due to the

reason of "*Sample(s) with High, Low or No Internal Standard*", which was pre-defined in Section 3.4 of the firm's re-assay SOP (b) (4) as "*Study samples whose IS response is less than 50% of the minimum or greater than 150% of the maximum IS response of the passing standards and quality control samples within the batch run are considered anomalous and must be flagged for repeat analysis. These samples will be repeated in single*". Based on the raw data submitted, the reviewer verified the firm followed the aforementioned criteria for the reassay. The peak areas of internal standard (ISTD Area) of these two samples ((b) (6) P1 2.0 h and (b) (6) P2 0.083 h) in the original run (Run #06) were far below the criteria (<50% of mean IS response), and sample repeats are acceptable. Therefore, the reassayed values were used in the final pharmacokinetic and statistical analyses.

- Investigational Repeat: there were also 2 samples [1 sample from the test treatment (0.09%) and 1 sample from the reference treatment (0.09%)] reanalyzed for nicotine in this fasting study due to the reason of "*Investigational Repeat*". However, no detailed reasons were reported, and this repeat reason was not defined in firm's re-assay SOP (No. (b) (4)). Therefore, from the bioequivalence standpoint, the reviewer considers these two sample reassays ((b) (6) P2 6.0 h and (b) (6) P2 3.0 h) as "PK repeats". However, based on the raw data submitted and the reviewer's calculation (the reviewer confirmed the original and reassay concentrations reported in above Table 4 "*Summary of Repeat Analysis*"), the original value for these two sample were 7.834 ng/ml and 3.102 ng/ml, whereas the duplicate reassay values were 7.845/7.873 ng/ml and 3.244/3.211 ng/ml, respectively, and the differences were less than 5%, which is considered acceptable. Thus, although the reviewer considers these two sample reassays as 'PK repeats', the reassay of these samples should not have any impact on the study outcome based on the closeness of the original and reassay values for these two samples, and also the consistency of duplicate reassay values (difference <5%).

- In addition to the individual reassayed samples as mentioned above, as documented in the Bioanalytical Report (Project No. AJ-1403, Report Date: 06/03/2014), for nicotine, there was one rejected run, Run#12 ((b) (6)), was identified due to the reason of all 3 Control Blank samples and both STD0 samples had responses at the retention time of nicotine between STD1 and STD3, and therefore failed to meet the acceptance criteria. These subject samples were repeated in subsequent Run#15.

- Overall, the firm's study sample reanalyses are **adequate**.

3.6 Waiver Request(s) For Immediate Release Dosage Forms

Strengths for which waivers are requested, if applicable	2 mg
Waiver regulation cited?	21 CFR § 320.22 (d) (2)
Strengths considered for 21 CFR 320.24 (b)(6)	N/A
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	The review of in vitro dissolution testing was completed recently on 01/11/2017 with deficiencies. However, the dissolution data are considered acceptable with respect to supporting the waiver request for the 2 mg strength of the test product.
Waivers granted?	**WAIVER GRANTED**
If not then why?	N/A

3.7 Deficiency Comments

Please refer to the deficiency comment specified in the letter attached.

3.8 Comments for Other OGD Disciplines

Discipline	Comment
N/A	N/A

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4. Study Information

Study Number	AJ-1403
Study Title	Nicotine Polacrilex 4 mg Mini Lozenge/Oral versus Nicorette® 4 mg Mini Lozenge/Oral (RLD) in a Randomized, Open-Label, Single-Dose, Two-Way Crossover Study in Healthy Smokers Under Fasted Conditions
Study Type	*In Vivo* BE
Clinical Site (Name & Address)	Phase One Solutions, Inc. 1405 NW 167th Street Miami Gardens, FL 33169 USA Phone: (305) 624-9191
Principal Investigator	Lawrence A. Galitz, MD lawrencegalitz@phase1solutions.com
Dosing Dates	**Period 1:** 14-May-2014 **Period 2:** 19-May-2014
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	
Analytical Director	
Storage Period of Biostudy Samples (a) Duration (No. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g.,-20°C to -80°C)	(a) Fourteen (14) days from the first sample collected on 14-May-2014 to the last sample extracted on 28-May-2014. (b) -20ºC±10ºC
Long-Term Storage Stability Coverage (no. days @ temp °C)	83 days at -20ºC±10ºC in K_2EDTA human plasma

Table 5. Product information

Product	Test	Reference
Treatment ID	T (A)	R (B)
Product Name	Nicotine Polacrilex 4.0 mg mini lozenge	Nicorette® 4.0 mg mini lozenge
Manufacturer	PLD Acquisitions, LLC D/B/A Avema Pharma Solutions	GSK
Batch/Lot No.	BM033299 / BP033725	14347
Manufacture Date	02/11/14	
Expiration Date	N/A	07/15
Strength	4.0 mg	4.0 mg
Dosage Form	Lozenge	Lozenge
Bio-Batch Size	(b) (4)	
Production Batch Size		
Potency (Assay)	98.8%*	98.1%†
Content Uniformity (AV)	98.0%, 1.3%	100.3%, 1.6%
Dose Administered	1 x 4 mg	1 x 4 mg
Route of Administration	Oral	Oral

*Obtained from the Certificate of Analysis (COA) of the test product (Batch# BP033725), located in Module 5, Section 3.2.P.5.4 Batch Analysis.
† Obtained from the COA of the reference product (Batch #14347), located in Module 5, Section 2.7.1.

Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	N/A

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	**Enrolled:** 29 **Dosed:** 29 **Completed:** 26 **Samples Analyzed:** 27 **Data Analyzed:** 26
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	5 days
Randomization Scheme (Sequence of T and R)	**Yes** Please see Appendix 16.1.7 for the subject randomization schedule and codes.

Blood Sampling Times	A total of twenty (20) blood samples will be collected during each period. Blood samples (6 mL) were collected in appropriately labeled blood collection tubes containing K_2EDTA as the anticoagulant within 90 minutes prior to dosing and at 5, 10, 15, 30, 40 and 50 minutes and 1.0, 1.25, 1.5, 1.75, 2.0, 2.33, 2.67, 3.0, 4.0, 6.0, 8.0, 10.0 and 12.0 hours after study drug administration in each study period.
Anticoagulant used	K_2EDTA
Blood Sample Processing & Storage (include storage temperature)	(b) (4)

Comments on Study Design:

- The study (#AJ-1403) was designed as an open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative oral bioequivalence study of the Test and Reference formulations of Nicotine Polacrilex mini lozenge 4 mg in normal healthy smokers, male and non-pregnant female, under fasting condition (Per the subject inclusion criteria: current cigarette smoker who has smoked cigarettes daily for at least 1 year; Please see *Section 4.1.1.4* for details).

- Per the study protocol (Protocol #AJ1403; Date: 04/30/2014)[9], within 30 days of qualifying screening examinations, the subjects will report to SITE's dormitory facility approximately 14 hrs or earlier prior to study drug administration. All subjects will be required to fast at least 10 hrs prior to dose and must abstain from smoking during their confinement. The assigned study drug will be placed in the subject's mouth by SITE staff and the subject will be instructed to allow lozenge to completely dissolve slowly over approximately 20-30 minutes. The subject will be asked not to chew or swallow the lozenge and move the lozenge around the mouth while it dissolves. No water will be

[9] ANDA 207868, View EDR: Clinical Study Protocol (#AJ1403; Date: 04/30/2014) in Module 5.3.1.2. Submission Date: 06/19/2014.

administered in conjunction with lozenge. The subject will be asked to minimize swallowing as the lozenge dissolves. The time the lozenge has completely dissolved will be noted by the SITE staff for each subject. After dosing, no food will be allowed until 4 hrs post-dose. No water may be consumed for 1 hr pre-dose through 1 hr post-dose. Drinking water will be *ad libitum* at all other times.

- A total of 29 volunteers were enrolled and all 29 volunteers dosed in both period I. 26 subjects were dosed in period II and 26 subjects completed the study. Final PK analysis was carried out on the 26 subjects.

- Per RLD labeling, Tmax for nicotine is about 1 hour after oral administration of lozenge, and the elimination half-life is approximately 2 hours. Therefore, the current sampling time up to 12 hours is adequate to cover the absorption, distribution and elimination phases, and continue for more than five times of the plasma half-life.

- The firm's fasting study design is **acceptable**.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. AJ-1403			
		Treatment Groups	
		Test Product N = 26	Reference Product N = 26
Age (years)	Mean ± SD	46.0 ± 13.8	46.0 ± 13.8
	Range	20 - 65	20 - 65
Age Groups	< 18	0 (0.0%)	0 (0.0%)
	18 – 40	6 (23.1%)	6 (23.1%)
	41 – 64	18 (69.2%)	18 (69.2%)
	65 – 75	2 (7.7%)	2 (7.7%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	Male	20 (76.9%)	20 (76.9%)
	Female	6 (23.1%)	6 (23.1%)
	Asian	0 (0.0%)	0 (0.0%)
	Black	0 (0.0%)	0 (0.0%)

	Caucasian	1 (3.8%)	1 (3.8%)
	Hispanic	25 (96.2%)	25 (96.2%)
	Other	0 (0.0%)	0 (0.0%)
Other Factors	N/A	N/A	N/A

Table 8. Dropout Information, Fasting Bioequivalence Study

Study No. AJ-1403				
Subject No/ Treatment	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Withdrew Consent	P2, prior to dosing	No	No
	Emesis/Withdrew Consent/Medical grounds per the Principal Investigator	P1, prior to 40 minute PK sample	No	No
	Vomiting, time thought to be insufficient for complete absorption of drug; subject number not assigned	P1, 17 minutes after dosing	No	No

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System/ Adverse Event	**Reported Incidence by Treatment Group**	
	Fasted Bioequivalence Study Study No. AJ-1403	
	Test	**Reference**
Gastrointestinal Disorders		
Nausea	1 (3.4%)	1 (3.4%)
Vomit	1 (3.4%)	1 (3.4%)
Total	2 (6.8%)	2 (6.8%)

Subjects Experiencing Emesis (Include in eCTD)

Subject Number*	**Test/Reference**	**Period**	**Duration Between Dosing and Emesis (hrs)**
(b) (6)	R	P1	40 min
	T	P1	17 min

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.

Yes. As submitted in the Clinical Study Report (Project No. AJ-1403, Version: Final, Report Date: 06/12/2014 01), a total of 4 adverse events (2 following Test, 2 following Reference) were reported by 2 of the subjects who participated in this study. All adverse events were considered mild and all were resolved. However, there is still not enough information to make a comparison only based on sparse occurrence of AEs in the different disease categories related to the fasting study due to the nature of relatively small number of study subjects; consequently, these AEs are not significant and/or should not have significant impact on the outcome of the fasting study.

Are there any serious adverse events or death? If so, are they reported to the OGD Safety Committee?

No deaths, serious adverse events, or significant adverse events reported or occurred for any subjects over the course of the fasting study.

Are there any other safety concerns based on the adverse event profile?

No

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Study No. AJ-1403		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Laboratory Assessment Deviations – blood samples collected late	(b) (6)	

Comments:

Dropouts:

- In the fasting study (Study No. AJ-1403), a total of 29 healthy, adult subjects were enrolled and 26 subjects completed both the periods of the study. Subject (b) (6) withdrew consent prior to Period 2. Subject (b) (6) was withdrawn from the study for medical reasons (nausea and vomiting) by the Principal Investigator prior to completion of Period 1. Subject 029 (screen#) vomited 17 minutes after dosing was initiated; the residence time of the lozenge in the oral cavity was thought to be insufficient for complete absorption of drug and for that reason a subject number was not assigned and blood samples were not collected. All these three subjects were never replaced with any substitute or were included in further analysis. Pharmacokinetic analysis was performed on data obtained from 26 subjects who completed the study.

Adverse Events:

- The subjects were monitored throughout the fasting study for any adverse experiences. There were no deaths, SAEs, or other significant AEs reported in the study.

- A total of 4 adverse events (2 following Test, 2 following Reference) were reported by 2 of the subjects who participated in this study. All adverse events were considered mild and all were resolved. The most frequent adverse events reported for the Test product were nausea and vomiting, reported by 2 and 2 subjects, respectively.

- Two emesis events occurred shortly after dosing (1 of which was not assigned a subject number) and were dropped from the study by the Principal Investigator (please see dropout subject for details), and therefore have no impact on the study outcome.

Protocol Deviations:

- As submitted in Appendix 16.2.2 and Section 10.2 of the fasting study report, details of the protocol deviations that occurred over the course of the study were also appended in Table 10 above. There were no early draws reported, however, there were some late draws during the study. Most of blood sampling time deviations in the study occurred less than 5% of the nominal time points (except for (b) (6) 50min, (b) (6) 1.75h, (b) (6) 30min, (b) (6) 1.0h, (b) (6) 1.0h, (b) (6) 50min, (b) (6) 1.25h, (b) (6) 5min, (b) (6) 50min for P1, (b) (6) 5min for P2, (b) (6) 30min, (b) (6) 10min, (b) (6) 30min, (b) (6) 40min, (b) (6) 5min and 40min, (b) (6) 5min, (b) (6) 5min and 10min, (b) (6) 10min, (b) (6) 30min and 1.0h, (b) (6) 5min, 30min and 40min). The detailed information of all deviations between the scheduled and actual times of sample collection is presented in the table below. However, the blood sample collection time point deviations should not have any impact on the outcome of the study since the actual blood sample collection times were utilized for the pharmacokinetic and statistical analysis.

Subject Number (b) (6)	Period	Drug	Time Point	Deviation	Time Late MM:SS
	2	A	1.75Hr	Blood sample collected late	0:02:44
	1	A	40min	Blood sample collected late	0:02:21
	2	B	5min	Blood sample collected late	0:01:23
	1	A	50min	Blood sample collected late	0:01:30
	2	B	5min	Blood sample collected late	0:01:53
	2	B	50min	Blood sample collected late	0:01:35
	2	A	5min	Blood sample collected late	0:06:11
	2	A	10min	Blood sample collected late	0:02:12
	2	A	40min	Blood sample collected late	0:01:10
	2	A	3.0Hr	Blood sample collected late	0:01:29
	2	A	4.0Hr	Blood sample collected late	0:02:10
	1	A	1.75Hr	Blood sample collected late	0:04:40
	2	B	10min	Blood sample collected late	0:01:02
	2	B	1.75Hr	Blood sample collected late	0:02:01
	2	A	1.0Hr	Blood sample collected late	0:01:02
	1	B	50min	Blood sample collected late	0:01:20
	1	B	1.0Hr	Blood sample collected late	0:04:20
	2	A	30 min.	Blood sample collected late	0:02:00
	2	A	1.75Hr	Blood sample collected late	0:03:05
	2	A	8.0Hr	Blood sample collected late	0:03:01
	1	A	40min	Blood sample collected late	0:04:00
	1	A	1.75Hr	Blood sample collected late	0:02:45
	1	A	10.0Hr	Blood sample collected late	0:06:00
	2	B	15min	Blood sample collected late	0:05:01
	2	B	30min	Blood sample collected late	0:03:02
	2	B	4.0Hr	Blood sample collected late	0:01:38

Subject Number	Period	Drug	Time Point	Deviation	Time Late MM:SS
(b) (6)	2	A	1.75Hr	Blood sample collected late	0:02:44
	1	A	40min	Blood sample collected late	0:02:21
	2	B	5min	Blood sample collected late	0:01:23
	1	A	50min	Blood sample collected late	0:01:30
	2	B	5min	Blood sample collected late	0:01:53
	2	B	50min	Blood sample collected late	0:01:35
	2	A	5min	Blood sample collected late	0:06:11
	2	A	10min	Blood sample collected late	0:02:12
	2	A	40min	Blood sample collected late	0:01:10
	2	A	3.0Hr	Blood sample collected late	0:01:29
	2	A	4.0Hr	Blood sample collected late	0:02:10
	1	A	1.75Hr	Blood sample collected late	0:04:40
	2	B	10min	Blood sample collected late	0:01:02
	2	B	1.75Hr	Blood sample collected late	0:02:01
	2	A	1.0Hr	Blood sample collected late	0:01:02
	1	B	50min	Blood sample collected late	0:01:20
	1	B	1.0Hr	Blood sample collected late	0:04:20
	2	A	30 min.	Blood sample collected late	0:02:00
	2	A	1.75Hr	Blood sample collected late	0:03:05
	2	A	8.0Hr	Blood sample collected late	0:03:01
	1	A	40min	Blood sample collected late	0:04:00
	1	A	1.75Hr	Blood sample collected late	0:02:45
	1	A	10.0Hr	Blood sample collected late	0:06:00
	2	B	15min	Blood sample collected late	0:05:01
	2	B	30min	Blood sample collected late	0:03:02
	2	B	4.0Hr	Blood sample collected late	0:01:38

- There was no other protocol deviation recorded during the study. Therefore, the listed protocol deviations did not have any significant impact on the outcome of the study.

Thus, the overall "Dropouts/Adverse Events/Protocol Deviations" did not compromise the integrity of the study and the firm's handling of these matters is **acceptable**.

4.1.1.3 Bioanalytical Results

Table 11. Sample Analysis Calibration and Quality Control

Bioequivalence Study No. AJ-1403 Analyte Name: Nicotine								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.2000	0.4000	1.000	2.000	5.000	10.00	20.00	25.00
Inter day Precision (%CV)	5.7	4.2	2.8	1.7	1.7	2.0	1.8	2.1
Inter day Accuracy (%Bias)	-0.4	-0.1	1.7	0.6	0.4	-0.6	-0.8	-0.9
Linearity	"r^2" values: 0.996004 to 0.999667							

Linearity Range (ng/mL)	0.2000 to 25.00 ng/mL
Sensitivity/LLOQ (ng/mL)	LLOQ 0.2000 ng/mL

Bioequivalence Study No. AJ-1403 Analyte Name: Nicotine				
Parameter	**Quality Control Samples**			
Concentration (ng/mL)	LQC 0.5000	MQC-1 2.500	MQC-2 12.50	HQC 18.75
Inter day Precision (%CV)	9.7	2.3	1.9	2.2
Inter day Accuracy (%Bias)	2.5	1.1	-0.2	-0.6

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Are there any concerns related to sample analysis (including reanalysis, run rejection, etc.)?	No

Were 20% of chromatograms included?	Yes.
Did the firm provide 100% numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log) in the instrument printout format?	Yes.

Table 12. SOP's Dealing with Sample Analysis

SOP No.	Effective Date of SOP	SOP Title
[redacted] (b) (4)		Sample Analysis (Chromatographic)
		Sample Reanalysis and Reporting Criteria
		Incurred Sample Reanalysis

Comments:

- The firm submitted representative original chromatograms for approximate 20% of total study samples (Subject [redacted] (b) (6)) for the fasting study (Study No. AJ-1403) in the Bioanalytical Report (Project No. AJ-1403, Report Date: 06/03/2014) in module 5.3.1.4.

- The firm also provided complete (100%) raw numerical data for all the subjects from all analytical runs (Run#01 to #18) of the fasting BE study as an attachment "*Study AJ-1403 Raw data*" in module 5.3.1.4.

- All data being reported for this study are from acceptable runs as per the firm's run acceptance criteria predefined in Section 8 of firm's SOP "*Sample Analysis*

(Chromatographic)". As documented in the Bioanalytical Report submitted by the firm, total 18 analytical runs (including 2 runs for incurred sample reanalysis and 2 runs for individual/batch repeats) were carried out for the analyte of nicotine, and only one rejected run, Run#12 (Subjects (b) (6)), was identified due to "All 3 Control Blank samples and both STD0 samples failed to meet acceptance criteria", and accordingly these two subject samples was re-assayed in the subsequent run.

- To confirm the reproducibility of bioanalytical method during study sample analysis, in this study, for nicotine, the firm used 121 samples out of 1059 (11.3% of the total samples analyzed) in its incurred samples reproducibility (ISR) testing. ISR testing was performed as per SOP (b) (4) (Reanalysis of Incurred Bioanalytical Samples; effective date: 02/14/2014). Of 121 ISR samples considered, 120 samples (99.2%) met the acceptance criteria: at least ⅔ of reanalyzed samples must have a relative difference for the repeat values of within ± 20%. The firm's selection for ISR samples was as per the current FDA Guidance (Guidance for Industry: Bioanalytical Method Validation; recommended September 2013)[10]. The firm's ISR analysis is acceptable and the method is reproducible.

- As a result, the firm's during study assay validation is considered **complete** (adequate).

4.1.1.4 Pharmacokinetic Results

Is there a Tmax difference between T and R	Yes. T/R = 1.104 for Nicotine. Acceptable, please see the comments below.
Are any CIs marginal?	No
Were the subjects dosed in groups?	No
Is the study design replicate and/or reference-scaled?	No
Is sampling time adequate?	Yes. Per RLD labeling, Tmax for nicotine is about 1 hour after oral administration of lozenge, and the elimination half-life is approximately 2 hours. In the current study, half-life for nicotine is approximately 3.20 hours for the test and 2.93 hours for the reference products. Blood samples were collected up to 12 hours after drug administration, and the sampling times are adequate to cover the absorption, distribution and elimination phases, and continue for more than four to five times of the plasma half-life.

Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE Studies for Nicotine for Fasting Study (No. AJ-1403)

Nicotine Polacrilex Mini Lozenges **Dose (1 × 4 mg), N=26 (Male=20 and Female=6; Completed)** **Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals** **Fasting Bioequivalence Study (Study No. AJ1403)**

[10] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf

Nicotine					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	34.7	37.9	91.56	84.50	99.21
AUC∞ (ng·hr/mL)	37.8	41.1	91.92	84.66	99.81
Cmax (ng/mL)	8.30	8.42	98.60	92.33	105.30

Nicotine Polacrilex Mini Lozenges Dose (1 × 4 mg), N=26 (Male=20 and Female=6; Completed) Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study (Study No. AJ1403)					
Baseline Corrected Nicotine					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	32.3	35.0	92.18	84.80	100.20
AUC∞ (ng·hr/mL)	35.1	38.0	92.23	84.66	100.47
Cmax (ng/mL)	7.87	7.87	100.03	93.95	106.50

Overall Comment:

- Per the recommendations in the currently BE draft guidance, for Nicotine Polacrilex Mini Lozenges, only one fasting BE study is recommended on the biostrength of Eq. 4 mg base in general population (healthy males and nonpregnant females), and bioequivalence should be established based on 90% CI of nicotine. The agency does not recommend correcting the data for baseline. However, since the current BE study was conducted in the normal healthy smokers (Per firm's subject inclusion criteria: current cigarette smoker who has smoked cigarettes daily for at least 1 year, please see Section 4.1.1.1 for details), and "*positive pre-dose nicotine levels were observed in at least one period in all subjects except Subject 107 (i.e. 50 subject-period cases)*" as reported by the firm, therefore, pharmacokinetic and statistical analyses were conducted using the data of both original/uncorrected and baseline-corrected nicotine concentrations (the measured nicotine concentration was corrected by subtracting the contribution from the pre-dose level), which are considered acceptable.

- The 90% CIs for the T/R ratio of least squares geometric means of $LnAUC_{0\text{-}t}$, $LnAUC_{0\text{-}\infty}$ and LnC_{max} for both nicotine and baseline-corrected nicotine reported by the firm are all within acceptable BE limits of 80.00-125.00%, and therefore meet the BE criteria.

- The ratio of median Tmax values for test (1.38 hours) vs. reference (1.25 hours) products is 1.104 for nicotine, with individual Tmax values ranging from 0.883 to 2.67 hours for the test product and from 0.500 to 6.00 hours for the reference product. Therefore, the median Tmax difference between the test and reference products is acceptable.

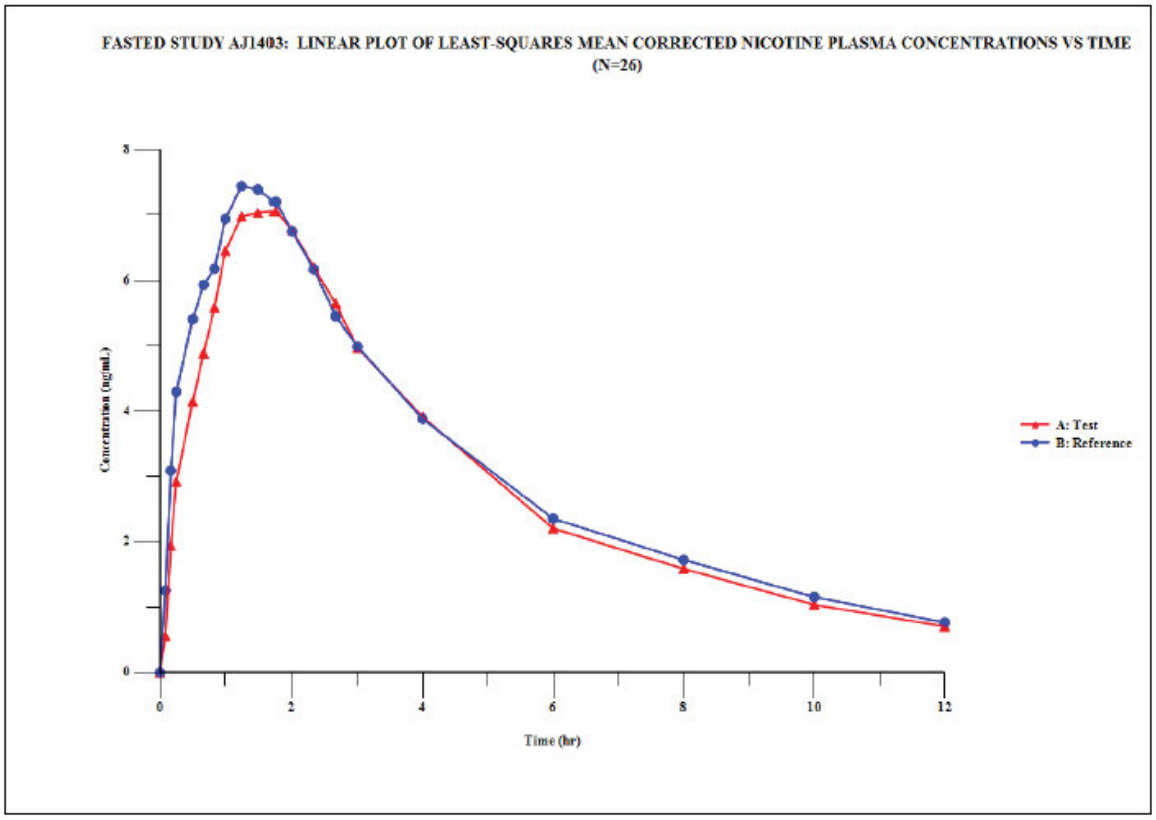
- The firm's *in vivo* fasting BE study is **adequate** (complete) as per comments above.

Table 13. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (Firm-Submitted Data in Firm's Format)

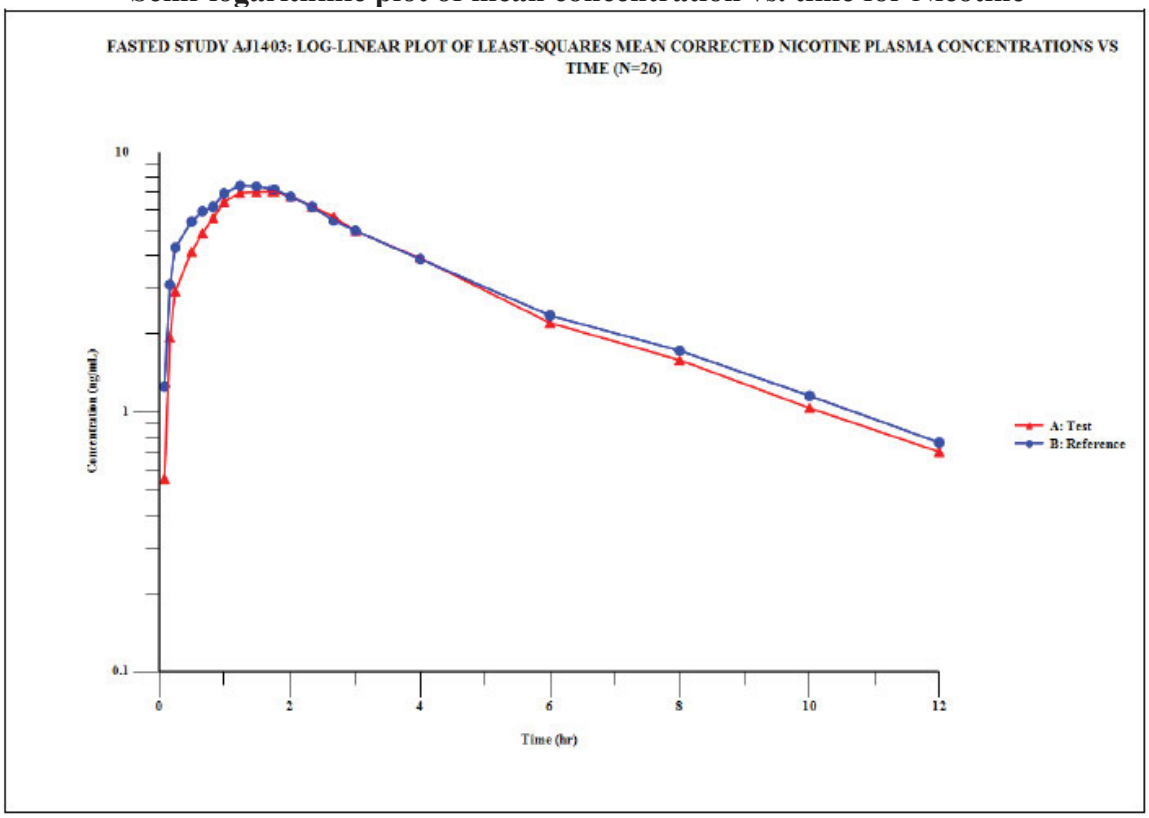
Collection (Hour)	Least-Squares Means (ng/mL)		P-Value*
	Test	Reference	
0.000	0.0000	0.0000	-
0.083	0.5537	1.2528	0.0383
0.167	1.9416	3.0899	0.0014
0.250	2.9182	4.2948	<0.0001
0.500	4.1436	5.4054	0.0002
0.667	4.8839	5.9314	0.0127
0.833	5.5815	6.1720	0.1522
1.000	6.4497	6.9361	0.3201
1.250	6.9759	7.4414	0.3023
1.500	7.0332	7.3876	0.1931
1.750	7.0569	7.1991	0.6268
2.000	6.7653	6.7457	0.9485
2.330	6.1972	6.1650	0.8995
2.670	5.6417	5.4525	0.4054
3.000	4.9692	4.9854	0.9374
4.000	3.9088	3.8789	0.8629
6.000	2.2034	2.3529	0.5662
8.000	1.5846	1.7223	0.5676
10.00	1.0359	1.1543	0.3710
12.00	0.7025	0.7628	0.4824

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (Firm-Submitted Plot)

Linear plot of mean concentration vs. time for Nicotine



Semi-logarithmic plot of mean concentration vs. time for Nicotine



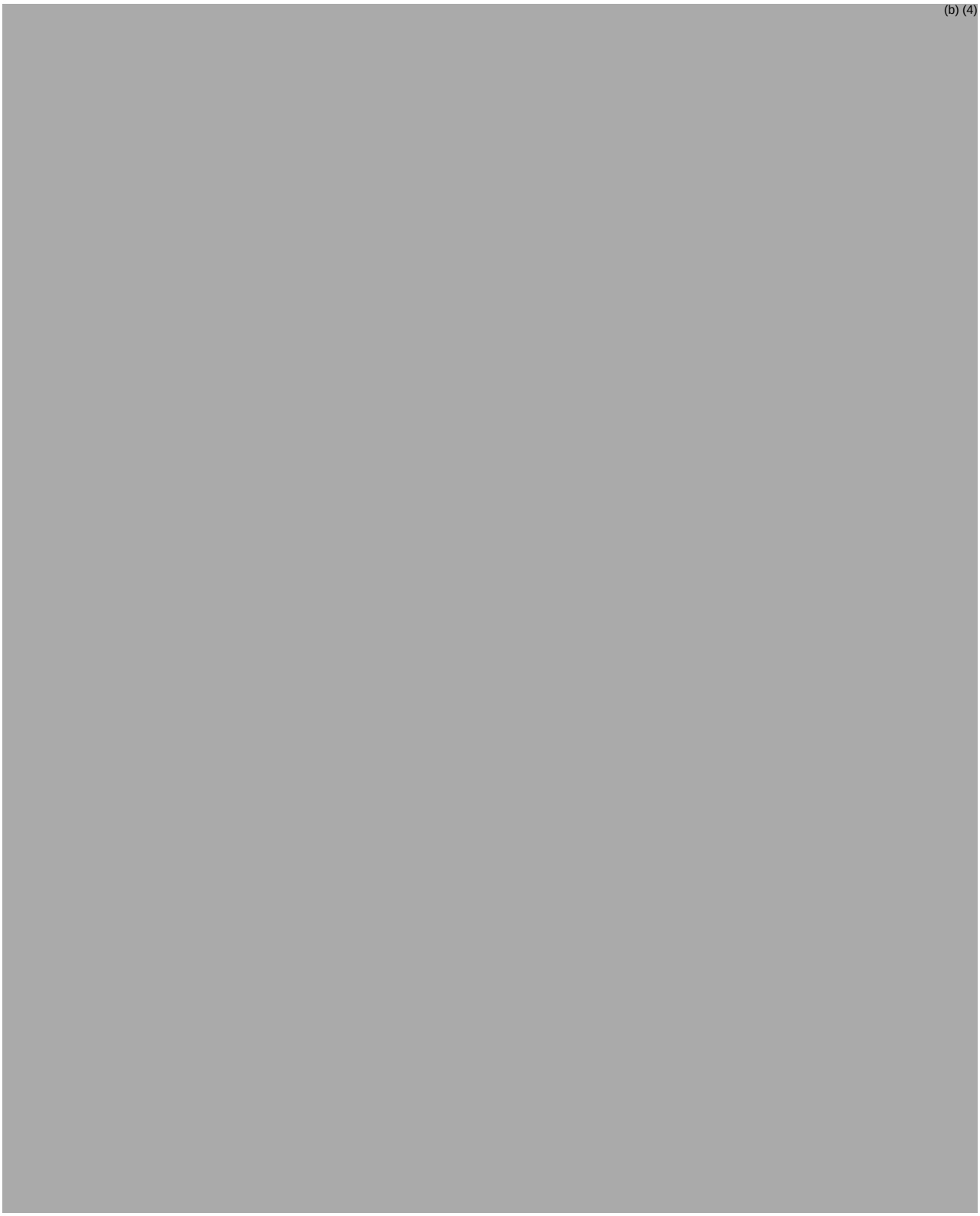
4.2 Formulation Data

Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg (Bio-strength)

Components	4 mg		2 mg		Pharmaceutical Function
	mg per unit	% w/w	mg per unit	% w/w	
Nicotine Polacrilex 15%	(b) (4)				Active
Mannitol					(b) (4)
Sodium Bicarbonate					
Sodium Stearyl Fumarate					
Maltodextrin					
(b) (4)					
Calcium Polycarbophil					
Xanthan Gum					
Aspartame					
Sodium Alginate					
Talc					
Total Weight	(b) (4)	100.00	(b) (4)	100.00	N/A

Reviewer's comments:

(b) (4)



[11] GDRP/Panorama for ANDA-207868-ORIG-1-RESUB-3, Parent: Filing Review (A207868N000DFR_CHK.docx; Beena Mathew); Date uploaded: 01/11/2016.

[12] DARRTS, ANDA 203690, REV-BIOEQ-01(General Review), Submit/Final Date: 4/4/2012.

[13] FDA IIG database: http://intranetapps.test fda.gov/scripts/iig/; last accessed: 12/1/2015.

Maximum Elemental Iron Content Calculation:

(b) (4) in (b) (4) This is in compliance to 21 CFR 73.1200.

Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD) within IIG (per unit) limits?	No
If no, are they all above/within IIG (per day) limits?	Within
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	YES
Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	YES

Reviewer's Additional Comments on Formulation:

- The formulation for the lower strength of the test product, Nicotine Polacrilex Mini Lozenges, 2 mg, is proportionally similar to that of the 4 mg strength of the test product, which underwent bioequivalence testing.
- The amount of elemental iron consumed is below FDA limit for elemental iron of 5 mg per day [21 CFR 73.1200 (c)].
- (b) (4)

- Thus, the test product formulations are now considered **adequate**.

4.3 Dissolution Data

Dissolution Review Path	As of the date of 08/23/2016, the *in vitro* dissolution testing has not yet been reviewed. The review of *in vitro* dissolution testing will be conducted separately by ONDP (Assessment of the Biopharmaceutics under the Quality Review) at a later time. ***Notes:*** The dissolution review was completed recently on 01/11/2017, the related part in the current review has been updated to 01/31/2017.

Table 24. Summary of In vitro Dissolution Studies – 4 mg strength

Dissolution Conditions	**Apparatus:**	Apparatus 1 (Basket)
	Speed of Rotation:	100 rpm
	Medium:	pH7.4 phosphate buffer, USP
	Volume:	900mL
	Temperature:	37 ± 0.5 °C
Firm's Proposed Specifications	NLT (b) (4) and NMT (b) (4) of Nicotine LC dissolved in 30min NLT and NMT of Nicotine LC dissolved in 60min NLT of Nicotine LC dissolved in 90min NLT of Nicotine LC dissolved in 120min NLT ((b) (4)) of Nicotine LC dissolved in 180minutes	
Dissolution Testing Site (Name, Address)	PLD Acquisitions, LLC D/B/A Avema Pharma Solutions, 10400 NW 29th Terrace, Miami, FL 33172, USA.	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**					**Study Report Location**
						30	**60**	**90**	**120**	**180**	
QC-309 Page- 166	06/06/14	Test: BM033299 (Manufacturing date:02/11/14)	4.0mg Lozenge	12	Mean (%)	31	55	76	91	99	Test results form PS003381 located in the corresponding finished product folder
					Range (%)	(b) (4)					
					%RSD	5.3	7.8	7.6	6.0	2.7	
QC-313	11/25/13	Reference: 14347 (Expiration date: 07/2015)	4.0mg	12	Mean (%)	27	46	63	80	103	Test results form PS003381 located in

					Range (%)	[redacted] (b) (4)					
					%RSD	4.9	3.9	3.6	5.2	1.0	

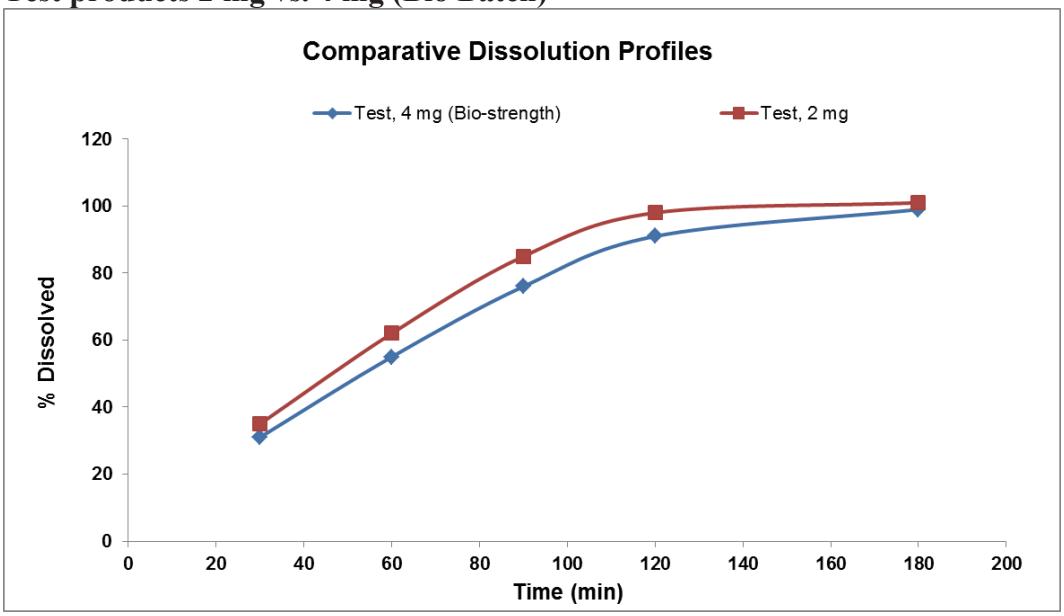
Summary of In vitro Dissolution Studies – 2mg strength

Dissolution Conditions	**Apparatus:**	Apparatus 1 (Basket)
	Speed of Rotation:	100 rpm
	Medium:	pH7.4 phosphate buffer, USP
	Volume:	900mL
	Temperature:	37 ± 0.5 °C
Firm's Proposed Specifications	NLT [redacted] (b) (4) and NM [redacted] (b) (4) of Nicotine LC dissolved in 30min NLT [redacted] and NM [redacted] f Nicotine LC dissolved in 60min NLT [redacted] of Nicotine LC dissolved in 90min NLT [redacted] of Nicotine LC dissolved in 120min NLT [redacted] (Q [redacted] (b) (4) of Nicotine LC dissolved in 180minutes	
Dissolution Testing Site (Name, Address)	PLD Acquisitions, LLC D/B/A Avema Pharma Solutions, 10400 NW 29th Terrace, Miami, FL 33172, USA.	

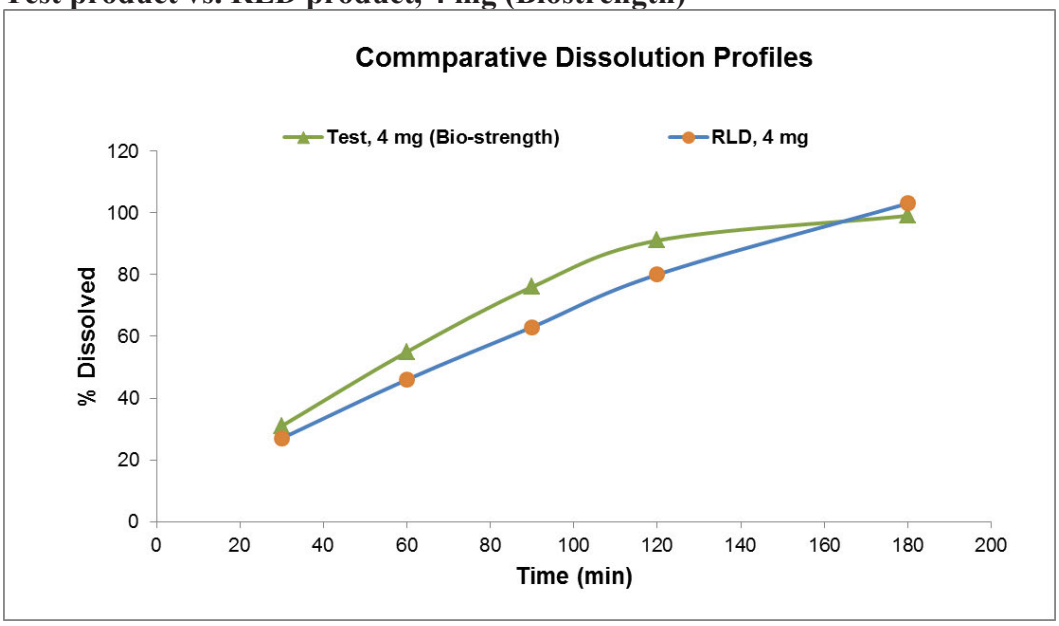
Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**					**Study Report Location**
						30	**60**	**90**	**120**	**180**	
QC-294 Page- 101	06/05/14	Test: BM033296 (Manufacture Date: 02/06/14)	2.0mg Lozenge	12	Mean (%)	35	62	85	98	101	Lab Notebook QC-294 Page- 101
					Range (%)	[redacted] (b) (4)					
					%RSD	3.4	4.0	4.7	2.4	1.1	
QC-394 Page-118	09/10/15	Reference: 14848 (Expiration date: 01/2017)	2.0mg Lozenge	12	Mean (%)	31	54	74	95	103	Lab Notebook QC-394 Page-118
					Range (%)	[redacted] (b) (4)					
					%RSD	4.5	4.2	4.3	3.2	1.5	

Comparative Dissolution Profile for Nicotine Polacrilex Mini Lozenges with FDA-recommended method (By reviewer):

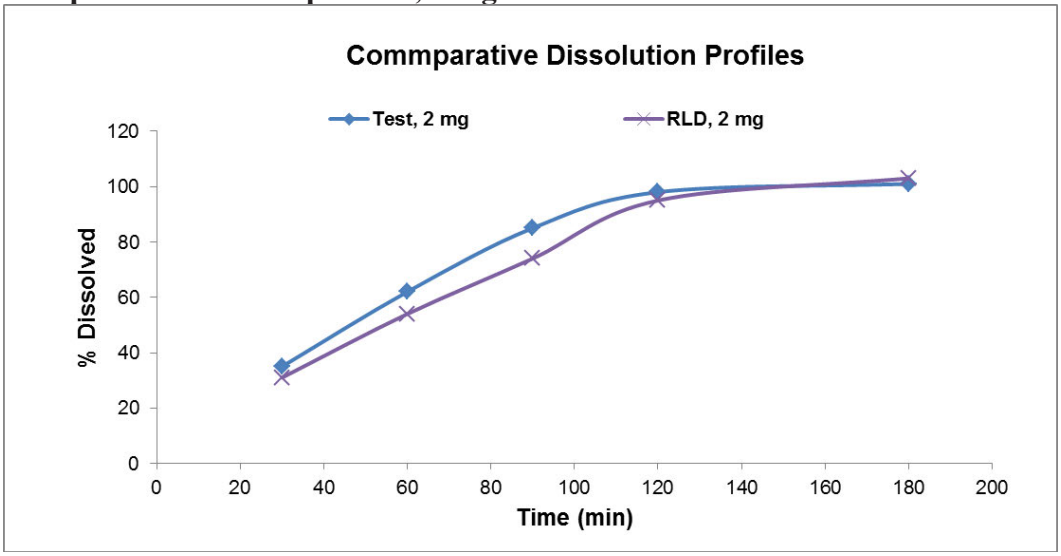
Test products 2 mg vs. 4 mg (Bio Batch)



Test product vs. RLD product, 4 mg (Biostrength)



Test product vs. RLD product, 2 mg



F2 metric, biostudy strengths compared to other strength(s)		
Dissolution Method: FDA-recommended method		
Biostudy Strength	**Other Strength**	**F2 metric between two test strengths**
4 mg (Bio-Lot# 2008026)	2 mg (Lot# 2007901)	57.58

F2 Metric Test vs RLD (all strengths)	
Dissolution Method: FDA-recommended method	
4 mg	52.21
2 mg	56.79

Please comment on whether dissolution data are adequate to support waiver requests.	Inadequate. Please see comments below

Overall Comment:

- The review of *in vitro* dissolution testing was conducted separately by the biopharmaceutics quality reviewer at the Office of New Drug Products (ONDP) in the Office of Pharmaceutical Quality (OPQ), which was completed recently on 01/11/2017 (http://panorama.fda.gov/task/view?ID=566154ad0141c025b3ecfb8c1188bb79).

- There is no USP method for Nicotine Polacrilex Mini Lozenges, but there is an FDA-recommended method posted on the FDA External Dissolution Database as follows[14] (*Note*: The dissolution method and specifications for this product has not yet been posted on the FDA internal dissolution database[15]):

[14] FDA External Dissolution Database: http://www.accessdata fda.gov/scripts/cder/dissolution/index.cfm; Search Term: Nicotine Polacrilex (updated date: 12/23/2010); last accessed: 08/22/2016.

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Nicotine Polacrilex	Lozenge (Mini)	I (Basket)	100	Phosphate Buffer, pH 7.4	900	30, 60, 90, 120 and 180	12/23/2010

- The firm conducted dissolution testing using the FDA-recommended method at the time points of 30, 60, 90, 120 and 180 min. The test products showed comparable dissolution profiles as the RLD products on the corresponding strength with similarity factor f2 values above 50 (Please see dissolution profiles and f2 values above for details). The *in vitro* dissolution testing and *in vivo* BE studies on the biostrength were conducted on the same Test (#BM033299) and RLD (#14347) lots.

- The reviewer verified that the summary dissolution data in the tables are in agreement with the individual unit data submitted by the firm. The variability of the dissolution data are less than 10% for all the dissolution sampling time points of both test and reference products.

- Based on the firm-provided *in vitro* dissolution summary data tables, the *in vitro* dissolution testing using FDA method was performed within 4 months since manufacture date of the test products. The reference products used in the dissolution test were before the RLD expiration date.

- As per the separate dissolution review, the firm's dissolution method was acceptable; however, deficiencies were identified related to the incomplete submission of dissolution raw data and unacceptable dissolution criteria/specifications. Please refer to the original dissolution review for details (http://panorama.fda.gov/task/view?ID=566154ad0141c025b3ecfb8c1188bb79).

- In the current BE review, the dissolution data were evaluated for the waiver request consideration only. Based on the comparative dissolution data submitted using FDA-recommended method, the dissolution profiles of the test products are considered comparable between the bio-strength, 4 mg, and the lower strength, 2 mg, with calculated similarity factor f2 values above 50 (Please see Figures and f2 values above for the dissolution profiles between the two test strengths). Please note that sampling time points of 30, 60, 90 and 120 min were used for calculation of f2 value between the test strengths.

- Therefore, at the time of this review, the dissolution data are **adequate** with respect to supporting the waiver request for the 2 mg strength of the test product.

[15] OGD Internal Dissolution Database; Search Term: Nicotine Polacrilex; last accessed: 08/22/2016.

4.4 The Office of Study Integrity and Surveillance (OSIS) Inspection

Reviewer's Comments for OSIS Inspection:

Based on OSIS site search "*OSI: Site Search*" [16], no OSIS inspection record was documented under the current ANDA at either clinical site (Phase One Solutions, Inc.) or analytical site (Bioanalytical Laboratory Services).

For the **analytical site** (b) (4), (b) (4) as per the memorandum provided by the Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) dated (b) (4) "*OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI)*". Thus, OSIS recommends accepting data without on-site inspection for the current ANDA 207868.

For the **clinical site** [Phase One Solutions, Inc. (1405 NW 167th Street, Miami Gardens, FL 33169, USA)], a memorandum of "*Review of Clinical Establishment Inspection Report (EIR)*" was recently documented by the DGDBE/OSIS in the GDRP/Panorama dated 02/13/2017[18].

As per this EIR review, the OSIS arranged an inspection for the BE studies of (b) (4) (b) (4) and AJ-1403 (ANDA 207868) conducted by Phase One Solutions, Inc. Since "*the firm is out-of-business (Phase One Solutions was closed in 2015), study records were audited at the* (b) (4) During the OSIS inspection from (b) (4) (b) (4) were audited, and an **FDA Form-483** was issued with four inspectional findings at the end of the inspection (please see below for details). However, "*due to delays in obtaining records, study AJ-1403 (ANDA 207868; the current application) was **not** audited*". Also, as stated in the EIR review, "*at the time of finalization of this review, no response to the Form FDA 483 observations was received by OSIS*". Therefore, the inspection was completed on 02/10/2017 with an outcome classified as "Voluntary Action Indicated (**VAI**)".

Thus, OSIS recommends that "*data from the clinical portions of studies* (b) (4) (b) (4) *are unacceptable for further Agency review because FDA could not verify the identity of investigation products used in the studies*". For the current ANDA 207868, OSIS recommends "*the review division request further information regarding whether the reserve sample issue for* (b) (4) *impacts study AJ-1403, including whether there are reserve samples available for collection*".

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[16] OSI Site Search: http://fdswv04385/bioprod/Bioequivalence_Project_Managment/Interface/ASPTest/DSI/index.asp, last assessed date: 08/23/2016; 02/15/2017

(b) (4)

(b) (4)

OSIS findings at the clinical site, OSIS assessment in the EIR and current BE reviewer's comments are summarized as follows:

(b) (4)

Reviewer's comment:

- For the current ANDA 207868, the clinical study dates (Dosing Date: PI, 05/14/2014; (b) (4)
(b) (4)

- The impact of this OSIS objectionable finding was considered systemic, thus the firm will be requested to address this inspectional finding identified from the audited studies under (b) (4) for its impact on the *in vivo* BE study of the current application, ANDA 207868.

OSIS Finding #2: (b) (4)
(b) (4)

OSIS Assessment:

- (b) (4)

Reviewer's comment:

- As per the clinical study report (Project No. AJ-1403, Version: Final, Report Date: 06/12/2014 01), for the pivotal fasting study (#AJ-1403) of the current ANDA 207868,

the IntegReview Institutional Review Board (IRB) approved Version 1.0 of the clinical study protocol (Protocol# AJ1403) on 05/02/2014, and Version 2.0 of the protocol was approved by the IRB on 05/08/2014. Copies of the approval forms from the IRB, as well as the approved protocols (Version 1.0 and Version 2.0), were provided as Appendix 16.1.1 in Module 5.3.1.2.

- In addition, the final English language Informed Consent Form (ICF) was approved by the IRB on 05/07/2014, and the Spanish language ICF was approved by the IRB on 05/09/2014.

- Based on the Case Report Forms of individual subject in the pivotal study (#AJ-1403) provided in Module 5.3.1.2, the reviewer verified that all the subjects enrolled/dosed were screened on 05/10/2014 and 05/12/2014. Therefore, for the current application, ANDA 207868, IRB approval was granted prior to clinical study dates, including the subject screening. Thus, the OSIS finding #2 was an isolated observation and does not affect the outcome of the current study.

OSIS Finding #3: (b) (4) .

(b) (4)

OSIS Assessment:

- Although generic (non-study specific) consent forms were used during screening, all subjects re-consented on IRB approved consent forms. This observation will have no significant impact on subject safety.

Reviewer's comment:

- For the pivotal fasting study (#AJ-1403), based on the Case Report Forms of individual subject provided in Module 5.3.1.2, the reviewer verified that, during the screening, all the subjects were either consented directly with the IRB approved study-specific consent form, or consented with generic consent form then re-consented with the study-specific consent form. Thus, the OSIS finding #3 was also an isolated observation and does not affect the outcome of the current study for the current application, ANDA 207868.

OSIS Finding #4: *Failure to permit an employee of FDA to copy records. Specifically, the firm failed to provide access to copying/scanning equipment to investigators as requested prior to the initiation of the inspection and failed to provide copies/scans of relevant records in a timely manner.*

OSIS Assessment:

- This observation will have no significant impact on study integrity.

Reviewer's comment:

- The impact of this OSIS finding was not considered systemic. Thus, the OSIS finding #4 does not affect the outcome of the current study for the current application, ANDA 207868.

Thus, based on the review of EIR and BE reviewer's evaluation, for considering the impact of similar studies conducted and site practices by the same facility on the BE studies, the above OSIS' observation#1 from (b) (4) study of the current ANDA 207868. The firm will be forwarded to address this inspectional finding for its impact on the *in vivo* BE study of the current application, ANDA 207868, and provide information and any necessary supporting documents (if applicable) regarding whether the samples of investigational product and reference product, specifically, Nicotine Polacrilex Mini Lozenges 4 mg produced by PLD Acquisitions LLC and Nicorette® Mini Lozenge 4 mg, used in the related *in vivo* BE study, were retained and can be released to FDA upon request.

Overall, this ANDA is a GDUFA CY4 submission, the OSIS inspection status for the current ANDA is **COMPLETE** (but the clinical site is inadequate this time *pending the firm's acceptable response*).

4.5 Attachments

4.5.1 Additional Studies (If applicable)

Are there any additional studies? (e.g. pilot, failed) **If yes, please provide the location of report (complete/summary).**	☒ Yes ☐ No Pilot fasting BE study (#AJ-1401)
Number of Subjects	15
Are the test formulations in the pilot/failed studies and pivotal studies similar[19]?	☒ Yes ☐ No ☐ N/A No detailed formulation was provided
What was the objective of pilot/failed study?	Investigate the influence of drug release profiles against the innovator product. One fast release formulation and one slow release formulation was compared for the purpose of pivotal study.
Please comment on reason(s) of failure.	N/A. BE criteria was passed
Any serious adverse events or deaths reported?	☐ Yes ☐ No ☒ N/A Information not provided

Table 7: Summary of Results for Statistical Tests on Nicotine for the Fasting Study (Fast Formulation)

Parameter	Test[1]	Reference[1]	Ratio[2]	CV%[3]	90% CI[4]
AUC_{0-t}	33.8	34.8	97.33	11.9	90.39 – 104.81
AUC_{0-inf}	36.7	37.8	97.24	12.9	89.76 – 105.34
C_{max}	7.94	8.36	93.70	15.1	85.31 – 102.91
T_{max}	1.36	1.56	87.33	-	-
λ_z	0.2261	0.2305	98.08	-	-
$t_{1/2}$	3.16	3.19	99.04	-	-

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; CV%, coefficient of variation

1. Results are presented as least-squares geometric means for AUC and Cmax and arithmetic means for other parameters.
2. Ratio calculated as Test least-squares mean divided by the Reference least-squares mean expressed as a percentage. None of the comparisons were detected as statistically significant by ANOVA (α=0.05).
3. Estimated intra-subject CV%=100*SQRT(e^{MSE}-1), where MSE is the mean square error term from the ANOVA.
4. CI on the ratio expressed as a percentage.

Table 8: Summary of Results for Statistical Tests on Nicotine for the Fasting Study (Slow Formulation)

Parameter	Test[1]	Reference[1]	Ratio[2]	CV%[3]	90% CI[4]
AUC_{0-t}	34.5	34.8	99.33	11.9	92.24 – 106.96
AUC_{0-inf}	37.4	37.8	98.87	12.9	91.27 – 107.10
C_{max}	8.30	8.47	97.95	15.1	89.18 – 107.58
T_{max}	1.66	1.56	106.05	-	-
λ_z	0.2446	0.2305	106.10	-	-
$t_{1/2}$	3.02	3.19	94.65	-	-

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; CV%, coefficient of variation

1. Results are presented as least-squares geometric means for AUC and Cmax and arithmetic means for other parameters.
2. Ratio calculated as Test least-squares mean divided by the Reference least-squares mean expressed as a percentage. None of the comparisons were detected as statistically significant by ANOVA (α=0.05).
3. Estimated intra-subject CV%=100*SQRT(e^{MSE}-1), where MSE is the mean square error term from the ANOVA.
4. CI on the ratio expressed as a percentage.

[19] Submission of Summary Bioequivalence Data for Abbreviated New Drug Applications

Figure 3: Nicotine Plasma Profile of the Proposed Product vs the RLD for the Fasted Study

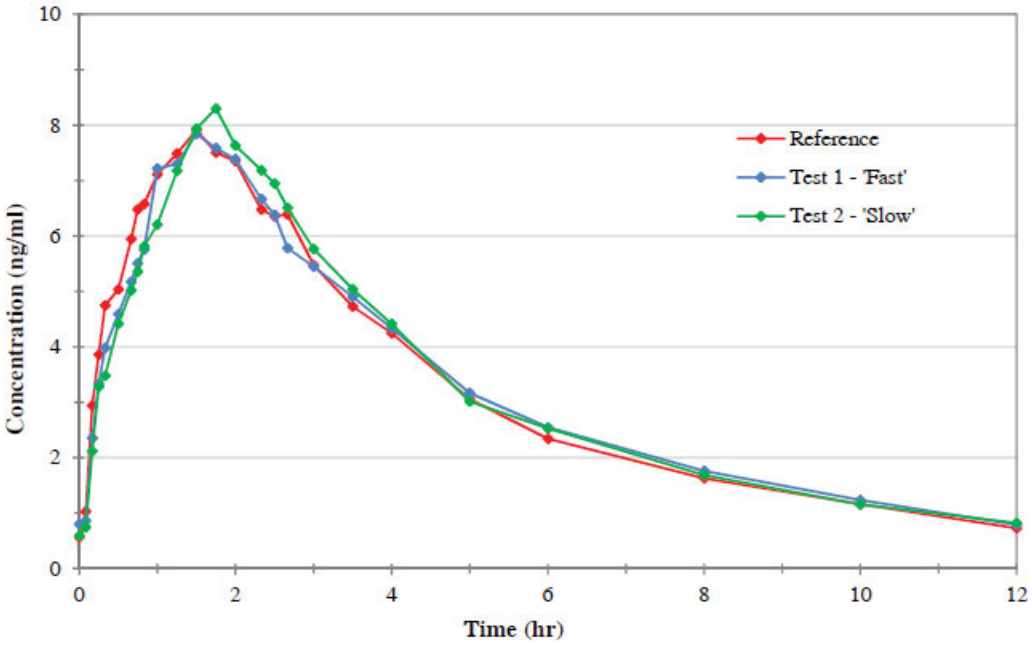
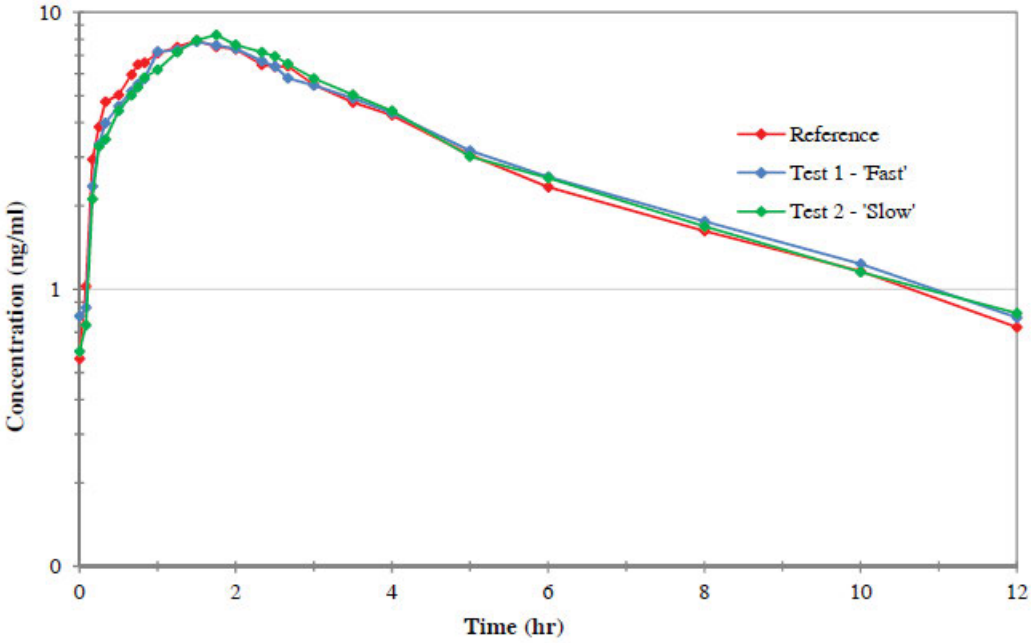


Figure 4: Log Linear Nicotine Plasma Profile of the Proposed Product vs the RLD for the Fasted Study



Reviewer's comments on pilot study

- As per Section 4.2 of the pharmaceutical development report (Report No.: D000684 Version 1; Date: 06/17/2014)[20], the firm stated "*from the product and process understanding gained throughout pharmaceutical development, two (2) separate pilot*

[20] ANDA 207868, View EDR: Pharmaceutical Development Report (#D000684; Date: 06/17/2014) in Module 3.2.P.2. Submission Date: 06/18/2014.

clinical batches, one (1) fast release formulation and one (1) slow release formulation, were manufactured", and in order to "*investigate the influence of drug release profiles against the innovator product*", a 3-way crossover, 15 patient fasted study was conducted (study# AJ-1401). However, the detailed formulations and batch information were not provided for the test product of the said pilot fasting study.

- Based on the PK results in the tables above, the 90% confidence intervals of C_{max}, AUC_{0-t} and AUC_{inf} are all within the acceptable BE limits of 80.00-125.00% for both test formulations. Therefore, both the fast and slow release formulations of the pilot clinical batches were found to be bioequivalent to the RLD.

- In addition, the median Tmax of the test products were considered comparable to that of the reference product for both test formulations, in this pilot fasting study (The range of Tmax were not provided).

	Tmax/Test (h)	**Tmax/Reference (h)**	**T/R Ratio**
Fast release formulation	1.36	1.56	0.873
Slow release formulation	1.66	1.56	1.061

- Therefore, as the firm stated that "*from the clinical data generated from the pilot bioequivalence study, the slow release formulation was selected*" for the pivotal study (study# AJ-1403).

- However, in addition to the information summarized above, no other information was provided for this pilot fasting study in the current submission. As per the Agency's current practice, the firm will be asked to provide the all BE data/information for this pilot study using the data summary tables for BE submissions (Table 1 to Table 16 if applicable) found at the following link: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf. The firm will also be asked to refer to the FDA's guidance "*Submission of Summary Bioequivalence Data for ANDAs* (http://www.fda.gov/downloads/Drugs/.../Guidances/UCM134846.pdf; May 2011)" for details.

- In addition, the firm will be asked to provide the details of all adverse events (AEs) observed in this pilot fasting study, including the severity/intensity of the AEs (i.e., mild, moderate, severe, serious etc.), onset and resolution times.

4.5.2 Easily Correctable Deficiency (ECD) Request

The DBIII's ECD Request to the Firm Dated 09/12/2016 (Reference# 10140263):

ANDA No.	207868
Drug Product Name	Nicotine Polacrilex Mini Lozenges
Strength(s)	EQ 2 mg Base and EQ 4 mg Base
Applicant Name	PLD Acquisitions LLC, D/B/A Avema Pharma Solutions
Applicant Address	10400 NW 29th Terrace Miami, FL 33172 USA
Applicant's Point of Contact	Mehul Govani
Contact's Telephone Number	(b) (4)
Contact's Fax Number	(516) 272-8203
Contact's Email Address	mgovani@pldevelopments.com
Original Submission Date(s)	12/02/2015 (Resubmission/After Refuse to Receive) *[06/19/2014 (Subject to a refuse to receive)]*
Submission Date(s) of Amendment(s) Under Review	09/17/2015 (Supp. Document #2) Quality/Response To Information Request 12/02/2015 (Supp. Document #3) Quality/Manufacture Information; User Fee/Coversheet; Resubmission/After Refuse to Receive; Labeling/Container-Carton Draft
Reviewer	Yi Zhang, Ph.D.
Study Number (s)	AJ-1403
Study Type (s)	Fasting
Strength (s)	1 x 4 mg
Clinical Site	Phase One Solutions, Inc.
Clinical Site Address	1405 NW 167th Street Miami Gardens, FL 33169 USA
Analytical Site	(b) (4)
Analytical Site Address	
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)** **Post October 1, 2014 ANDAs** ☒ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☐ **Complete**
OVERALL REVIEW RESULT	**INADEQUATE**
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**
COMMUNICATION	☒ **ECD** ☐ **IR**

	☐ NOT APPLICABLE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 2 & 3	**Fasting**	**4 mg**	**INADEQUATE**
1, 2 & 3	**Waiver**	**2 mg**	**INADEQUATE**

The deficiency below represents *EASILY CORRECTABLE DEFICIENCY* identified during the full ANDA review and the current ANDA review cycle will remain open. The following comment/deficiency with respect to the inactive ingredients in the formulation exceeding the IIG limits should be communicated to the firm via a Division of Bioequivalence III (DBIII)'s ECD request.

1. You stated in the Section of "*Description and Composition of the Drug Product*" in Module 2.3 of "*Quality Overall Summary*" and Module 3.2.P of "*Drug Product*" in the current submission dated 12/02/2015, that "*all excipients fall below IIG or other applicable limits for oral route of administration*", as shown in the table below:

However, as per the approved reference listed drug (RLD) labeling for Nicorette® (nicotine polacrilex) Mini Lozenges, the patient should be advised to "*place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 - 30 minutes). Minimize swallowing. Do not chew or swallow lozenge*". Therefore, the maximum daily intake (MDI) of each excipient present in the test product formulation should be calculated based on the same route of administration (e.g. troche/lozenge, buccal or sublingual).

The MDI levels of the respective Sodium Stearyl Fumarate, Maltodextrin, and Talc present in your test formulation were (b) (4), respectively, and they exceed the maximum amounts listed in the FDA's Inactive Ingredient Guide (IIG) based on the maximum daily dose (MDD) of 20 lozenges for Nicotine Polacrilex Mini Lozenges intended for the above said route of administration. Therefore, please provide your justification along with supportive data that the amounts of Sodium Stearyl Fumarate, Maltodextrin, and Talc present in your test formulation would not significantly compromise the safety and/or efficacy of your test drug product.

Firm's Email Inquiry dated 09/13/2016

Hello Linda,

(b) (4)

Thanks,
Mehul

Mehul Govani, Regulatory Affairs Manager
PL Developments | http://www.PLDevelopments.com
w|516-986-1700 (b) (4)
email| mgovani@pldevelopments.com
609-2 Cantiague Rock Road | Westbury, NY | 11590

Reviewer's Note:

- The BE review team prepared a DBIII's Response to firm's email inquiry. However, as per the current regulatory practice as suggested by the DBIII upper management and the RPM that "*We will not process or review a partial response. Facsimile or e-mail responses will not be accepted*", the firm was asked to respond to the best of their ability to the ECD request directly[21].

Firm's Response to the DBIII's ECD Request Dated 10/26/2016 (Supp. Document #8):

Response to Question 1:

As per the FDA guidance ANDA submissions- Refuse to receive standards and as per the confirmation from FDA-Substance Registration System team, it is our understanding that the potency described in the IID database corresponds to "per dosage unit" and not the "maximum daily intake".

Based on the FDA guidance ANDA submissions- Refuse to receive standards, "Applicants can justify inactive ingredient levels by reference to the IID, which is a listing of inactive ingredients and their maximum levels of use (per dosage unit or percent composition), arranged by either route of administration or dosage form."

It is also our understanding that maximum daily intake (MDI) is calculated using the following formula:

$$MDI = \frac{MDD}{A} \times P$$

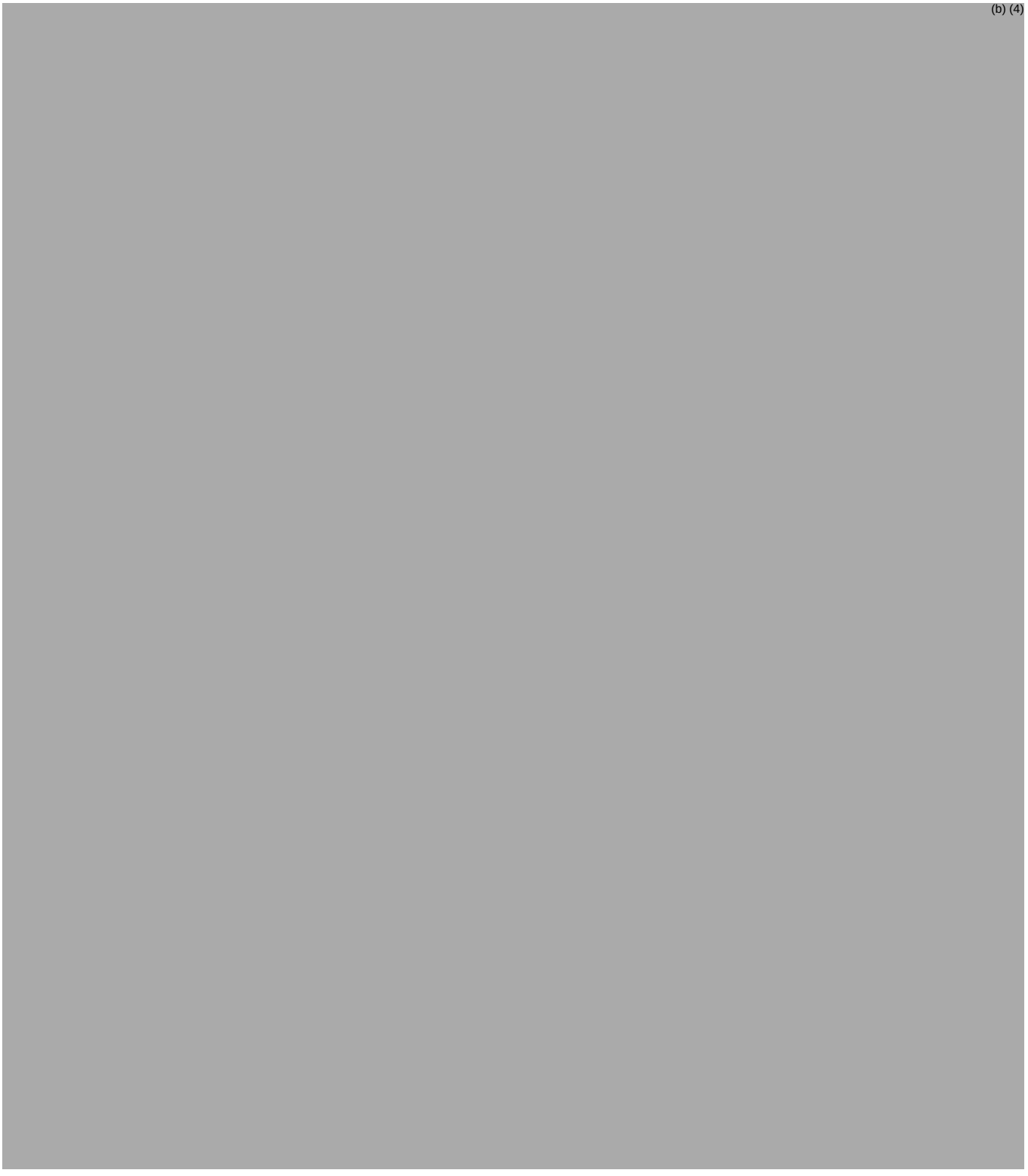
Where,
MDD: Highest recommended daily dose of the drug identified in the approved drug labeling.
P: Potency of the inactive ingredient per dosage unit.
MDD/A is the maximum number of dosage units that could be consumed per day.

The reference source for the formula above is the "Inactive Ingredient Database - FDA

[21] GDRP/Panorama for ANDA-207868-ORIG-1-RESUB-3, ECD extension (http://panorama fda.gov/task/view?ID=58065659001fbe9e5cb8bec83e888097&activeTab=list-task-documents; Linda Park) Date uploaded: 10/18/2016.

Update" presentation by **Robert Iser**.

If we were to calculate MDI based on this formula then the calculations would be as mentioned below.



compromise the safety and/or efficacy of our test drug product. This information has been provided in Module 1.11.2.

Reviewer's Note:

- Based on the maximum daily dose (MDD) of 20 lozenges/per day for Nicotine Polacrilex Mini Lozenges, the firm's proposed maximum daily intake (MDI) amounts for three of the inactive ingredients, Sodium Stearyl Fumarate, Maltodextrin, and Talc [redacted], [redacted]), in the test product formulations, as calculated by the BE reviewer, exceed the maximum daily intake levels of the same inactive ingredients in previously FDA-approved drug products intended for the same route of administration (i.e. troche/lozenge, buccal or sublingual).

- Based on the administration route of the lozenges, the justification of IID levels should use troche/lozenge, buccal or sublingual routes, since these dosage forms are all dissolved in the mouth, other than passing through down to the digestive track. Therefore, the firm's justification using other orally administered dosage forms (e.g., oral routes via digestive track) for the lozenge is not acceptable unless appropriate supportive data/safety information are provided. Thus, the usage of the oral route of administration for the calculation of reference/approved MDI as IIG limit justification is not acceptable.

- The firm's calculation of MDI in its test product is consistent with reviewer's calculation. However, the calculation method to determine the maximal MDI from reference/approved drug products is incorrect. As the formula firm described above, "P (Potency of the inactive ingredient per dosage unit)" and "MDD/A (maximum number of dosage units that could be consumed per day)" firm used were from different drug products, i.e., in firm's calculation, "P" [redacted]) was chosen from IID database of other approved drug product, however, [redacted]" is the maximum units/lozenges per day for the current test product, which is not acceptable.

- In the current response dated 10/26/2016, the firm also provided supportive documents, including a summary of "*Nonclinical Information Amendment*" along with clinical/research literatures and reports in Module 1.11.2, and claimed that "*the amounts of Sodium Stearyl Fumarate, Maltodextrin, and Talc present in our test formulation would not significantly compromise the safety and/or efficacy of our test drug product.*" The DBIII is seeking expert opinion/comments from the Division of Clinical Review (DCR) for the evaluation of the firm's current responses to the safety concern and clinical significance due to the [redacted] amounts of these three excipients. The BE review outcome will be pending for DCR's consult review.

4.6 Consult Reviews

The DBIII's Safety/Efficacy Consult to the Division of Clinical Review (DCR) Dated 11/18/2016 [22]:

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		**REQUEST FOR CONSULTATION**		
TO (Division/Office): Daiva Shetty, M.D., Acting Director, Division of Clinical Review Office of Bioequivalence Office of Generic drugs			FROM: Yi Zhang, Ph.D., Reviewer, DBIII/Team 36 Through Nilufer Tampal, Ph.D. Acting Director, Division of Bioequivalence III (DBIII) Office of Bioequivalence Office of Generic Drugs	
DATE November 18, 2016	IND NO. N/A	ANDA NO. 207868	TYPE OF DOCUMENT Consult	DATE OF DOCUMENT December 2, 2015 (Original) October 26, 2016 (ECD response)
NAME OF DRUG Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base		PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG Smoking Cessation Therapeutic Agent	DESIRED COMPLETION DATE **01/06/2016** **(TAD of the ANDA: 02/20/2017)**
NAME OF FIRM: PLD Acquisitions LLC, D/B/A Avema Pharma Solutions				
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): Original ANDA
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):	

[22] GDRP/Panorama for ANDA-207868-ORIG-1-RESUB-3: Bioequivalence ECD/IR and Consults//Send Consult Request (A207868N000DB_C11032016.docx); Date uploaded: 11/18/2016; (http://panorama.fda.gov/task/view?ID=581b8881004658643ab857434fe8f650).

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

Introduction:

On June 19, 2014, the firm, PLD Acquisitions LLC, D/B/A Avema Pharma Solutions, submitted an abbreviated new drug application (ANDA) for Nicotine Polacrilex Mini Lozenges, 2mg and 4 mg. The application was refused to received (RTR) due to incomplete information and was subsequently accepted for filing on December 2, 2015. As per the current product specific guidance[23], the original submission contained the results of an *in vivo* fasting bioequivalence (BE) study (Study No. AJ1403) comparing it's test product, Nicotine Polacrilex Mini Lozenges, 4 mg, to the corresponding reference product, GlaxoSmithKline Consumer Healthcare's Nicorette® Mini Lozenge, 4 mg [NDA 022360, approved on 05/18/2009; Over the Counter (OTC)][24], along with a waiver request for the 2 mg strength. Upon the initial BE review, the only deficiency identified during the full ANDA review (***Attachment 1***) by the Division of Bioequivalence III (DBIII) was related to the proposed maximum daily intake (MDI) amounts of the following three inactive ingredients: Sodium Stearyl Fumarate, Maltodextrin, and Talc, in the test formulation. The individual amounts for all three of the inactive ingredients exceeded the inactive ingredients limits (IIG) limits for the troche/lozenge, buccal or sublingual route of administration. Please see information below for details.

Issue Details:

As per the RLD labeling for Nicorette®, the directions state "*Do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day*"[25] for both strengths of the drug product. Therefore, based on the MDD (20 lozenges/per day), the amounts of the three inactive ingredients in test products are as follows:

Inactive ingredient(s)	Unit amount (mg per unit) in 2 mg or 4 mg strength test products	Proposed MDI (mg) based on MDD for Nicotine Polacrilex Lozenges (× 20 units)	Maximum level (mg) listed in the FDA IIG database for Approved Drug Products with the same route of administration	Ref. No/Note
Sodium Stearyl Fumarate	(b) (4)			

[23] FDA Product-Specific Recommendations for Generic Drug Development, http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240974.pdf; Recommended Jan 2011. Last accessed: 11/14/2016.

[24] Electronic Orange Book (Updated Through 06/2016): http://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=022360#; Search Term: NDA 022360.

[25] Labeling and clinical pharmacology (online database), https://dailymed nlm nih.gov/dailymed/drugInfo.cfm?setid=991704ed-781a-489b-8b56-0b558e8fc385 (Updated: 06/07/2016); Search Term: Nicorette®.

Maltodextrin(1)	(b) (4)
Talc	

(b) (4)

Based on the data currently available to the Agency for the same route of administration (i.e. troche/lozenge, buccal or sublingual), the proposed amounts for these three inactive ingredients, Sodium Stearyl Fumarate, Maltodextrin and Talc, in the test formulations, appeared to potentially exceed the maximum daily intake levels (Please see Section 4.2 of BE review for details (***Attachment 1***). Thus, a deficiency was communicated to the firm via an ECD request dated 09/12/2016. The firm was asked to provide its justification along with supportive data that the amounts of Sodium Stearyl Fumarate, Maltodextrin, and Talc present in the test formulation would not significantly compromise the safety and/or efficacy of the test drug product (***Attachment 2***).

On 09/13/2016, the firm submitted an email inquiry to the DBIII regarding the issued ECD request (***Attachment 3***). In preparing a response to the firm's inquiry, the BE review team informally consulted the Pharm/Tox team in the Division of Clinical Review (DCR) (***Attachment 4***). However, this information was not communicated to the applicant, due to the recommendations put forth by DBIII management and Regulatory Project Manager (RPM) in OGD that "*We will not process or review a partial response. Facsimile or e-mail responses will not be accepted*"[26].

On 10/26/2016, the firm submitted a complete response to the above deficiency comment made by DBIII (***Attachment 5***). However, the firm's justification is based on the usage of the oral route of administration (e.g., oral routes via digestive track) for calculation of the MDI and IIG limits. In addition, the firm incorrectly calculated the maximal MDI from approved drug products based on the equation provided in its response. Also, the firm provided supportive documents, including a summary of "*Nonclinical Information Amendment*" along with additional clinical/research literatures and reports in Module 1.11.2 (***Attachment 6 and 7***), and claimed that "*the amounts of Sodium Stearyl Fumarate, Maltodextrin, and Talc present in our test formulation would not significantly compromise the safety and/or efficacy of our test drug product.*"

Consult Request:

DBIII seeks your expert opinion/advice for the evaluation of the safety and toxicity and overall acceptability of the firm's formulations of Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg based on the route of administration for the excipients: Sodium Stearyl Fumarate, Maltodextrin and Talc. Please comment on the following question:

Is there any safety concern and/or clinical significance on the proposed MDI levels of Sodium Stearyl Fumarate (b) (4) Maltodextrin (b) (4) and Talc (b) (4) on the MDD of this drug (up to 20 lozenges per day), by the troche/lozenge, buccal or sublingual route(s) of administration used in the test formulation for the Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg?

Attachments:

1) ***Attachment 1***: DBIII BE review document can be found at:
   http://panorama.fda.gov/task/view?ID=566154ac0141beee6e16a23c11cb43fa

   A207868N000DB_N1 2022015.docx

[26] GDRP/Panorama for ANDA-207868-ORIG-1-RESUB-3, ECD extension (http://panorama fda.gov/task/view?ID=580656590001fbe9e5cb8bec83e888097&activeTab=list-task-documents; Linda Park) Date uploaded: 10/18/2016.

2) ***Attachment 2***: DBIII ECD request (Date: 09/12/2016):
http://panorama.fda.gov/task/view?ID=57d75f910141f3c9ad5691ff7370fbb6

A207868N000DB_ECD 08312016.docx

3) ***Attachment 3***: The firm's email inquiry to ECD request (Reference#10140263; Date: 09/13/2016)
http://panorama.fda.gov/issue/view?ID=57d8498d014bbe515990013d8297e7d3

Firm's Email Inquiry.docx

4) ***Attachment 4***: E-mail communication between DBIII and DCR (Not to be released under FOIA)

RE MDI limit of IIGs for Nicotine Polacrilex

5) ***Attachment 5***: The firm's response to ECD request (Supp. Document #8; Date: 10/26/2016):
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-2-cover-letters\cover-letter-0007-10262016.pdf

cover-letter-0007-10262016.pdf

6) ***Attachment 6***: Summary Report of "*Nonclinical Information Amendment*" provided in the current response:
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\1112-safety-amendment.pdf

1112-safety-amendment.pdf

7) ***Attachment 7***: Several clinical/research literatures/reports and other supportive documents were provided in Module 1.11.2:
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\bergfeld-2012cir.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\fda-scogs-61.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\freers-2012.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\hajiar-1992-epa-talc.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\kibbe-2012.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\moreton-2012.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\nicorettepi20160609.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\robert-iser-2013.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\spectrum-msds.pdf

Thank you for your consideration. Please address comments/questions to Nilufer.Tampal@fda.hhs.gov	
SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Consult Response from the Division of Clinical Review (DCR) Dated 01/30/2017 [27]:

[27] GDRP/Panorama for ANDA-207868-ORIG-1-RESUB-3: Bioequivalence ECD/IR and Consults//Response to Consult Request (A207868_DCR_0_ClinPT_Nicotine Polacrilex Mini Lozenges_three excipients.pdf); Date uploaded: 01/30/2017; (http://panorama fda.gov/task/view?ID=581b88810046586d00366cea3ab3a56f).

Division of Clinical Review Consultation

Nicotine Polacrilex Mini Lozenges, 2 mg Base and 4 mg Base

Drug Product:	Nicotine Polacrilex Mini Lozenges. EQ 2 mg Base and EQ 4 mg Base
ANDA:	207868
ANDA Sponsor:	PLD Acquisitions LLC, D/B/A Avema Pharma Solutions
Reference Listed Drug (RLD) **NDA, Approval Date** **RLD Sponsor:**	Nicorette® Mini Lozenge 4 mg, 2 mg strength NDA 022360, Approved 5/18/2009 GlaxoSmithkline Consumer Healthcare
Pharmacology-Toxicology Primary Reviewer:	Mi Young Yang, PhD Pharmacologist Division of Clinical Review (DCR) Office of Generic Drugs (OGD)
Pharmacology-Toxicology Secondary Reviewer:	Robert Dorsam, PhD Pharmacology/Toxicology Team Leader DCR, OGD
Medical Officer Primary Reviewer:	Shahreen Hussain-Malik , MD Medical Officer DCR, OGD
Medical Officer Secondary Reviewer:	Nancy Snow, DO Acting Team Leader DCR, OGD
Tertiary Reviewer	Daiva Shetty, MD Deputy Director DCR, OGD
To:	Yi Zhang, PhD Reviewer Division of Bioequivalence III (DB III)/Team 36
Reason for Consult:	Is there any safety concern and/or clinical significance on the proposed MDI levels of Sodium Stearyl Fumarate (b) (4) Maltodextrin (b) (4) and Talc (b) (4) based on the MDD of this drug (up to 20 lozenges per day), by the troche/lozenge, buccal or sublingual route(s) of administration used in the test formulation for the Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg.
Date of Submission:	12/2/2015
Date of Consult:	11/18/2016
Date Assigned:	12/5/2016
Date of Completion:	1/27/2017
Conclusion:	DCR concludes from clinical and nonclinical perspectives, that the levels of sodium stearyl fumarate, maltodextrin and talc in the proposed generic nicotine lozenge drug product are acceptable.

1. Executive Summary:

This review addresses a consult from DBIII requesting DCR to assess the safety and acceptability of the levels of three excipients, sodium stearyl fumarate, maltodextrin and talc, in the proposed generic nicotine lozenges drug product.

PLD Acquisitions LLC, D/B/A/ Avema Pharma Solutions, submitted an ANDA on 6/19/2014 for a generic Nicotine Polacrilex Mini Lozenges drug product, 2mg and 4 mg. The reference listed drug (RLD) is Nicorette® Mini Lozenge 2 mg and 4 mg, NDA 022360, approved on 5/18/2009. Nicotine Lozenges are indicated for the reduction of withdrawal symptoms, including nicotine craving, associated with quitting smoking. The maximum daily dose (MDD) is 20 lozenges. The proposed generic drug product contains three excipients not found in the RLD, sodium stearyl fumarate, maltodextrin and talc. The maximum daily intake (MDI) levels of each excipient in the proposed generic drug product are (b) (4) for sodium stearyl fumarate, (b) (4) for maltodextrin and (b) (4) for talc.

DCR reviewed the safety and acceptability of the three excipients in question from both clinical and Pharmacology/Toxicology perspectives, and considered not only systemic absorption of the excipient, but also local effects on the oral mucosa. From a clinical perspective, the proposed MDIs of the three excipients were compared to their MDIs in FDA-approved drug products with a similar clinical context of use. Clinical safety information available from the literature for each excipient was also considered in the current evaluation. From a Pharmacology/Toxicology perspective, DCR reviewed the safety of each excipient, with an emphasis on their genetic toxicity, chronic oral toxicity, and local toxicity using relevant animal studies.

From both a clinical and nonclinical perspective, DCR concludes that the levels of sodium stearyl fumarate, maltodextrin and talc in the proposed generic nicotine lozenge drug product are acceptable and would not pose an increased risk for adverse events when the generic drug product is taken in place of the RLD.

2. Recommendation:
DCR concludes that the proposed levels of sodium stearyl fumarate (b) (4) maltodextrin (b) (4) and talc (b) (4) in the generic nicotine lozenge drug product are acceptable.

3. **The following comments/deficiencies and/or recommendations should be conveyed to the ANDA applicant:**
Not applicable. There is nothing to be conveyed to the sponsor.

DBIII Reviewer's Comments on DCR Consult Response:

- Although the firm's proposed maximum daily intake (MDI) amounts for Sodium Stearyl Fumarate (b) (4) Maltodextrin (b) (4) and Talc (b) (4) based on the maximum daily dose (MDD) of this drug product (up to 20 lozenges per day), in the test product formulations, exceed the MDI levels of the same inactive ingredients in previously FDA-approved drug products intended for the same route of administration (i.e. troche/lozenge, buccal or sublingual); However, as per the DCR's consult response dated 01/30/2017, from clinical and nonclinical perspectives, considering their local and systemic safety attributes in Pharmacology/Toxicology, "*the proposed maximum daily intake levels of sodium stearyl fumarate, maltodextrin and talc from the current generic drug product do not pose an increased risk for adverse events, as compared to the RLD*"[24]. Therefore, the proposed formulations of the test products with these three excipients are considered acceptable (Please see DCR's consult response and ***Section 4.2*** of the current BE review for details).

- The related part of the current BE review has been updated as per the recommendation of the DCR consult response.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:	207868
APPLICANT:	PLD Acquisitions LLC, D/B/A Avema Pharma Solutions
DRUG PRODUCT:	Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base

[The following deficiencies/comments should be communicated to the firm via a CR letter]

The Division of Bioequivalence III (DBIII) has completed its review and has identified the following deficiencies:

Deficiencies Related to *In Vivo* Pilot Fasting Bioequivalence (BE) Study

1. As stated in your pharmaceutical development report (Report No.: D000684 Version 1; in Module 3, Section 3.2.P.2, Date: 06/17/2014), you conducted a three-way crossover *in vivo* pilot fasting bioequivalence (BE) study (Study No. AJ-1401) with two investigational test formulations, one fast release formulation and another slow release formulation, against the reference-listed drug (RLD) product. However, you did not provide the detailed formulation and batch information on these two investigational test lots. Per the current Guidance for Industry: Submission of Summary Bioequivalence Data for ANDAs (issued May 2011; see the link below for details: http://www.fda.gov/downloads/Drugs/GuidancesCompliance Regulatory Information/Guidances/UCM134846.pdf), please submit complete 16 eCTD-formatted data summary tables for the said pilot BE study (Study No. AJ-1401) conducted using the table templates shown at the following link: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf.

2. In addition to BE Summary Table 8 "*Incidence of Adverse Events in Individual Studies*" requested above, please provide the details of all adverse events (AEs) observed in your pilot BE study (Study No. AJ-1401), including the severity/intensity of the AEs (i.e., mild, moderate, severe, serious etc.), onset and resolution times. Please use the following summary guide table in response to this deficiency:

Subject #	Test/ Reference	Period	Adverse Reaction(AE)	AE Severity/Intensity (e.g. mild, moderate,	Time and Date of	Time and Date	Duration Between Dosing and Start of AE	Time and Date of Resolution	Additional Comments

				severe, etc.)	dosing	of AE	(hours)		

Deficiency Related to the Office of Study Integrity and Surveillance (OSIS) Inspection

3. During November 22 to 25, 2016, the FDA Office of Study Integrity and Surveillance (OSIS)'s Division of Bioequivalence and GLP Compliance (DBGLPC) conducted (audited) a surveillance inspection for the clinical site, Phase One Solutions, Inc. (1405 NW 167th Street, Miami Gardens, FL 33169, USA). During the OSIS inspection, clinical study records from this site were audited for the studies from another application. This clinical site is the same as used for the *in vivo* BE study in the current application. FDA Form-483 was issued to this clinical site following the inspection. For considering the impact of similar study conducted and site practices by the same facility on the BE study of the current ANDA, DBIII reviewed the OSIS inspection reports and found that the following objectionable finding by the OSIS at the above mentioned clinical site could potentially compromise the integrity of the study of the current ANDA as well:

   Observation #1
   Samples of the test article, reference standard used in a bioequivalence study were not retained.

   Please address the above specific finding identified by the OSIS with respect to its impact on all related *in vivo* BE studies in the current ANDA, providing information and any necessary supporting documents (if applicable) in your response regarding whether the study samples of the investigational products, specifically, Nicotine Polacrilex Mini Lozenges 4 mg manufactured by PLD Acquisitions LLC, and the reference product, Nicorette® Mini Lozenge 4 mg, used in your *in vivo* BE study, were retained and thus can be released to the FDA upon request.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.7 Outcome Page

ANDA: 207868 Original BE Review

Completed Assignment for 207868 ID: 28725

Reviewer: Zhang, Yi **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base; PLD Acquisitions LLC, D/B/A Avema Pharma Solutions

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
28725	12/2/2015	BIO	ANDA Original [1]	1	1
28725	12/2/2015	Parallel	Dissolution-Based Waiver (IR) (For all waiver strengths) [0.25]	0.25	0.25
28725	12/2/2015	Parallel	Fasting Study (Abbreviated Template) (No extra credit for additional analytes) [0.75]	0.75	0.75
28725	8/23/2016	BIOQUALITY	Quality Assessment [1-5]	5	5
				Total:	7

ANDA: 207868, DCR Consult and Consult Response Review (REF# 11137918)

Completed Assignment for 207868 ID: 30138

Description: Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base; PLD Acquisitions LLC, D/B/A Avema Pharma Solutions--DCR consult and response

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Score	Subtotal
30138	1/30/2017	BIO	Consult Review (For Consults to Other Office) [1]	1	1
30138	1/30/2017	Parallel	Review of the Consult Response and Formal Consult [1]	1	1
30138	2/2/2017	BIOQUALITY	Quality Assessment [1-5]	4	4
				Total:	6

ANDA: 207868, Review for OSIS EIR/Inspection Report

Completed Assignment for 207868 ID: 30251

Description: Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base; PLD Acquisitions LLC, D/B/A Avema Pharma Solutions--OSIS Review

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
30251	2/13/2017	BIO	OSIS Inspection Report Review [1]	1	1
30251	2/13/2017	Parallel	OSIS Inspection Report: Review of Parent (Per application) [1]	1	1
30251	2/16/2017	BIOQUALITY	Quality Assessment [1-5]	4	4
				Total:	6

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207868

OTHER REVIEW(s)

Division of Clinical Review Consultation

Nicotine Polacrilex Mini Lozenges, 2 mg Base and 4 mg Base

Drug Product:	Nicotine Polacrilex Mini Lozenges. EQ 2 mg Base and EQ 4 mg Base
ANDA:	207868
ANDA Sponsor:	PLD Acquisitions LLC, D/B/A Avema Pharma Solutions
Reference Listed Drug (RLD) **NDA, Approval Date** **RLD Sponsor:**	Nicorette® Mini Lozenge 4 mg, 2 mg strength NDA 022360, Approved 5/18/2009 GlaxoSmithkline Consumer Healthcare
Pharmacology-Toxicology Primary Reviewer:	Mi Young Yang, PhD Pharmacologist Division of Clinical Review (DCR) Office of Generic Drugs (OGD)
Pharmacology-Toxicology Secondary Reviewer:	Robert Dorsam, PhD Pharmacology/Toxicology Team Leader DCR, OGD
Medical Officer Primary Reviewer:	Shahreen Hussain-Malik , MD Medical Officer DCR, OGD
Medical Officer Secondary Reviewer:	Nancy Snow, DO Acting Team Leader DCR, OGD
Tertiary Reviewer	Daiva Shetty, MD Deputy Director DCR, OGD
To:	Yi Zhang, PhD Reviewer Division of Bioequivalence III (DB III)/Team 36
Reason for Consult:	Is there any safety concern and/or clinical significance on the proposed MDI levels of Sodium Stearyl Fumarate (b) (4) Maltodextrin (b) (4) and Talc (b) (4) based on the MDD of this drug (up to 20 lozenges per day), by the troche/lozenge, buccal or sublingual route(s) of administration used in the test formulation for the Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg.
Date of Submission:	12/2/2015
Date of Consult:	11/18/2016
Date Assigned:	12/5/2016
Date of Completion:	1/27/2017
Conclusion:	DCR concludes from clinical and nonclinical perspectives, that the levels of sodium stearyl fumarate, maltodextrin and talc in the proposed generic nicotine lozenge drug product are acceptable.

1 Executive Summary:

This review addresses a consult from DBIII requesting DCR to assess the safety and acceptability of the levels of three excipients, sodium stearyl fumarate, maltodextrin and talc, in the proposed generic nicotine lozenges drug product.

PLD Acquisitions LLC, D/B/A/ Avema Pharma Solutions, submitted an ANDA on 6/19/2014 for a generic Nicotine Polacrilex Mini Lozenges drug product, 2mg and 4 mg. The reference listed drug (RLD) is Nicorette® Mini Lozenge 2 mg and 4 mg, NDA 022360, approved on 5/18/2009. Nicotine Lozenges are indicated for the reduction of withdrawal symptoms, including nicotine craving, associated with quitting smoking. The maximum daily dose (MDD) is 20 lozenges. The proposed generic drug product contains three excipients not found in the RLD, sodium stearyl fumarate, maltodextrin and talc. The maximum daily intake (MDI) levels of each excipient in the proposed generic drug product are (b) (4) for sodium stearyl fumarate, (b) (4) for maltodextrin and (b) (4) for talc.

DCR reviewed the safety and acceptability of the three excipients in question from both clinical and Pharmacology/Toxicology perspectives, and considered not only systemic absorption of the excipient, but also local effects on the oral mucosa. From a clinical perspective, the proposed MDIs of the three excipients were compared to their MDIs in FDA-approved drug products with a similar clinical context of use. Clinical safety information available from the literature for each excipient was also considered in the current evaluation. From a Pharmacology/Toxicology perspective, DCR reviewed the safety of each excipient, with an emphasis on their genetic toxicity, chronic oral toxicity, and local toxicity using relevant animal studies.

From both a clinical and nonclinical perspective, DCR concludes that the levels of sodium stearyl fumarate, maltodextrin and talc in the proposed generic nicotine lozenge drug product are acceptable and would not pose an increased risk for adverse events when the generic drug product is taken in place of the RLD.

2 Recommendation:

DCR concludes that the proposed levels of sodium stearyl fumarate ((b) (4)), maltodextrin ((b) (4)) and talc (b) (4) in the generic nicotine lozenge drug product are acceptable.

The following comments/deficiencies and/or recommendations should be conveyed to the ANDA applicant:

Not applicable. There is nothing to be conveyed to the sponsor.

3 Regulatory Background:

The RLD is Nicorette® Mini Lozenge 4 mg, 2 mg strength, NDA 022360, approved 5/18/2009 is indicated for the reduction of withdrawal symptoms, including nicotine craving, associated with quitting smoking.

The applicant submitted ANDA 207868 on 6/19/2014 for a generic Nicotine Polacrilex Mini Lozenges drug product, 2mg and 4 mg. The application was refused to receive (RTR) due to

incomplete information but was subsequently accepted for filing on 12/2/2015. The submission contained the results of an *in vivo* fasting bioequivalence (BE) study (Study No. AJ1403) comparing the test product, Nicotine Polacrilex Mini Lozenges, 4 mg, to the corresponding reference product, GlaxoSmithKline Consumer Healthcare's Nicorette® Mini Lozenge, 4 mg [NDA 022360, approved on 05/18/2009; Over the Counter (OTC)]. The applicant received a waiver for the 2 mg strength.

During the initial BE review, the only deficiency identified by DBIII related to the proposed maximum daily intake (MDI) amounts of the three inactive ingredients, sodium stearyl fumarate, maltodextrin and talc because they exceeded the maximum daily intake levels of products found in the IIG. A deficiency was communicated to the firm via an easily correctable deficiency (ECD) request dated 09/12/2016 and the firm was asked to provide justification and supportive data that the amounts of Sodium Stearyl Fumarate, Maltodextrin, and Talc present in the test formulation would not significantly compromise the safety and/or efficacy of the test drug product.

On 10/26/2016, the applicant submitted a response to the above deficiency comment made by DBIII. The firm's justification is based on the usage of the oral route of administration (e.g., oral route via digestive track) for calculation of the MDI and IIG limits. The firm provided supportive documents, including a summary of "Nonclinical Information Amendment" along with additional clinical/research literature and reports in Module 1.11.2 and claimed that "the amounts of Sodium Stearyl Fumarate, Maltodextrin, and Talc present in our test formulation would not significantly compromise the safety and/or efficacy of our test drug product."[1]

Subsequently, DBIII consulted DCR with the following request:

DBIII seeks your expert opinion/advice for the evaluation of the safety and toxicity and overall acceptability of the firm's formulations of Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg based on the route of administration for the excipients: Sodium Stearyl Fumarate, Maltodextrin and Talc. Please comment on the following question:

Is there any safety concern and/or clinical significance on the proposed MDI levels of Sodium Stearyl Fumarate (b) (4) *Maltodextrin* (b) (4) *and Talc* (b) (4) *based on the MDD of this drug (up to 20 lozenges per day), by the troche/lozenge, buccal or sublingual route(s) of administration used in the test formulation for the Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg?*

3.1 Current or Draft Guidance

There is a product specific bioequivalence guidance for nicotine polacrilex lozenge/oral at the "Bioequivalence Recommendations for Specific Products" website:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240974.pdf

[1]Consult request from DB III to DCR ANDA 207868
http://panorama.fda.gov/document/view?ID=581cb6fd0050647d27b514a1bf8685ac

3.2 Controls or Protocols

There are no open or closed controls or protocols in the OGD's databases for Nicotine Polacrilex lozenges relevant to the consult.

3.3 Orange Book Information

There are 12 marketed prescription entries in the Orange Book for Nicotine Polacrilex Lozenge (see Table 1 below).

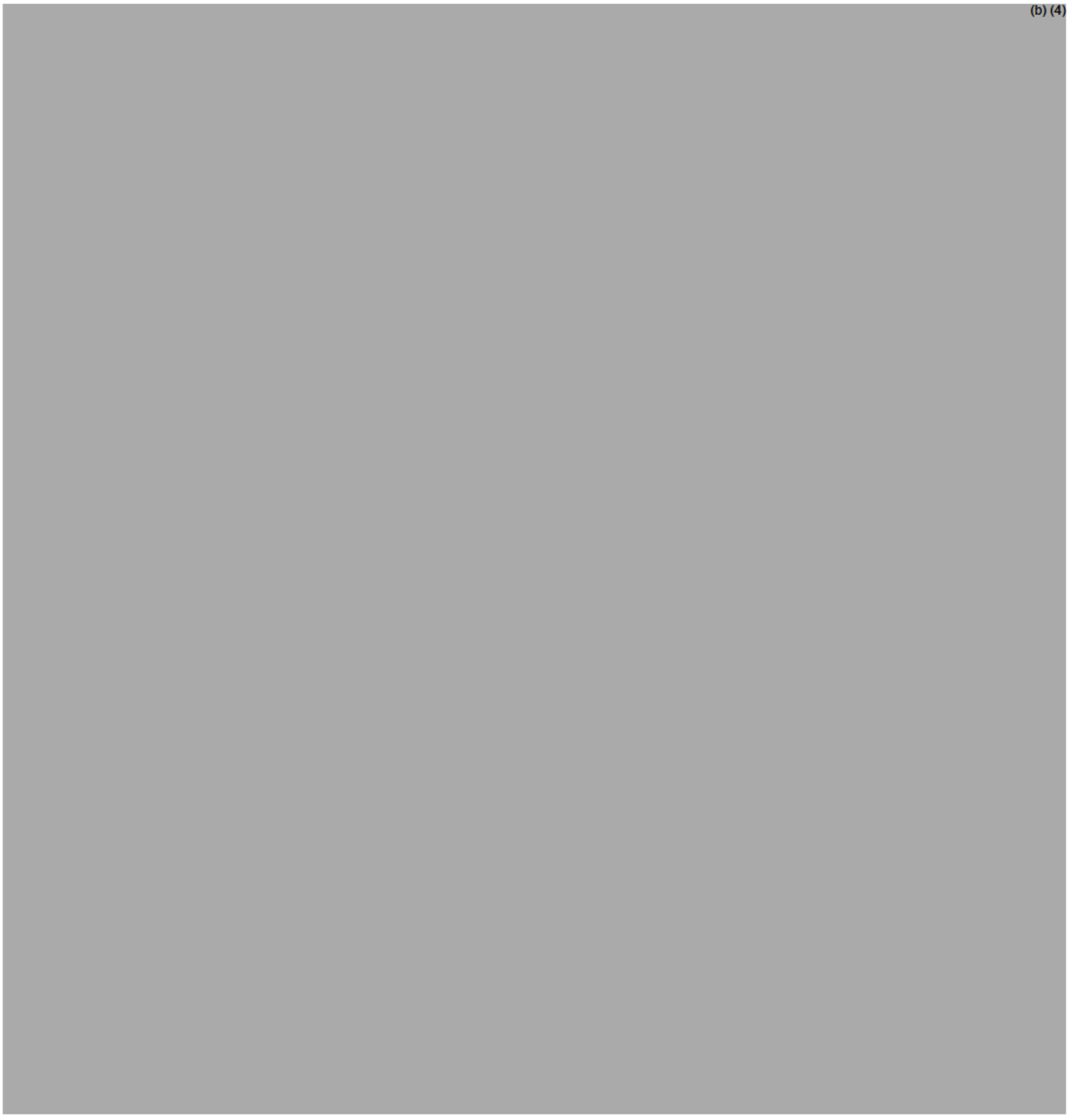
Table 1: Orange Book Currently Approved Applications for Nicotine Polacrilex Lozenges(n= 12)

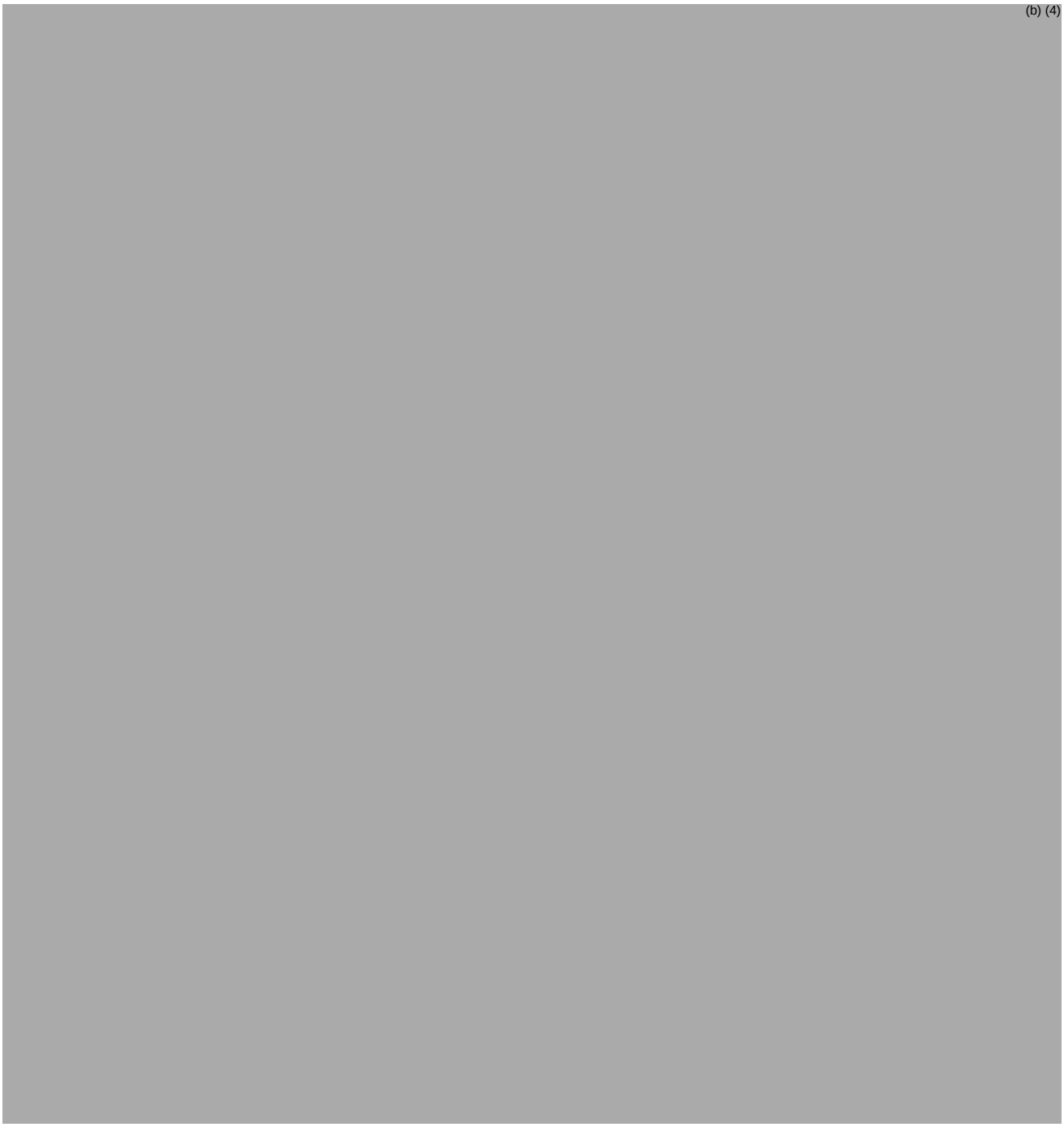
Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N021330		No	Nicotine Polacrilex	Troche/Lozenge	2 mg Base	Commit	Glaxosmithkline Consumer Healthcare
N021330		Yes	Nicotine Polacrilex	Troche/Lozenge	4 mg Base	Commit	Glaxosmithkline Consumer Healthcare
N022360		No	Nicotine Polacrilex	Troche/Lozenge	2 mg Base	Nicorette	Glaxosmithkline Consumer Healthcare
N022360		Yes	Nicotine Polacrilex	Troche/Lozenge	4 mg Base	Nicorette	Glaxosmithkline Consumer Healthcare
A077007		No	Nicotine Polacrilex	Troche/Lozenge	2 mg Base	Nicotine Polacrilex	Perrigo R and D Co
A077007		No	Nicotine Polacrilex	Troche/Lozenge	4 mg Base	Nicotine Polacrilex	Perrigo R and D Co
A090711		No	Nicotine Polacrilex	Troche/Lozenge	2 mg Base	Nicotine Polacrilex	Perrigo R and D Co
A090711		No	Nicotine Polacrilex	Troche/Lozenge	4 mg Base	Nicotine Polacrilex	Perrigo R and D Co
A090821		No	Nicotine Polacrilex	Troche/Lozenge	2 mg Base	Nicotine Polacrilex	Perrigo R and D Co
A090821		No	Nicotine Polacrilex	Troche/Lozenge	4 mg Base	Nicotine Polacrilex	Perrigo R and D Co
A203690		No	Nicotine Polacrilex	Troche/Lozenge	2 mg Base	Nicotine Polacrilex	Perrigo R and D Co
A203690		No	Nicotine Polacrilex	Troche/Lozenge	4 mg Base	Nicotine Polacrilex	Perrigo R and D Co

Source: Search on 12/22/2016 by this reviewer of the Orange Book, website http://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

3.4 RLD Formulation

The RLD formulation for Nicorette® Mini Lozenge 4 mg, 2 mg strength formulation, NDA 022360, was obtained from Module 3.2.P.1 of the applicant's submission.


(b) (4)


(b) (4)

3.5 Proposed Generic Formulation

The proposed generic formulation was obtained from Section 1.11.2 in the application submission dated 10/26/2016.[2]

Table 4: Nicotine Polacrilex Mini Lozenge Drug Product Composition and Function of Excipients

Ingredient	Function	4.0-mg Dose (mg/unit)	2.0-mg Dose (mg/unit)	Maximum Daily Intake[a] (mg)
Nicotine polacrilex 15%	Active			
Mannitol				
Sodium bicarbonate				
Calcium polycarbophil				
Xanthan gum				
Aspartame				
Sodium alginate				
NA = not applicable.				

(b) (4)

Reviewer's comment: The RLD does not contain sodium stearyl fumarate, maltodextrin or talc.

4 Labeling:

The current product label for Nicorette® Mini Lozenge 4 mg, 2 mg strength NDA 022360, was approved on 5/18/2009.[3] There are no black box warnings.

4.1 Indications

Reduces withdrawal symptoms, including nicotine craving associated with quitting smoking.

[2] ANDA 207868 EDR module 1.11.2 Nonclinical Information Amendment; \\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\1112-safety-amendment.pdf

[3] Label for Nicorette® Mini Lozenge, NDA 022360, DARRTS https://elist.fda.gov/prpllr/public/spl/f524f3ab-9af6-4244-91ca-11fb31842f68/f524f3ab-9af6-4244-91ca-11fb31842f68.view , accessed 1/4/17

4.2 Off-Label Uses

According to the literature, off-label uses of nicotine replacement therapy (NRT) include non-cessation reasons such as less intention to stop smoking and more intention to reduce smoking.[4]

4.3 Dosage and Administration

Directions (2mg Lozenge)

- **if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.**

- before using this product, read the enclosed User's Guide for complete directions and other important information
- begin using the lozenge on your quit day
- **if you smoke your first cigarette within 30 minutes of waking up,** use 4 mg nicotine lozenge
- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2 mg nicotine lozenge

according to the following 12 week schedule:

Weeks 1to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- **nicotine lozenge is a medicine and must be used a certain way to get the best results**
- place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation
- occasionally move the lozenge from one side of your mouth to the other until completely dissolved
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.**
- it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.

Directions (4mg Lozenge)

- **if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this Product will work for you**
- before using this product, read the enclosed User's Guide for complete directions and other important information
- begin using the lozenge on your quit day
- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2 mg nicotine lozenge
- **if you smoke your first cigarette within 30 minutes of waking up,** use 4 mg nicotine lozenge according to the following 12 week schedule:

Weeks 1to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- **nicotine lozenge is a medicine and must be used a certain way to get the best results**
- place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation

[4] Hughes, J. Significant of Off-Label Use of NRT. Addiction. 2008 Oct; 103 (10): 1704-1705

- occasionally move the lozenge from one side of your mouth to the other until completely dissolved
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.**
- It is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.

4.4 Significant Warnings and Precautions

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider.

Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Ask a doctor before use if you have
- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes
- history of seizures

Ask a doctor or pharmacist before use if you are
- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if
- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)

Keep out of reach of children and pets.

Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

5 Discussion:

DBIII consulted DCR to determine the safety and acceptability of the proposed levels of sodium stearyl fumarate, maltodextrin and talc used in the generic nicotine lozenges drug product.

The verbatim consult states:
DBIII seeks your expert opinion/advice for the evaluation of the safety and toxicity and overall acceptability of the firm's formulations of Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg based on the route of administration for the excipients: Sodium Stearyl Fumarate, Maltodextrin and Talc. Please comment on the following question:

Is there any safety concern and/or clinical significance on the proposed MDI levels of Sodium Stearyl Fumarate (b) (4) *Maltodextrin* (b) (4) *and Talc* (b) (4) *based on the MDD of this drug (up to 20 lozenges per day), by the troche/lozenge, buccal or sublingual route(s) of administration used in the test formulation for the Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg?*

(b) (4)

The clinical review considered the MDI levels of each of the three excipients and compared their daily intake levels to FDA-approved drug products with a similar context of use. The P/T review considered relevant genetic toxicity, chronic oral toxicity, and local toxicity studies in the evaluation of the safety of each of the excipients in question.

Evaluation of proposed levels of sodium stearyl fumarate (b) (4)

Sodium stearyl fumarate, a fine and white powder with agglomerates, is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.[5] Sodium stearyl fumarate is a food additive permitted for direct addition to food for human consumption as a conditioning or stabilizing agent up to 0.2 – 1.0% by weight of the food (21 CFR 172.826).

(b) (4)

Also, they state that sodium stearyl fumarate is an inactive ingredient in at least 14 FDA-approved orally disintegrating drug product formulations, and is listed on the FDA EAFUS

[5] Hand book of Pharmaceutical Excipients, 6th Edition (2009), Edited by Rowe RC, Sheskey PJ, and Quinn ME.

(Everything Added to Food in the United States) database for use as a multipurpose direct food additive. Finally, it is generally regarded as nontoxic and nonirritant material and is not a novel excipient.[6]

Clinical review:

The medical literature was reviewed regarding human health effects of sodium stearyl fumarate. Sodium stearyl fumarate's laxative effect was studied in a group of 26 patients with the diagnosis of constipation. Oral doses of sodium fumarate ranging from (b) (4) (b) (4) t) produced laxative effects within approximately 10 hours after administration.[7]

DCR looked for approved drugs containing these inactive ingredients that would support the systemic safety as well as the local effects on the oral mucosa of the inactive ingredients. A search of the FDA inactive ingredients database (IID) for sodium stearyl fumarate on 12/06/16 identified two drug products that would support the local effects of sodium stearyl fumarate.

Prednisolone Sodium Phosphate orally disintegrating tablets (ANDA 202179; rheumatology agents; Mylan Pharmaceuticals Inc; approved on 4/10/2013) and Escitalopram Oxalate sublingual tablets (NDA 22328; sedative and hypnotics; Purdue Pharma Products LP; approved on 11/23/2011).

Per the drug product's labeling information[8], prednisolone sodium phosphate is indicated in the treatment of allergic conditions, such as atopic dermatitis and seasonal allergic rhinitis. It is also indicated for asthma. This drug product provides sodium stearyl fumarate of (b) (4) The level of sodium stearyl fumarate in the proposed nicotine lozenges (b) (4) exceeds that of prednisolone orally disintegrating tablets (ANDA 202179). Escitalopram oxalate is given sublingually, but the MDI of (b) (4) of sodium stearyl fumarate is insufficient to support the MDI (b) (4) in the proposed nicotine polacrilex drug product.

However, several FDA-approved oral drug products contain sodium stearyl fumarate at a maximum daily intake (MDI) that exceeds the proposed level (see Table 5 below). For example, ANDA 203135 for calcium acetate oral capsules contains sodium stearyl fumarate at an MDI of (b) (4), higher than the MDI of (b) (4) in the proposed nicotine lozenge.

[6] ANDA 207868 Module 1.11.2

[7] Bodansky, O. et al. The Toxicity and Laxative Action of Sodium Fumarate. Journal of the American Pharmaceutical Association.Volume XXXI, No.1, January 1942, pp 1-8.

[8] Prednisolone sodium phosphate labeling: \\cdsesub1\evsprod\anda202179\0008\m1\us\pred-fnl-pkg-insrt.pdf

Table 5: Sodium Stearyl Fumarate Maximum Daily Intake for Proposed Product and Approved FDA Oral Products

App	Drug Name	Dosage Form	Indication/ Use	MDD (mg/day)	Sodium Stearyl Fumarate	Sodium Stearyl Fumarate MDI (mg/day)
NDA 22328	Escitalopram oxalate	Tablet, Sublingual	Sedative and Hypnotics	[redacted] (b) (4)		
ANDA 202179	Prednisolone sodium phosphate	Tablet, Orally Disintegrating	Rheumatology Agents			
NDA 22044	Janumet	Tablet, Oral	Hypoglycemic agents			
NDA 201917	Incivek	Tablet, Oral	Antiviral/Systemic/Hepatitis			
ANDA 203135	Calcium acetate	Capsule, Oral	Hyperphosphatemia			
ANDA 202738	Ritonavir	Tablet, Oral	Antiretroviral/Systemic/HIV/ Nucleoside Reverse Transcriptase			
ADNA 207868*	Nicotine polacrilex	Lozenge, Sublingual	Nicotine Replacement Therapy			

* Current Review

Pharmacology/Toxicology review:

The available FDA guidance, published literature, prior approved drug products, and evidence of prior exposure were reviewed to assess the safety of [redacted] (b) (4) of sodium stearyl fumarate in the proposed generic nicotine lozenges drug product.

Sodium stearyl fumarate is a food additive permitted for direct addition to food for human consumption as a conditioning or stabilizing agent up to 0.2 – 1.0% by weight of the food (21 CFR 172.826).

[redacted] (b) (4)

A literature search revealed limited available information for this excipient. Metabolic studies of sodium stearyl fumarate indicated that approximately 80% of the dose in rats and 35% of the dose in dogs were rapidly absorbed and metabolized to stearyl alcohol and fumaric acid, with stearyl alcohol further oxidized to stearic acid. The unabsorbed fraction of administered sodium

stearyl fumarate was excreted in the feces in rats and dogs.[9] Stearyl alcohol and stearic acid are naturally occurring constituents in various food products and fumaric acid is a normal constituent of body tissue.[5] The World Health Organization (WHO) has assigned an acceptable daily intake (ADI) for man of "not limited" for stearic acid and salts because these molecules are *"normal products of the metabolism of fats and their metabolic fate is well established"*.[10] The WHO has also assigned an ADI of unspecified for fumaric acid because "*fumaric acid is a normal constituent of tissues and is metabolized by the body"*.[11]

Higher levels of sodium stearyl fumarate are obtained in other drug products and food, therefore the proposed levels of sodium stearyl fumarate do not raise concerns for systemic toxicity. Buccal tissues are exposed to sodium stearyl fumarate via a variety of other drug products and food. In consideration of exposure information from approved drugs, its presence in food, and rapid metabolism, sodium stearyl fumarate also does not appear to pose a risk for local toxicity. In addition, patients are instructed to occasionally move the lozenge from one side of the mouth to the other side. This reduces the likelihood that any single local site would be exposed to the maximum dose.

Risk assessment and conclusion for sodium stearyl fumarate:

Published literature indicates sodium stearyl fumarate is rapidly absorbed and metabolized to stearyl alcohol and fumaric acid. Stearyl alcohol, stearic acid and fumaric acid are naturally occurring components in various food products or normal constituents or metabolite of body tissue. In addition, sodium stearyl fumarate is one of food additives permitted for direct addition to food for human consumption as a conditioning or stabilizing agent up to 0.2 – 1.0% by weight of the food. Thus, the buccal tissues are exposed to sodium stearyl fumarate via a variety of other drug products and food.

Based on the exposure and metabolism profiles, and non-toxic characteristics, the proposed MDI of 125 mg/day sodium stearyl fumarate does not appear to pose systemic or local toxicity concerns from clinical or Pharmacology/Toxicology perspectives.

Evaluation of proposed levels of maltodextrin (b) (4)

Maltodextrin is a nutritive saccharide polymer consisting of D-glucose units. Maltodextrin is used as a binder, diluent, tablet film former and viscosity increasing agent in pharmaceutical formulations. According to the Handbook of Excipients, maltodextrin is generally regarded as a nonirritant and nontoxic material as an excipient.[5] Maltodextrin is generally recognized as safe (GRAS) by the FDA (21 CFR 184.1444) and it is used in food with no limitation other than current good manufacturing practice in accordance with 21CFR 184.1(b).

[9] Figdor SK and Pinson R., The absorption and metabolism of orally administered tritium labelled sodium stearyl fumarate in the rat and dog. *J. Agric. Food Chem.* 1970; **18(5)**: 872–877

[10] FAO/WHO, Toxicological evaluation of certain food additives with a review of general principles and of specifications, Seventeenth report of the joint FAO/WHO expert committee on food additives, *World Health Organ. Tech. Rep. Ser.*, 1974; No. 539.

[11] FAO/WHO, Evaluation of certain food additives and contaminants, Thirty-fifth report of the FAO/WHO expert committee on food additives, *World Health Organ. Tech. Rep. Ser.*, 1990; No. 789.

Applicant's justification:
The applicant states that although it is not listed in the IID as approved for a lozenge, buccal or sublingual formulation, the RLD, Nicorette®, contains maltodextrin as an inactive ingredient. It is an inactive ingredient in 2231 products including 2 FDA-approved orally disintegrating drug product formulations. Maltodextrin is in the FDA EAFUS database, and is listed as a direct food substance that is GRAS and that can be safely used in food with no limitation, is regarded as generally nonirritant and nontoxic and is not a novel excipient.[6]

(b) (4)

Clinical review:
The medical literature regarding the safety of maltodextrin in humans was reviewed. Glucose is obtained from the digestion of maltodextrin and is readily absorbed in the small intestine and used in metabolism.[12] There has been a link to increased health risk due to an increase in consumption of refined carbohydrate sources. The regular intake of calorie dense, low fiber/protein foods or drinks with high levels of refined added carbohydrates such as maltodextrin can induce a persistent positive energy balance resulting in weight gain, impaired insulin sensitivity along with increased blood cholesterol and lipids.[13] Therefore, it's recommended that consumers consume carbohydrates in moderation. The amount of maltodextrin to be ingested from the proposed drug product as an excipient is minimal and is not expected to increase the daily carbohydrate and glucose load.

Furthermore, a search of the FDA IID for maltodextrin on 12/06/16 identified Cetirizine Hydrochloride orally disintegrating tablets (ANDA 205490; antihistamine; Par Pharmaceuticals Inc; approved on 9/02/2015) and Loperamide Hydrochloride/ Simethicone chewable tablets (ANDA 076029; anticholinergics/antispasmodics; Perrigo Co; approved on 08/30/2002). Cetirizine hydrochloride orally disintegrating tablet is over-the-counter (OTC) and used for the temporary relief of allergic symptoms due to hay fever or other upper respiratory allergies.[14] Loperamide hydrochloride/ simethicone is indicated to relieve diarrhea, gas and bloating.[15] This drug product provides maltodextrin of (b) (4) which exceeds the level of maltodextrin in the proposed nicotine lozenge. Moreover, several FDA-approved oral drug products contain maltodextrin and the MDIs of maltodextrin in these products exceed the proposed amount (see Table 6 below).

[12] Cabre, E. et al. Effect of total enteral nutrition on the short-term outcome of severely malnourished cirrhotics. A randomized controlled trial. Gastroenterology. 98: 715-720/
[13] Gross, L. et al. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecological assessment. Amer J Clin. Nutr. 79: 774-779
[14] Cetirizine Hydrochloride labeling;
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205490Orig1s000lbl.pdf
[15] Loperamide hydrochloride/ simethicone labeling;
http://darrts fda.gov:9602/darrts/ViewDocument?documentId=090140af80193395

Table 6: Maltodextrin Maximum Daily Intake for Proposed Product and Approved FDA Oral Products

App	Drug Name	Dosage Form	Indication/ Use	MDD (mg/day)	Maltodextrin	Maltodextrin MDI (mg/day)
ANDA 205490	Cetirizine Hydrochloride	Tablet, Orally Disintegrating	Antihistamine			(b) (4)
			(b) (4)			
ANDA 065250	Clarithromycin	Tablet, Oral	Macrolide antibiotics			
NDA 050698	Biaxin (clarithromycin)	Suspension, Oral	Macrolide antibiotics			
			(b) (4)			
ANDA 20786*	Nicotine polacrilex	Lozenge, Sublingual	Nicotine Replacement Therapy			

* Current Review
^ assumption of average weight 60 to 69 kg

Therefore, from a clinical safety perspective there is sufficient support in approved drug products for systemic and local effects of maltodextrin in the proposed generic drug product.

Pharmacology/Toxicology review:

The available FDA guidance, published literature, and previous evaluation of maltodextrin by DCR were reviewed to assess the safety of (b) (4) of maltodextrin in the proposed generic nicotine lozenges drug product.

Maltodextrin is listed as GRAS by the FDA and it is used in food with no limitation other than current good manufacturing practice in accordance with 21CFR 184.1(b).

Maltodextrin was reported to be non-mutagenic in Ames study.[16]

(b) (4)

(b) (4) In another recent review by DCR under ANDA 205954

[16] Yoshikawa Y et al., Assessment of the safety of hydrogenated resistant maltodextrin: reverse mutation assay, acute and 90-day subchronic repeated oral toxicity in rats, and acute no-effect level for diarrhea in humans, *J*

(b) (4)

Risk assessment and conclusion for maltodextrin:
The safety margins between nonclinical vs. clinical doses for maltodextrin from the current proposed generic drug product was calculated and there is approximately 278-fold safety margins when the NOAEL of 5000 mg/kg from the 90-day repeated dose toxicity study was used. Thus, currently proposed level of maltodextrin does not raise systemic toxicity concerns. Furthermore, maltodextrin is present in FDA-approved drug products and the MDI levels of maltodextrin from approved drug products with same route of administration are higher than the MDI from the current proposed generic drug product. Therefore, the proposed levels of maltodextrin do not pose systemic or local toxicity concerns. Additionally, maltodextrin is GRAS and may be used in food without limitation.

Based on the exposure profiles, non-toxic characteristics, clinical and non-clinical toxicity data, the proposed MDI of (b) (4) maltodextrin does not pose systemic or local toxicity concerns from clinical and Pharmacology/Toxicology perspectives.

Evaluation of proposed levels of talc (MDI: 50 mg/day)

Talc is a clay mineral made up of hydrated magnesium silicate. The chemical formulation of talc is $3MgO{\cdot}4SiO2{\cdot}H2O$. Talc is listed as GRAS when migrating from cotton and cotton fabrics used in dry food packaging and migrating to food from paper and paperboard products (21 CFR § 182.70 and 21 CFR § 182.90) by the FDA. Talc is also an indirect food additive (21 CFR § 176.170 and 21 CFR §178.3297).

Applicant's justification
The applicant states that although the MDI of talc in the proposed generic drug product is above the maximum potency of a buccal or sublingual product, it is within the approved potency for an oral product in the IID. It is in the FDA EAFUS and listed as a GRAS substance as both a color additive and an indirect food additive. They note that talc is an excipient in at least 2 FDA-approved buccal drug product formulations and at least 6 FDA-approved orally disintegrating drug product formulations. It is also regarded as nontoxic material and is not a novel excipient.[6]

[19] ANDA 205954, buprenorphine/naloxone sublingual film, Clinical and P/T joint review, dated 6/14/2016

Clinical review:
The medical literature regarding safety of talc in humans was reviewed. In a case of intestinal talcosis, a 27 year old man was treated for pulmonary tuberculosis with tablets that contained talc which amounted to a total of 183 g talc over a period of 28 months. Eighteen years later, the patient was hospitalized for abdominal pain that was refractory to antacids, and had to undergo a right hemicolectomy. Microscopic examination showed prominent fibrosis of the intestinal wall. Analysis of these particles showed various elements including talc. [20] This case demonstrates that although significant side effects can occur with talc ingestion, these occur at extremely high and excessive levels, beyond what is ingested as an excipient in drug products.

A search of the FDA IID for talc on 12/06/16 identified Lansoprazole orally disintegrating tablets (ANDA 078730; miscellaneous ulcer agents; Ani Pharmaceuticals Inc; approved on 10/15/2010). Lansoprazole is a proton pump inhibitor indicated for duodenal ulcer, H. pylori eradication to reduce the risk of duodenal ulcer recurrence, benign gastric ulcer, NSAID-associated gastric ulcer and gastroesophageal reflux disease.[21] This drug product provides an MDI of talc of (b) (4) at the MDD of 90 mg, which exceeds the level of talc in the proposed nicotine lozenges. Moreover, several FDA-approved oral drug products contain talc and the MDIs of talc in these drug products exceed the proposed amount of talc (see Table 7 below).

Table 7: Talc Maximum Daily Intake for Proposed Product and Approved FDA Oral Products

App	Drug Name	Dosage Form	Indication/ Use	MDD (mg/day)	Talc	Talc MDI (mg/day)
NDA 021543	Striant® (Testosterone)	Tablet, Buccal	Androgens/Testosterone	(b) (4)		
ANDA 078730	Lansoprazole	Tablet, Orally Disintegrating	Ulcer agents			
ANDA 065150	Azithromycin	Tablet, Oral	Macrolides			
ANDA 071644	Ibuprofen	Tablet, Oral	Acute Pain, Non-opioid			
ANDA 20786*	Nicotine polacrilex	Lozenge, Sublingual	Nicotine Replacement Therapy			

* Current Review

Pharmacology/Toxicology review:
The available FDA guidance and published literature were reviewed to assess the safety of (b) (4) mg/day of talc in the proposed generic nicotine lozenges drug product.

Talc is listed as a GRAS by the FDA. Talc is also one of indirect food additive (21 CFR § 176.170 and 21 CFR §178.3297).

[20] Anani,, P.A., et al. "Unusual intestinal talcosis". Am J Surg Pathol 11 (11): 890-894 (1987).
[21] Lansoprazole delayed-release orally disintegrating tablets labeling; \\cdsesub1\evsprod\anda078730\0005\m1\us\9762-rev-11-16.pdf

Talc was assessed by the United States Environmental Protection Agency (US EPA).[22] Talc was not mutagenic in Salmonella or Saccharomyces , not clastogenic in rat bone marrow cells, and not mutagenic by the dominant lethal assay although the study details were not available.[23] Two oral absorption studies of talc in mice, rats, guinea pigs, and hamsters indicated more than 95% of the dose of orally administered talc was not absorbed; most of the dosed talc was excreted in the feces. [24, 25] Biodisposition of talc after intravaginal administration was studied by two groups but the study results were equivocal; Talc was not translocated to the uterus or beyond in monkeys whereas talc migrated to the ovaries in rats.[26, 27] Although several repeated dose toxicity studies of talc were available in animals by inhalation, intratracheal, and intraperitoneal administration, only one repeated oral dose toxicity study of talc in rats was reported. The oral administration of talc (100 mg/kg/day) for 101 days induced stomach tumor in one rat out of 32 (reviewed by US EPA).

Talc administered by inhalation or intratracheal instillation was not carcinogenic in rats and hamsters.

Taken together, these non-clinical data indicate that the proposed levels of talc have limited potential for systemic toxicity.

Risk assessment and conclusion for talc:

Talc was not mutagenic and more than 95% of orally administered talc was not absorbed in published nonclinical studies. Talc is present in FDA-approved drug products and the MDI levels of talc from approved drug products with same route of administration are higher than the MDI from currently proposed generic drug product. Therefore, currently proposed levels of talc do not pose systemic or local toxicity concerns. Additionally, talc is GRAS by the FDA and is also an indirect food additive.

Based on the exposure profiles, non-toxic characteristics, clinical and non-clinical toxicity data, the proposed MDI of (b) (4) talc does not pose any systemic or local toxicity concerns from clinical and Pharmacology/Toxicology perspectives.

[22] Hajiar *et al*., Health assessment document for talc, Research Triangle Park, NC: Environmental Protection Agency, US Office of Research and Development; 1992.
[23] Lord GH., The biological effects of talc in the experimental animal: a literature review, *Fd. Cosmet. Toxicol.* 1978; **16**: 51-57.
[24] Wehner *et al*., Absorption of ingested talc by hamsters. *Fd. Cosmet. Toxicol*. 1977; **15**: 453-455.
[25] Phillips et al., Studies on the absorption and disposition of ^{3}H-labelled talc in the rat, mouse, guinea-pig and rabbit, *Fd. Cosmet. Toxicol*. 1978; **16**: 161-163.
[26] Wehner *et al*., On talc translocation from the vagina to the oviducts and beyond, *Fd. Chern. Toxicol*. 1986; **24**: 329-338.
[27] Henderson et al., (1986) The demonstration of the migration of talc from the vagina and posterior uterus to the ovary in the rat, *Environ. Res*. 1986; **40**: 247-250.

6 Conclusion:

The proposed maximum daily intake levels of sodium stearyl fumarate, maltodextrin and talc from the current generic drug product do not pose an increased risk for adverse events, as compared to the RLD. Hence, the proposed levels of each excipient are acceptable from clinical and Pharmacology/Toxicology perspectives.

7 References:

See Footnotes

Robert Dorsam

Digitally signed by Robert Dorsam
Date: 1/30/2017 08:45:18AM
GUID: 5048c79e00001d1a860d88bc481f8883

Daiva Shetty

Digitally signed by Daiva Shetty
Date: 1/30/2017 10:25:48AM
GUID: 5081924f00008b85e43df3f5824475e5

Nancy Snow

Digitally signed by Nancy Snow
Date: 1/30/2017 08:42:57AM
GUID: 508da6f100027b2a80a136409d193d74

Shahreen Hussain-Malik

Digitally signed by Shahreen Hussain-Malik
Date: 1/30/2017 09:52:35AM
GUID: 5423006c00721eab0bcec403cf7af2db

Mi Young Yang

Digitally signed by Mi Young Yang
Date: 1/30/2017 08:42:47AM
GUID: 561ff0060016d57c06873af71ffbfbe6

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207868

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)**

RPM: Gwen Murphy Team Leader: Kevin Denny

☐ **PI** ☐ **PII** ☐ **PIII** ☒ **PIV** (*eligible for 180 day exclusivity* ☐ **Yes** ☐ **No)** ☐ **MOU** ☐ **RX or** ☒ **OTC**

ANDA #: 207868 Applicant: PLD Acquisitions LLC, D/B/A Avema Pharma Solutions
Established Product Name: Nicotine Polacrilex Lozenges, 2 mg and 4 mg (Mini)

Basis of Submission (RLD): N022360 Nicorette
Basis Of Submission Discontinued? Yes ☐ No ☒
If yes, has FR published indicating the Agency determined the product was not withdrawn for reasons of safety or effectiveness?
Yes ☐ FR Notice dated _____; Document Citation _____; FR. _____(Example: 78 FR 67365)
No ☐ Consult completed but not yet published in FR

(Is ANDA based on an approved Suitability Petition? ☐ Yes ☒ No, if yes, use SP language in template)

Does the ANDA contain REMS? ☐ Yes ☒ No *(If YES, initiate approval action 6 weeks prior to target action date)*

Regulatory Project Manager Evaluation: **Date: 1/30/2019**

☒ Date (Received) Acceptable for Filing -- Date **12/2/2015**
☒ Date last Complete Response (CR) letter was issued -- Date **10/25/2018**
☐ Previously reviewed and tentatively approved (if applicable) --- Date _____

YES	NO		
☒	☐	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A)	
		Date of Acceptable Bioequivalence **9/23/2018** • Date of BE Guidance (if any) **9/2018** Date of Acceptable Labeling **2/1/2019** • Date of last RLD labeling update **6/5/2018** Date of Acceptable Quality **1/30/2019** • DMF No(s) (b) (4) Date(s) Acceptable **5/23/2011** • No outstanding DMF review amendments ☒ • Date of Acceptable Overall Manufacturing Inspection **11/27/2018**	If applicable: Date of Acceptable Microbiology **N/A** Date of Acceptable Clinical Review **N/A** Date of Acceptable Dissolution **1/25/2019** Date of Acceptable REMS **N/A**
☒	☐	**MMA:** All amendments submitted to the Agency on or after December 5, 2016 contain (1) a patent certification or section viii statement, (2) a recertification, or (3) a verification statement per 21 CFR 314.96(d).	
☐	☒	Are consults pending for any discipline?	
☒	☐	OSIS Clinical Endpoint and Bioequivalence Site Inspections are acceptable	
☐	☒	Is there a pending legal or regulatory issue (refer to Policy Alert Tracker)? If YES → OGD Policy Lead confirmed ANDA may proceed ☐; Memo uploaded (if applicable) ☐	
☐	☒	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES→Verify a second filing review was completed (if applicable) and that all disciplines completed new reviews ☐	
☒	☐	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff or Division liaison 30 to 60 days prior to approval, Date emailed _____	

Review Discipline/Division and RPM TL Endorsements

☒	☐	Applicable review discipline/division endorsements completed
☒	☐	RPM Team Leader endorsement completed

Additional Notes (if applicable)

See Labeling memo (email) uploaded to current project confirming that 6/5/18 RLD Labeling update does not need to be addressed by this applicant for approval of ANDA 207868.

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 2/1/2019
Name: IM

Patent/Exclusivity Certification:

☐ **PI** ☐ **PII** ☐ **PIII** ☒ **PIV** ☐ **section viii**

If Paragraph IV Certification- did applicant:

Notify patent holder/NDA holder:	Yes ☒	No ☐
Was applicant sued w/in 45 days:	Yes ☒	No ☐
Has case been settled:	Yes ☐	No ☐
Applicant addressed all listed exclusivities	Yes ☐	No ☐
Do the patent and exclusivity certifications align?	Yes ☐	No ☐
Have there been any revisions to the use code since the original submission?	Yes ☐	No ☐

RLD = **Nicorette** NDA# **22360** ☐ **RX or** ☒ **OTC**

Date Checked in Orange Book#: **2/1/2019**

Type of Letter:

☒ APPROVAL

☐ TENTATIVE APPROVAL

☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH)

LETTER RECOMMENDED FOR DRUGS@FDA Yes ☐ No ☐

Forfeiture Information

Is a forfeiture memo needed for the first applicant: Yes ☒ No ☐

If yes, the date forfeiture memo was completed

Date 6/4/2018 ANDA # 207868

180 Day Exclusivity Information

Is applicant eligible for 180 day exclusivity Yes ☒ No ☐

☒ Sole

☐ Shared

ANDA Exclusivity for each strength: Yes ☒ No ☐

Which strength(s) eligible _____

Comments:

BOS = Nicorette (NDA 22360) Application submission 6/19/2014 with a PIV certification to the '164 patent. Amendment 9/17/2015 with an updated patent certification statement to include a PIV certification to the '772 patent. RTR letter issued 9/29/2015. Response to RTR received 12/2/2015. Acknowledgment letter signed 1/14/2016 with a revised ANDA receipt date of 12/2/2015.

Amendment 2/18/2016 with USPS PIV return receipts sent to GlaxoSmithKline Consumer Healthcare (PA) and signed 1/25/2016. PLD states they were unable to deliver to addresses on the USPTO site for additional deliveries, though after confirming correct addresses notice was sent 2/9/2016 to GlaxoSmithKline LLC (PA) and GlaxoSmithKline (PA) and signed, but not dated, but delivered 2/11/2016 per PLD.
Amendment 3/31/2016 PLD states there was no legal action taken on the PIV certifications within the statutory 45 day time period.

There are no additional unexpired patents and no unexpired exclusivities listed in the OB to the NDA. There is no pending CP for the drug product. With respect to 180-day exclusivity, this ANDA is the first application received to the NDA with a PIV certification and would be eligible for 180-day exclusivity. The ANDA did not receive a TA within 30 months of the 12/2/2015 receipt date and may have forfeited the exclusivity. The agency determined 6/4/2018 that the cause for the application not receiving the 30-month TA was caused by a change in the review requirements and therefore Avema has not forfeited 180-day exclusivity (see memo in ANDA program).
Of note, there are already approved ANDAs based on the same NDA. However, those applications were submitted and approved prior to the submission of the '164 (request for listing 9/5/2013) and '772 (request for listing 2/25/2015) patents and were not eligible for 180-day exclusivity. This is the first ANDA received to have a PIV certification to NDA 22360.

PLD's ANDA is eligible for Full Approval with an award of 180-day exclusivity.

180 Day Exclusivity Status/Landscape: Granted to this ANDA
Citizen Petitions Impact: N/A

First Legally Approvable Date: 3/31/2016, upon notice of no legal action on the PIV certifications
If Tentative Approval, anticipated full approval date: N/A

2. Final Decision

Date: 2/7/2019
Name: sgk

ANDA received on **12/2/2015** for the **2 mg and 4 mg** strengths
RTR'd? Yes ☐ No ☒ If yes, RTR'd on Enter date
Priority Status? Yes ☒ No ☐ If yes, prioritization factor is **First Generic**
Basis of Submission (RLD)

Drug Name	**Nicorette Mini Lozenge**
NDA #	**022360**
Applicant Name	**GlaxoSmithKline Consumer Healthcare**

☒ Verified the following:

1. Completion of the following endorsement tasks, if applicable:
    a. Division of Legal and Regulatory Support Endorsement
    b. Paragraph IV Evaluation
    c. REMS Endorsement
    d. Quality Endorsement
    e. Bioequivalence Endorsement
    f. Clinical-Bioequivalence Endorsement
    g. Labeling Endorsement
    h. RPM Team Leader Endorsement
2. All applicable endorsement tasks are completed in the platform within 30 days of potential approval.
3. No updates to patents and/or exclusivities in Orange Book since the Division of Legal and Regulatory Support Endorsement
4. No Reference Listed Drug updates at Drugs@FDA since the Labeling Endorsement
5. No issues listed on the current version of the Policy alert list since the RPM Team Leader Endorsement
6. No new alerts in the Submission Facility Status View since the Quality Endorsement
7. Overall Inspection Recommendation of Approve of the current project (see screenshot below)
8. No new DMF amendments since Quality Endorsement
9. No amendments received since the RPM Team Leader Endorsement

This ANDA is ready for **FULL** APPROVAL.

****INCLUDE SNIP OF SUBMISSION FACILITY STATUS VIEW AT THE TIME OF APPROVAL****

(b) (4)

[redacted]

(b) (4)

[redacted]

REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form
02	10/03/2017	Kevin Denny	Reviser	• Update form to reflect revisions to SOP 4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA, Version 04 • Remove content adequately captured in the platform • Update information captured in the Division of Legal and Regulatory Support Endorsement section • Other minor administrative corrections to format and content
03	1/24/18	Kevin Denny	Reviser	• Update Final Decision section

ANDA 207868

INFORMATION REQUEST

PLD Acquisitions LLC
D/B/A Avema Pharma Solutions
Attention: Mehul Govani
Regulatory Affairs Manager
609-2 Cantiague Rock Road
Westbury, NY 11590

Dear Mehul Govani:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 19, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Nicotine Polacrilex Mini Lozenges 2 mg and 4 mg.

We also refer to your April 30, 2018 submission, containing your response to the Agency's Complete Response Letter.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than **October 1, 2018**, in order to continue our evaluation of your ANDA.

Comments and information requests:

A. Drug Product

1. (b) (4)
2.
3.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

(b) (4)

4.

(b) (4)

5.

6.

C (b) (4)

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Adrienne Belton, Regulatory Business Process Manager, at 240-402-4024 or Adrienne.Belton@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Adrienne M. Belton, Pharm.D
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Adrienne Belton

Digitally signed by Adrienne Belton
Date: 9/20/2018 02:45:32PM
GUID: 56c337af019cd6b2700d9d7298b7db01

M E M O R A N D U M

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

DATE: 5/22/2018

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: ANDA 207868

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Novum Pharmaceutical Research Services	3760 Pecos McLeod, Las Vegas, NV

M E M O R A N D U M

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

DATE: 5/22/2018

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: ANDA 207868

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

ANDA 207868

INFORMATION REQUEST

PLD Acquisitions LLC, D/B/A Avema Pharma Solutions
10400 NW 29th Terrace
Miami, FL 33172
Attention: Mehul Govani

Dear Mehul Govani:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on June 19, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base.

We are reviewing the BIOEQUIVALENCE section of your submission and have the following information request:

1. In the current amendment dated 04/30/2018, you submitted a new pivotal *in vivo* bioequivalence (BE) study (#11879301) conducted on the new test (#CM097374/RD039-24) and reference (#15376) bio-batches. As per the "*Inclusion Criteria*" in your clinical study protocol (Protocol# PLDA000218; Date: 02/08/2018) and report (Study# 11879301; Date: 04/24/2018), you state that "*Subject is a current smoker and has smoked regularly for at least 1 year before initial dosing*", and positive pre-dose nicotine concentrations were observed for at least one period in 29 subjects, which accounts for 72.5% of total 40 subjects who completed the study. Also, based on the raw data submitted and your study report, the measurable pre-dose nicotine concentrations in 7 subjects (Subject No (b) (6), (b) (6)) were greater than 5% of the respective measured Cmax values, and therefore "*these 7 subjects were excluded from statistical analysis*". Therefore, considering your subject recruitment of "*current smoker*" and predominant measurable pre-dose nicotine concentrations observed, please re-conduct your pharmacokinetic (PK) and statistical analyses using the data of **baseline-corrected** nicotine concentrations (the measured nicotine concentration at each time point should be corrected by subtracting the contribution from the corresponding pre-dose level), and resubmitted the study outcomes, including BE Summary Table 2 and 3, and corresponding part of your study report and statistical report.

   Please also submit related SAS transport (.xpt) datasets for plasma concentration and PK parameters in the following format:

   Plasma Concentration Data

SUB	SEQ	PER	GRP	TRT	C1	C2…	Cn	T1	T2…	Tn	KE_FIRST	KE_LAST

Definition Table for SAS Transport Dataset of Individual Plasma Concentration Data

Variable Name	Variable Label	Type	Notes
SUB	Subject Identification Number	Char/Num	Unique subject identifier (3001, 3002, …)
PER	Period	Numeric	Period identifier
SEQ	Sequence	Numeric	Sequence identifier (1=RT; 2=TR)
TRT	Treatment	Numeric	Treatment group (1=Test; 2=Reference)
GRP	Group Identification Number	Numeric	Dosing group identifier if subjects are dosed in more than one group
C1	Concentration Time 1	Numeric	Concentration at the first time point*
C2	Concentration Time 2	Numeric	Concentration at the second time point*
Cn	Concentration Time n	Numeric	Concentration at the nth time point*
T1	Time Point 1	Numeric	First **Actual** Sampling Time (e.g., 0 hour)
T2	Time Point 2	Numeric	Second **Actual** Sampling Time (e.g., 0.167 hour)
Tn	Nth Time Point	Numeric	Nth **Actual** Sampling Time (e.g., 12 hours)
KE_FIRST	First time point for KE calculation	Numeric	First time point of the elimination segment (of the concentration-time curve) selected for calculating KE**
KE_LAST	Last time point for KE calculation	Numeric	Last time point of the elimination segment (of the concentration-time curve selected for calculating KE**

NOTE:
*, C1, C2, …, Cn should be baseline-corrected nicotine concentrations.
**, KE_FIRST and KE_LAST should be given as the sequential numbers of the time points, and NOT the time values themselves. For example:
KE_FIRST = 10 which means the 10th time point, not "10 hours"
KE_LAST = 24 which means the 24th time point, not "24 hours"

PK Parameter Data

SUB	SEQ	PER	GRP	TRT	Tmax	Cmax	AUCt	AUCi	Ke	Thalf

Definition Table for SAS Transport Dataset of Individual PK Parameter Data

Variable Name	Variable Label	Type	Notes
SUB	Subject Identification Number	Char/Num	Unique subject identifier
PER	Period	Numeric	Period identifier
SEQ	Sequence	Numeric	Sequence identifier (1=RT; 2=TR)
TRT	Treatment	Numeric	Treatment group (1=Test; 2=Reference)
GRP	Group Identification Number	Numeric	Dosing group identifier if subjects are dosed in more than one group
AUCt	Area Under the Curve from zero hour (0) to the last time point with measurable concentration (t)	Numeric	Area under the curve from time 0 to t
AUCi	Area Under the Curve from zero hour (0) to infinity	Numeric	Area under the curve from time 0 to infinity
Cmax	Cmax	Numeric	Maximum concentration
Tmax	Tmax	Numeric	Time at maximum concentration
Thalf	Half-life	Numeric	Half-life calculated from the terminal phase of the elimination
Ke	Ke	Numeric	Elimination rate constant

2. Based on your current submission, the Table 14.2.1 of "*Concentration Values for Individual Subjects*" in your study report (Study# 11879301; Page 57-62; Date: 04/24/2018) is incomplete, which only includes concentrations of sampling time points until 120 min. Please resubmit a complete table including data from all sampling time points.

We request a complete written response no later than September 17, 2018 to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
BIOEQUIVALENCE

If you do not submit a complete written response by September 17, 2018, the listed information requests may be incorporated in a complete response letter.

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the

Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter , these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review of your entire application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact Linda Park, Bioequivalence Project Manager, at linda.park1@fda.hhs.gov or (240) 402-5120.

Sincerely,

Linda Park, Pharm.D.
OFFICE OF GENERIC DRUGS
OFFICE OF BIOEQUIVALENCE
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DBIII's Response to an Amendment to the Post-CR Meeting Request (MR) Written Response

Date: December 11, 2017

From: Yi Zhang, Ph.D. (Primary Reviewer)
Li Gong, Ph.D. (Secondary Reviewer)
April C. Braddy, Ph.D. (Tertiary Reviewer)

Through: Nilufer M. Tampal, Ph.D.
Director, DBIII/OB/OGD

To: Mehul Govani
Regulatory Affairs Manager
PLD Acquisitions LLC, D/B/A Avema Pharma Solutions

Subject: Amendment to the Post- CR meeting request about bioequivalence (BE) deficiency regarding the violation of reserve sample regulations in the CR letter (dated 07/14/2017)

ANDA: 207868
(Platform/GDRP: ANDA-207868-GI-1-MEETING-12)

Applicant: PLD Acquisitions LLC, D/B/A Avema Pharma Solutions

Drug Product: Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base

Subject of Request:

The applicant is requesting the Office of Generic Drugs (OGD) to reconsider the bioequivalence (BE) deficiency identified in the CR Letter dated July 14, 2017, that relates to the violation of reserve sample regulations, so that its BE studies can be proved to be valid and acceptable to support the approvability of ANDA 207868.

Date of request: July 28, 2017 (Post-CR MR)
October 19, 2017 (Amendment)

I. Background

On 12/02/2015, the firm, PLD Acquisitions LLC, originally submitted ANDA 207868 containing a pivotal (#AJ-1403) and a pilot (#AJ-1401) fasting BE studies comparing a test product, Nicotine Polacrilex Mini Lozenges, EQ 4 mg base, to the corresponding reference product, GlaxoSmithKline Consumer Healthcare's Nicorette® (nicotine polacrilex) Mini Lozenge, EQ 4 mg base [NDA 022360, approved on 05/18/2009; Over-the-Counter (OTC)]. The application also contains a waiver request for the EQ 2 mg base strength.

As per the original BE review[1] and the subsequent BE amendment review[2], the firm's pivotal and pilot fasting BE studies were both considered adequate (complete). However, during the review of the Office of Study Integrity and Surveillance (OSIS)' inspections, based on the information provided, the clinical site, Phase One Solutions, Inc., did not retain reserve samples appropriately as require by 21 CFR 320.38 and 320.63. The retained samples of the investigational products for the BE studies have been destroyed. Hence, the authenticity of the test and reference drug products used in the pivotal (AJ-1403) and pilot (AJ-1401) BE studies cannot be confirmed due to the lack of reserve samples. Thus, the following BE deficiency was communicated to the firm in the Complete Response (CR) Letter dated 07/14/2017:

> ***Deficiency Related to the OSIS Inspection***
>
> *As per 21 CFR 320.38 and 320.63, "The applicant of an abbreviated application or a supplemental application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act, or, if bioequivalence testing was performed under contract, the contract research organization shall retain reserve samples of any test article and reference standard used in conducting an in vivo or in vitro bioequivalence study required for approval of the abbreviated application or supplemental application. The applicant or contract research organization shall retain the reserve samples in accordance with, and for the period specified in, 320.38 and shall release the reserve samples to FDA upon request in accordance with 320.38". In the absence of reserve samples at the study site or an independent third party, the authenticity of test and reference drug products used in studies cannot be ensured.*
>
> *Based upon the information you provided in the current post-complete response (CR) amendment (dated 05/02/2017), the clinical site, Phase One Solutions, Inc., did not retain reserve samples properly of the investigational products used in the related bioequivalence (BE) studies for the current ANDA as require by 21 CFR 320.38 and 320.63, as you stated that "During the week of 02/20/17 we were informed by Phase One over the phone that* ***the retain samples which were stored at the temporary location were destroyed****"; and that you were "not informed about this and you were not provided with a certificate of destruction." Therefore, the authenticity of the test and reference drug products used in your pivotal (Study No. AJ-1403) and pilot (Study No. AJ-1401) BE studies cannot be confirmed due to lack of reserve samples. As a result, the in vivo BE study data from the current studies, #AJ-1403*

[1] GDRP/Panorama, ANDA 207868 (ANDA-207868-ORIG-1-RESUB-3): Bioequivalence Discipline Review (Bioequivalence Primary Review: A207868N000DB_N12022015.docx); Last Update: 02/18/2017. http://panorama.fda.gov/task/view?ID=566154ac0141beee6e16a23c11cb43fa.

[2] GDRP/Panorama, ANDA 207868 (ANDA-207868-ORIG-1-AMEND-11): Bioequivalence Discipline Review (Bioequivalence Primary Review: A207868N000DB_NA05022017.docx); Last Update: 06/13/2017. http://panorama.fda.gov/task/view?ID=590cc9b8005b538a64f58ba9363ebbca.

*and #AJ-1401, are **not** acceptable since the reliability of data has been impaired by the violation of reserve sample regulations.*

On 07/28/2017, the firm submitted a post-CR meeting request to the Office of Generic Drugs (OGD) to seek Agency's reconsideration of the above deficiency identified in the CR letter regarding the violation of reserve sample regulations (***Attachment #1***). The firm provided a number of documents related to samples from the lots of products used in the BE studies that remained in the firm's possession and asserted that its retention of these samples satisfied the requirement to maintain samples from the BE study. With DBIII's re-evaluation, a written response was granted on 09/29/2017 (***Attachment #2***) to respond to the firm's meeting request briefly as below:

You failed to meet the regulatory requirements for the CRO to reserve samples [21 CFR 320.38 and 320.63] for in vivo BE studies; Please be advised to repeat your pivotal fasting BE study using unexpired batches of the test and reference products.

Also, as requested by the Office of Generic Drug Policy (OGDP), additional details were communicated to the firm dated 10/12/2017 (as a supplemental letter to the above mentioned Post-CR MR written response; ***Attachment #3***). This letter reiterated the deficiency stated in both the complete response letter and written response to the meeting request, noting in addition that:

For CRO site (POS): The firm did not provide

(1) Drug inventory or accountability of both test and reference;
(2) Record of transferring reserved samples from the CRO site to the temporarily stored facility;
(3) Record for the disposal/destruction of reserved samples, such as numbers of unit of drugs being destroyed.

The supplemental letter stated in addition that the firm's "retention of samples for studies performed at a contract research organization (CRO) on its face does not meet the regulatory requirement for the CRO to reserve sample." The letter also noted that even if this was not the case:

For PLD site/in-house samples (as requested by the OGDP): The firm did not provide

(1) SOPs for in-house sample retention and storage;
(2) Complete on-site inventory records for both test and reference to allow for reconciliation and accountability of the drug products.

In the current Amendment to Post-CR Meeting Request dated 10/19/2017, the firm responded to the comments related to PLD site (in-house sample retention & storage), and provided (1) "*RLD and test usage documentation*" demonstrating the same batches of test and reference products were reserved at the PLD site; and (2) "*SOPs and quality policies*" indicating the in-house samples were stored at well-controlled conditions. However, the firm still did not provide documentation requested for the CRO site. (Please see ***Attachment #4*** for details). The purpose of reserve samples is to deter possible bias and fraud in the BE studies and to assure that the reserved samples be a portion of the samples tested at the clinical site, the storage conditions well-controlled, and the chain of custody unbroken. However, the retained samples and the currently submitted SOPs at PLD site (i.e. manufacturing site) were not considered a portion of the samples tested for the BE studies because the *in vivo* BE studies were conducted at the CRO site. And the chain of custody

was also broken at the CRO site due to the lack of complete documentation mentioned above.

Moreover, an OB-OGDP internal meeting was held on 12/11/2017 to discuss the issue of sample retention for the current ANDA 207868 (***Attachment #5*** for meeting minutes[3]).

II. Questions and Responses

Firm's Request:

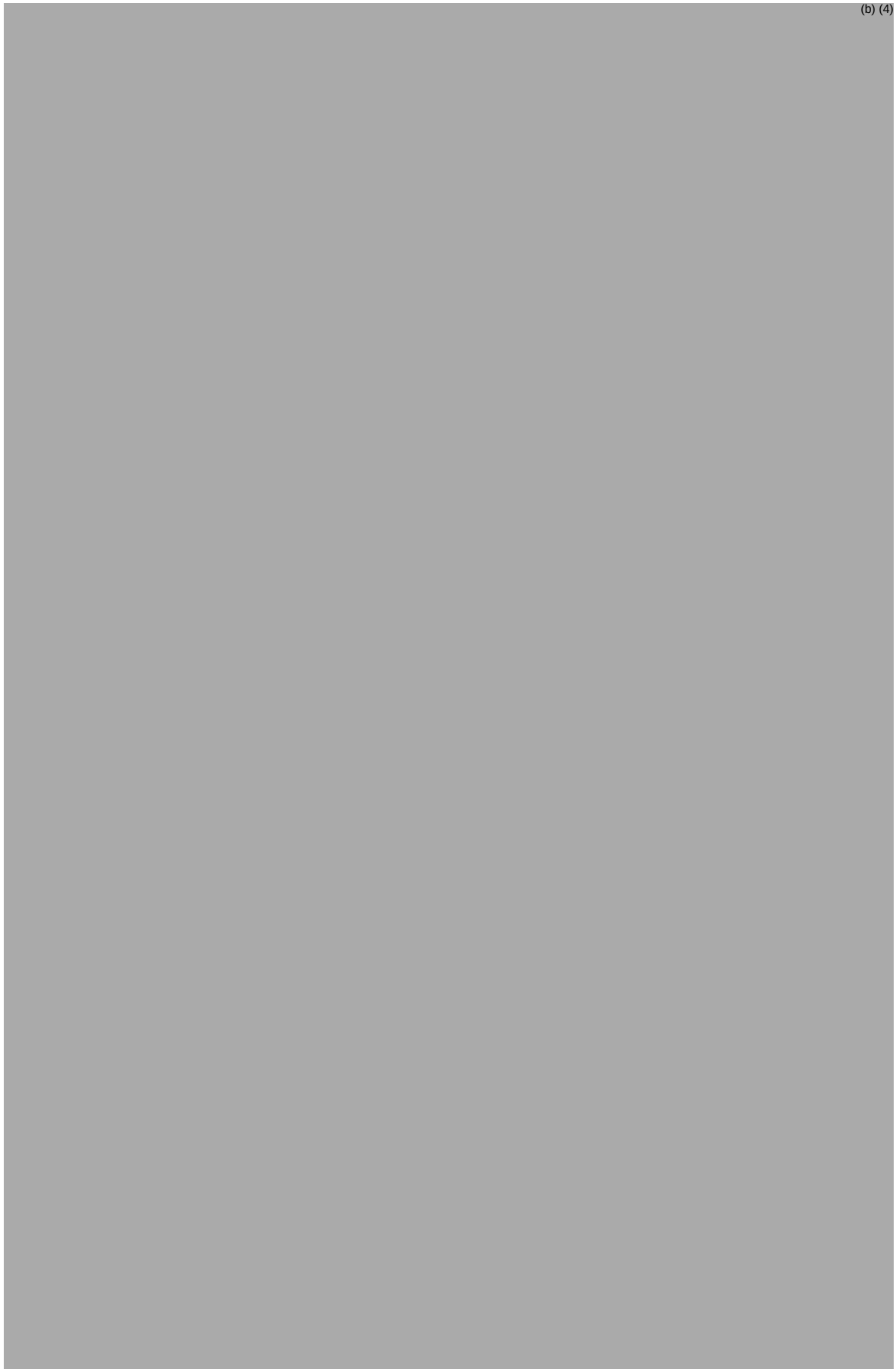
PLD Acquisitions LLC d/b/a Avema Pharma Solutions is submitting an amendment to the Supplement to post CRL meeting request written response dated September 29, 2017. This amendment intends to address the concerns raised regarding assurance of the authenticity of the test and reference products.

1) The first concern raised by OGD was regarding PLD's documentation of standard procedures for in-house sample retention and storage.
   Response: PLD is providing the below mentioned policies and procedures that address the in-house sample retention and storage requirements. These procedures are applicable to the samples used in the bioequivalence ("BE") testing as PLD did not intend to conduct its own bioequivalence study. In accordance with our sample retention and storage procedures, we do have retention samples retained in an area segregated from the testing area with controlled access limited to authorized personnel.
   Please see the attached links to our SOPs that govern our sample retention and storage procedures.

SOP000051: Retention samples
SOP000120: Raw material (API) and bulk product security
SOP000091: Login, tracking and Disposition of QC laboratory samples
SOP000028: Stability Program
SOP000026: Control and retention of records
QP000007: Document Management Policy
QP000017: Stability Policy

2) The second concern raised by OGD was regarding a complete on-site inventory records for both test article and reference standard to allow for reconciliation and accountability of the drug products.
   Response: In this response, we are providing documentation to support actual usage of test article and the reference standard.

[3] Meeting Minutes: GDRP/Panorama, FDA Correspondence - Project; http://panorama.fda.gov/task/view?ID=5a37e28700096069a6c2bbddb80c2ea2.


(b) (4)

DBIII's Response:

As we previously communicated to you in our Complete Response (CR) Letter dated 07/14/2017 and our Post-CR Meeting Request Written Response dated 09/29/2017, the contract research organization that conducted your *in vivo* pivotal (Study No. AJ-1403) and pilot (Study No. AJ-1401) BE studies failed to retain samples of the drug products used in the studies. Therefore, the in vivo BE study data from the current studies are not acceptable. To deter possible bias and fraud in the studies and to assure that the reserved samples be a portion of the samples used in the BE studies, the storage conditions well-controlled, and the chain of custody unbroken, as per 21 CFR 320.38 and 320.63, the reserve samples should be retained and stored at a study site, or at an independent third party site. Because the reserved samples for ANDA 207868 have been destroyed at the CRO site, the authenticity of the test and reference drug products used in your BE studies cannot be assured. Retention by PLD of samples from the same batches used in testing neither provides the necessary assurances of study integrity nor satisfies applicable regulation.

Please be advised to repeat your pivotal fasting BE study using unexpired batches of the test and reference products. Please refer to draft guidance on Nicotine Polacrilex Lozenge for details (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240974.pdf; Recommended Jan 2011). Please note that sufficient quantities of the drug products used in the study should be retained as per FDA Guidance for Industry: Handling and Retention of BA and BE Testing Samples (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf; May 2004).

You may consider this correspondence as a division level denial of a request for reconsideration of the BE deficiency identified in the July 14, 2017 complete response letter. If you wish to appeal to this decision you may submit a request for formal dispute resolution. The guidance for industry on *Formal Dispute Resolution: Sponsor Appeals Above the Division Level* (Nov. 2017, Rev. 1) recommends that an applicant should contact the formal dispute resolution coordinator located on the CDER Formal Dispute Resolution web page, located at https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ContactCDER/ucm444092.htm, for a reconsideration request beyond the division level.

III. Attachments

Attachment #1: Post-CR meeting request dated 07/28/2017
\\cdsesub1\evsprod\anda207868\0011\m1\us\1-2-cover-letters\cover-letter-0011-07282017.pdf

Attachment #2: DBIII's written response dated 09/29/2017

A207868N000DPM-WrittenResponses01.pd

Attachment #3: DBIII's supplemental response dated 10/12/17

A207868N000DPM-R
esponse01-PostCRMF

Attachment #4: Amendment to Post-CR meeting request dated 10/19/2017
\\cdsesub1\evsprod\anda207868\0012\m1\us\1-2-cover-letters\cover-letter-0012-10192017.pdf

Attachment #5: OB-OGDP meeting minutes[3]

ANDA
207868-Internal Meet

Outcome Page

Completed Assignment for 207868 ID: 33372

Reviewer:	Zhang, Yi	**Date Completed:**	
Verifier:		**Date Verified:**	
Division:	Division of Bioequivalence III		
Description:	Response to Amendment (Post-CR MR) for ANDA 207868 (Sample retention), Nicotine Polacrilex Mini Lozenges		

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
33372	10/19/2017	BIO	Post CR Meeting Request Review [1]	1	1
33372	10/19/2017	Parallel	Post CR Meeting Request [1]	1	1
33372	12/16/2017	BIOQUALITY	Quality Assessment [1-5]	4.5	4.5
				Total:	6.5

Response to a Post-CR meeting request from the Applicant

Date: September 11, 2017

From: Yi Zhang, Ph.D. (Primary Reviewer)
Li Gong, Ph.D. (Secondary Reviewer)
April C. Braddy, Ph.D. (Tertiary Reviewer)

Through: Nilufer M. Tampal, Ph.D.
Director, DBIII/OB/OGD

To: Mehul Govani
Regulatory Affairs Manager
PLD Acquisitions LLC, D/B/A Avema Pharma Solutions

David Rosen, BS Pharm., JD
Foley & Lardner LLP

Subject: Post-Complete Response (CR) meeting request about bioequivalence (BE) deficiency regarding the violation of reserve sample regulations in the CR letter (dated 07/14/2017)

ANDA: 207868
(Platform/GDRP: ANDA-207868-GI-1-MEETING-12)

Applicant: PLD Acquisitions LLC, D/B/A Avema Pharma Solutions

Drug Product: Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base

Subject of Request:

The applicant is requesting the Office of Generic Drugs (OGD) to reconsider the bioequivalence (BE) deficiency identified in the CR Letter dated July 14, 2017, that relates to the reserve samples so that the BE studies can be relied up to support the approvability of ANDA 207868.

Date of request: July 28, 2017

I. Background

On 12/02/2015, the firm, PLD Acquisitions LLC, originally submitted ANDA 207868 containing a pivotal (#AJ-1403) and a pilot (#AJ-1401) fasting BE studies comparing a test product, Nicotine Polacrilex Mini Lozenges, EQ 4 mg base, to the corresponding reference product, GlaxoSmithKline Consumer Healthcare's Nicorette® (nicotine polacrilex) Mini Lozenge, EQ 4 mg base [NDA 022360, approved on 05/18/2009; Over-the-Counter (OTC)] . The application also contains a waiver request for the EQ 2 mg base strength.

As per the original BE review[1] and the subsequent BE amendment review[2], the firm's pivotal and pilot fasting BE studies were both considered adequate (complete). However, during the review of the Office of Study Integrity and Surveillance (OSIS)' inspections, based on the information provided, the clinical site, Phase One Solutions, Inc., did not retain reserve samples appropriately as require by 21 CFR 320.38 and 320.63. The retained samples of the investigational products for the BE studies have been destroyed. Hence, the authenticity of the test and reference drug products used in the pivotal (AJ-1403) and pilot (AJ-1401) BE studies cannot be confirmed due to the lack of reserve samples. As a result, the following BE deficiency was communicated to the firm in the Complete Response (CR) Letter dated 07/14/2017:

> ***Deficiency Related to the OSIS Inspection***
>
> *As per 21 CFR 320.38 and 320.63, "The applicant of an abbreviated application or a supplemental application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act, or, if bioequivalence testing was performed under contract, the contract research organization shall retain reserve samples of any test article and reference standard used in conducting an in vivo or in vitro bioequivalence study required for approval of the abbreviated application or supplemental application. The applicant or contract research organization shall retain the reserve samples in accordance with, and for the period specified in, 320.38 and shall release the reserve samples to FDA upon request in accordance with 320.38". In the absence of reserve samples at the study site or an independent third party, the authenticity of test and reference drug products used in studies cannot be ensured.*
>
> *Based upon the information you provided in the current post-complete response (CR) amendment (dated 05/02/2017), the clinical site, Phase One Solutions, Inc., did not retain reserve samples properly of the investigational products used in the related bioequivalence (BE) studies for the current ANDA as require by 21 CFR 320.38 and 320.63, as you stated that "During the week of 02/20/17 we were informed by Phase One over the phone that **the retain samples which were stored at the temporary location were destroyed**"; and that you were "not informed about this and you were not provided with a certificate of destruction." Therefore, the authenticity of the test and reference drug products used in your pivotal (Study No. AJ-1403) and pilot (Study No. AJ-1401) BE studies cannot be confirmed due to lack of reserve samples. As a result, the in vivo BE study data from the*

[1] GDRP/Panorama, ANDA 207868 (ANDA-207868-ORIG-1-RESUB-3): Bioequivalence Discipline Review (Bioequivalence Primary Review: A207868N000DB_N12022015.docx); Last Update: 02/18/2017. http://panorama.fda.gov/task/view?ID=566154ac0141beee6e16a23c11cb43fa.

[2] GDRP/Panorama, ANDA 207868 (ANDA-207868-ORIG-1-AMEND-11): Bioequivalence Discipline Review (Bioequivalence Primary Review: A207868N000DB_NA05022017.docx); Last Update: 06/13/2017. http://panorama.fda.gov/task/view?ID=590cc9b8005b538a64f58ba9363ebbca.

*current studies, #AJ-1403 and #AJ-1401, are **not** acceptable since the reliability of data has been impaired by the violation of reserve sample regulations.*

On 07/28/2017, the firm submitted a post-CR meeting request to the Office of Generic Drugs (OGD) to seek Agency's reconsideration/reversion of the above deficiency identified in the CR letter regarding the violation of reserve sample regulations. A written response has been granted to respond to the firm's meeting request. The firm's request and DBIII's response are provided below.

Please note that the same OSIS deficiency/issue related to sample retention has been identified at the same clinical site (Phase One Solutions, Inc.) (b) (4) (b) (4).

II. Questions and Responses

Firm's Request:

We would like to propose OGD to reconsider the bioequivalence deficiency mentioned in the Complete Response Letter based on the attached letter (please see *key points* attached below)[5] from David Rosen, BS Pharm., JD of Foley & Lardner LLP who is authorized to speak on behalf of PLD Acquisitions LLC, D/B/A Avema Pharma Solutions, owner of ANDA 207868. Mr. Rosen's letter also includes pedigree history for the PLD test batch and Glaxo SmithKline RLD batch 14347 for Pivotal BE study AJ-1403 to support ANDA207868 Nicotine Polacrilex lozenge, 2 mg and 4 mg.

"*The CRL identified a deficiency related to the fact that the retained samples for the bioequivalence ("BE") studies were not properly maintained by the contract laboratory Phase One Solutions, Inc. Miami Gardens, Florida, that conducted the studies, (pivotal Study No. AJ-1403) and pilot Study No. AJ-1401). While Phase One Solutions ceased operations, in the interim, Phase One Solutions made arrangements with another company to temporarily maintain the samples at another secured, climate controlled location, in* (b) (4)*, until Phase One Solutions or a successor company resumed operations. Unfortunately, the company who accepted responsibility for maintaining the retained BE samples, without informing PLD, destroyed the BE samples and did not provide PLD with a certificate of destruction.*

PLD has in its controlled access, environmentally-controlled and monitored facility, samples of the test and reference products, Nicotine Polacrilex Lozenge, 4 mg, Lot No.

(b) (4)

[5] ANDA 207868, View EDR: Package of Post-CR meeting request, dated 07/28/2017; \\cdsesub1\evsprod\anda207868\0011\m1\us\1-2-cover-letters\cover-letter-0011-07282017.pdf.

BP033725 and Nicorette Mini Lozenge 4 mg, Lot 14347, respectively, that were used in the BE studies. Although the retained samples at the CRO were not maintained, the samples were hand delivered by PLD from its facility. Documentation of the change of custody is enclosed as noted below. Given that samples from the lots of products used in the BE studies were continuously in PLD's possession in a well-controlled and secured facility, we believe PLD meets the requirement to maintain reliable and secure representative samples from the BE study.

The intent of the requiring the retention of samples used in BE studies is to ensure that the reserve samples are representative of the batches provided by the drug manufacturer for the testing and to deter possible bias and fraud. In view of the extensive documentation provided as exhibits to this letter and the fact that PLD has actual samples of the test and reference products, Nicotine Polacrilex Lozenge, 4 mg, Lot No. BP033725 and Nicorette Mini Lozenge 4 mg, Lot 14347, respectively, that were used in the BE studies, PLD firmly believes that adequate evidence exists for the Agency to conclude that the products used in the BE studies tested are representative of the batches provided for testing and that the BE studies can be relied upon to support approval of ANDA 207868.

On behalf of PLD, I respectfully request that the Agency review the enclosed documentation, reverse the deficiency identified in the CRL that relates to the retained samples so that the BE studies can be relied up to support approval of ANDA 207868."

DBIII's Response:

As we previously communicated to you in our CR letter dated 07/14/2017, you failed to meet the regulatory requirements for retention of reserve samples [21 CFR 320.38 and 320.63] for your *in vivo* fasting BE studies of the current application, ANDA 207868. Based on 21 CFR 320.38 and 320.63, samples should be retained and stored at study site, or at independent third party site. In the absence of reserve samples at the study site or an independent third party site, the authenticity of the test and reference drug products used in the studies cannot be assured. Therefore, the data from your current pivotal (Study No. AJ-1403) and pilot (Study No. AJ-1401) BE studies are not acceptable.

Please be advised to repeat your pivotal fasting BE study using unexpired batches of the test and reference products. Please refer to draft guidance on Nicotine Polacrilex Lozenge for details (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240974.pdf; Recommended Jan 2011). Please note that sufficient quantities of the drug products used in the study should be retained as per FDA Guidance for Industry: Handling and Retention of BA and BE Testing Samples (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf; May 2004).

Outcome Page

Completed Assignment for 207868 ID: 32269

Reviewer: Zhang, Yi **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence III

Description: Response to Post-CR meeting request for ANDA 207868 (Sample retention), Nicotine Polacrilex Mini Lozenges

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
32269	7/28/2017	BIO	Post CR Meeting Request Review [1]	1	1
32269	7/28/2017	Parallel	Post CR Meeting Request [1]	1	1
32269	9/12/2017	BIOQUALITY	Quality Assessment [1-5]	4	4
				Total:	6

List of Deficiencies for Complete Response # 2

A. Drug Product Deficiencies

1. The Division of Biopharmaceutics has recommended new dissolution acceptance criteria. If you accept the new dissolution acceptance criteria, please revise and submit updated release and stability specification.

2. The Division of Bioequivalence has considered your bioequivalence studies unacceptable. If new batches are manufactured to address Bioequivalence deficiencies, please provide quality information (certificate of analysis for raw materials and finished product, executed batch record, and stability data) pertinent to the new batches.

B. Biopharmaceutics Deficiencies

1. Your proposed acceptance criteria are too liberal. The following acceptance criteria are recommended based on the dissolution data submitted:

Time in minutes	% Release
30	Between (b) (4) %
60	Between (b) (4) %
180	Not less than (b) (4) %

We request that you acknowledge your acceptance of the recommended dissolution acceptance criteria. Implement the recommended dissolution acceptance criteria for the proposed drug product, and provide the revised specifications table with the updated acceptance criterion for the dissolution test.

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name and Date:

Suhas Patankar

Digitally signed by Suhas Patankar
Date: 7/11/2017 09:41:48AM
GUID: 508da70600028a4abf9ab8b19093cd0d

M E M O R A N D U M

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

DATE: February 10, 2017

TO: Dale P. Conner, Pharm.D.
Acting Director
Office of Bioequivalence
Office of Generic Drugs

FROM: Melkamu Getie-Kebtie, R.Ph., Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Elise A. Murphy
Acting Deputy Division Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of clinical establishment inspection report (EIR), covering ANDA (b) (4) (b) (4) ANDA 207868, Nicotine Polacrilex Mini Lozenge, sponsored by Avema Pharma Solutions, Inc.

Inspection summary:

The Office of Study Integrity and Surveillance (OSIS) arranged for an inspection of the following clinical studies (b) (4) (b) (4) and AJ-1403 (ANDA 207868) conducted by Phase One Solutions, Inc., Miami Gardens, FL. Because the firm is out-of-business, study records were audited at the (b) (4) (b) (4) At the conclusion of the inspection, four observations were issued on Form FDA 483.

The ORA investigators recommended an OAI classification for the inspection. However, following discussions between OSIS and the Office of Scientific Investigations, it was determined that the Form FDA 483 observations did not warrant an OAI classification for the site.

This reviewer recommends that data from the clinical portions of studies (b) (4) are unacceptable for further Agency review because FDA could not

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

REQUEST FOR CONSULTATION

TO (Division/Office):
Daiva Shetty, M.D.,
Acting Director, Division of Clinical Review
Office of Bioequivalence
Office of Generic drugs

FROM:
Yi Zhang, Ph.D., Reviewer, DBIII/Team 36
Through
Nilufer Tampal, Ph.D.
Acting Director, Division of Bioequivalence III (DBIII)
Office of Bioequivalence
Office of Generic Drugs

DATE	IND NO.	ANDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 18, 2016	N/A	207868	Consult	December 2, 2015 (Original) October 26, 2016 (ECD response)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nicotine Polacrilex Mini Lozenges, EQ 2 mg Base and EQ 4 mg Base	High	Smoking Cessation Therapeutic Agent	**01/06/2016** **(TAD of the ANDA: 02/20/2017)**

NAME OF FIRM: PLD Acquisitions LLC, D/B/A Avema Pharma Solutions

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): Original ANDA

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

Introduction:

On June 19, 2014, the firm, PLD Acquisitions LLC, D/B/A Avema Pharma Solutions, submitted an abbreviated new drug application (ANDA) for Nicotine Polacrilex Mini Lozenges, 2mg and 4 mg. The application was refused to received (RTR) due to incomplete information and was subsequently accepted for filing on December 2, 2015. As per the current product specific guidance[1], the original submission contained the results of an *in vivo* fasting bioequivalence (BE) study (Study No. AJ1403) comparing it's test product, Nicotine Polacrilex Mini Lozenges, 4 mg, to the corresponding reference product, GlaxoSmithKline Consumer Healthcare's Nicorette® Mini Lozenge, 4 mg [NDA 022360, approved on 05/18/2009; Over the Counter (OTC)][2], along with a waiver request for the 2 mg strength. Upon the initial BE review, the only deficiency identified during the full ANDA review (***Attachment 1***) by the Division of Bioequivalence III (DBIII) was related to the proposed maximum daily intake (MDI) amounts of the following three inactive ingredients: Sodium Stearyl Fumarate, Maltodextrin, and Talc, in the test formulation. The individual amounts for all three of the inactive ingredients exceeded the inactive ingredients limits (IIG) limits for the troche/lozenge, buccal or sublingual route of administration. Please see information below for details.

Issue Details:

As per the RLD labeling for Nicorette®, the directions state "*Do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day*"[3] for both strengths of the drug product. Therefore, based on the MDD (20 lozenges/per day), the amounts of the three inactive ingredients in test products are as follows:

Inactive ingredient(s)	Unit amount (mg per unit) in 2 mg or 4 mg strength test products	Proposed MDI (mg) based on MDD for Nicotine Polacrilex Lozenges (× 20 units)	Maximum level (mg) listed in the FDA IIG database for Approved Drug Products with the same route of	Ref. No/Note
Sodium Stearyl Fumarate	(b) (4)			
Maltodextrin(1)				
Talc				

(b) (4)

[1] FDA Product-Specific Recommendations for Generic Drug Development, http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240974.pdf; Recommended Jan 2011. Last accessed: 11/14/2016.

[2] Electronic Orange Book (Updated Through 06/2016): http://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=022360#; Search Term: NDA 022360.

[3] Labeling and clinical pharmacology (online database), https://dailymed nlm nih.gov/dailymed/drugInfo.cfm?setid=991704ed-781a-489b-8b56-0b558e8fc385 (Updated: 06/07/2016); Search Term: Nicorette®.

amounts of Sodium Stearyl Fumarate, Maltodextrin, and Talc present in the test formulation would not significantly compromise the safety and/or efficacy of the test drug product (***Attachment 2***).

On 09/13/2016, the firm submitted an email inquiry to the DBIII regarding the issued ECD request (***Attachment 3***). In preparing a response to the firm's inquiry, the BE review team informally consulted the Pharm/Tox team in the Division of Clinical Review (DCR) (***Attachment 4***). However, this information was not communicated to the applicant, due to the recommendations put forth by DBIII management and Regulatory Project Manager (RPM) in OGD that "*We will not process or review a partial response. Facsimile or e-mail responses will not be accepted*"[4].

On 10/26/2016, the firm submitted a complete response to the above deficiency comment made by DBIII (***Attachment 5***). However, the firm's justification is based on the usage of the oral route of administration (e.g., oral routes via digestive track) for calculation of the MDI and IIG limits. In addition, the firm incorrectly calculated the maximal MDI from approved drug products based on the equation provided in its response. Also, the firm provided supportive documents, including a summary of "*Nonclinical Information Amendment*" along with additional clinical/research literatures and reports in Module 1.11.2 (***Attachment 6 and 7***), and claimed that *"the amounts of Sodium Stearyl Fumarate, Maltodextrin, and Talc present in our test formulation would not significantly compromise the safety and/or efficacy of our test drug product."*

Consult Request:

DBIII seeks your expert opinion/advice for the evaluation of the safety and toxicity and overall acceptability of the firm's formulations of Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg based on the route of administration for the excipients: Sodium Stearyl Fumarate, Maltodextrin and Talc. Please comment on the following question:

Is there any safety concern and/or clinical significance on the proposed MDI levels of Sodium Stearyl Fumarate (b) (4) Maltodextrin (b) (4) and Talc (b) (4) based on the MDD of this drug (up to 20 lozenges per day), by the troche/lozenge, buccal or sublingual route(s) of administration used in the test formulation for the Nicotine Polacrilex Mini Lozenges, 2 mg and 4 mg?

Attachments:

1) ***Attachment 1***: DBIII BE review document can be found at:
http://panorama fda.gov/task/view?ID=566154ac0141beee6e16a23c11cb43fa

A207868N000DB_N1 2022015.docx

2) ***Attachment 2***: DBIII ECD request (Date: 09/12/2016):
http://panorama fda.gov/task/view?ID=57d75f910141f3c9ad5691ff7370fbb6

A207868N000DB_ECD 08312016.docx

3) ***Attachment 3***: The firm's email inquiry to ECD request (Reference#10140263; Date: 09/13/2016)
http://panorama fda.gov/issue/view?ID=57d8498d014bbe515990013d8297e7d3

[4] GDRP/Panorama for ANDA-207868-ORIG-1-RESUB-3, ECD extension (http://panorama fda.gov/task/view?ID=58065659001fbe9e5cb8bec83e888097&activeTab=list-task-documents; Linda Park) Date uploaded: 10/18/2016.

Firm's Email Inquiry.docx

4) ***Attachment 4***: E-mail communication between DBIII and DCR (Not to be released under FOIA)

RE MDI limit of IIGs for Nicotine Polacrilex

5) ***Attachment 5***: The firm's response to ECD request (Supp. Document #8; Date: 10/26/2016):
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-2-cover-letters\cover-letter-0007-10262016.pdf

cover-letter-0007-10262016.pdf

6) ***Attachment 6***: Summary Report of "*Nonclinical Information Amendment*" provided in the current response:
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\1112-safety-amendment.pdf

1112-safety-amendment.pdf

7) ***Attachment 7***: Several clinical/research literatures/reports and other supportive documents were provided in Module 1.11.2:
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\bergfeld-2012cir.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\fda-scogs-61.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\freers-2012.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\hajiar-1992-epa-talc.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\kibbe-2012.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\moreton-2012.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\nicorettepi20160609.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\robert-iser-2013.pdf
\\cdsesub1\evsprod\anda207868\0007\m1\us\1-11-information-amendment\1-11-2-safety-information-amendment\spectrum-msds.pdf

Thank you for your consideration. Please address comments/questions to Nilufer.Tampal@fda hhs.gov

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs/Office of Bioequivalence/Division of Bioequivalence III (DBIII)

Memorandum

Date: September 21, 2016

From: Yi Zhang, Ph.D. (Primary Reviewer)
Li Gong, Ph.D. (Secondary Reviewer)
April Braddy, Ph.D. (Tertiary Reviewer)
DBIII Reviewers

Through: Nilufer M. Tampal, Ph.D.
Director (Acting),
DBIII/OB/OGD

To: Mehul Govani, Regulatory Affairs Manager
PLD Acquisitions LLC, D/B/A Avema Pharma Solutions

Subject: Email Inquiry about BE ECD (date sent: 9/12/16) for ANDA 207868
Date of request: 09/13/2016

Subject of Request:

Questions regarding the limits of maximum daily intake (MDI) of three inactive ingredients (Sodium stearyl fumarate, maltodextrin and talc) in DBIII's Easily Correctable Deficiencies (ECD) Bioequivalence reference# 10140263

Applicant: PLD Acquisitions LLC, D/B/A Avema Pharma Solutions

Application# & DP: ANDA 207868, Nicotine Polacrilex Mini Lozenges

Bioequivalence (DBIII) Reviewer Response:

On September 13, 2016, you submitted an email inquiry to the Division of Bioequivalence III (DBIII)'s Easily Correctable Deficiency (ECD) dated 09/12/2016 (Reference# 10140263) for your application, ANDA 207868, regarding the three inactive ingredients (i.e., Sodium Stearyl Fumarate, Maltodextrin, and Talc) present in your test formulations exceeding the Inactive Ingredient Database (IID) limits based on data available on FDA's public IID database and maximum daily intake (MDI).

In your above email inquiry, you referred to the value of "*Amount per dosage unit*" listed in the current FDA's public IID database to the "*Maximum potency*" of each inactive ingredient for your proposed generic drug product. However, as per the Agency's current practice, listed levels in the IID database are used for safety purposes, and should be used to justify on the basis of the amount of MDI per the RLD label of each individual inactive ingredient in the test formulation with the same route of administration, rather than on each unit amount only.

As we previously communicated to you in our ECD letter dated 09/12/2016, the MDI levels of Sodium Stearyl Fumarate, Maltodextrin, and Talc (b) (4), respectively) present in your test formulation exceed the daily intake levels of the corresponding inactive ingredients in the FDA-approved drug products for the same route of administration. Based on the administration route of the lozenges, the justification of IID levels should use troche/lozenge, buccal or sublingual routes, since these dosage forms are all dissolved in the mouth, other than passing through down to the digestive track. Therefore, your justification using other orally administered dosage forms (e.g., oral routes via digestive track) for the lozenge is not acceptable unless appropriate supportive data/safety information are provided. Thus, the usage of the oral route of administration is not acceptable.

Furthermore, your calculation method to determine the MDI is incorrect. It should be calculated as follows:

> MDI = Amount of each inactive ingredient/dosage unit (test product), adjusted with maximum daily dose (MDD; per RLD label).

Based on the above information, the safety of the excipients (i.e., Sodium Stearyl Fumarate, Maltodextrin, and Talc) for the buccal route of administration warrants further safety evaluation. Therefore, please provide information to facilitate our assessment which will focus on the safety of these excipients for the proposed dose, buccal route, and duration of use for this specific patient population. Please submit safety information to characterize the potential for local toxicity of the oral mucosa. Safety information may be based on prior approved drugs with a similar context of use, prior evidence of human exposure, and nonclinical information to support the general toxicity and genetic toxicity of the proposed excipients. If citing published literature, please provide a copy of the cited article.

Attachment 1: **Firm's Email Inquiry dated 09/13/2016**

Hello Linda,

We have some questions regarding Easily correctable deficiency Bioequivalence reference# 10140263.

The deficiency talks about 3 inactive ingredients (Sodium stearyl fumarate, maltodextrin and talc) exceeding the Maximum daily intake (MDI). Based on the FDA guidance "ANDA submissions- Refuse to receive standards"

Applicants can justify inactive ingredient levels by reference to the IID, which is a listing of inactive ingredients and their maximum levels of use (per dosage unit or percent composition), arranged by either route of administration or dosage form

(b) (4)

Please let us know if the above explanation satisfies your concerns.

Thanks,
Mehul

Mehul Govani, Regulatory Affairs Manager
PL Developments | http://www.PLDevelopments.com

w|516-986-1700 (b) (6)
email| mgovani@pldevelopments.com
609-2 Cantiague Rock Road | Westbury, NY | 11590

Attachment 2: **DBIII's ECD letter dated 9/12/2016**

The deficiency below represents *EASILY CORRECTABLE DEFICIENCY* identified during the full ANDA review and the current ANDA review cycle will remain open. The following comment/deficiency with respect to the inactive ingredients in the formulation exceeding the IIG limits should be communicated to the firm via a Division of Bioequivalence III (DBIII)'s ECD request.

1 (b) (4)

However, as per the approved reference listed drug (RLD) labeling for Nicorette® (nicotine polacrilex) Mini Lozenges, the patient should be advised to "*place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 - 30 minutes). Minimize swallowing. Do not chew or swallow lozenge*". Therefore, the maximum daily intake (MDI) of each excipient present in the test product formulation should be calculated based on the same route of administration (e.g. troche/lozenge, buccal or sublingual).

The MDI levels of the respective Sodium Stearyl Fumarate, Maltodextrin, and Talc present in your test formulation were (b) (4) respectively, and they exceed the maximum amounts listed in the FDA's Inactive Ingredient Guide (IIG) based on the maximum daily dose (MDD) of 20 lozenges for Nicotine Polacrilex Mini Lozenges intended for the above said route of administration. Therefore, please provide your justification along with supportive data that the amounts of Sodium Stearyl Fumarate, Maltodextrin, and Talc present in your test formulation would not significantly compromise the safety and/or efficacy of your test drug product.

(b) (4)


(b) (4)

Outcome Page

Review Response for Email Inquiry Reference# 10153680

Completed Assignment for 10153680 ID: 29055

Reviewer: Zhang, Yi **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence III

Description: Review Response for Email Inquiry for ANDA 207868, Nicotine Polacrilex Mini Lozenges

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
29055	9/13/2016	BIO	Consult Review (For Consults to DBs) [1]	1	1
29055	9/13/2016	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1
29055	9/20/2016	BIOQUALITY	Quality Assessment [1-5]	5	5
				Total:	7