CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 076880

Name: Nicotine Polacrilex Gum USP, 2 mg (base) (Original Flavor)

Sponsor: IVAX Pharmaceuticals Inc.

Approval Date: February 18, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076880

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076880

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 76-880

IVAX Pharmaceuticals Inc.
Attention: Patricia Jaworski
Sr. Director, Regulatory Affairs
Two University Plaza, Suite 220
Hackensack, NJ 07601

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated October 23, 2003, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Nicotine Polacrilex Gum USP, 2 mg (base) (Original Flavor).

Reference is also made to your amendments dated March 16, March 19, May 16, and September 27, 2007; and September 12 (2 submissions), October 13, October 31, and November 13, 2008.

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 use as recommended in the submitted over-the-counter (OTC) labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Nicotine Polacrilex Gum USP, 2 mg (base) (Original Flavor) to be bioequivalent to the reference listed drug, Nicorette Gum, 2 mg (base) (Original Flavor), of GlaxoSmithKline. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as ***"Miscellaneous Correspondence – SPL for Approved ANDA 76-880"***.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Robert L. West
2/18/2009 02:21:13 PM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076880

LABELING

NDC 0172-6730-00

NICOTINE POLACRILEX GUM USP

2 mg (nicotine)

Peppermint

1 piece

KEEP OUT OF REACH OF CHILDREN

Mfd for: Ivax Pharmaceuticals, Inc.

Miami, FL 33137 0108A

Made in Uruguay

Lot: Exp.

NDC 0172-6730-00
NICOTINE POLACRILEX GUM USP
2 mg (nicotine)
Peppermint
1 piece
KEEP OUT OF REACH OF CHILDREN
Mfd for: Ivax Pharmaceuticals, Inc.
Miami, FL 33137 0108A
Made in Uruguay
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Drug Facts

Active ingredient (in each chewing piece)	***Purpose***
Nicotine polacrilex (equal to 2 mg nicotine)	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.

Do not use
- if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing products.

Ask a doctor before use 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 blood pressure.
- stomach ulcer or diabetes.

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, teeth or jaw problems occur.
- irregular heartbeat or palpitations occur.
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat.

Keep out of reach of children and pets. Pieces of nicotine gum may have enough nicotine to make children and pets sick. Wrap used pieces of gum 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**
- before using this product, read the enclosed User's Guide for complete directions and other important information
- stop smoking completely when you begin using the gum
- **if you smoke less than 25 cigarettes a day;** use 2 mg nicotine gum
- **if you smoke 25 or more cigarettes a day;** use according to the following 12 week schedule:

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

- nicotine gum is a medicine and must be used a certain way to get the best results
- chew the gum slowly until it tingles. Then park it between your cheek and gum. When the tingle is gone, begin chewing again, until the tingle returns.
- repeat this process until most of the tingle is gone (about 30 minutes)
- do not eat or drink for 15 minutes before chewing the nicotine gum, or while chewing a piece
- to improve your chances of quitting, use at least 9 pieces per day for the first 6 weeks
- if you experience strong or frequent cravings, you may use a second piece within the hour. However, do not continuously use one piece after another since this may cause you hiccups, heartburn, nausea or other side effects.
- do not use more than 24 pieces a day
- it is important to complete treatment. Stop using the nicotine gum at the end of 12 weeks. If you still feel the need to use nicotine gum, talk to your doctor.

Other Information **• each piece contains:** calcium 61 mg, sodium 6.84 mg
- Store at 20°-25°C (68°-77°F) • Protect from light

Inactive Ingredients corn starch, gum base, noncrystallizing sorbitol solution, peppermint oil, sodium bicarbonate, sorbitol

Questions or comments call IVAX Pharmaceuticals, Inc. Medical Affairs Department at 1-888-838-2872 weekdays (8:30 a.m.-5:00 p.m. EST).

PLACE ANTI-THEFT STICKER HERE

THEFT SURVEILLANCE TAG AREA

EAS Tagged

3 0172-6730-272

NICOTINE POLACRILEX GUM USP

2 mg

(nicotine)

Peppermint

NICOTINE POLACRILEX GUM USP

2 mg

(nicotine)

Peppermint

This product is protected in sealed blisters. **Do not use if individual blisters or printed backings are broken, open or torn.**

- **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**

Lot:

Exp.

IVAX Pharmaceuticals, Inc. NDC 0172-6730-27

Compare to the active ingredient in Nicorette®*

NICOTINE POLACRILEX GUM USP

Peppermint

2 mg

(nicotine)

Stop Smoking Aid

For those who smoke **less than** 25 cigarettes a day

If you smoke 25 or more cigarettes a day: use nicotine polacrilex gum USP 4 mg

108 pieces, 2 mg each

Free Audio CD upon request. See inside.

To remove the gum, tear off single unit.

Peel off backing starting at corner with loose edge.

Push gum through foil.

TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to quit.
2. **Use Enough** - Chew **at least 9 pieces** of nicotine polacrilex gum per day during the first six weeks.
3. **Use Long Enough** - use nicotine polacrilex gum for the full 12 weeks.
4. **Use with a support program** as directed in the enclosed User's Guide.

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

Manufactured for
Ivax Pharmaceuticals, Inc.
Miami, FL 33137
by: Laboratorios Haymann SA
Montevideo, Uruguay

Made in Uruguay

0108A

Nicotine Polacrilex Gum USP

2 mg and 4 mg User's Guide

HOW TO USE NICOTINE POLACRILEX GUM TO HELP YOU QUIT SMOKING

KEYS TO SUCCESS

1. You must really want to quit smoking for **nicotine polacrilex gum** to help you.
2. You can greatly increase your chances for success by using at least 9 to 12 pieces every day when you start using **nicotine polacrilex gum**. See page 12 for details.
3. You should continue to use **nicotine polacrilex gum** as explained in the User's Guide for 12 full weeks.
4. **Nicotine polacrilex gum** works best when used together with a support program - See page 3 for details.
5. If you have trouble using **nicotine polacrilex gum**, ask your doctor or pharmacist or call the IVAX Pharmaceuticals, Inc. Medical Affairs Department at 1-888-838-2872 weekdays (8:30 a.m. – 5:00 p.m. EST).
6. To request a free audio CD containing tips to help make quitting easier, call the toll free number listed above. (ONE CD PER CUSTOMER)

- **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 for
Ivax Pharmaceuticals, Inc.
Miami, FL 33137
by: Laboratorios Haymann S.A.
Montevideo, Uruguay

0172
01/08
B1

Made in Uruguay

SO YOU DECIDED TO QUIT

Congratulations. Your decision to stop smoking is an important one. That's why you've made the right choice in choosing **nicotine polacrilex gum**. Your own chances of quitting smoking depend on how much you want to quit, how strongly you are addicted to tobacco, and how closely you follow a quitting program like the one that comes with **nicotine polacrilex gum**.

QUITTING SMOKING IS HARD!

If you've tried to quit before and haven't succeeded, don't be discouraged! Quitting isn't easy. It takes time, and most people try a few times before they are successful. The important thing is to try again until you succeed. This User's Guide will give you support as you become a non-smoker. It will answer common questions about **nicotine polacrilex gum** and give tips to help you stop smoking, and should be referred to often.

WHERE TO GET HELP

You are more likely to stop smoking by using **nicotine polacrilex gum** with a support program that helps you break your smoking habit. 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.

If you find you cannot stop smoking or if you start smoking again after using **nicotine polacrilex gum**, remember breaking this addiction doesn't happen overnight. You may want to talk to a health care professional who can help you improve your chances of quitting the next time you try **nicotine polacrilex gum** or another method.

LET'S GET ORGANIZED

Your reason for quitting may be a combination of concerns about health, the effect of smoking on your appearance, and pressure from your family and friends to stop smoking.

Or maybe you're concerned about the dangerous effect of second-hand smoke on the people you care about. All of these are good reasons. You probably have others. Decide your most important reasons, and write them down on the wallet card in your kit. Carry this card with you. In difficult moments, when you want to smoke, the card will remind you why you are quitting.

WHAT YOU'RE UP AGAINST

Smoking is addictive in two ways. Your need for nicotine has become both physical and mental. You must overcome both addictions to stop smoking. So while **nicotine polacrilex gum** will lessen your body's physical addiction to nicotine, you've got to want to quit smoking to overcome the mental dependence on cigarettes. Once you've decided that you're going to quit, it's time to get started. But first, there are some important warnings you should consider.

SOME 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.

Do not use

- if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing products.

Ask a doctor before use 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 use if you are

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

Stop use and ask a doctor if

- mouth, teeth or jaw problems occur.
- irregular heartbeat or palpitations occur.
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat.

Keep out of reach of children and pets. Pieces of nicotine gum may have enough nicotine to make children and pets sick. Wrap used pieces of gum in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

LET'S GET STARTED

Becoming a non-smoker starts today. First, check that you bought the right starting dose.

If you smoke 25 or more cigarettes a day, use 4 mg nicotine gum. **If you smoke less than 25 cigarettes a day,** use 2 mg nicotine gum.

Next, read through the entire User's Guide carefully. Then, set your personalized quitting schedule. Take out a calendar that you can use to track your progress, and identify four dates, using the stickers in the center of the User's Guide.

STEP 1 (weeks 1 through 6): Your quit date (and the day you'll start using nicotine polacrilex gum).

Choose your quit date (it should be soon). This is the day you will quit smoking cigarettes entirely and begin using **nicotine polacrilex gum** to satisfy your cravings for nicotine. For the first six weeks, you'll use a piece of **nicotine polacrilex gum** every hour or two. Be sure to follow the directions in the User's Guide. Place the Step 1 sticker on this date.

STEP 2 (weeks 7 through 9): The day you'll start reducing your use of nicotine polacrilex gum.

After six weeks, you'll begin gradually reducing your **nicotine polacrilex gum** usage to one piece every two to four hours. Place the Step 2 sticker on this date (the first day of week seven).

STEP 3 (weeks 10 through 12): The day you'll further reduce your use of nicotine polacrilex gum.

Nine weeks after you begin using **nicotine polacrilex gum,** you will further reduce your nicotine intake by using one piece every four to eight hours. Place the Step 3 sticker on this date (the first day of week ten). For the next three weeks, you'll use a piece of **nicotine polacrilex gum** every four to eight hours.

End of treatment: The day you'll complete nicotine polacrilex gum therapy.
Nicotine polacrilex gum should not be used for longer than twelve weeks. Identify the date thirteen weeks after the date you chose in Step 1 and place the "EX-SMOKER" sticker on your calendar.

PLAN AHEAD

Because smoking is an addiction, it is not easy to stop. After you've given up cigarettes, you will still have a strong urge to smoke. Plan ahead NOW for these times, so you're not defeated in a moment of weakness. The following tips may help:

- Keep the phone numbers of supportive friends and family members handy.
- Keep a record of your quitting process. Track the number of **nicotine polacrilex gum** pieces you use each day, and whether you feel a craving for cigarettes. In the event that you slip, immediately stop smoking and resume your quit attempt with the **nicotine polacrilex gum** program.
- Put together an Emergency Kit that includes items that will help take your mind off occasional urges to smoke. Include cinnamon gum or lemon drops to suck on, a relaxing CD, and something for your hands to play with, like a smooth rock, rubber band, or small metal balls.

- Set aside some small rewards, like a new magazine or a gift certificate from your favorite store, which you'll 'give' yourself after passing difficult hurdles.
- Think now about the times when you most often want a cigarette, and then plan what else you might do instead of smoking. For instance, you might plan to take your coffee break in a new location, or take a walk right after dinner, so you won't be tempted to smoke.

HOW NICOTINE POLACRILEX GUM WORKS

Nicotine polacrilex gum's sugar-free chewing pieces provide nicotine to your system - they work as a temporary aid to help you quit smoking by reducing nicotine withdrawal symptoms. **Nicotine polacrilex gum** provides a lower level of nicotine to your blood than cigarettes, and allows you to gradually do away with your body's need for nicotine. Because **nicotine polacrilex gum** does not contain the tar or carbon monoxide of cigarette smoke, it does not have the same health dangers as tobacco. However, it still delivers nicotine, the addictive part of cigarette smoke. Nicotine can cause side effects such as headache, nausea, upset stomach and dizziness.

HOW TO USE NICOTINE POLACRILEX GUM

If you are under 18 years of age, ask a doctor before use. Before you can use **nicotine polacrilex gum** correctly, you have to practice! That sounds silly, but it isn't. **Nicotine polacrilex gum isn't like ordinary chewing gum.** It's a medicine, and must be chewed a certain way to work right. Chewed like ordinary gum, **nicotine**

polacrilex gum won't work well and can cause side effects. An overdose can occur if you chew more than one piece of **nicotine polacrilex gum** at the same time, or if you chew many pieces one after another. Read all the following instructions before using **nicotine polacrilex gum.** Refer to them often to make sure you're using **nicotine polacrilex gum** correctly. If you chew too fast, or do not chew correctly, you may get hiccups, heartburn, or other stomach problems. Don't eat or drink for 15 minutes before using **nicotine polacrilex gum** or while chewing a piece. The effectiveness of **nicotine polacrilex gum**

may be reduced by some foods and drinks, such as coffee, juices, wine or soft drinks.

1. Stop smoking completely before you start using **nicotine polacrilex gum**.
2. To reduce craving and other withdrawal symptoms, use **nicotine polacrilex gum** according to the dosage schedule on page 12.
3. Chew each **nicotine polacrilex gum** piece very slowly several times.
4. Stop chewing when you notice a peppery taste, or a slight tingling in your mouth. (This usually happens after about 15 chews, but may vary from person to person.)
5. Park the **nicotine polacrilex gum** piece between your cheek and gum and leave it there.
6. When the peppery taste or tingle is almost gone (in about a minute), start to chew a few times slowly again. When the taste or tingle returns, stop again.
7. Park the **nicotine polacrilex gum** piece again (in a different place in your mouth).
8. Repeat steps 3 to 7 (chew, chew, park) until most of the nicotine is gone from the **nicotine polacrilex gum** piece (usually happens in about half an hour; the peppery taste or tingle won't return).
9. Wrap the used **nicotine polacrilex gum** piece in paper and throw away in the trash.

The following chart outlines the recommended dosage schedule for **nicotine polacrilex gum**:		
Weeks 1 to 6	**Weeks 7 to 9**	**Weeks 10 to 12**
1 piece every 1 to 2 hours	1 piece every 2 to 4 hours	1 piece every 4 to 8 hours
DO NOT USE MORE THAN 24 PIECES PER DAY		

To improve your chances of quitting, use at least 9 pieces of **nicotine polacrilex gum** a day. If you experience strong or frequent cravings, you may use a second piece within the hour.

However, do not continuously use one piece after another, since this may cause you hiccups, heartburn, nausea, or other side effects.

HOW TO REDUCE YOUR NICOTINE POLACRILEX GUM USAGE

The goal of using **nicotine polacrilex gum** is to slowly reduce your dependence on nicotine. The schedule for using **nicotine polacrilex gum** will help you reduce your nicotine craving gradually as you reduce and then stop your use of **nicotine polacrilex gum**. Here are some tips to help you cut back during each step and then stop using **nicotine polacrilex gum**:

- After a while, start chewing each **nicotine polacrilex gum** piece for only 10 to 15 minutes, instead of half an hour. Then, gradually begin to reduce the number of pieces used.
- Or, try chewing each piece for longer than half an hour, but reduce the number of pieces you use each day.
- Substitute ordinary chewing gum for some of the **nicotine polacrilex gum** pieces you would normally use. Increase the number of pieces of ordinary gum as you cut back on the **nicotine polacrilex gum** pieces.

- Check how well you've reduced your daily usage of **nicotine polacrilex gum** in Weeks 10 to 12. You should only be using about 3 to 5 pieces a day. Get ready to stop.

STOP USING NICOTINE POLACRILEX GUM AT THE END OF WEEK 12. The following tips may help you with stopping **nicotine polacrilex gum** at the end of 12 weeks.

- Set a stop date.
- Use the same number of pieces of confectionery gum or mints as you were using **nicotine polacrilex gum** per day.

At the times when you have an urge to use **nicotine polacrilex gum,** use a strong flavored gum or mint such as cinnamon or peppermint.

- Reduce the number of pieces of gum or mints you use by one piece per day until you do not need to use any gum or mints.

Talk to your doctor if you:

- still feel the need to use **nicotine polacrilex gum** at the end of week 12
- start using **nicotine polacrilex gum** again after stopping
- start smoking again

TIPS TO MAKE QUITTING EASIER

Within the first few weeks of giving up smoking, you may be tempted to smoke for pleasure, particularly after completing a difficult task, or at a party or bar. Here are some tips to help get you through the important first stages of becoming a non-smoker:

On your Quit Date:

- Ask your family, friends, and co-workers to support you in your efforts to stop smoking.
- Throw away all your cigarettes, matches, lighters, ashtrays, etc.
- Keep busy on your quit day. Exercise. Go to a movie. Take a walk. Get together with friends.

- Figure out how much money you'll save by not smoking. Most ex-smokers can save more than $1,000 a year.
- Write down what you will do with the money you save.

- Know your high-risk situations and plan ahead how you will deal with them.
- Keep **nicotine polacrilex gum** near your bed, so you'll be prepared for any nicotine cravings when you wake up in the morning.
- Visit your dentist and have your teeth cleaned to get rid of the tobacco stains.

Right after Quitting:

- During the first few days after you've stopped smoking, spend as much time as possible at places where smoking is not allowed.
- Drink large quantities of water and fruit juices.
- Try to avoid alcohol, coffee and other beverages you associate with smoking.
- Remember that temporary urges to smoke will pass, even if you don't smoke a cigarette.
- Keep your hands busy with something like a pencil or a paper clip.
- Find other activities which help you relax without cigarettes.
- Swim, jog, take a walk, play basketball.

- Don't worry too much about gaining weight. Watch what you eat, take time for daily exercise, and change your eating habits if you need to.
- Laughter helps. Watch or read something funny.

WHAT TO EXPECT Your body is now coming back into balance. During the first few days after you stop smoking, you might feel edgy and nervous and have trouble concentrating. You might get headaches, feel dizzy and a little out of sorts, feel sweaty or have stomach upsets. You might even have trouble sleeping at first. These are typical withdrawal symptoms that will go away with time. Your smoker's cough will get worse before it gets better. But don't worry, that's a good sign. Coughing helps clear the tar deposits out of your lungs.

After a Week or Two:
By now you should be feeling more confident that you can handle those smoking urges. Many of your withdrawal symptoms have left by now, and you should be noticing some positive signs: less coughing, better breathing and an improved sense of taste and smell, to name a few.

After a Month:
You probably have the urge to smoke much less often now. But urges may still occur, and when they do, they are likely to be powerful ones that come out of nowhere. Don't let them catch you off guard. Plan ahead for these difficult times.

Concentrate on the ways non-smokers are more attractive than smokers. Their skin is less likely to wrinkle. Their teeth are whiter, cleaner. Their breath is fresher. Their hair and clothes smell better. That cough that seems to make even a laugh sound more like a rattle is a thing of the past. Their children and others around them are healthier, too.

What To Do About Relapse:
What should you do if you slip and start smoking again? The answer is simple. A lapse of one or two or even a few cigarettes has not spoiled your efforts! Discard your cigarettes, forgive yourself and try again. If you start smoking again, keep your box of **nicotine polacrilex gum** for your next quit attempt.

If you have taken up regular smoking again, don't be discouraged. Research shows that the best thing you can do is to try again. The important thing is to learn from your last attempt.

- Admit that you've slipped, but don't treat yourself as a failure.
- Try to identify the `trigger' that caused you to slip, and prepare a better plan for dealing with this problem next time.
- Talk positively to yourself - tell yourself that you have learned something from this experience.
- Make sure you used **nicotine polacrilex gum** correctly over the full 12 weeks to reduce your craving for nicotine.
- Remember that it takes practice to do anything, and quitting smoking is no exception.

WHEN THE STRUGGLE IS OVER Once you've stopped smoking, take a second and pat yourself on the back. Now do it again. You deserve it. Remember now why you decided to stop smoking in the first place. Look at your list of reasons. Read them again. And smile. Now think about all the money you are saving and what you'll do with it. All the non-smoking places you can go, and what you might do there. All those years you may have added to your life, and what you'll do with them.

Remember that temptation may not be gone forever. However, the hard part is behind you, so look forward with a positive attitude, and enjoy your new life as a non-smoker.

QUESTIONS & ANSWERS

1. How will I feel when I stop smoking and start using nicotine polacrilex gum?

You'll need to prepare yourself for some nicotine withdrawal symptoms. These begin almost immediately after you stop smoking, and are usually at their worst during the first three to four days.

Understand that any of the following is possible:

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

Nicotine polacrilex gum can help provide relief from withdrawal symptoms such as irritability and nervousness, as well as the craving for nicotine you used to satisfy by having a cigarette.

2. Is nicotine polacrilex gum just substituting one form of nicotine for another?
Nicotine polacrilex gum does contain nicotine. The purpose of **nicotine polacrilex gum** is to provide you with enough nicotine to help control the physical withdrawal symptoms so you can deal with the mental aspects of quitting. During the 12-week program, you will gradually reduce your nicotine intake by switching to

fewer pieces each day. Remember, don't use **nicotine polacrilex gum** together with nicotine patches or other nicotine containing products.

3. Can I be hurt by using nicotine polacrilex gum?
For most adults, the amount of nicotine in the gum is less than from smoking. Some people will be sensitive to even this amount of nicotine and should not use this product without advice from their doctor (see page 5). Because **nicotine polacrilex gum** is a gum-based product, chewing it can cause dental fillings to loosen and aggravate other mouth, tooth and jaw problems. **Nicotine polacrilex gum** can also cause hiccups, heartburn and other stomach problems especially if chewed too quickly or not chewed correctly.

4. Will I gain weight?
Many people do tend to gain a few pounds in the first 8 to 10 weeks after they stop smoking. This is a very small price to pay for the enormous gains that you will make in your overall health and attractiveness. If you continue to gain weight after the first two months, try to analyze what you're doing differently. Reduce your fat intake, choose healthy snacks, and increase your physical activity to burn off the extra calories.

5. Is nicotine polacrilex gum more expensive than smoking?
The total cost of **nicotine polacrilex gum** for the twelve-week program is about equal to what a person who smokes one and a half packs of cigarettes a day would spend on cigarettes for the same period of time.

Also, use of **nicotine polacrilex gum** is only a short-term cost, while the cost of smoking is a long-term cost, because of the health problems smoking causes.

6. What if I slip up?
Discard your cigarettes, forgive yourself and then get back on track. Don't consider yourself a failure or punish yourself. In fact, people who have already tried to quit are more likely to be successful the next time.

GOOD LUCK!

Recommended Dosage Schedule for Nicotine Polacrilex Gum

STEP 1	STEP 2	STEP 3
Weeks 1 to 6	**Weeks 7 to 9**	**Weeks 10 to 12**
1 piece every	1 piece every	1 piece every
1 to 2 hours	2 to 4 hours	4 to 8 hours

Wallet Card

My most important reasons to quit smoking are:

_____

_____

_____

_____

_____

0108A

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

Step 1

1 piece every 1 to 2 hours

At the beginning of week #1 (Quit Date)

Step 2

1 piece every 1 to 2 hours

At the beginning of week #7

Step 3

1 piece every 1 to 2 hours

At the beginning of week #10

Step 4

an EX-SMOKER

12 weeks after quit date

CALENDAR STICKERS

(can be found in center of User's Guide)

At the beginning of
week #1 (Quit Date)

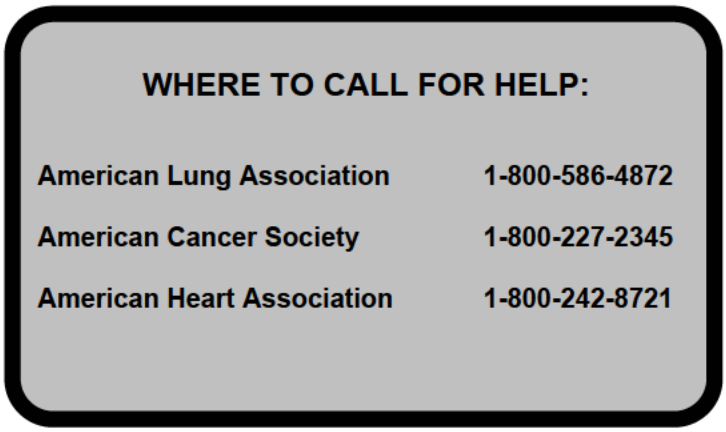
At the beginning of
week #7

At the beginning of
week #10

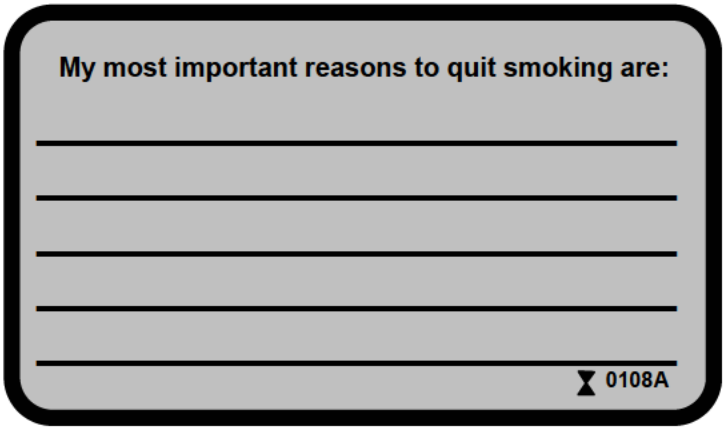
12 weeks after
quit date

(wallet card appears on back cover of user's guide)

Wallet Card (Front)



Wallet Card (Back)



Nicotine Polacrilex Gum USP
(CD Text)

Ivax Pharmaceutical's Inc.

CD TRACK 1

SFX: Sound of various voices from happy crowd.

ANNCR: Congratulations on your decision to become a non-smoker. This is one of the most important decisions you will ever make. And one of the best.

(VOICES: "Yeah! Right! Way to go!)

The nicotine polacrilex gum User's Guide and this CD are designed to help make it as easy as possible to break the habit. But keep in mind that this program won't work unless you are really committed to becoming a non-smoker. Maybe you tried before and failed. If so, don't be discouraged. Remember, lots of people make several tries before they succeed. This time, nicotine polacrilex gum will help relieve the physical symptoms of quitting, so you are better equipped to manage the mental part.

(VOICE: "Yeah – you can do it!")

Even though nicotine polacrilex gum is easy to use, it's not used like ordinary chewing gum. <u>It's serious medicine!</u> Like any medicine, you should use it only as directed. We'll get to the directions later, but you should also know that there are some people who shouldn't use nicotine polacrilex gum or any product containing nicotine without checking with their doctor; women who are pregnant or nursing, for example.

And anyone with a history of heart trouble, high blood pressure that can't be controlled with medication, takes insulin for diabetes or has a stomach ulcer should get medical advice first. Quitting smoking can also affect the way your body reacts to certain other medications you may be taking for asthma or depression – so - check with your doctor if any of these things apply to you.

Be sure to read the User's Guide that comes in this kit for other important information about using nicotine polacrilex gum.

Even though nicotine polacrilex gum contains nicotine, it doesn't contain any of the thousands of other harmful chemicals that are in cigarette smoke. And it's designed to get you off nicotine for good.

Support group. Adults. Group leader is authoritative, but pleasant woman. Among students are Older Woman (OW), Young Woman (YW), Young Man (YM), and cynical Older Man with gruff voice (OM).

(SFX: Murmurs, conversation. Leader taps on desk for attention.)

LEADER: All right everybody; quiet now, we're ready to start. This support group is all about how to use nicotine polacrilex gum to help you quit smoking.

OM: So who needs a support group? It's a chewing gum. You chew it. We might as well have to take a class on how to breathe.

LEADER: "How to Breathe" is Mr. Tanaka's group, down the hall. You'll be in that one later. But this comes first because nicotine polacrilex gum isn't ordinary chewing gum. You have to use it the right way or it won't work the way it's supposed to.

OM: Hey, chewing gum is kid stuff.

LEADER: But chewing nicotine polacrilex gum isn't. It's only for people who are at least 18 and who really want to quit smoking. Younger people should talk to a doctor first.

Okay, so let's begin. First, has everybody read the nicotine polacrilex gum User's Guide?

OW: I read it, yeah. It didn't take long and it made the whole quitting process a lot clearer to me.

LEADER: Right. There's nothing mysterious or complicated about it. But there's a right way to do it, and the only way you can expect to get the results you want is to use nicotine polacrilex gum the way it's supposed to be used.

Now, who remembers the very first instruction?

OW: Buy nicotine polacrilex gum?

LEADER: Well, actually, there's an even earlier step. Before using nicotine polacrilex gum you have to stop smoking – and I mean completely. That's important! And you mustn't chew tobacco or use snuff or nicotine patches either.

You start using nicotine polacrilex gum on the day you stop smoking, and you never smoke and use nicotine polacrilex gum together. That could give an overdose of nicotine, which is pretty powerful stuff. The results could make you sick.

YW: I know. Sometimes if I smoke two or three cigarettes in a row, like if I am nervous, I get dizzy.

LEADER: Sure. So the next question is: when are you going to stop? Has everybody picked a Quit Date?

OM: Yeah, I have. I have to attend a seminar on Monday, in a non-smoking building. I figure if nicotine polacrilex gum can get me through the first day, it'll be easier from then on.

LEADER: Not a bad idea. Just be careful, because when you walk out of the building, there's going to be a terrific desire to have a smoke, so you have to be prepared for that. The nicotine polacrilex gum User's Guide includes a list of tips for handling those temptations. Anybody else?

OW: Oh I'm going to quit as soon as possible. After I take today's classes I'm going to stop smoking. I already marked tomorrow on my calendar.

LEADER: Yeah, that's it. Pick a date and stick with it. How about you, miss?

YW: My cousin is visiting this weekend. I figured I'll be so busy showing her around, I won't have time to think about wanting to smoke! And if I am tempted to slip, she could talk me out of it.

LEADER: Actually, the idea of having support when you need it is a good one. A friend or a family member, maybe even a coworker, can provide moral support. Several national organizations offer support groups like this one – there's a list of their toll-free phone numbers in the nicotine polacrilex gum user's guide.

YM: So, the first step is to pick a Quit Date, and mark it on our calendar.

LEADER: Right. Now, we have to learn how to use nicotine polacrilex gum.

OM: What's the big deal about that?

LEADER: Well, as I said before, nicotine polacrilex gum isn't ordinary chewing gum, so you don't chew it the way you're used to. The big difference is that it contains nicotine, which you release by chewing it. The idea is to chew it so it releases the nicotine gradually – not too fast, not too slow.

OW: Oh, I know, I know – it was in the book. You chew it until you get a tingling feeling in your mouth. Then you <u>park</u> it between your cheek and your gum until the tingling feeling goes away. You keep it there until you don't get anymore tingling.

LEADER: Right again, first you chew, then you park. Then you chew, then you park. You do that until the zing is gone. It takes about 15 chews to develop the tingling, and it takes a minute or so for it to go away. So the method is to chew, park, chew, park. Let's all repeat that.

CLASS: (not quite together): Chew, park, chew, park, chew, park…

LEADER: Uh, pretty good, but let's do it together a little bit better. One more time – and a one, and a two, and a…

CLASS: (in unison): Chew, park, chew, park, chew, park, chew.

LEADER: OK, that's terrific!

OM: So when do we use this stuff? After meals, or what?

LEADER: The recommended schedule is a piece every hour or two while you're awake for the first six weeks. That's 8 to 16 pieces a day. You'll have the best chance of staying smoke-free if you use at least 9 pieces a day. If you experience strong or frequent cravings, you may use a second piece within the hour. However, do not continuously use one piece after another since this may cause you hiccups, heartburn, nausea and other side effects.

YM: So you mean if I start with 16 pieces a day, I have to use 16 pieces a day for six weeks?

LEADER: No. The idea is to cut down gradually on your body's need for nicotine. So if you start with 16 pieces a day, try to cut down after the first week to 14 pieces. After another week you may be able to cut down to 12. It would be ideal if you could get yourself down to 8 to 10 pieces a day by the end of the first six weeks.

OW: Well now, the book says to use a piece every two to four hours during weeks seven to nine. And the book also includes calendar stickers to mark week seven now, so we'll be reminded when to start decreasing the amount we use.

LEADER: Right.

OW: And the kit also includes calendar stickers to mark week seven now, so we'll be reminded when to start decreasing the amount we use.

LEADER: Yes it does. Again, the idea is to start with the recommended dosage, and to decrease it gradually, at a rate that you feel comfortable with. Then, for the last three weeks – that's weeks 10 through 12 – you should be able to get along with a piece every 4 to 8 hours. At the end of the 12 weeks you shouldn't need nicotine polacrilex gum any longer.

YW: It sounds pretty easy. Anything else we should know?

LEADER: Yes, if you have kids or pets at home make sure you throw away the used pieces of nicotine polacrilex gum safely. Wrap used pieces of gum in paper and throw away in the trash. There will still be some nicotine in used pieces of gum – enough to make children or small animals sick.

And – also some foods and drinks can make nicotine polacrilex gum less effective, so you shouldn't eat or drink for 15 minutes before using a piece. And you shouldn't drink anything while you're chewing. If you do, the nicotine polacrilex gum won't be able to do its job.

YW: Gee, all I have to do is use nicotine polacrilex gum the right way and I can kick my smoking habit?

YM: There's got to be more to it than that.

LEADER: Well, there is. Even though nicotine polacrilex gum helps with the physical part of your addiction to cigarettes, it can't deal with the mental part. For many people, mental addiction is the hardest part to fight.

But don't panic because lots of people make a few tries before they succeed. And there are some pretty effective techniques for dealing with the mental addiction and for boosting your willpower.

And that's the subject of you next support group right down the hall. In fact, it's just about to start so good luck to you all!

(People get up and begin shuffling out of the room.)

(END OF CD TRACK 1)

(CD TRACK 2)

(Music: Peaceful and soothing. Perhaps "space music" with vaguely oriental harmonies.)

Mr. Tanaka's classroom. The students have filed in, and are strangely quiet. (Music down.)

Mr. Tanaka has almost no accent, and speaks somewhat precisely in a soft voice that is reassuring and comforting.

TANAKA: Good afternoon. I notice that you are all rather quiet. That is because of the music. It is true that peaceful music brings a quiet and relaxed state of mind. *(Music stops)* One of the things you will see as you go through the program to end your smoking habit is that relaxation is important in relieving the mental stress you may feel.

But before we become too relaxed, I would like each of you to tell me your most important reason for wanting to quit. Let us begin with you, miss.

YW: Oh. Well, I guess I want to quit because I don't want to smell like smoke all the time. I put on this expensive perfume, but I still smell like smoke. Uh, I don't now because I haven't had a cigarette for a couple of hours while I'm in school here.

TANAKA: Things will smell even better to you after you have been off cigarettes for a while. Things will smell better and taste better. But that probably isn't your most important reason for quitting, sir.

YM: Oh, no. I want to quit basically because I figure it will be a lot better for my health. Right now, when I work out or play a little basketball I get winded pretty easy.

TANAKA: That's the best reason of all. You have all read the many reports that tie cigarette smoking to some serious diseases and health problems. As soon as you stop smoking, your risk of getting these diseases begins to decrease.

OW: Well, I'm quitting for my health too. But I also have my niece and her two children living with me, and I don't think living in a smoky house is good for them. So I guess I'm doing it for all of us.

OM: Yeah, well my wife is the one who started bugging me. She makes me go out on the back porch whenever I want a smoke, and that's no fun when the weather's lousy. So, I'm trying to quit. Look, I know quitting will be good for me if I can stick to it. And I know it'll save me some money. Besides, I may even get a little peace and quiet.

TANAKA: Excellent. The reasons you all have given are very important ones. It is good to review them in your mind when you feel the need to smoke. Remind yourself of the many reasons why you decided to quit. You might even write them down and look at them every day. In fact, there is even a wallet card in your user's guide with space for you to do just that. Whenever you need help to overcome the urge, you can take it out and read what you wrote.

OM: I know one problem I'm going to have. I spend a lot of time at Harper's – uh, this bar in my neighborhood – because my buddies hang out there. They all smoke so it's going to be tough for me not to.

TANAKA: Yes, indeed it will. Perhaps you will decide not to go to Harper's for a week or so. But never lose sight of this: you want to give up smoking – you <u>don't</u> want to give up your lifestyle. So sooner or later you will go back to Harper's. When you do so, it must be in a frame of mind that makes it possible for you to resist the temptation that will be all around you.

OM: How do I do that?

TANAKA: Let us see if we can find an answer. At Harper's, do you have a friend who has given up smoking?

OM: Yeah, Jack. He used to smoke more than anybody there. But I guess he got worried about his health, so he quit. I think he joined some kind of group. He didn't show up at Harper's for a couple of weeks, but he's back to being a regular.

TANAKA: There is your answer. Your friend Jack joined a support group of people who were going through the same difficulties he was. And he avoided Harper's for a while because he knew that the temptation to smoke might be more than he could resist. But after a while he had conquered his addiction well enough to come back and meet with his friends.

OM: Yeah, I guess that might work.

TANAKA: Don't forget, the first weeks are the hardest, so that's when you should avoid temptation if you can. After that, the mental part of your dependence on cigarettes should be coming under control, and you can resume doing some of the things you may have given up for a while. Soon, you will find yourself taking pride in your ability to be comfortable in situations where others are smoking.

OM: So when I do feel ready to go back to Harper's I have to go with my mind made up not to smoke – and I have to keep reminding myself of my reasons?

TANAKA: Exactly. If you tell your friends you are quitting smoking, they will probably be glad to help support you in your decision, if they think you are sincere.

OW: Oh, I think I'll get a lot of support just by looking at the kids. If I remind myself that I'm doing it for them it will be easier than if I were just doing it for myself.

TANAKA: An excellent thought.

YW: With me I guess it's more of a habit than anything else. Pretty often I find myself smoking and I don't even remember reaching for the cigarette and lighting it.

TANAKA: That happens to most smokers. If there aren't any cigarettes around, you won't be able to smoke without thinking about it. That's why most people who want to quit throw away their cigarettes, lighters and ashtrays.

YW: Well, actually I kind of like to smoke. I guess it gives me pleasure, even though it makes my clothes smell.

TANAKA: That is the greatest hurdle to overcome. Smokers get pleasure out of smoking. Not out of every cigarette – many of them are just from habit. But that first cigarette in the morning is satisfying. And a cigarette with coffee or after a meal is pleasurable for many people. Perhaps the best way to deal with this is to find a

substitute pleasure that works for you. Find something to do that is pleasant and that doesn't go well with smoking.

YM: I smoke when I get nervous. Is there anything I can do about that?

TANAKA: Yes, there are techniques you can use to help you relax. For example, breathing.

STUDENTS: *Huh? What? Hey, I do that all the time.*

TANAKA: I thought that would surprise you. I am not talking about ordinary breathing – the kind we do without thinking about it. I am talking about deep, relaxing breathing – breathing upon which you concentrate all your attention. Perhaps, young lady, you will assist me in demonstrating.

YW: But I don't know anything about that.

TANAKA: That doesn't matter. It's really quite simple. The first thing to do is sit up straight, but without straining yourself.

YW: Like this?

TANAKA: Yes, but you must relax. Try letting you arms dangle loosely. Shake them a bit to relax the muscles. Make sure your leg and back muscles are relaxed too. Move your head around a little to relax your neck. How does that feel?

YW: Pretty good.

TANAKA: Fine. Now, breathe out and then take a slow breath as deeply as you can.

YW: *(Exhales. Inhales very deeply.)*

TANAKA: Now, hold that breath for a few seconds. Then let it all out slowly. Wait a second and take another deep breath.

YW: *(Breathes.)*

TANAKA: How does that feel?

YW: Gee. I never knew you could get such a feeling from just breathing.

TANAKA: It is amazing, is it not? Now, to assure that deep breathing truly relaxes you, close your eyes and picture a scene that you find very pleasurable and soothing.

YW: Like walking on the beach?

TANAKA: If that is the scene that makes you feel good, yes.

YM: I'll go along with that. Except I like to do my walking in the woods.

TANAKA: Now, let's all try it. Sit straight but relaxed. Take slow, deep breaths, and think of something that makes you feel at ease.

(Students shift around, shake, and breathe a few times.)

OM: Man, I never knew I could get such a kick out of breathing.

OW: Me, too.

TANAKA: That is one of the keys to helping you resist smoking at those critical times. Find something to do that occupies your mind and body fully. This can help you not think about smoking. Your routine may be as simple as this breathing exercise, but the important thing is to find some easy activity that is right for you.

YM: Boy, that's great. Anything else to help us resist temptation?

TANAKA: Basically, anything that helps you relax. As I said at the start of the class, soothing and peaceful music is a great aid to relaxation. If you're at home and feel the need for a smoke, try putting on some soft music. Sit in a comfortable chair, relax your muscles, breathe deeply and just let yourself float.

You are beginning a process that will not be easy. But if you use nicotine polacrilex gum properly, as it is explained in the User's Guide, and if you remember these tips to help you get past the mental hurdles, you will greatly increase your chances for success.

Now, we're going to spend the rest of the period just practicing muscle relaxation, deep breathing and calm, soothing mental pictures. Make yourselves comfortable and I will put on some music to help you put all thought of smoking out of your minds. I am sure you will enjoy it.

(Music up. Plays to end of Track.)

0172
02/08
Draft text 3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076880

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Numbers: 77-850 (4 mg, original)
76-880 (2 mg, peppermint)

Date of Submission: September 12, 2008

Applicant's Name: Ivax Pharmaceuticals, Inc.

Established Name: Nicotine Polacrilex Gum, USP

Labeling Deficiencies:

1. CARTON

Please include on your labeling the amount of calcium contained in your gum. (See 21 CFR 201.70)

2. User's Guide

Please relocate the stickers to be placed on your calendar to appear at the end of the User's Guide.

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. 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

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your previous labeling with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTE TO THE CHEMIST:

1. ANDA 76-880 - list the amount of sodium as 6.84 mg, is this correct? Also, they have not listed any calcium, is there any calcium in the gum?

2. ANDA 77-850 - list the amount of sodium as 8.44 mg, is this correct? Also, they have not listed any calcium, is there any calcium in the gum?

From: Skanchy, David
Sent: Wednesday, October 22, 2008 10:31 AM
To: Dillahunt, Michelle
Subject: RE: 76-880, 77-850

Michelle,

The amounts of sodium listed are correct. The gum base does contain calcium carbonate and since the gum base is the major component, the amount of calcium may be significant. We should ask the firm to declare the calcium content based on typical amounts present in the gum base. Would you like me to call the firm first to see if the levels are significant? Is there a reporting threshold for labeling (i.e. level below which a labeling declaration is not required)?

Dave S.

From: Skanchy, David
Sent: Monday, October 27, 2008 10:42 AM
To: Dillahunt, Michelle
Subject: RE: 76-880, 77-850

Michelle,

I spoke with the firm Friday afternoon and they indicate that they will exceed 20 mg calcium. Are there any other labeling deficiencies? You can add this one to the list if there are. I will have the firm send me the information regarding the calculation of the precise amount as a telephone amendment and you can close out labeling with the deficiency letter. Let me know if this is ok.

Dave S.

FOR THE RECORD:

1. MODEL LABELING - NDA 18-612/S-050 (2 mg); NDA 20-066/S-031 (4 mg) (Nicorette® gum) approved on June 13, 2008. This supplement provides for a new cinnamon flavor.
   A new mint flavor uncoated gum was approved 4/23/04. Labeling text for the new cinnamon flavor was used for the review since this flavor contains revised text that applies to all flavors.
   The audiotape/CD was also last approved on August 9, 2002 (S-031).
   NDA 18-612/S-035 (2 mg); NDA 20-066/S-017 (4 mg), approved June 23, 2004 was used as the model labeling for the user's guide.

2. This drug product is the subject of a USP monograph.

3. There is no specific labeling requirement for this product in USP.

4. The listing of inactive ingredients on the carton appears to be consistent with the listing of inactive ingredients found in the statement of components and composition. Vol 1.1 pg. 24

From chemistry review #6
*******Peppermint oil is used to mask the nicotine bitter taste and does not impart a strong**

mint flavor, the formulation is intended to mimic the RLD original flavor (March 4, 2004 amendment).

5. PATENTS/EXCLUSIVITIES

None

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD - Store at 20 to 25° C (68 to 77° F) - Protect from light

ANDA: Store at 20 to 25° C (68 to 77°F) - Protect from light.

7. In the approval letter of NDA 18-612/S-031, approved August 9, 2002, it appeals that the innovator's "committed Smoker's Enrollment Form" was approved. I asked Helen Cothran of OTC to find out that this is also required for the approval of generic applications for this drug product. Helen indicated in the e-mail dated 9/26/02 that the committed smoker's enrollment program is a voluntary, individualized support program initiated by the manufacturer and this program is not required by the Agency for approval of NTR product. (See file folder for detail)

8. Packaging - p. 267, vol. 1.2

(b) (4)

9. Package sizes:
RLD -20s, 40s, 50s, 110s and 170s
ANDA - 108s

10. The Audio CD and User's guide do not specify the flavors. We find this acceptable.

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11. The drug product will be manufactured for Ivax Pharmaceuticals Inc. by the firm shown below:

Site	Function		
Laboratorios Haymann S. A. Gianelli 1489 Montevideo Uruguay	Manufacturing. (b) (4) (b) (4)	Vol. 1.2 p. 8	

12. Description of gum
4 mg - Rectangular biconvex pieces, of yellow color with smooth white dots and mint odor
2 mg - Rectangular biconvex pieces, of beige color with smooth white dots and mint odor

. Ivax does not have imprint information on their gum. The RLD does not have imprint information on their gum. See emails from previous Nicotine application (b) (4)

Michelle,
Please see the following table for the status of all the coated gum products in-house. So far Perrigo is the only firm with approved coated gums (4). All of Watson's are pending. Since any consult on the printing issue could affect those Perrigo products already approved I think (and Tom Hinchliffe concurred) we should consult with Lille Golson and cc Peter Rickman on the issue. We could potentially be put in the uncomfortable position of having to go to Perrigo and ask them to add a printing step to their process for product already on the market for up to two years, depending on the result of the consult. It is also worth noting that Watson uses the approved Perrigo product as a justification for the waiver, under the assumption that a waiver was approved for Perrigo. It appears that this assumption may not be valid. I looked at the older uncoated gums and it appears neither the RLD nor any of the generics have imprinting on the pieces (printing with inks actually wouldn't work well on the rougher surfaced uncoated cores). So at some point, it appears, a waiver was granted or the imprinting requirement was never applied to the uncoated gums (maybe the requirement didn't exist when the first NDA's for nicorrette were approved 15 or more years ago). I am happy to type up a narrative summarizing the situation and forward to Golson and cc Rickman after Perrigo confirms whether they ever included a waiver request (I'll bet they didn't). Once we send out the consult we lose control of the situation and have to live with someone else's decision. Let me know what you think.
Dave S.

ANDA Firm Strength/flavor Status/date Printing on gum (Y/N) W.aiver requested for printing on gum**
78-546 Perrigo 4 mg (coated, Tutti Frutti) Approved 5/2007 No No
78-547 Perrigo 2 mg (coated, Tutti-Frutti) Approved 5/2007 No No
76-777* Perrigo 2 mg (coated, Mint) Approved 6/2006 No No
76-779* Perrigo 4 mg (coated, Mint) Approved 6/2006 No No
78-967 Perrigo 2 mg (coated, orange) CMC AP w/TL, Bio and labeling pending No No
78-968 Perrigo 4 mg (coated, orange) CMC AP w/TL, Bio and labeling pending No No
78-697 Watson 4 mg (coated, orange) CMC deficient, Bio and labeling pending Yes Yes
78-699 Watson 2 mg (coated, orange) CMC deficient, Bio and labeling pending Yes Yes
79-038 Watson 4 mg (coated, fruit) Not yet reviewed Not known, but probably Not known
79-044 Watson 2 mg (coated, fruit) Not yet reviewed Not known, but probably Not known
79-216 Watson 2 mg (coated, cinnamon) Not yet reviewed Not known, but probably Not known
79-219 Watson 4 mg (coated, cinnamon) Not yet reviewed Not known, but probably Not known

*These ANDA's were originally the uncoated mint gum. Supplement 5 reformulated to the coated mint gum and the
original uncoated core became the subject of a new ANDA. Approval date is for the coated formulation in Supplement 5.

**To the best of the chemist's recollection, no waiver was included in the CMC portion of the application for absence of printing on the gum pieces.

From: Golson, Lillie D
Sent: Tuesday, January 15, 2008 12:40 PM
To: Dillahunt, Michelle
Subject: RE: Coated Nicotine gums: imprinting issue

Thanks. Go ahead and let it go based on the fact that we approved Perrigo's product w/o the imprinting. Include this email in you FTR.

Date of Review: 10/27/08 **Date of Submission: 9/12/08**

Primary Reviewer: Michelle Dillahunt **Date:**

Team Leader: Lillie Golson **Date:**

---

cc:

ANDA: 77-850
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSAM\IVAXPharm\LTRS&REV\77850na2.labeling.doc
Review

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

/s/

Michelle Dillahunt
11/3/2008 09:28:58 AM
LABELING REVIEWER

Lillie Golson
11/3/2008 05:50:39 PM
LABELING REVIEWER

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Numbers: 77-850 (4 mg, original) Date of Submission: November 13, 2008

76-880 (2 mg, peppermint)

Applicant's Name: Ivax Pharmaceuticals, Inc.

Established Name: Nicotine Polacrilex Gum, USP

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No, electronic

1. BLISTER - 2 x 5

   2 mg and 4 mg - Satisfactory in FPL as of the September 12, 2008 submission.

2. CARTON- 40s, 100s, 110s, 160s

   2 mg and 4 mg - Satisfactory in FPL as of the November 13, 2008 submission.

3. USER'S GUIDE

   Satisfactory in FPL as of the November 13, 2008 submission.

4. Audio CD

   Satisfactory in FPL as of the September 12, 2008 submission.

5. CD audio script

   Satisfactory in FPL as of the September 12, 2008 submission.

6. Marketing and Surveillance Plan

   Satisfactory as of the September 12, 2008 submission.

BASIS OF APPROVAL:

Patent Data –18-612 and 20-066

No	Expiration	Use Code	Use	File
		There are no unexpired patents		

Exclusivity Data - 18-612 and 20-066

Code/sup	Expiration	Use Code	Description	Labeling Impact
			There are no unexpired exclusivities	

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: NDA 18-612/S-050 (2 mg); NDA 20-066/S-031 (4 mg) (Nicorette® gum) approved on June 13, 2008.
NDA 18-612/S-035 (2 mg); NDA 20-066/S-017 (4 mg), approved June 23, 2004 was used as the model labeling for the user's guide.
It appears that the innovator's audiotape was also last approved on August 9, 2002 (S-013). See FTR

NDA Number: 18-612 and 20-066

NDA Drug Name: Nicorette® Gum

NDA Firm: GlaxoSmith Kline

Date of Approval of NDA Insert and supplement #:
NDA 18-612/S-050 (2 mg); NDA 20-066/S-031 (4 mg) approved on June 13, 2008.

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Carton Labeling: Side-by-side comparisons

NOTE TO THE CHEMIST:

1. ANDA 76-880 - list the amount of sodium as 6.84 mg, is this correct? Also, they have not listed any calcium, is there any calcium in the gum?

2. ANDA 77-850 - list the amount of sodium as 8.44 mg, is this correct? Also, they have not listed any calcium, is there any calcium in the gum?

From: Skanchy, David
Sent: Wednesday, October 22, 2008 10:31 AM
To: Dillahunt, Michelle
Subject: RE: 76-880, 77-850

Michelle,

The amounts of sodium listed are correct. The gum base does contain calcium carbonate and since the gum base is the major component, the amount of calcium may be significant. We should ask the firm to declare the calcium content based on typical amounts present in the gum base. Would you like me to call the firm first to see if the levels are significant? Is there a reporting threshold for labeling (i.e. level below which a labeling declaration is not required)?

Dave S.

From: Skanchy, David

Sent: Monday, October 27, 2008 10:42 AM
To: Dillahunt, Michelle
Subject: RE: 76-880, 77-850

Michelle,

I spoke with the firm Friday afternoon and they indicate that they will exceed 20 mg calcium. Are there any other labeling deficiencies? You can add this one to the list if there are. I will have the firm send me the information regarding the calculation of the precise amount as a telephone amendment and you can close out labeling with the deficiency letter. Let me know if this is ok.

Dave S.

From: Dillahunt, Michelle
Sent: Thursday, December 04, 2008 3:52 PM
To: Skanchy, David
Subject: RE: RE: 76-880, 77-850

Ivax has revised their labeling to indicate that there is 61 mg of calcium in their 2 mg and 4 mg nicotine gum.
Is this accurate?

From: Skanchy, David
Sent: Friday, December 05, 2008 5:59 AM
To: Dillahunt, Michelle
Subject: RE: RE: 76-880, 77-850

This is correct.

Dave S.

FOR THE RECORD:

1. MODEL LABELING - NDA 18-612/S-050 (2 mg); NDA 20-066/S-031 (4 mg) (Nicorette® gum) approved on June 13, 2008. This supplement provides for a new cinnamon flavor.
   A new mint flavor uncoated gum was approved 4/23/04. Labeling text for the new cinnamon flavor was used for the review since this flavor contains revised text that applies to all flavors.
   The audiotape/CD was also last approved on August 9, 2002 (S-031).
   NDA 18-612/S-035 (2 mg); NDA 20-066/S-017 (4 mg), approved June 23, 2004 was used as the model labeling for the user's guide.

2. This drug product is the subject of a USP monograph.

3. There is no specific labeling requirement for this product in USP.

4. The listing of inactive ingredients on the carton appears to be consistent with the listing of inactive ingredients found in the statement of components and composition. Vol 1.1 pg. 24

   From chemistry review #6
   ********Peppermint oil is used to mask the nicotine bitter taste and does not impart a strong mint flavor, the formulation is intended to mimic the RLD original flavor (March 4, 2004 amendment).**

5. PATENTS/EXCLUSIVITIES

   None

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD - Store at 20 to 25° C (68 to 77° F) - Protect from light

ANDA: Store at 20 to 25° C (68 to 77°F) - Protect from light.

7. In the approval letter of NDA 18-612/S-031, approved August 9, 2002, it appeals that the innovator's "committed Smoker's Enrollment Form" was approved. I asked Helen Cothran of OTC to find out that this is also required for the approval of generic applications for this drug product. Helen indicated in the e-mail dated 9/26/02 that the committed smoker's enrollment program is a voluntary, individualized support program initiated by the manufacturer and this program is not required by the Agency for approval of NTR product. (See file folder for detail)

8. Packaging - p. 267, vol. 1.2

9. Package sizes:
RLD -20s, 40s, 50s, 110s and 170s
ANDA - 108s

10. The Audio CD and User's guide do not specify the flavors. We find this acceptable.

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11. The drug product will be manufactured for Ivax Pharmaceuticals Inc. by the firm shown below:

Site	Function		
Laboratorios Haymann S. A. Gianelli 1489 Montevideo Uruguay	Manufacturing, (b) (4) (b) (4)	Vol. 1.2 p. 8	

12. Description of gum
4 mg - Rectangular biconvex pieces, of yellow color with smooth white dots and mint odor
2 mg - Rectangular biconvex pieces, of beige color with smooth white dots and mint odor

. Ivax does not have imprint information on their gum. The RLD does not have imprint information on their gum. See emails from previous Nicotine application (b) (4)

Michelle,
Please see the following table for the status of all the coated gum products in-house. So far Perrigo is the only firm with approved coated gums (4). All of Watson's are pending. Since any consult on the printing issue could affect those Perrigo products already approved I think (and Tom Hinchliffe concurred) we should consult with Lille Golson and cc Peter Rickman on the issue. We could potentially be put in the uncomfortable position of having to go to Perrigo and ask them to add a printing step to their process for product already on the market for up to two years, depending on the result of the consult. It is also worth noting that Watson uses the approved Perrigo product as a justification for the waiver, under the

assumption that a waiver was approved for Perrigo. It appears that this assumption may not be valid. I looked at the older uncoated gums and it appears neither the RLD nor any of the generics have imprinting on the pieces (printing with inks actually wouldn't work well on the rougher surfaced uncoated cores). So at some point, it appears, a waiver was granted or the imprinting requirement was never applied to the uncoated gums (maybe the requirement didn't exist when the first NDA's for nicorrette were approved 15 or more years ago). I am happy to type up a narrative summarizing the situation and forward to Golson and cc Rickman after Perrigo confirms whether they ever included a waiver request (I'll bet they didn't). Once we send out the consult we lose control of the situation and have to live with someone else's decision. Let me know what you think.
Dave S.

ANDA Firm Strength/flavor Status/date Printing on gum (Y/N) W.aiver requested for printing on gum**
78-546 Perrigo 4 mg (coated, Tutti Frutti) Approved 5/2007 No No
78-547 Perrigo 2 mg (coated, Tutti-Frutti) Approved 5/2007 No No
76-777* Perrigo 2 mg (coated, Mint) Approved 6/2006 No No
76-779* Perrigo 4 mg (coated, Mint) Approved 6/2006 No No
78-967 Perrigo 2 mg (coated, orange) CMC AP w/TL, Bio and labeling pending No No
78-968 Perrigo 4 mg (coated, orange) CMC AP w/TL, Bio and labeling pending No No
78-697 Watson 4 mg (coated, orange) CMC deficient, Bio and labeling pending Yes Yes
78-699 Watson 2 mg (coated, orange) CMC deficient, Bio and labeling pending Yes Yes
79-038 Watson 4 mg (coated, fruit) Not yet reviewed Not known, but probably Not known
79-044 Watson 2 mg (coated, fruit) Not yet reviewed Not known, but probably Not known
79-216 Watson 2 mg (coated, cinnamon) Not yet reviewed Not known, but probably Not known
79-219 Watson 4 mg (coated, cinnamon) Not yet reviewed Not known, but probably Not known

*These ANDA's were originally the uncoated mint gum. Supplement 5 reformulated to the coated mint gum and the
original uncoated core became the subject of a new ANDA. Approval date is for the coated formulation in Supplement 5.

**To the best of the chemist's recollection, no waiver was included in the CMC portion of the application for absence of printing on the gum pieces.

From: Golson, Lillie D
Sent: Tuesday, January 15, 2008 12:40 PM
To: Dillahunt, Michelle
Subject: RE: Coated Nicotine gums: imprinting issue

Thanks. Go ahead and let it go based on the fact that we approved Perrigo's product w/o the imprinting. Include this email in you FTR.

Date of Review: 12/15/08 **Date of Submission: 11/13/08**

Primary Reviewer: Michelle Dillahunt **Date:**

Team Leader: Lillie Golson **Date:**

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cc:

ANDA: 77-850
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSAM\IVAXPharm\LTRS&REV\77850AP1.labeling.doc
Review

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

Michelle Dillahunt
12/18/2008 10:06:23 AM
LABELING REVIEWER

Lillie Golson
12/19/2008 01:05:22 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076880

CHEMISTRY REVIEWS

ANDA 76-880

Nicotine Polacrilex Gum USP
2 mg (Original Flavor)

IVAX Pharmaceuticals, Inc.

David Skanchy

Office of Generic Drugs/Division of Chemistry II

Executive Summary Section

Table of Contents

Executive Summary Section

Executive Summary Section

Chemistry Review Data Sheet

1. ANDA 76-880

2. REVIEW #: 1

3. REVIEW DATE: March 23, 2004

4. REVIEWER: David Skanchy

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	October 23, 2003
Amendment (telephone)	March 4, 2004

7. NAME & ADDRESS OF APPLICANT:

Name: IVAX Pharmaceuticals, Inc.
Address: 140 Legrand Avenue
Northvale, New Jersey
07647

Representative: Patricia Jaworski
Telephone: (201) 767-1700 ext 323 or 146

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Nicotine Polacrilex Gum USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for this submission is the approved listed drug, Nicorette® 2 mg, the subject of NDA #18-612, held by GlaxoSmithKline. The referenced drug product has no unexpired patents or exclusivity. A Paragraph I Certification and Exclusivity Statement are provided on pages 10015 and 10016, respectively.

10. PHARMACOL. CATEGORY:

Indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms.

11. DOSAGE FORM: Chewing Gum

12. STRENGTH/POTENCY: 2 mg

13. ROUTE OF ADMINISTRATION: Buccal

14. Rx/OTC DISPENSED: ___ Rx __X_ OTC

15. **Error! Reference source not found.**

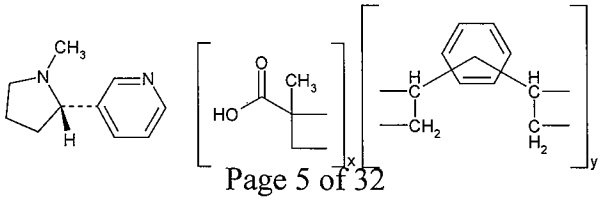
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Nicotine Polacrilex

Molecular Formula $C_{10}H_{14}N_2(C_{18}H_{22}O_4)_n$



Executive Summary Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Nicotine Polacrilex 20% w/w	1	Inadequate	3/8/04	Reviewed by DSkanchy
	III		(b) (4)	4	N/A	N/A	
	III			4	N/A	N/A	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] 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
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Pending		
Methods Validation	Not required		
Labeling	Not Acceptable	2/19/2004	MDillahunt
Bioequivalence	Pending		
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

Executive Summary Section

19. ORDER OF REVIEW

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

Executive Summary Section

The Chemistry Review for ANDA 76-880

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to minor deficiencies.

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

None.

II. Summary of Chemistry Assessments

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

Nicotine is a volatile strongly alkaline oily liquid. It is colorless when pure but becomes yellow when exposed to air, boiling point is 247°C. It is optically active containing a single chiral center and has an $[\alpha]_d$ of -139° to -151° . Nicotine is supplied ionically bound to Polacrilex Resin which contains 20% nicotine. The resin is a weak cation exchange polymer made from vinylacrylic acid and divinyl benzene. The nicotine containing resin is blended with inactive ingredients such as Gum base, sorbitol, peppermint oil, and starch to produce a sugar free chewing gum containing 2 mg of nicotine. The drug is delivered for buccal absorbtion by chewing a 1 gram dosage unit. The reference listed drug for this product is Nicorette® Gum 2 mg by GlaxoSmithKline (NDA 18-612).

The manufacturer of the drug substance, Polacrilex Resin 20% Nicotine, is (b) (4) (DMF # (b) (4) . A two-year expiration dating period is proposed for this product. This is supported by accelerated stability data in the container/closure proposed for marketing.

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

Nicotine Gum's sugar free chewing pieces provide nicotine to the body, working as a temporary aid to help quit smoking by reducing nicotine withdraw symptoms. Nicotine Polacrilex Gum provides a lower level of nicotine to the blood stream than cigarettes, and allows people to gradually do away with the body's need for

nicotine. The recommended usage schedule and instruction on gradually decreasing nicotine polacrilex gum use are provided in the User's Guide.

C. Basis for Approvability or Not-Approval Recommendation

The applicant referenced a Drug Master File No. (b) (4) from (b) (4) to support the manufacturing of the drug substance. This DMF was reviewed and found inadequate. The applicant needs to (b) (4) (b) (4)

The bioequivalence review is pending. The labeling review noted deficiencies. Establishment inspections are currently pending. The analytical methods will not need to be validated by a FDA laboratory according to the current policy.

In light of the magnitude of issues pertaining to the drug substance and the drug product that impact on the safety and efficacy, the application is not approvable due to minor deficiencies.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-640/DSkanchy/3/23/04; 3/31/04 Bin Wu for D. Skanchy 4/6/04
HFD-640/SRosencrance/3/30/04; 3/31/04 for Susan Rosencrance 4/6/04
HFD-617/THinchliffe/4/1/04 4/6/04

C. CC Block

ANDA 76-880 Original
ANDA 76-880 DUP
DIV FILE
Field Copy

22 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Chemistry Assessment Section

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-880 APPLICANT: IVAX

DRUG PRODUCT: Nicotine Polacrilex Gum USP, 2 mg (Original Flavor)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.
9.

Chemistry Assessment Section

10. (b) (4)

11.

12.

Kvist, C., et. al., *International Journal of Pharmaceutics*, 189 (1999) 57-65.
European Pharmacopeia, *4.06, 2.9.25, Chewing gum, medicated, drug release from.*

13. (b) (4)

14.

15.

16.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Chemistry Assessment Section

1. Please provide all available room temperature stability data in your next amendment.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Chemistry Assessment Section

cc: ANDA 76-880 Original
ANDA 76-880 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/DSkanchy/03/23/2004; 3/31/04 Pris w/in for D. Skanchy 4/6/04
HFD-640/SRosencrance/3/30/04; 3/31/04 Pris w/in for Susan Rosencrance 4/6/04
HFD-617/THinchliffe/4/1/04 4/6/04

F/T by: EW 4/6/04

\\CDS013\OGDS11\FIRMSAM\IVAX\LTRS&REV\76880.CR01.doc

TYPE OF LETTER: NOT APPROVABLE - Minor

~~ANDA 76-880~~

Nicotine Polacrilex Gum USP, 2 mg (Original Flavor)

IVAX Pharmaceuticals, Inc.

David Skanchy

Office of Generic Drugs/Division of Chemistry II

Executive Summary Section

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Executive Summary Section

Executive Summary Section

Chemistry Review Data Sheet

1. ANDA 76-880

2. REVIEW #: 2

3. REVIEW DATE: September 15, 2005

4. REVIEWER: David Skanchy

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	October 23, 2003
Amendment (telephone)	March 4, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (response to deficiencies)	May 23, 2005

7. NAME & ADDRESS OF APPLICANT:

Name: IVAX Pharmaceuticals, Inc.
Address: 125 Wells Avenue
Congers, New York 10920
07647

Representative: Patricia Jaworski
Telephone: (845)267-2444 ext. 200 or 201
Fax: (845)268-0117

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Nicotine Polacrilex Gum USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for this submission is the approved listed drug, Nicorette® 2 mg, the subject of NDA #18-612, held by GlaxoSmithKline. The referenced drug product has no unexpired patents or exclusivity. A Paragraph I Certification and Exclusivity Statement are provided on pages 10015 and 10016, respectively.

10. PHARMACOL. CATEGORY:

Indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms.

11. DOSAGE FORM: Chewing Gum

12. STRENGTH/POTENCY: 2 mg

13. ROUTE OF ADMINISTRATION: Buccal

14. Rx/OTC DISPENSED: ___ Rx __X__ OTC

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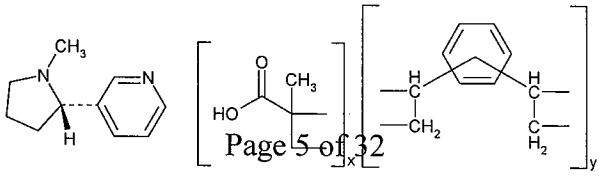
__X__Not a SPOTS product

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

Nicotine Polacrilex
Molecular Formula $C_{10}H_{14}N_2(C_{18}H_{22}O_4)_n$



Executive Summary Section

17. RELATED/SUPPORTING DOCUMENTS:

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DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
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	III			4	N/A	N/A	
	III			4	N/A	N/A	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] 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
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Pending		
Methods Validation	Not required		
Labeling	***Not Acceptable***	***2/19/2004***	***MDillahunt***
Bioequivalence	***Not Acceptable***	***4/19/05***	***PSeo***
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

Executive Summary Section

19. ORDER OF REVIEW

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

Executive Summary Section

The Chemistry Review for ANDA 76-880

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to minor deficiencies.

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

None.

II. Summary of Chemistry Assessments

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

Nicotine is a volatile strongly alkaline oily liquid. It is colorless when pure but becomes yellow when exposed to air, boiling point is 247°C. It is optically active containing a single chiral center and has an $[\alpha]_d$ of -139° to -151° . Nicotine is supplied ionically bound to Polacrilex Resin which contains 20% nicotine. The resin is a weak cation exchange polymer made from vinylacrylic acid and divinyl benzene. The nicotine containing resin is blended with inactive ingredients such as Gum base, sorbitol, peppermint oil, and starch to produce a sugar free chewing gum containing 2 mg of nicotine. The drug is delivered for buccal absorbtion by chewing a 1 gram dosage unit. The reference listed drug for this product is Nicorette® Gum 2 mg by GlaxoSmithKline (NDA 18-612).

The manufacturer of the drug substance, Polacrilex Resin 20% Nicotine, is [redacted] (b) (4) (DMF # [redacted] (b) (4) A two-year expiration dating period is proposed for this product. This is supported by accelerated stability data in the container/closure proposed for marketing.

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

Nicotine Gum's sugar free chewing pieces provide nicotine to the body, working as a temporary aid to help quit smoking by reducing nicotine withdraw symptoms. Nicotine Polacrilex Gum provides a lower level of nicotine to the blood stream than cigarettes, and allows people to gradually do away with the body's need for

nicotine. The recommended usage schedule and instruction on gradually decreasing nicotine polacrilex gum use are provided in the User's Guide.

C. Basis for Approvability or Not-Approval Recommendation

The applicant needs to tighten the stability specifications for impurities/related substances. The bioequivalence review is pending. The labeling review noted deficiencies. Establishment inspections are currently pending. In light of the magnitude of issues pertaining to the drug substance and the drug product that impact on the safety and efficacy, the application is not approvable due to minor deficiencies.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-640/DSkanchy/09/15/2005;9/19/05 9/20/05
HFD-640/NYa/9/19/05 for 9/20/05
HFD-617/THinchliffe/YKong for 9/20/05

C. CC Block

ANDA 76-880 Original
ANDA 76-880 DUP
DIV FILE
Field Copy

24 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Chemistry Assessment Section

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-880 APPLICANT: IVAX

DRUG PRODUCT: Nicotine Polacrilex Gum USP, 2 mg (Original Flavor)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please commit to provide a [redacted] (b) (4) (b) (4)

2. We again ask that you [redacted] (b) (4) (b) (4)

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Chemistry Assessment Section

cc: ANDA 76-880 Original
ANDA 76-880 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/DSkanchy/09/15/2005;9/19/05 Dfinal 9/20/05
HFD-640/NYa/9/19/05 Dfinal 9/20/05
HFD-617/THinchliffe/YKong for 9/20/05 Wfor Toh 9/20/05

F/T by rad9/20/05

\\CDS013\OGDS11\FIRMSAM\IVAX\LTRS&REV\76880_CR02.doc

TYPE OF LETTER: NOT APPROVABLE – Minor

ANDA 76-880

Nicotine Polacrilex Gum USP
2 mg (Original Flavor)

IVAX Pharmaceuticals, Inc.

David Skanchy

Office of Generic Drugs/Division of Chemistry II

Chemistry Assessment Section

Table of Contents

Chemistry Assessment Section

Chemistry Assessment Section

Chemistry Review Data Sheet

1. ANDA 76-880

2. REVIEW #: 3

3. REVIEW DATE: July 26, 2006

4. REVIEWER: David Skanchy

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	October 23, 2003
Amendment (telephone)	March 4, 2004
Amendment (response to deficiencies)	May 23, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (response to deficiencies)	May 15, 2006
Amendment (gratuitous)	February 2, 2006

7. NAME & ADDRESS OF APPLICANT:

Name: IVAX Pharmaceuticals, Inc.
Address: 140 Legrand Avenue
Northvale, New Jersey
07647
Representative: Patricia Jaworski
Telephone: (201) 767-1700 ext 323 or 146

Chemistry Assessment Section

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Nicotine Polacrilex Gum USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for this submission is the approved listed drug, Nicorette® 2 mg, the subject of NDA #18-612, held by GlaxoSmithKline. The referenced drug product has no unexpired patents or exclusivity. A Paragraph I Certification and Exclusivity Statement are provided on pages 10015 and 10016, respectively.

10. PHARMACOL. CATEGORY:
Indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms.

11. DOSAGE FORM: Chewing Gum

12. STRENGTH/POTENCY: 2 mg

13. ROUTE OF ADMINISTRATION: Buccal

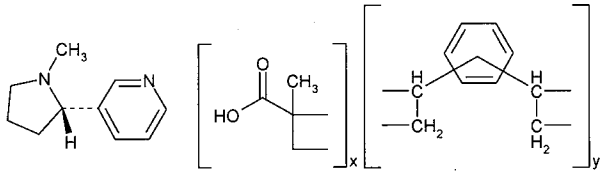
14. Rx/OTC DISPENSED: ___ Rx ___X__ OTC

15. Spots Product
_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

Nicotine Polacrilex
Molecular Formula $C_{10}H_{14}N_2(C_{18}H_{22}O_4)_n$



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Nicotine Polacrilex 20% w/w	1	Adequate	9/15/05	Reviewed by DSkanchy
	III		(b) (4)	4	N/A	N/A	
	III			4	N/A	N/A	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] 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
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	12/23/2005	OC
Methods Validation	Not required		
Labeling	***Not Acceptable***	***2/19/2004***	***MDillahunt***
Bioequivalence	***Not Acceptable***	***6/1/05***	***PSeo***
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

Chemistry Assessment Section

19. ORDER OF REVIEW

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

Chemistry Assessment Section

The Chemistry Review for ANDA 76-880

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable - major due to deficient labeling and a new bio study. *A DSI investigation of the clinical site resulted in DBE request for a new bioequivalence study which has not yet been submitted.*

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

None.

II. Summary of Chemistry Assessments

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

Nicotine is a volatile strongly alkaline oily liquid. It is colorless when pure but becomes yellow when exposed to air, boiling point is 247°C. It is optically active containing a single chiral center and has an $[\alpha]_d$ of -139° to -151° . Nicotine is supplied ionically bound to Polacrilex Resin which contains 20% nicotine. The resin is a weak cation exchange polymer made from vinylacrylic acid and divinyl benzene. The nicotine containing resin is blended with inactive ingredients such as Gum base, sorbitol, peppermint oil, and starch to produce a sugar free chewing gum containing 2 mg of nicotine. The drug is delivered for buccal absorbtion by chewing a 1 gram dosage unit. The reference listed drug for this product is Nicorette® Gum 2 mg by GlaxoSmithKline (NDA 18-612).

The manufacturer of the drug substance, Polacrilex Resin 20% Nicotine, is [redacted] (b) (4) (DMF [redacted] (b) (4) A two-year expiration dating period is proposed for this product. This is supported by accelerated stability data in the container/closure proposed for marketing.

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

Nicotine Gum's sugar free chewing pieces provide nicotine to the body, working as a temporary aid to help quit smoking by reducing nicotine withdraw symptoms. Nicotine Polacrilex Gum provides a lower level of nicotine to the blood stream

than cigarettes, and allows people to gradually do away with the body's need for nicotine. The recommended usage schedule and instruction on gradually decreasing nicotine polacrilex gum use are provided in the User's Guide.

C. Basis for Approvability or Not-Approval Recommendation

Not approvable - major due to deficient labeling and a new bio study. *A DSI investigation of the clinical site resulted in DBE request for a new bioequivalence study.*

23 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Chemistry Assessment Section

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-880 APPLICANT: IVAX

DRUG PRODUCT: Nicotine Polacrilex Gum USP, 2 mg (Original Flavor)

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. We note in a June 2005 deficiency letter issued by the Division of Bioequivalence (DBE) that a new bioequivalence study was requested. To date your response to the DBE letter has not been received and the current review cycle must now be closed. Please submit a Chemistry Amendment to re-open review of this ANDA when you submit your response to the DBE letter.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Chemistry Assessment Section

cc: ANDA 76-880 Original
ANDA 76-880 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/DSkanchy/7/26/2006
HFD-640/NYa/8/28/06
HFD-617/THinchliffe/

F/T by rad8/29/06

\\CDS013\OGDS11\FIRMSAM\IVAX\LTRS&REV\76880_CR03.doc

TYPE OF LETTER: Not Approvable- Major

ANDA 76-880

Nicotine Polacrilex Gum USP
2 mg (Original Flavor)

IVAX Pharmaceuticals, Inc.

David Skanchy

Office of Generic Drugs/Division of Chemistry II

Executive Summary Section

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Executive Summary Section

Executive Summary Section

Chemistry Review Data Sheet

1. ANDA 76-880

2. REVIEW #: 4

3. REVIEW DATE: July 24, 2007

4. REVIEWER: David Skanchy

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	October 23, 2003
Amendment (telephone)	March 4, 2004
Amendment (response to deficiencies)	May 23, 2005
Amendment (response to deficiencies)	May 15, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (response to Major due to DBE)	June 19, 2007
Telephone Amendment	July 6, 2007

7. NAME & ADDRESS OF APPLICANT:

Name: IVAX Pharmaceuticals, Inc.

Executive Summary Section

Address: 140 Legrand Avenue
Northvale, New Jersey
07647

Representative: Patricia Jaworski
Telephone: (215) 293-6150

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Nicotine Polacrilex Gum USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for this submission is the approved listed drug, Nicorette® 2 mg, the subject of NDA #18-612, held by GlaxoSmithKline. The referenced drug product has no unexpired patents or exclusivity. A Paragraph I Certification and Exclusivity Statement are provided on pages 10015 and 10016, respectively.

10. PHARMACOL. CATEGORY:

Indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms.

11. DOSAGE FORM: Chewing Gum

12. STRENGTH/POTENCY: 2 mg

13. ROUTE OF ADMINISTRATION: Buccal

14. Rx/OTC DISPENSED: ___ Rx __X__ OTC

15. Spots Product

_____SPOTS product – Form Completed

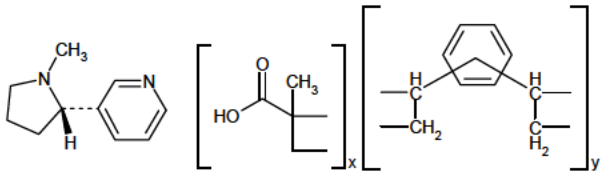
__X__Not a SPOTS product

Executive Summary Section

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

Nicotine Polacrilex

Molecular Formula $C_{10}H_{14}N_2(C_{18}H_{22}O_4)_n$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Nicotine Polacrilex 20% w/w	1	Adequate	9/15/05	Reviewed by DSkanchy
	III		(b) (4)	4	N/A	N/A	
	III			4	N/A	N/A	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] 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
None		

18. STATUS:

Executive Summary Section

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES*	Acceptable	12/23/2005	OC
Methods Validation	Not required		
Labeling	***Not Acceptable***	***2/19/2004***	***MDillahunt***
Bioequivalence	***Pending Dissolution Acknowledgement***	***7/20/07***	***PSeo***
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

**Ivax AC in 2003, needs update.*

19. ORDER OF REVIEW

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

Executive Summary Section

The Chemistry Review for ANDA 76-880

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable from a Chemistry perspective. Acceptable labeling and DBE review are pending. *A DSI investigation of the clinical site resulted in DBE request for a new bioequivalence study which has been submitted and found acceptable, only acknowledgement of the dissolution conditions/specification is pending.*

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

None.

II. Summary of Chemistry Assessments

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

Nicotine is a volatile strongly alkaline oily liquid. It is colorless when pure but becomes yellow when exposed to air, boiling point is 247°C. It is optically active containing a single chiral center and has an $[\alpha]_d$ of -139° to -151° . Nicotine is supplied ionically bound to Polacrilex Resin which contains 20% nicotine. The resin is a weak cation exchange polymer made from vinylacrylic acid and divinyl benzene. The nicotine containing resin is blended with inactive ingredients such as Gum base, sorbitol, peppermint oil, and starch to produce a sugar free chewing gum containing 2 mg of nicotine. The drug is delivered for buccal absorbtion by chewing a 1 gram dosage unit. The reference listed drug for this product is Nicorette® Gum 2 mg by GlaxoSmithKline (NDA 18-612).

The manufacturer of the drug substance, Polacrilex Resin 20% Nicotine, is (b) (4) (DMF (b) (4). A two-year expiration dating period is proposed for this product. This is supported by accelerated stability data in the container/closure proposed for marketing.

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

Nicotine Gum's sugar free chewing pieces provide nicotine to the body, working as a temporary aid to help quit smoking by reducing nicotine withdraw symptoms.

Executive Summary Section

Nicotine Polacrilex Gum provides a lower level of nicotine to the blood stream than cigarettes, and allows people to gradually do away with the body's need for nicotine. The recommended usage schedule and instruction on gradually decreasing nicotine polacrilex gum use are provided in the User's Guide.

C. Basis for Approvability or Not-Approval Recommendation

Approvable from a Chemistry perspective. Acceptable labeling and DBE review are pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-640/DSkanchy/
HFD-640/NYa/
HFD-617/THinchliffe/

C. CC Block

ANDA 76-880 Original
ANDA 76-880 DUP
DIV FILE
Field Copy

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Chemistry Assessment Section

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-880 APPLICANT: IVAX

DRUG PRODUCT: Nicotine Polacrilex Gum USP, 2 mg (Original Flavor)

Please note that there are currently no Chemistry, Manufacturing, and Controls (CMC) deficiencies to communicate at this time. This application, however, is still pending satisfactory Bioequivalence and Labeling reviews. We note that Labeling issues were communicated on or about July 10, 2007 by telephone. We also note that Division of Bioequivalence (DBE) deficiencies were issued on or about July 27, 2007 under separate cover. When you have responded to the issues raised in the Labeling and DBE communications, please submit a MINOR Chemistry amendment to re-open review of this ANDA.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Chemistry Assessment Section

cc: ANDA 76-880 Original
ANDA 76-880 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/DSkanchy/7/24/2007
HFD-640/NYa/
HFD-617/THinchliffe/10/2/07

F/T by

M:\Temp files\76880_cr04.doc

TYPE OF LETTER: Not Approvable MINOR

Chemistry Assessment Section

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

/s/

David Skanchy
10/2/2007 02:10:36 PM
CHEMIST

Thomas Hinchliffe
10/3/2007 09:00:11 AM
CSO

Naiqi Ya
10/5/2007 02:16:02 PM
CHEMIST

Chemistry Assessment Section

ANDA 76-880

Nicotine Polacrilex Gum USP
2 mg (Original Flavor)

IVAX Pharmaceuticals, Inc.

David Skanchy

Office of Generic Drugs/Division of Chemistry II

Chemistry Assessment Section

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Chemistry Assessment Section

Chemistry Assessment Section

Chemistry Review Data Sheet

1. ANDA 76-880

2. REVIEW #: 5

3. REVIEW DATE: January 2, 2008

4. REVIEWER: David Skanchy

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	October 23, 2003
Amendment (telephone)	March 4, 2004
Amendment (response to deficiencies)	May 23, 2005
Amendment (response to deficiencies)	May 15, 2006
Amendment (response to Major due to DBE)	June 19, 2007
Telephone Amendment	July 6, 2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (re-open CMC)	November 13, 2007

7. NAME & ADDRESS OF APPLICANT:

Name: IVAX Pharmaceuticals, Inc.

Chemistry Assessment Section

Address: Two University Plaza
Suite 220
Hackensack, New Jersey
07601

Representative: Patricia Jaworski
Telephone: (215) 293-6150

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Nicotine Polacrilex Gum USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for this submission is the approved listed drug, Nicorette® 2 mg, the subject of NDA #18-612, held by GlaxoSmithKline. The referenced drug product has no unexpired patents or exclusivity. A Paragraph I Certification and Exclusivity Statement are provided on pages 10015 and 10016, respectively.

10. PHARMACOL. CATEGORY:

Indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms.

11. DOSAGE FORM: Chewing Gum

12. STRENGTH/POTENCY: 2 mg

13. ROUTE OF ADMINISTRATION: Buccal

14. Rx/OTC DISPENSED: ___ Rx __X__ OTC

15. Spots Product

_____SPOTS product – Form Completed

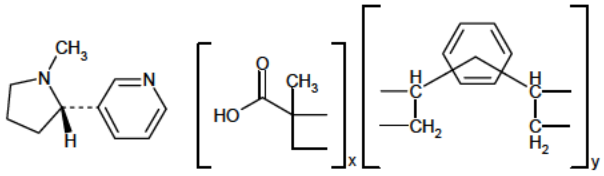
__X__Not a SPOTS product

Chemistry Assessment Section

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

Nicotine Polacrilex

Molecular Formula $C_{10}H_{14}N_2(C_{18}H_{22}O_4)_n$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Nicotine Polacrilex 20% w/w	1	Adequate	9/15/05*	Reviewed by DSkanchy
	III		(b) (4)	4	N/A	N/A	
	III			4	N/A	N/A	

*DMF holder was reminded to submit annual reports

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] 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
None		

18. STATUS:

Chemistry Assessment Section

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES*	Acceptable	12/23/2005	OC
Methods Validation	Not required		
Labeling*	***Pending***		
Bioequivalence	***Pending***		
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

*Ivax AC in 2003, needs update. Request submitted by T. Hinchliffe 1/02/2008.
**Firm indicates final labeling to be submitted by 1/31/2008.

19. ORDER OF REVIEW

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

Chemistry Assessment Section

The Chemistry Review for ANDA 76-880

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable from a Chemistry perspective. Acceptable labeling and DBE review are pending.

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

None.

II. Summary of Chemistry Assessments

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

Nicotine is a volatile strongly alkaline oily liquid. It is colorless when pure but becomes yellow when exposed to air, boiling point is 247°C. It is optically active containing a single chiral center and has an $[\alpha]_d$ of -139° to -151° . Nicotine is supplied ionically bound to Polacrilex Resin which contains 20% nicotine. The resin is a weak cation exchange polymer made from vinylacrylic acid and divinyl benzene. The nicotine containing resin is blended with inactive ingredients such as Gum base, sorbitol, peppermint oil, and starch to produce a sugar free chewing gum containing 2 mg of nicotine. The drug is delivered for buccal absorbtion by chewing a 1 gram dosage unit. The reference listed drug for this product is Nicorette® Gum 2 mg by GlaxoSmithKline (NDA 18-612).

The manufacturer of the drug substance, Polacrilex Resin 20% Nicotine, is [redacted] (b) (4) (DMF # [redacted] (b) (4)). A two-year expiration dating period is proposed for this product. This is supported by accelerated stability data in the container/closure proposed for marketing.

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

Nicotine Gum's sugar free chewing pieces provide nicotine to the body, working as a temporary aid to help quit smoking by reducing nicotine withdraw symptoms. Nicotine Polacrilex Gum provides a lower level of nicotine to the blood stream than cigarettes, and allows people to gradually do away with the body's need for

nicotine. The recommended usage schedule and instruction on gradually decreasing nicotine polacrilex gum use are provided in the User's Guide.

C. Basis for Approvability or Not-Approval Recommendation

Approvable from a Chemistry perspective. Acceptable labeling review is pending.

III. Administrative

Endorsement Block

HFD-640/DSkanchy/
HFD-640/NYa/
HFD-617/THinchliffe/

25 Pages has been Withheld in Full as b4 (CCI/TS) immediately following this page

Chemistry Assessment Section

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-880 APPLICANT: IVAX

DRUG PRODUCT: Nicotine Polacrilex Gum USP, 2 mg (Original Flavor)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

There are currently no Chemistry, Manufacturing, and Controls (CMC) deficiencies to communicate at this time. However, this application is still pending a satisfactory Labeling review. We note that Labeling comments were communicated to you on or about July 10, 2007 by telephone and you have still failed to respond. Do not respond to this communication until you have responded to the issues raised in the Labeling communications. Please submit a MINOR Chemistry amendment to re-open review of this ANDA.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Chemistry Assessment Section

cc: ANDA 76-880 Original
ANDA 76-880 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/DSkanchy/1/02/2008
HFD-640/NYa/1/22/08
HFD-617/THinchliffe/1/22/08

F/T by

M:\Temp files\76880_cr05.doc

TYPE OF LETTER: Minor – Failure to respond to labeling

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

/s/

David Skanchy
1/22/2008 10:10:23 AM
CHEMIST

Thomas Hinchliffe
1/22/2008 11:46:07 AM
CSO

Naiqi Ya
1/22/2008 02:46:14 PM
CHEMIST

Chemistry Assessment Section

ANDA 76-880

Nicotine Polacrilex Gum USP
2 mg (Original Flavor)

IVAX Pharmaceuticals, Inc.

David Skanchy

Office of Generic Drugs/Division of Chemistry II

Chemistry Assessment Section

Table of Contents

Chemistry Assessment Section

Chemistry Assessment Section

Chemistry Review Data Sheet

1. ANDA 76-880

2. REVIEW #: 6

3. REVIEW DATE: January 02, 2009

4. REVIEWER: David Skanchy

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	October 23, 2003
Amendment (telephone)	March 4, 2004
Amendment (response to deficiencies)	May 23, 2005
Amendment (response to deficiencies)	May 15, 2006
Amendment (response to Major due to DBE)	June 19, 2007
Telephone Amendment	July 6, 2007
Amendment (re-open CMC)	November 13, 2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (re-open CMC, <467>)	September 12, 2008
Telephone Amendment	October 14, 2008
Telephone Amendment	October 31, 2008

7. NAME & ADDRESS OF APPLICANT:

Chemistry Assessment Section

Name: Teva (formerly IVAX Pharmaceuticals, Inc.)
Address: Two University Plaza
Suite 220
Hackensack, New Jersey
07601

Representative: Patricia Jaworski
Telephone: (215) 293-6150

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Nicotine Polacrilex Gum USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for this submission is the approved listed drug, Nicorette® 2 mg, the subject of NDA #18-612, held by GlaxoSmithKline. The referenced drug product has no unexpired patents or exclusivity. A Paragraph I Certification and Exclusivity Statement are provided on pages 10015 and 10016, respectively.

10. PHARMACOL. CATEGORY:

Indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms.

11. DOSAGE FORM: Chewing Gum

12. STRENGTH/POTENCY: 2 mg

13. ROUTE OF ADMINISTRATION: Buccal

14. Rx/OTC DISPENSED: ___ Rx __X_ OTC

15. Spots Product

_____SPOTS product – Form Completed

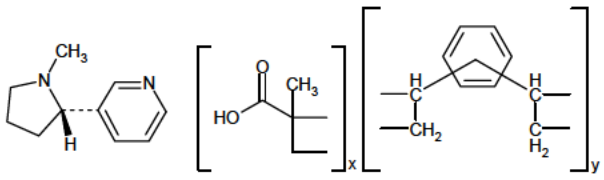
__X__Not a SPOTS product

Chemistry Assessment Section

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

Nicotine Polacrilex

Molecular Formula $C_{10}H_{14}N_2(C_{18}H_{22}O_4)_n$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Nicotine Polacrilex 20% w/w	1	Adequate	10/24/08	Reviewed by DSkanchy
	III		(b) (4)	4	N/A	N/A	
	III			4	N/A	N/A	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] 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
None		

Chemistry Assessment Section

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES*	Acceptable	12/23/2005; 01/31/2008	OC
Methods Validation	Not required		
Labeling	Acceptable	12/19/2008	M. Dillahunt
Bioequivalence	Acceptable	10/30/2008	S. Mazella, P. Seo
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

*Ivax AC in 2003, updated 01/31/2008.

19. ORDER OF REVIEW

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

Chemistry Assessment Section

The Chemistry Review for ANDA 76-880

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable from a Chemistry perspective.

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

None.

II. Summary of Chemistry Assessments

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

Nicotine is a volatile strongly alkaline oily liquid. It is colorless when pure but becomes yellow when exposed to air, boiling point is 247°C. It is optically active containing a single chiral center and has an $[\alpha]_d$ of -139° to -151° . Nicotine is supplied ionically bound to Polacrilex Resin which contains 20% nicotine. The resin is a weak cation exchange polymer made from vinylacrylic acid and divinyl benzene. The nicotine containing resin is blended with inactive ingredients such as Gum base, sorbitol, peppermint oil, and starch to produce a sugar free chewing gum containing 2 mg of nicotine. The drug is delivered for buccal absorbtion by chewing a 1 gram dosage unit. The reference listed drug for this product is Nicorette® Gum 2 mg by GlaxoSmithKline (NDA 18-612).

The manufacturer of the drug substance, Polacrilex Resin 20% Nicotine, is (b) (4) (DMF (b) (4) A two-year expiration dating period is proposed for this product. This is supported by accelerated stability data in the container/closure proposed for marketing.

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

Nicotine Gum's sugar free chewing pieces provide nicotine to the body, working as a temporary aid to help quit smoking by reducing nicotine withdraw symptoms. Nicotine Polacrilex Gum provides a lower level of nicotine to the blood stream than cigarettes, and allows people to gradually do away with the body's need for

nicotine. The recommended usage schedule and instruction on gradually decreasing nicotine polacrilex gum use are provided in the User's Guide.

C. Basis for Approvability or Not-Approval Recommendation

Approvable from a Chemistry perspective.

III. Administrative

Endorsement Block

HFD-640/DSkanchy/01/02/2009
HFD-640/NYa/1/27/09
HFD-617/THinchliffe/1/30/09

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Chemistry Assessment Section

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-880 APPLICANT: IVAX

DRUG PRODUCT: Nicotine Polacrilex Gum USP, 2 mg (Original Flavor)

N/A

Chemistry Assessment Section

Attachment 1. CHEMISTRY COMMENTS PROVIDED TO THE APPLICANT for Telephone Amendment (faxed 10/03/2008; response received 10/14/2008)

ANDA: 76-880 and 77-850 APPLICANT: IVAX
DRUG PRODUCT: Nicotine Polacrilex Gum USP, 2 mg and 4 mg (Original Flavor)

*The deficiencies presented below represent MINOR deficiencies and the current review cycle will remain open. You should respond completely to these deficiencies with a "**Telephone Amendment**" within ten days **or** provide us with an estimated time frame for when a complete response can be submitted. If you have questions regarding these deficiencies please contact the Chemist at 240-276-8552 or the Project Manager, Tom Hinchliffe, at 240-276-8536. Please submit documentation by fax to the attention of the Project Manager at 240-276-8582. Please also submit official hard copies of any faxed documentation to the OGD Document Room.*

1. Please provide a commitment to update the USP<467> information upon a change in supplier or method of manufacture for any of the formulation components.

2. Please update your finished product specifications and Certificate of Analysis format to include a statement that the product complies with USP <467> requirements.

3. Please provide data from a representative lot of the [redacted] (b) (4)

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

/s/

David Skanchy
2/12/2009 07:34:49 AM
CHEMIST

Naiqi Ya
2/18/2009 01:43:09 PM
CHEMIST

Thomas Hinchliffe
2/18/2009 01:45:31 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076880

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-880
Drug Product Name	Nicotine Polacrilex Chewing Gum, USP
Strength(s)	2 mg
Applicant Name	Ivax Pharmaceuticals, Inc. A wholly owned subsidiary of Teva Pharmaceuticals USA
Address	Two University Plaza, Suite 220, Hackensack, NJ 07601
Applicant's Point of Contact	Patricia Jaworski
Contact's Telephone Number	215-293-6150
Contact's Fax Number	201-489-1403
Original Submission Date(s)	10/23/2003
Submission Date(s) of Amendment(s) Under Review	3/16/2007
DSI Status	Clinical Site: VAI, inspected (b) (4) Analytical Site: VAI, inspected (b) (4)
Reviewer	Paul Seo, Ph.D.

Review of an Amendment

1 EXECUTIVE SUMMARY

This amendment was submitted in response to the DBE's concerns regarding several bioanalytical method deficiencies in the original submission dated 10/23/2003. At the Agency's recommendation, the firm has repeated the bioequivalence study under fasting conditions and is therefore submitting the current amendment which references Nicorette® Gum (regular flavor) and includes a new fasting bioequivalence (BE) study (study #AA27587). The previous BE deficiencies (letter dates 9/28/2004, 3/17/2005, 6/13/2005) regarding study #AA01926 are therefore no longer relevant.

The fasting study is a single-dose two-way crossover study using 11 male and 11 female normal healthy volunteers (smokers of at least 10-20 cigarettes/day) given a dose of 2 mg. The results (point estimate, 90% CI) of the fasting BE study are LAUCt of 1.07, 101.21-113.75%; LAUCi of 1.09, 104.20-114.88%; and LCmax of 1.00, 93.29-106.71%. The fasting study is incomplete due to lack of several biosummary tables and dissolution deficiency.

The firm performed in-vitro dissolution studies on its nicotine polacrilex chewing gum. The firm conducted dissolution testing using 40 mL of 0.1% SLS using chewing gum apparatus (b) (4) at 40 strokes/min. The firm's dissolution testing was not conducted as per EP. Although this is not required, the firm should provide a description (and figure if available) of apparatus (b) (4) used in the dissolution testing. Additionally, the firm should submit SOPs for dissolution testing. Dissolution conditions will be finalized after review of the requested information. The application is incomplete.

The DSI status is VAI. Both the clinical and analytical sites were inspected in (b) (4) and (b) (4) respectively.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 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	No	
BCS Waivers	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

3.2 Pre-Study Bioanalytical Method Validation

Table 3. Bioanalytical Method Validation For Nicotine VAL 39.6

Information requested	Data
Bioanalytical method validation report location	\\Cpu-103\Bio_Archive\VAL\Effective\val 39\VAL 39.6.doc
Analyte	Nicotine
Internal standard (IS)	(b) (4)
Method description	High performance liquid chromatographic mass spectrometric method, (b) (4)
Limit of quantitation	0.167 ng/mL
Average recovery of drug	Low QC: 101.1% High QC: 93.1%
Average recovery of IS	86.4%
Standard curve concentrations	0.167, 0.333, 0.555, 1.11, 5.55, 11.1, 22.2, 44.4, 55.5 ng/mL
QC concentrations	0.166, 0.498, 3.32, 16.6 ,41.6 ng/mL
QC Intra-Batch precision range	**Batch: 02CUS** **Precision** **Accuracy** LLOQ QC: 12.1% 7.8% Low QC: 8.5% 0.4% Medium-Low QC: 3.5% 0.6% Medium-High QC: 2.8% 2.4% High QC: 3.1% 1.2% **Batch: 04CUS** **Precision** **Accuracy** LLOQ QC: 4.0% 12.7% Low QC: 5.7% 7.8% Medium-Low QC: 1.7% 3.0% Medium-High QC: 1.5% 4.2% High QC: 3.6% 1.4% **Batch: 05CUS** **Precision** **Accuracy** LLOQ QC: 9.1% 7.8% Low QC: 4.8% 4.8% Medium-Low QC: 7.0% 3.0% Medium-High QC: 3.5% 0.6% High QC: 2.5% 0.0%
QC Inter-Batch precision range	**Batch:** **Precision** **Accuracy** LLOQ QC: 8.7% 9.6% Low QC: 6.7% 4.4% Medium-Low QC: 4.5% 2.1% Medium-High QC: 3.0% 2.4% High QC: 3.0% 1.0%
Short-term stability	58 hours at Ambient Temperature
Stock solution stability	266 days at 1.00 mg/mL in 0.02% Acetic Acid at -20°C 371 days at 0.0167 mcg/mL in Milli-Q water at -20°C
Internal Standard Stock solution stability	454 days at 54 mcg/mL in Milli-Q water at -20°C 364 days at 1.1 mcg/mL in Milli-Q water at -20°C
Post-preparative stability	108 hours Ambient Temperature
Freeze-thaw stability	4 cycles at -20°C
Long-term storage stability	815 days at -20°C
Processed sample integrity	120 hours at Ambient Temperature
Dilution integrity	up to 149 ng/mL
Selectivity	Nicotine is present in the environment and even in non-smoker donors. Therefore, Nicotine was found present in non-smoker donors tested: 25% showed interference of less than 50% of the LLOQ standard

SOPs submitted	Yes
Bioanalytical method is acceptable	Yes

Comments on the Pre-Study Method Validation:

The firm's dilution integrity was shown at for 68.9 ng/ml (using milliQ water since nicotine is present in the environment) and exhibited a %nominal and %CV of 92.0% and 2.8%, respectively for 2x, and 88.7% and 6.2%, respectively for 5x. The dilution

integrity was also shown for 149 ng/ml (using human plasma with EDTA) and exhibited a % nominal and %CV of 98.1% and 2.4%, respectively for 2x, and 107.7% and 6.6%, respectively for 5x.

The firm conducted a method validation for the determination of nicotine in chewed gum cuds, but did not submit an electronic summary table. The firm should also submit an electronic summary table of bioanalytical methods for the determination of nicotine in chewed gum cuds (e.g. VAL 118.3).

3.3 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No.(M/F) Age and Weight: Mean (Range)	Mean Parameters (± SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\ t}$ (ng·h/mL)	AUC_{∞} (ng·h/mL)	T½ (h)	K_{el} (1/h)	
AA27587	Comparative, Open-Label, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Ivax and GlaxoSmithKline (Nicorette®) 2 mg Nicotine Polacrilex Regular Flavored Chewing Gum in Healthy Adult Smokers under Fasting Conditions	Randomized Single-dose Crossover Uncorrected Data	Test product: nicotine polacrilex regular flavored chewing gum; 2 mg dose, oral Lot No.: US5684050006 Reference product: Nicorette® 2 mg regular flavored chewing gum; 2 mg dose, oral Lot No.: FI151A	22 healthy adult volunteers (11 males and 11 females) completed the study Mean age and weight based on 22 subjects completing the study: 23 years (18 - 34 years) Mean Weight: 70.6 kg (55.5 – 99.2 kg) Pharmacokinetic and statistical analyses were performed on data from 22 subjects	5.4427 ± 2.00875 5.2968 ± 1.71956	0.8565 0.7784	20.267 ± 10.0637 18.430 ± 8.9326	21.486 ± 10.7647 19.673 ± 9.6075	3.941 3.863	0.22793 0.23106	Vol. p.
AA27587	Comparative, Open-Label, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Ivax and GlaxoSmithKline (Nicorette®) 2 mg Nicotine Polacrilex Regular Flavored Chewing Gum in Healthy Adult Smokers under Fasting Conditions	Randomized Single-dose Crossover PK Corrected Data	Test product: nicotine polacrilex regular flavored chewing gum; 2 mg dose, oral Lot No.: US5684050006 Reference product: Nicorette® 2 mg regular flavored chewing gum; 2 mg dose, oral Lot No.: FI151A	22 healthy adult volunteers (11 males and 11 females) completed the study Mean age and weight based on 22 subjects completing the study: 23 years (18 - 34 years) Mean Weight: 70.6 kg (55.5 – 99.2 kg) Pharmacokinetic and statistical analyses were performed on data from 22 subjects	5.3364 ± 1.96451 5.2009 ± 1.68030	0.8565 0.7784	19.334 ± 9.6671 17.640 ± 8.4531	21.008 ± 10.5423 19.210 ± 9.1281	3.655 3.493	0.23599 0.24042	Vol. P.

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer (On Non-Baseline Corrected Data, Dropped Subject #s 1, 14, 16, and 21 due to >5%Cmax)

Drug Dose (1 x 2 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study (Study No.AA27587)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng hr/ml)	17.92	16.70	1.07	101.21-113.75
AUC∞ (ng hr/ml)	20.76	18.98	1.09	104.20-114.88
Cmax (ng/ml)	5.06	5.07	1.00	93.29-106.71

Note: DBE does not recommend baseline correction for chewing gum studies

Table 3. Reanalysis of Study Samples

AA27587 Additional Information in Volume(s), Page(s)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
LSR – Lowest Standard Remove	40	41	4.81	4.93	40	40	4.81	4.81
LIP – Lost in Processing	6	5	0.72	0.60	6	5	0.72	0.60
UCR – Unacceptable Chromatography	2	2	0.24	0.24	2	2	0.24	0.12
DCU – Diluted Concentration Unreliable	12	7	1.44	0.84	12	7	1.44	0.84
Value Requiring Confirmation	1	0	0.12	0.00	1	0	0.12	0.00
Total	61	55	7.33	6.61	61	54	7.33	6.37

Did use of recalculated plasma concentration data change study outcome? "Value Requiring Confirmation" may potentially be a PK repeat. Therefore the reviewer recalculated the data with and without the reassay in question. The study outcome did not change.

Comments from the Reviewer: Acceptable

3.4 Formulation

Same as original submission dated 10/23/2003

3.5 In Vitro Dissolution

Location of DBE Dissolution Review	None
Source of Method (USP, FDA or Firm)	Firm
Medium	0.1% SLS
Volume (mL)	40 mL
Apparatus type	(b) (4) chewing gum apparatus
Rotation (rpm)	40 strokes/min
DBE-recommended specifications	NLT (b) (4) (Q) in 30 minutes-EP 2.9.25
If a modified-release tablet, was testing done on ½ tablets?	NA
F2 metric calculated?	No
If no, reason why F2 not calculated	Only single strength
Is method acceptable?	**INCOMPLETE**
If not then why?	*See note below

*Note: The original submission (dated 10/23/2003) did not provide any dissolution data. The firm's dissolution testing was not conducted as per EP. Although this is not required, the firm should provide a description (and figure if available) of apparatus (b) (4) used in the dissolution testing. Additionally, the firm should submit SOPs for dissolution testing. Dissolution conditions will be finalized after review of the requested information.

3.6 Waiver Request(s)

NONE

3.7 Deficiency Comments

1. The firm's dissolution testing was not conducted as per EP. Although this is not required, the firm should provide a description (and figure if available) of apparatus (b) (4) used in the dissolution testing. Additionally, the firm should submit SOPs for dissolution testing. Dissolution conditions will be finalized after review of the requested information.

2. The firm conducted a method validation for the determination of nicotine in chewed gum cuds, but did not submit an electronic summary table. The firm should also submit an electronic summary table of bioanalytical methods for the determination of nicotine in chewed gum cuds (e.g. VAL 118.3).

3.8 Recommendations

1. The bioequivalence study conducted under fasting conditions by IVAX Pharmaceuticals, Inc. on its test product, Nicotine Polacrilex 2 mg gum (regular flavor), lot #US5684050006 comparing it to the reference product, Nicorette® 2 mg gum (regular flavor), lot #F1151A, manufactured by GlaxoSmithKline is incomplete.

2. The multi-dose chew-out study (previously reviewed in 76880N0307.doc) conducted by IVAX Pharmaceuticals, Inc. on its nicotine polacrilex 2 mg gum (regular flavor), lot US5684030001 comparing it to Nicorette® 2 mg gum (regular flavor), lot DA050A manufactured by GlaxoSmithKline is acceptable.

3. The dissolution testing is incomplete. The firm should provide a description (and figure if available) of apparatus (b) (4) used in the dissolution testing. Additionally, the firm should submit SOPs for dissolution testing. Dissolution conditions will be finalized after review of the requested information.

The firm should be informed of the deficiency comments and recommendations

3.9 Comments for Other OGD Disciplines

Discipline	Comment
	NONE

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	AA27587
Study Title	Comparative, Open-Label, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Ivax and Glaxosmithkline (Nicorette®) 2 mg Nicotine Polacrilex Regular Flavored Chewing Gum in Healthy Adult Smokers Under Fasting Conditions
Clinical Site (Name & Address)	MDS Pharma Services, 22-24 Lisburn Road, Belfast, N. Ireland, BT9 6AD
Principal Investigator	Stephen P. Smith, MB, MRCGP
Dosing Dates	Period 1: 9/8/2005 Period 2: 9/22/2005
Analytical Site (Name & Address)	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	Plasma: 10/28/2005 – 3/22/2006 Gum: 10/29/2005
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	195 days (long term stability was shown for 815 days @ -20°C)

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Nicotine Polacrilex Chewing Gum (regular)	Nicorette® (regular)
Manufacturer	IVAX Pharmaceuticals, Inc.	GlaxoSmithKline
Batch/Lot No.	US5684050006	F1151A
Manufacture Date	05/2005	
Expiration Date		2/2007
Strength	2 mg	2 mg
Dosage Form	Chewing Gum	Chewing Gum
Bio-Batch Size	(b) (4) pieces	
Production Batch Size	(b) (4) pieces	

Potency (Assay)	107%	105%
Content Uniformity (mean, %CV)	107.5%, 1.8%	
Dose Administered	1x2 mg	1x2 mg
Route of Administration	Buccal	Buccal

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	23 enrolled (smokers of at least 10-20 cigarettes per day), 22 completing, 22 analyzed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 1, 2, 3, 4, 7, 8, 13, 14, 19, 20, 22, 23 BA: 5, 6, 9, 10, 11, 12, 15, 16, 17, 18, 21, 24
Blood Sampling Times	-0.25, -0.167, -0.0833, and 0 hours predose, and at 0.0833, 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 2, 3, 6, 9, 12, 16, and 24 hours post-dose
Blood Volume Collected/Sample	1 x 10 ml in tubes containing EDTA
Blood Sample Processing/Storage	Samples were collected and processed on ice prior to storing. Plasma samples were separated by centrifugation, then frozen at -20°C and kept frozen until assayed
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	At least 10 hours prior to dosing and for at least 4 hours thereafter
Length of Confinement	At least 36 hours prior to dosing until after the 24-hour blood draw
Method of Administration	Subjects chewed the gum for 30 minute duration. The gum was chewed 3 times every 4 seconds. The subjects were required to chew the gum 3 times on one side of the mouth and then move the gum to the other side of the mouth to chew 3 times on that side of the mouth
Smoking Restrictions	During confinement, subjects were not allowed to smoke. To avoid contamination of the subjects with additional nicotine by smoking, their surroundings were totally free of cigarette smoke
Safety Monitoring	Seated blood pressure and carbon monoxide testing

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

	Test Product N=22	Reference Product N=22
Age (Years)		
Mean±SD	23.2 ± 4.0	23.2 ± 4.0
Range	18 - 34	18 - 34
Age Groups (Years)		
18-39	22 (100.0%)	22 (100.0%)
Sex		
Female	11 (50.0%)	11 (50.0%)
Male	11 (50.0%)	11 (50.0%)
Race		
Caucasian	22 (100.0%)	22 (100.0%)

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
3	Subject was dropped due to difficult venipuncture	2	N

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Adverse Event (Classified according to MedDRA Version 8.1) System Organ Class Preferred Term	Test		Reference		Total	
Number of Subjects Dosed	23	(100%)	23	(100%)	23	(100%)
Number of Subjects With Adverse Events	22	(95.7%)	19	(82.6%)	22	(95.7%)
Number of Subjects Without Adverse Events	1	(4.3%)	4	(17.4%)	1	(4.3%)
Respiratory, thoracic and mediastinal disorders	18	(78.3%)	13	(56.5%)	19	(82.6%)
Cough	13	(56.5%)	11	(47.8%)	16	(69.6%)
Throat irritation	10	(43.5%)	6	(26.1%)	11	(47.8%)
Hiccups	3	(13%)	3	(13%)	4	(17.4%)
Nasal congestion	2	(8.7%)	0	(0%)	2	(8.7%)
Increased upper airway secretion	0	(0%)	1	(4.3%)	1	(4.3%)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
At screening on 9/6/2005, this subject's height/weight% was 20%. The protocol required that subjects were within ±15% of their ideal weights. Client approval was obtained to continue this subject in the study	22	
On 9/8/2005, PK samples were not obtained for the subject at 8:20, 8:40, and 14:00 hours	19	
On 9/22/2005, PK samples were not obtained for the subject at 9:15, and 10:00 hours		3
On 9/22/2005, PK sample was not obtained for the subject at 8:05 hours	17	
Due to recruitment issues, only 23 subjects were dosed in period 1 instead of 24		
Sample time deviations		

Comments on Dropouts/Adverse Events/Protocol Deviations:
No major adverse events or protocol deviations occurred such that the study outcome was altered. There were a few sampling time deviations. Actual times were used for calculating PK parameters.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Analyte 1									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	0.149	0.298	0.497	0.993	4.97	9.93	19.9	39.7	49.7
Inter day Precision (%CV)	5.0	3.5	4.2	3.5	2.9	3.8	3.0	2.4	2.3
Inter day Accuracy (%Actual)	107.4	100.7	100.0	92.0	95.4	103.7	100.0	102.0	98.2
Linearity	0.9972 – 0.9998								
Sensitivity/LOQ (ng/mL)	0.149								

Parameter	**Quality Control Samples**		
Concentration (ng/mL)	0.450	3.00	15.0
Inter day Precision (%CV)	5.6	2.3	2.6
Inter day Accuracy (%Actual)	110.9	103.3	100.0

Reviewer's note: For several of the batches, the analyses of the study samples were frequently outside the acceptance criteria. Moreover, in some batches, several low QC samples were outside the acceptance criteria and the batches were rejected.

To resolve this problem, the firm prepared new intermediate stock solutions and working solutions on 1/16/2006. The linearity of the working solutions was verified and the results found acceptable. Since the working solutions were acceptable, STD and QC samples were prepared on 1/24/2006 using these working solutions. This is the reason for discrepancy between assay validation and reported pre-validation.

Comments on Study Assay Validation: Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Randomly, subject #s 6, 7, 10, 11, 12, 13

Comments on Chromatograms: Acceptable

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
GL-BIO-10602-01	8/23/2004	Chromatographic and Spectrometric Methods: Calibration Curve Preparation, Specifications and Acceptance Criteria
GL-BIO-10603-01	8/23/2004	Reporting of Data Generated from the Analysis of Biological Matrices and the Reassay of Samples

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:
Acceptable

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters (Data w/o correction for baseline and dropped subject #s 1, 14, 16, and 21 due to >5%Cmax)

Mean plasma concentrations are presented in Table 18 and Figure 1

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	20.22	55.18	6.10	52.78	18.41	53.64	7.65	51.69	1.10
AUCI	ng hr/mL	22.41	49.22	11.15	54.36	20.89	47.15	13.85	52.89	1.07
CMAX	ng/mL	5.42	40.37	2.73	9.91	5.33	34.73	3.07	9.84	1.02
TMAX	hr	0.83	.	0.33	2.00	0.67	.	0.50	1.25	1.25
KE	hr-1	0.20	36.02	0.00	0.31	0.18	39.36	0.00	0.29	1.11
THALF	hr	3.46	24.14	2.26	4.81	3.48	13.15	2.42	4.59	0.99

* Tmax values are presented as median, range.

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Nicotine Dose (2 mg) Geometric Means*, Ratio of Means, and 90% Confidence Intervals				
Bioequivalence Study (Uncorrected Data)				
Parameter	Test	Reference	Ratio (%)	90% C.I.
AUC_{0-t}	18.3470	16.9944	108.0	102.4% - 113.8%
AUC∞	19.4350	18.1880	106.9	101.5% - 112.5%
C_{max}	5.13541	5.06478	101.4	95.9% - 107.2%
Bioequivalence Study (Baseline-Corrected Data)				
Parameter	Test	Reference	Ratio (%)	90% C.I.
AUC_{0-t}	17.5490	16.3110	107.6	101.7% - 113.8%
AUC∞	19.1471	17.9144	106.9	101.2% - 112.9%
C_{max}	5.03581	4.97526	101.2	95.7% - 107.1%

* Geometric least-squares means are reported

Table 16. Geometric Means and 90% Confidence Intervals (w/o baseline correction, Dropped subject #s 1, 14, 16, and 21 due to >5%Cmax) - Reviewer Calculated

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	17.92	16.70	1.07	101.21	113.75

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCI	20.76	18.98	1.09	104.20	114.88
LCMAX	5.06	5.07	1.00	93.29	106.71

Table 17. Additional Study Information, Fasting Study No.

Root mean square error, AUC0-t	0.1004	
Root mean square error, AUC∞	0.0763	
Root mean square error, Cmax	0.1155	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	22(firm), 18 (reviewer)	22(firm), 18 (reviewer)
Do you agree or disagree with firm's decision?	Disagree (see comments below)	Disagree (see comments below)
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	8*	11*
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Treatment	Mean	Minimum	Maximum
TEST	0.93	0.84	0.98
REFERENCE	0.93	0.89	0.98

*Subjects #1 (test and reference), #2 (test and reference), #9 (test and reference), #11 (test and reference), #13 (reference), #14 (reference), #16 (test and reference), #17 (test and reference), #19 (test), #21 (reference), #22 (test and reference), and #23 (reference) exhibited measurable drug concentrations at 0 hour. Subjects #1 #14, #16, and #21 exhibited ≥5%$Cmax_{invidivual}$. The other subjects' 0-hour concentrations were <5%$Cmax_{individual}$.

Comments on Pharmacokinetic and Statistical Analysis:
The firm included 22 subjects in its statistical analysis. However, four subjects (#1, #14, #16, and #21) exhibited 0 hour drug concentrations that were ≥5%$Cmax_{invidivual}$, and therefore the reviewer repeated the statistical analysis (n=18) without these four subjects (as per *FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations).*

For information purposes, the firm also submitted baseline (pre-dose values) corrected data. The Division of Bioequivalence does not recommend correcting the data for baseline. The reviewer therefore did not repeat statistical analysis on the firm's baseline corrected data.

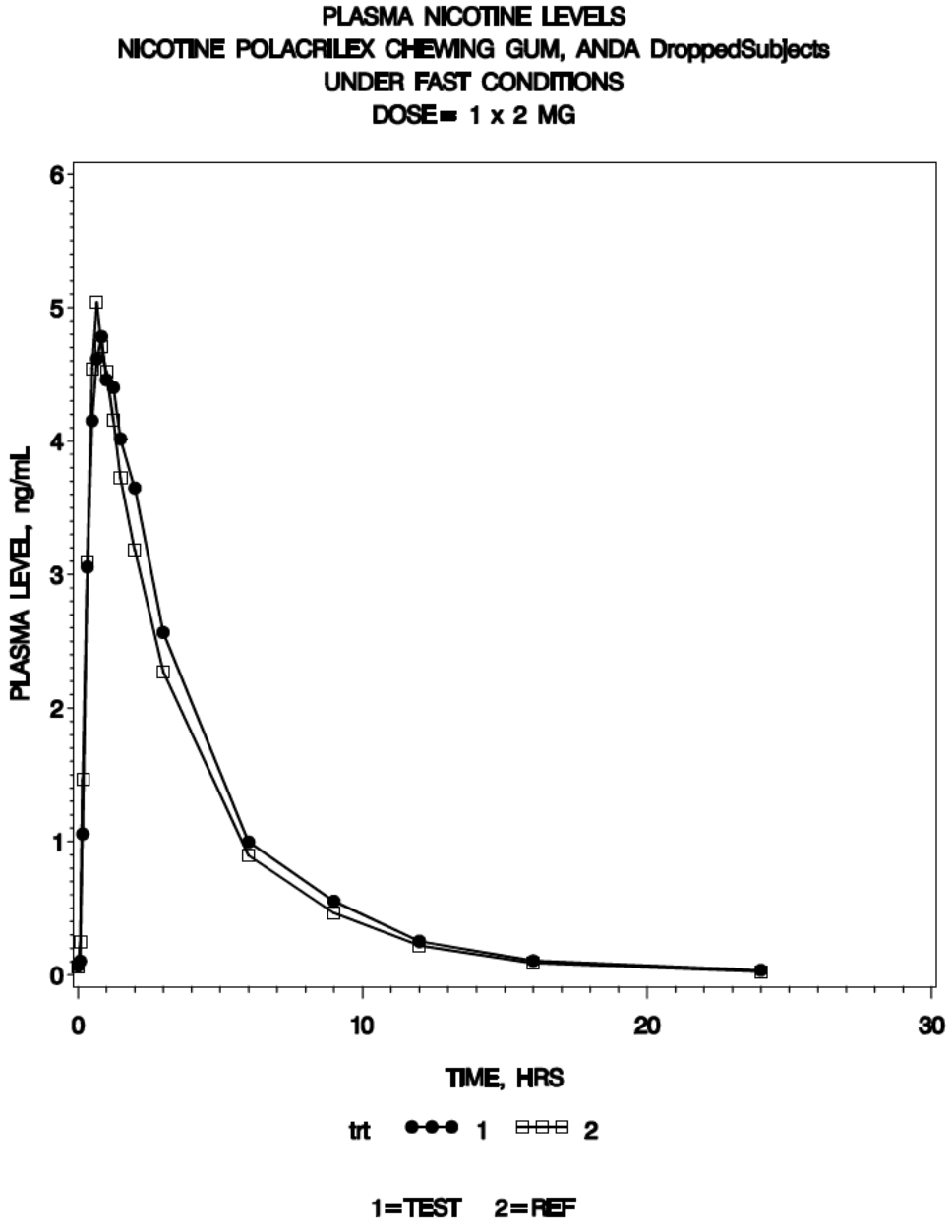
The reviewer recalculated the pharmacokinetic parameters and repeated statistical analysis for the firm's datasets using uncorrected (no baseline correction) data. The study outcome did not change.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:
The single-dose fasting bioequivalence study is incomplete due to lack of several biosummary tables and dissolution deficiency.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=18)		Reference (n=18)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.07	159.63	0.06	179.35	1.20
0.08	0.10	133.62	0.25	68.33	0.42
0.17	1.06	58.90	1.46	53.42	0.72
0.33	3.06	59.89	3.10	31.99	0.99
0.50	4.15	45.95	4.54	30.00	0.91
0.67	4.61	46.35	5.04	35.47	0.92
0.83	4.78	31.97	4.70	32.80	1.02
1.00	4.46	27.25	4.52	30.96	0.99
1.25	4.40	32.13	4.15	37.58	1.06
1.50	4.02	35.87	3.72	41.30	1.08
2.00	3.65	48.18	3.18	43.23	1.15
3.00	2.57	50.63	2.27	46.63	1.13
6.00	1.00	75.65	0.89	74.89	1.11
9.00	0.55	77.19	0.46	83.27	1.19
12.00	0.25	120.63	0.22	103.81	1.14
16.00	0.11	166.59	0.09	190.18	1.18
24.00	0.04	238.43	0.02	297.40	1.50

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.2 Dissolution Data

Dissolution Review Path	None

Table 19. Dissolution Data

Dissolution Conditions	**Apparatus:**	(b) (4) Chewing gum apparatus
	Speed of Rotation:	40 strokes/min
	Medium:	0.1% SLS
	Volume:	40 mL
	Temperature:	37°C
Firm's Proposed Specifications	Not proposed	

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved [Range], % RSD					Study Report Location
					5 min	10 min	20 min	30 min	45 min	
RE/8-Rev.0	Nicotine Polacrilex Chewing Gum, 2 mg Lot #: 5684050006	Gum, 2 mg	Dissolution Tester for Chewing Gum (b) (4) Medium: 0.1% sodium lauryl sulfate Volume: 40 ml Gap: 1.6 mm Twisting angle: 20° Chew Frequency: 40 strokes/minute Temperature: 37.4°C ± 0.3 °C Sample: gum piece between two rigid nylon nets	12	31	57	80	89	94 (b) (4)	Bioequivalence amendment, Vol. 1 Exhibit 5
					11	7	4	2	2	
RE/8-Rev.0	Nicorette® Gum 2 mg Lot #: FI 151	Gum, 2 mg		12	61	84	93	96	99 (b) (4)	
					14	5	3	3	3	

4.3 Consult Reviews

NONE

4.4 SAS Output

4.4.1 Fasting Study Data

FAST CONCENTRATION DATASET

(b) (4)

5 Pages has been Withheld in Full as b4 (CCI/TS) immediately following this page

4.5 Additional Attachments

NONE

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-880

APPLICANT: Ivax Pharmaceuticals, Inc. (A wholly owned subsidiary of Teva Pharmaceuticals USA)

DRUG PRODUCT: Nicotine Polacrilex Chewing Gum, 2 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

1. Please provide a description (and figure if available) of the chewing apparatus (b) (4) used in the dissolution testing. Additionally, p submit SOPs for dissolution testing. Dissolution conditions will be finalized after review of the requested information.

2. Please submit an electronic summary table of bioanalytical methods for the determination of nicotine in chewed gum cuds (e.g. VAL 118.3).

3. Please note for future studies, your selection of 20% sample chromatograms should be serially selected.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.6 Outcome Page

ANDA: 76-880

3.	**Study Amendment**	Strength(s):	2 mg
	(STA-New Fasting study)	Outcome:	**IC**
	Submission Date(s)	**3/16/2007**	
	Clinical Site:	MDS Pharma Services, 22-24 Lisburn Road, Belfast, N. Ireland, BT9 6AD	
	Analytical Site:	(b) (4)	

BIOEQUIVALENCE OUTCOME DECISIONS:	AC – Acceptable IC – Incomplete UN – Unacceptable WC – Without Credit

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

/s/

Paul Seo
4/18/2007 10:03:23 AM
BIOPHARMACEUTICS

Yih Chain Huang
4/18/2007 10:06:55 AM
BIOPHARMACEUTICS

Barbara Davit
4/18/2007 03:36:04 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-880
Drug Product Name	Nicotine Polacrilex Chewing Gum, USP
Strength(s)	2 mg
Applicant Name	Ivax Pharmaceuticals, Inc. A wholly owned subsidiary of Teva Pharmaceuticals USA
Address	Two University Plaza, Suite 220, Hackensack, NJ 07601
Applicant's Point of Contact	Patricia Jaworski
Contact's Telephone Number	215-293-6150
Contact's Fax Number	201-489-1403
Original Submission Date(s)	10/23/2003
Submission Date(s) of Amendment(s) Under Review	5/16/2007
DSI Status	Clinical Site: VAI, inspected (b) (4) Analytical Site: VAI, inspected (b) (4)
Reviewer	Paul Seo, Ph.D.

Review of an Amendment

1 EXECUTIVE SUMMARY

This amendment was submitted in response to a request from the Division of Bioequivalence (DBE) about dissolution testing and biosummary tables. The firm provided a description and figure (as part of the operating manual) of the chewing apparatus (b) (4) as requested. The firm also submitted SOPs, analytical validation report, and analytical validation protocol for dissolution testing. The firm also submitted an electronic summary table of bioanalytical methods for the determination of nicotine in chewing gum cuds.

The dissolution testing is acceptable. The firm should acknowledge the DBE-recommended specification of NLT (b) (4) in 30 min. The application is incomplete pending dissolution method and specification acknowledgement.

The DSI has inspected the analytical and clinical facilities. The outcomes were VAI.

2 REVIEW OF SUBMISSION

Deficiency 1: Please provide a description (and figure if available) of the chewing apparatus (b) (4) used in the dissolution testing. Additionally, please submit SOPs for dissolution testing. Dissolution conditions will be finalized after review of the requested information.

Firm's Response: The firm states that the (b) (4) dissolution apparatus consists of two vertically opposed surfaces contained in a thermostatted glass cylinder. The bottom surface, including the test cell, is raised and lowered so as to come into close contact with the upper surface. The upper surface is attached to a cylinder that rotates slightly with each vertical

"chew" event. Laboratorios Haymann S.A., the manufacturer of Nicotine Polacrilex Chewing Gum USP, 2 mg, has currently a (b) (4) version of the device. Additional testing capabilities (6-cell device) can be added as sample requirements dictate.

Moreover, the firm submitted the operating manual, instrument qualification, and operation qualification of the dissolution tester for chewing (b) (4)

Reviewer's Comment: Typically for chewing gum dosage forms, DBE has recommended the "EP chewing gum apparatus", however, the EP apparatus is not commercially/readily available. The (b) (4) shares many similarities with typical chewing gum dissolution apparatuses (e.g. EP Apparatus type: A machine is used to simulate gum chewing. Each piece of gum is placed in a small chamber at 37^0C containing 20 ml of "saliva" (chewing buffer). Two horizontal pistons "chew" the gum at a constant speed. A "tongue" (vertical position) ensures that the gum remains in the correct place). Based on the submitted documentation and firm's statement, it is the reviewer's opinion that the dissolution tester (b) (4) is sufficiently adequate in performing dissolution testing on nicotine polacrilex chewing gum.

The firm should acknowledge the FDA-recommended dissolution method and specification as follows:

Apparatus:	(b) (4)
Medium:	0.1% SLS
Volume:	40 mL
Gap:	1.6 mm
Twist Angle:	20^o
Speed:	40 strokes/min
Specification:	NLT (b) (4) (Q) in 30 minutes

Deficiency 2: Please submit an electronic summary table of bioanalytical methods for the determination of nicotine in chewed gum cuds (e.g. VAL 118.3).

Firm's Response: The firm submitted an electronic biosummary table of bioanalytical methods for the determination of nicotine in chewing gum cuds. The table is presented below.

Information Requested	Data
Bioanalytical method validation report title and number	VALIDATION REPORT OF AN LC/MS METHOD FOR THE DETERMINATION OF NICOTINE IN CHEWED GUM CUDS (2 MG AND 4 MG) (b) (4) VAL 118.3
Analyte	Nicotine (b) (4)
Internal standard (IS)	
Method description	The calibration standard and QC samples were prepared in solution although the analysis of study samples are in gum. The repeatability tests had proven that nicotine concentration in gum cuds can be evaluated over a calibration curve prepared in solution. Procedures of extraction: • The calibration curves were prepared as follows: An aliquot of standard and QC samples containing Nicotine plus an internal standard is diluted. • The gum samples were prepared as follows: A gum containing Nicotine plus an internal standard is extracted using a solid/liquid extraction procedure. Calibration standard and QC samples together with the extracted gum samples were injected into an HPLC equipped with a (b) (4) (b) (4) Quantitation is by peak area ratio. A weighted linear regression is used to determine the concentration of the compound.
Limit of quantitation	10.0 ng/mL (equivalent to 0.102 mg in gum)
Average recovery of drug in gum cuds	Low 118.6 % High 105.3 %
Average recovery of IS in gum cuds	83.6 %
Standard curve concentrations (final concentration in vial)	10.0, 20.0, 44.3, 70.6, 88.6, 176, 353 and 443 ng/mL
QC concentrations (final concentration in vial)	QC LLOQ : 9.90 ng/mL QC Low : 31.8 ng/mL QC Medium : 159 ng/mL QC High : 318 ng/mL
QC LLOQ Intraday precision range	7.5 %
QC LLOQ Intraday accuracy range	81.8 %
QC Low Intraday precision range	3.2 %
QC Low Intraday accuracy range	96.5 %
QC Medium Intraday precision range	2.9%
QC Medium Intraday accuracy range	106.9 %
QC High Intraday precision range	2.5 %

QC High Intraday accuracy range	103.1 %
QC Low Interday precision range	10.6 %
QC Low Interday accuracy range	95.3 %
QC Medium Interday precision range	12.7 %
QC Medium Interday accuracy range	98.7 %
QC High Interday precision range	11.0 %
QC High Interday accuracy range	108.8 %
Bench-top stability in gum cuds	25.0 hours at ambient temperature
Primary Stock Solution stability at 45.1 mg/mL	415 days in 0.02% acetic acid at -20ºC
Intermediate Stock Solution stability at 10.1 mcg/mL	366 days in 0.02% acetic acid at -20ºC
Intermediate Stock Solution stability at 22.5 mg/mL	119 days in Methanol / 0.02% acetic acid (50/50, v/v) at -20ºC
Intermediate Stock Solution stability at 0.505 mg/mL	358 days in Methanol / 0.02% acetic acid (50/50, v/v) at -20ºC
Primary Internal Standard Stock stability at 50.0 mg/mL	175 days in Methanol at -20ºC
Processed sample integrity	136 hours at ambient temperature
Post-preparative stability	73.0 hours at ambient temperature
Freeze-thaw stability in gum cuds	1 cycle at -20ºC
Long-term storage stability in gum cuds	91 days at -20ºC
Repeatability in gum cuds (4 mg)	2.4 %
Repeatability in gum cuds (2 mg)	5.4 %
Dilution integrity	N/AP
Selectivity	N/AP

Reviewer's Comment: The response is satisfactory.

Deficiency 3: Please note for future studies, your selection of 20% sample chromatograms should be serially selected.

Firm's Response: The firm acknowledges the Agency's comment that for future studies, the selection of 20% sample chromatograms should be serially selected.

Reviewer's Comment: The response is satisfactory.

Reviewer's Comments:

1. The dissolution testing is incomplete. The firm should acknowledge the FDA-recommended dissolution method and specification as follows:

Apparatus: (b) (4)
Medium: 0.1% SLS
Volume: 40 mL
Gap: 1.6 mm
Twist Angle: 20^{o}
Speed: 40 strokes/min
Specification: NLT (b) (4) (Q) in 30 minutes

Recommendations:

1. The bioequivalence study conducted under fasting conditions (previously reviewd in 76880A0307) by IVAX Pharmaceuticals, Inc. on its test product, Nicotine Polacrilex 2 mg gum (regular flavor), lot #US5684050006 comparing it to the reference product, Nicorette® 2 mg gum (regular flavor), lot #F1151A, manufactured by GlaxoSmithKline is acceptable.

2. The multi-dose chew-out study (previously reviewed in 76880N0307.doc) conducted by IVAX Pharmaceuticals, Inc. on its nicotine polacrilex 2 mg gum (regular flavor), lot US5684030001 comparing it to Nicorette® 2 mg gum (regular flavor), lot DA050A manufactured by GlaxoSmithKline is acceptable.

3. The dissolution testing is incomplete. The dissolution testing should be conducted using the FDA-recommended method: 40 ml of 0.1% SLS using chewing gum apparatus (b) (4) at 1.6 mm gap, 20° twist angle, and 40 strokes/min. The dissolution testing should meet the specification of NLT (b) (4) (Q) in 30 minutes.

The firm should be informed of the above comments and recommendations.

Comments to other OGD Disciplines

Discipline	Comment
All	Clinical Site: VAI, inspected (b) (4) Analytical Site: VAI, inspected (b) (4)

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-880

APPLICANT: Ivax Pharmaceuticals, Inc. (A wholly owned subsidiary of Teva Pharmaceuticals USA)

DRUG PRODUCT: Nicotine Polacrilex Chewing Gum, 2 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

You did not propose a dissolution specification. The dissolution testing should be conducted as follows:

Apparatus:	(b) (4)
Medium:	0.1% SLS
Volume:	40 mL
Gap:	1.6 mm
Twist Angle:	20°
Speed:	40 strokes/min

The test products should meet the following specification:

Not less than (b) (4) (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

With your response to the above deficiency, please indicate if you accept the above dissolution method and specification.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

3 OUTCOME PAGE

ANDA: 76-880

1.	**Study Amendment**	Strength(s):	2 mg
	(STA)	Outcome:	**IC (Pending dissolution acknowledgement)**
	Submission Date(s)	**5/16/2007**	
	Clinical Site:	MDS Pharma Services, 22-24 Lisburn Road, Belfast, N. Ireland, BT9 6AD	
	Analytical Site:	(b) (4)	

BIOEQUIVALENCE OUTCOME DECISIONS:	AC – Acceptable IC – Incomplete UN – Unacceptable WC – Without Credit

NOTE: The DSI has inspected the analytical and clinical facilities. The outcomes were VAI.

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/s/

Paul Seo
7/12/2007 04:03:42 PM
BIOPHARMACEUTICS

Yih Chain Huang
7/13/2007 09:04:30 AM
BIOPHARMACEUTICS

Barbara Davit
7/13/2007 05:29:50 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	76-880
Drug Product Name	Nicotine Polacrilex Chewing Gum
Strength	2 mg
Applicant Name	Teva Pharmaceuticals, USA
Submission Date	September 27, 2007
Reviewer	Steven Mazzella,R.Ph.

EXECUTIVE SUMMARY

This is a review of the dissolution specification acknowledgement from the firm.

The firm has accepted the FDA-recommended dissolution method and specification.

The application is complete.

COMMENTS:

None

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for *in-vivo* bioequivalence and *in-vitro* dissolution testing and the application is approvable.

I. Completed Assignment for 76880 ID: 782

Reviewer: Mazzella, Steven **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
782	9/27/2007	Dissolution Data	Dissolution Acknowledgement	1	0
				Bean Total:	0

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

/s/

Steven Mazzella
10/30/2007 12:41:22 PM
BIOPHARMACEUTICS

Lizzie Sanchez
10/30/2007 01:33:20 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076880

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IVAX
Pharmaceuticals, Inc.
140 Legrand Avenue
Northvale, New Jersey • 07647
Telephone: 201-767-1700
www.IVAXPharmaceuticals.com

76-880

OCT 23 2003

N-000

Via Federal Express

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ABBREVIATED NEW DRUG APPLICATION

Re: Nicotine Polacrilex Gum USP, 2 mg
Original ANDA Submission

Dear Mr. Buehler:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, and in compliance with 21 CFR §314.94, IVAX Pharmaceuticals, Inc., herewith submits an Abbreviated New Drug Application (ANDA) for Nicotine Polacrilex Gum USP, 2 mg.

IVAX has organized its ANDA in accordance with the OGD Guidance of February 1999, entitled, *Organization of an ANDA*. In support of this application, the information outlined below is provided:

- Table of Contents
- Form FDA 356h
- Basis for Submission
- Patent Certification and Exclusivity Statement
- Comparison between the proposed drug and the reference listed drug (Nicorette® Gum 2 mg, NDA held by Glaxo SmithKline)
- Draft Labeling (Four copies each in the archival [blue] binder, chemistry review [red] binder and the pharmacokinetic and bioavailability review [orange] binder.)
- Certification of Financial Interests and Arrangements of Clinical Investigators (Form FDA 3454)
- *In Vivo* Bioequivalence Studies (Fasted and Salivary Dissolution):

  Protocol No. AA01926: A Comparative Randomized, Single-Dose, Two-Way Crossover Bioavailability Study of Nicotine Polacrilex Gum 2mg in Healthy Adult Volunteers under Fasting Conditions

  Protocol No. AA02381: A Comparative Randomized, Two-Way Salivary Dissolution Crossover Bioavailability Study of Nicotine Polacrilex Gum 2 mg in Healthy Adult Volunteers.

The Diskettes are included in the front covers of the pharmacokinetic and bioavailability review (orange) binders: Volumes 2 of 6 and 5 of 6, respectively.

RECEIVED
OCT 27 2003
OGD/CDER

- Chemistry, Manufacturing and Controls Information
- Debarment, Conviction and Field Copy Certifications
- Methods Validation Package: Three (3) separately bound and identified copies are provided. IVAX Pharmaceuticals, Inc., commits to satisfactorily resolve any issues which might be identified during review of the methods validation, whether this occurs before or after ANDA approval.

This ANDA seeks approval for Nicotine Polacrilex Gum USP, 2 mg. Section VI of this application contains comparative analytical data for IVAX's Nicotine Polacrilex Gum USP, 2 mg, versus the innovator's 2 mg strength.

The archival copy of this application consists of eight (8) volumes. The chemistry review copy consists of three (3) volumes. The pharmacokinetic and bioavailability review copy consists of six (6) volumes.

The exhibit batch for this application was manufactured and packaged for (b) (4)

(b) (4)

IVAX Pharmaceuticals, Inc., requests that all information in this file be treated as confidential within the meaning of 21 CFR §314.430, and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office. We have made a concerted effort to ensure that this application contains all of the information that the Office of Generic Drugs may require. Should you have any questions, or require additional information, please contact our office at your convenience at (201) 767-1700, extension 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Director, Regulatory Affairs

cc: District Office

PJ/sh

Archival

IVAX Pharmaceuticals, Inc.

140 Legrand Avenue
Northvale, New Jersey • 07647
Telephone: 201-767-1700
www.IVAXPharmaceuticals.com

11/17/2003

Via Federal Express

NOV 0 5 2003

NEW CORRESP

Mr. Gary Buehler, Director
Office of Generic Drugs – HFD 600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE

Re: ANDA 76-880 for Nicotine Polacrilex Gum USP, 2 mg
Electronic Media

Dear Mr. Buehler:

Reference is made to IVAX's Abbreviated New Drug Application for Nicotine Polacrilex Gum USP, 2 mg, filed on October 23, 2003 and to a facsimile received October 30, 2003 from the Electronic Document Room Staff advising IVAX that several files submitted with the biostudy disc were not in PDF format

Pursuant to the Agency's instructions we are herewith submitting two electronic disc in the requested format.

IVAX Pharmaceuticals, Inc., has made every effort to ensure that the information contained herein is satisfactory. Should the Office of Generic Drugs have any questions please contact our office at your convenience at (201) 767-1700, extension 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Director, Regulatory Affairs

/sh

RECEIVED
NOV 0 6 2003
OGD/CDER

Will be sent on consult – SMD.

12/17/03 Archival NCE for filing SOS SMiddleton

NEW CORRESP NC

IVAX Pharmaceuticals, Inc.

140 Legrand Avenue
Northvale, New Jersey • 07647
Telephone: 201-767-1700
www.IVAXPharmaceuticals.com

Via Federal Express

DEC 12 2003

Mr. Gary Buehler, Director
Office of Generic Drugs – HFD 600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

Re: ANDA 76-880 for Nicotine Polacrilex Gum USP, 2 mg
Requested Data

Dear Mr. Buehler:

Reference is made to IVAX's Abbreviated New Drug Application for Nicotine Polacrilex Gum USP, 2 mg, filed on October 23, 2003 and to a December 1, 2003 telephone conversation with Saundra Middleton of your office. As advised by Ms. Middleton, the additional information is being submitted as a telephone amendment.

Ms. Middleton's requests are provided in italics and our responses following in plain typeface.

Requested Information:

1. *The actual studies (>90 days) referenced in Section IV, in support of the amount of sorbitol, sorbitol solution, and sodium bicarbonate used in the formulation.*

Response to item 1:

Regarding Sorbitol and Sorbitol Solution–

(b) (4)

Regarding Sodium Bicarbonate –

[1] 21 CFR 184
[2] *Sorbitol*, JECFA TRS 683-JECFA 26/27

RECEIVED
DEC 15 2003
OGD/CDER

(b) (4)

[redacted]

2. *Clarification on content of Peppermint Oil.*

Response to Item 2:

(b) (4)

[redacted]

3. *Corrections to cover page on the number of units tested for dissolution [content uniformity] referenced in Section VI.*

Response to Item 3:

(b) (4)

[redacted]

IVAX Pharmaceuticals, Inc., has made every effort to ensure that the information contained herein is satisfactory. Should the Office of Generic Drugs have any questions please contact our office at your convenience at (201) 767-1700, extension 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Director, Regulatory Affairs

---

[3] 21 CFR 184.1736

[4] *TOXILOGICAL EVALUATION OF SOME ANTIMICROBIALS, ANTIOXIDANTS, EMULSIFIERS, STABILIZERS, FLOUR-TREATMENT AGENTS, ACIDS AND BASES.*, FAO Nutrition Meetings Report Series No. 40 A,B,C. WHO./Food Add./67.29 (1967).

Archival

2.1

IVAX Pharmaceuticals, Inc.

140 Legrand Avenue
Northvale, New Jersey • 07647
Telephone: 201-767-1700
www.IVAXPharmaceuticals.com

Via Federal Express

Mr. Gary Buehler, Director
Office of Generic Drugs – HFD 600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AC

MAR 0 4 2004

TELEPHONE AMENDMENT

Re: ANDA 76-880 for Nicotine Polacrilex Gum USP, 2 mg
Requested Data

Dear Mr. Buehler:

Reference is made to IVAX's Abbreviated New Drug Application for Nicotine Polacrilex Gum USP, 2 mg, filed on October 23, 2003 and to the February 24, 2004 telephone communication with your office. As advised, the additional information is being submitted as a Telephone Amendment.

The agency's comments are provided in italics and our responses following in plain typeface.

1. *Ivax needs to obtain a letter from* (b) (4) *with the assigned DMF number,* (b) (4)

Response to item 1:
Attached please find a DMF authorization letter dated March 4, 2004 referencing DMF number (b) (4)

2. *Inquiry whether the peppermint oil in the formulation creates a "mint" flavor.*

Response to Item 2:
The flavor profile in this ANDA formulation is intended to mimic the innovator's "original" flavor. The use of peppermint oil in our formulation masks the bitter taste of the nicotine by imparting a slight, initial mint flavor which quickly vanishes. It does not impart a sustained mint flavor.

IVAX Pharmaceuticals, Inc., has made every effort to ensure that the information contained herein is satisfactory. Should the Office of Generic Drugs have any questions please contact our office at your convenience at (201) 767-1700, extension 323 or 348.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Director, Regulatory Affairs

PJ/sh

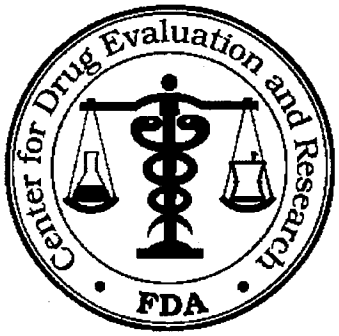
RECEIVED
MAR 0 8 2004
OGD/CDER

MINOR AMENDMENT

ANDA 76-880

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APR 06 2004



APPLICANT: Ivax Pharmaceuticals, Inc.

TEL: 201-767-1700 X323

ATTN: Patricia Jaworski

FAX: 201-767-3804

FROM: Thomas Hinchliffe

PROJECT MANAGER: (301) 827-5771

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated October 23, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nicotine Polacrilex Gum USP, 2 mg.

Reference is also made to your amendment(s) dated: March 4, 2004.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided here. Labeling and Bioequivalence comments, if any, will follow under separate cover when their reviews have been completed.

APR 06 2004

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-880 APPLICANT: IVAX

DRUG PRODUCT: Nicotine Polacrilex Gum USP, 2 mg (Original Flavor)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.
9.

10. [redacted] (b) (4)

11.

12.

Kvist, C., et. al., *International Journal of Pharmaceutics*, 189 (1999) 57-65.
European Pharmacopeia, *4.06, 2.9.25, Chewing gum, medicated, drug release from.*

13. [redacted] (b) (4)

14.

15.

16.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available room temperature stability data in your next amendment.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

IVAX Pharmaceuticals, Inc.
Regulatory Affairs Department
125 Wells Avenue
Congers, New York • 10920
Telephone: 845-267-2444
www.IVAXPharmaceuticals.com

MAY 23 2005

Via Federal Express

Mr. Gary Buehler, Director
Office of Generic Drugs – HFD 600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

MINOR AMENDMENT - Chemistry

Re: ANDA 76-880 for Nicotine Polacrilex Gum USP, 2 mg

Dear Mr. Buehler:

Reference is made to IVAX's Abbreviated New Drug Application for Nicotine Polacrilex Gum USP, 2 mg, filed on October 23, 2003 and to the Agency's April 6, 2004 "Not Approvable" letter. Pursuant to 21 CFR 314.96 and 21 CFR 314.120, Ivax is amending the application. As instructed, this response is considered a Minor Amendment. Please note, for ease of review, we have restated the Agency's observations in bold typeface followed by our response in plain typeface.

A. Deficiencies:

(b) (4)

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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MAY 24 2005
OGD / CDER

16. Please provide any (b) (4)

(b) (4)

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available room temperature stability data in your next amendment.

Response:
The updated stability data is provided in **Exhibit 9**.

CHANGE IN MAILING ADDRESS
IVAX's Regulatory Affairs Department has moved from Northvale, New Jersey to Congers, New York. Therefore, we request that effective immediately all correspondence related to this ANDA be sent to our new mailing address at 125 Wells Avenue, Congers, New York 10920. We also request that all faxed correspondence be sent to our new fax number: (845) 268-0117.

IVAX Pharmaceuticals, Inc. has made a concerted effort to ensure that this response is complete and that the information contained herein is satisfactory. Should you have any questions or require additional information, please contact our office at your convenience at (845) 267-2444, ext. 200 or 201.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Director, Regulatory Affairs

PJ/amh

IVAX Pharmaceuticals, Inc.
Regulatory Affairs Department
125 Wells Avenue
Congers, New York • 10920
Telephone: 845-267-2444
www.IVAXPharmaceuticals.com

MAY 23 2005

Via Federal Express

Food and Drug Administration
5600 Fishers Lane, Room 1364
Rockville, MD 20857

Attn: Ms. Irma Rivera, Program Specialist

MINOR CHEMISTRY AMENDMENT

Re: ANDA 76-880 Nicotine Polacrilex Gum

Dear Ms. Rivera:

In accordance with 21 CFR §314.96(b) regarding submission of a Field Copy of the technical section of any amendment to an unapproved Abbreviated New Drug application, we are forwarding a true and accurate copy of our Chemistry Amendment to the above referenced ANDA.

Should you have any questions or require additional information, please contact my office at (845) 267-2444, ext. 200 or 201.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Director, Regulatory Affairs

PJ/amh

MINOR AMENDMENT

ANDA 76-880

SEP 21 2005

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: IVAX Pharmaceuticals, Inc

TEL: 845-267-2444 ext. 201

ATTN: Patricia Jaworski

FAX: 845-268-0117

FROM: Thomas Hinchliffe

PROJECT MANAGER: (301) 827-5771

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated October 23, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nicotine Polacrilex Gum USP, 2 mg (original flavor).

Reference is also made to your amendment dated May 23, 2005.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachment (__1__ page). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

1K for TOH 9/21/05

Chemistry Assessment Section

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-880 APPLICANT: IVAX

DRUG PRODUCT: Nicotine Polacrilex Gum USP, 2 mg (Original Flavor)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please commit to provide a [redacted] (b) (4)

2. We again ask that you [redacted] (b) (4)

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

IVAX Pharmaceuticals, Inc.
Regulatory Affairs Department
125 Wells Avenue
Congers, New York • 10920
Telephone: 845-267-2444
www.IVAXPharmaceuticals.com

ORIG AMENDMENT
N-000 AM

MAY 15 2006

RECEIVED
MAY 16 2006
OGD / CDER

Via Federal Express

Mr. Gary Buehler, Director
Office of Generic Drugs – HFD 600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT – Chemistry

Re: ANDA 76-880 Nicotine Polacrilex Gum USP, 2 mg

Dear Mr. Buehler:

Reference is made to IVAX Pharmaceuticals Inc.'s Abbreviated New Drug Application for Nicotine Polacrilex Gum USP, 2 mg, submitted October 23, 2003 and to our minor amendment response dated May 23, 2005. Further reference is made to the Agency's September 21, 2005 letter. Pursuant to 21 CFR 314.96 and 21 CFR 314.120, Ivax is amending our application. As instructed, this response is considered a Minor Amendment.

Please note that for ease of review we have restated the Agency's observations in bold typeface followed by our response in plain typeface.

A. Deficiencies:

1. Please commit to provide a (b) (4)

(b) (4)

Response:

(b) (4)

Response:

(b) (4)

[redacted]

IVAX Pharmaceuticals, Inc. has made a concerted effort to ensure that this response is complete and that the information contained herein is satisfactory. Should you have any questions or require additional information, please contact our office at your convenience at (845) 267-2444, ext. 200 or 201.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Director, Regulatory Affairs

PJ/amh

IVAX

Archival

IVAX Pharmaceuticals, Inc.
Regulatory Affairs Department
125 Wells Avenue
Congers, New York • 10920
Telephone: 845-267-2444
www.IVAXPharmaceuticals.com

76-880

ORIGINAL

Via Facsimile to Saundra Middleton: 301-827-5911

MAY 23 2006

VIA FEDERAL EXPRESS

N/Mc

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Buehler:

This letter is in reference to your correspondence dated May 8, 2006 in which several IVAX Pharmaceutical Inc.'s pending applications were identified as requiring amendments. A copy of your letter is provided for reference.

Please note that for several of the listed applications IVAX has provided amendments to those products' respective non-approvable letters. Those files are listed in the table below along with the date of their responses.

ANDA	PRODUCT	NON-APPROVABLE DATE	RESPONSE DATE
(b) (4)			
76-880	Nicotine Polacrilex Gum USP, 2 mg (mint)	9/21/05	05/15/06

Additionally, please be informed that we intend to amend the following ANDA's as presented below:

ANDA	PRODUCT	NON-APPROVABLE DATE	PROJECTED RESPONSE DATE
(b) (4)			
77-170	Cetirizine Hydrochloride and Pseudophedrine Hydrochloride Extended Release Tablets, 5 mg/120 mg	11/24/04	07/31/06

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MAY 24 2006
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ANDA	PRODUCT	NON-APPROVABLE DATE	PROJECTED RESPONSE DATE
77-307	Trandolapril Tablets, 1 mg, 2 mg and 4 mg	1/11/05	11/30/06
77-319	Levetiracetam Tablets, 250 mg, 500 mg and 750 mg	2/25/05	11/30/06
			(b) (4)
77-433	Pamidronate Disodium for Injection, 30 mg/vial, 60 mg/vial and 90 mg/vial	5/23/05	11/30/06
			(b) (4)
77-518	Donepezil Hydrochloride Tablets, 5 mg and 10 mg	6/27/05	07/31/06
77-523	Fluconazole for Oral Suspension 10 mg/mL and 40 mg/mL	7/7/05	06/30/06
			(b) (4)
77-543	Risperidone Tablets, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg	7/14/05	11/30/06
77-205	Irbesartan Tablets, 75 mg, 150 mg and 300 mg	7/22/05	11/30/06
			(b) (4)

Lastly, we are currently considering the withdrawal of the ANDA's listed in the following table. The decision to do so will be made within the next two weeks. At that time the appropriate notification will be provided.

ANDA	PRODUCT	NON-APPROVABLE DATE
		(b) (4)

IVAX Pharmaceuticals has made a concerted effort to ensure that issues have been addressed satisfactorily. Should you have any questions or require any additional information, please contact our office at your convenience at (845) 267-2444 ext. 201 or 200.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Director, Regulatory Affairs

PJ/GO

IVAX

Archival

IVAX Pharmaceuticals, Inc.
Regulatory Affairs Department
125 Wells Avenue
Congers, New York • 10920
Telephone: 845-267-2444
www.IVAXPharmaceuticals.com

ORIGINAL

N/AA

FEB 2 2006

Via Federal Express

Mr. Gary Buehler, Director
Office of Generic Drugs – HFD 600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

GRATUITOUS AMENDMENT

Withdrawal of [redacted] (b) (4) **as a contract test laboratory for raw materials**

Re: ANDA 76-880 Nicotine Polacrilex Gum USP, 2 mg

Dear Mr. Buehler:

Reference is made to IVAX Pharmaceuticals, Inc.'s pending Abbreviated New Drug Application for Nicotine Polacrilex Gum USP, 2 mg, filed on October 23, 2003.

Pursuant to 21 CFR Part 314.96 Ivax is amending its application by withdrawing [redacted] (b) (4) as a contract test laboratory for microbiological testing of raw materials. If at some future date we wish to reinstate consideration of same, the application will be amended appropriately.

IVAX Pharmaceuticals, Inc. has made a concerted effort to ensure that this amendment is complete and that the information contained herein is satisfactory. Should you have any questions or require additional information, please contact our office at your convenience at (845) 267-2444, ext. 200 or 201.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Director, Regulatory Affairs

PJ/amh

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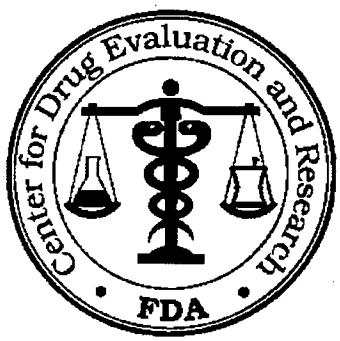
FEB 0 3 2006
OGD / CDER

MAJOR AMENDMENT

ANDA 76-880

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

SEP 0 1 2006



APPLICANT: IVAX Pharmaceuticals, Inc

TEL: 845-267-2444 ext. 201

ATTN: Patricia Jaworski

FAX: 845-268-0117

FROM: Thomas Hinchliffe

PROJECT MANAGER: (301) 827-5771

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated October 23, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nicotine Polacrilex Gum, USP 2 mg.

Reference is also made to your amendment dated February 2, 2006 and ~~March~~ May 15, 2006. 9/18/06

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-880 APPLICANT: IVAX

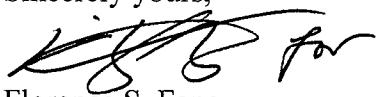
DRUG PRODUCT: Nicotine Polacrilex Gum USP, 2 mg (Original Flavor)

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. We note in a June 2005 deficiency letter issued by the Division of Bioequivalence (DBE) that a new bioequivalence study was requested. To date your response to the DBE letter has not been received and the current review cycle must now be closed. Please submit a Chemistry Amendment to re-open review of this ANDA when you submit your response to the DBE letter.

Sincerely yours,



Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

FDA FAX

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: IVAX Pharmaceuticals, Inc. TEL: 845-267-2444 ext. 201 or 200

ATTN: Patricia Jaworski FAX: 845-268-0117

Dear Madam:

This facsimile is in reference to your abbreviated new drug applications submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

Pages (including cover): __5__

SPECIAL INSTRUCTIONS:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

IVAX Pharmaceuticals, Inc. U.S. Agent for: IVAX-CR a.s.
Attention: Patricia Jaworski
125 Wells Avenue
Congers, New York, 10920

Dear ANDA Holder/Applicant:

We are writing to you as the sponsor of pending abbreviated new drug application(s) (ANDAs) supported by bioequivalence studies in which the bioanalytical analysis was conducted by (b) (4)

FDA has conducted several comprehensive inspections of bioequivalence studies conducted by (b) (4) since 2000. The findings of these inspections raise significant concerns about the validity of the reported results of these analytical studies conducted in support of drug applications for marketing. Our findings from these inspections include, but are not limited to, the following:

- (b) (4)

As a result of these findings, (b) (4) agreed to conduct an audit of data from all its bioequivalence studies generated from January 2000 to December 2004. However, FDA identified significant deficiencies with the (b) (4) audit during its most recent inspection. Thus, serious questions remain about the validity of bioequivalence data generated by (b) (4) in studies during this time period that have not been inspected by FDA, including the studies you have submitted in support of your applications. In view of these findings, FDA is informing holders of pending ANDA(s) of these issues and would like to know what steps are being taken by you to assure the accuracy of data submitted in these applications and confirm the validity of (b) (4) analytical studies that were conducted from January 2000 through December 2004 and subsequently submitted to the

FDA. Accordingly, with respect to these studies submitted in your application(s), we request that you do one of the following, in order of FDA preference:

1. Repeat the bioequivalence studies.

2. Re-assay the samples at a different bioanalytical facility. For this option, the integrity of the original samples must be demonstrated for the frozen storage period.

3. Commission a scientific audit by a qualified independent expert, who is knowledgeable in the area of bioequivalence studies and bioanalytical data, and selected by your company rather than by (b) (4), to verify the results obtained by (b) (4)

In addition, because one of the agency's significant findings for the inspected (b) (4) studies was the presence of anomalous results, we are requesting for all of the above options that the blood/plasma level results obtained in the studies be compared to any published literature or other relevant information that is publicly available. If you are unable to complete one of these options within the recommended six month time frame, please inform us of the reason(s) and your estimated time of completion.

If you choose to conduct an audit, we request that the completed audit reports be maintained at your site. If the audit finds the study acceptable, we request that you submit a certification to your application that formally attests in writing to the validity of the results obtained by (b) (4) upon which your application relies. If the audit finds the study to be unacceptable, you should either repeat the bioequivalence study and submit the information within 6 months of the completed audit or withdraw the application. Please note that these audits would also be subject to validity assessment by the agency upon submission.

The audit criteria provided below includes, but is not limited to, examples of areas that should be evaluated.

- The audit criteria for reviewing pre-study validation data should address whether accuracy and stability were demonstrated with appropriate validation experiments and documentation, and under the conditions of sample processing used for the analysis of samples from study subjects.

- The audit criteria for reviewing the results of the bioequivalence studies should address whether anomalous results were investigated and issues related to contamination were identified and corrected. It should also determine if a comparison of all available original and repeat results demonstrated assay reproducibility, and whether analytical runs were accepted in accordance with established procedures and without bias.

The new bioequivalence data or the re-analysis of the existing data should be submitted to your application as an amendment. If the new information does not support a finding of bioavailability/bioequivalence, the FDA may refuse to approve your application(s). Please find attached the list of your pending applications with studies conducted a (b) (4) during the specified

time period.

If you have any questions regarding this letter, please contact Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at 240-276-9310.

Sincerely,

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

IVAX Pharmaceuticals, Inc. U.S. Agent for: IVAX-CR a.s. ANDAs with studies conducted at (b) (4)

(b) (4)

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

/s/

Gary Buehler

1/10/2007 08:32:16 AM

TEVA PHARMACEUTICALS USA
Two University Plaza, Suite 220
Hackensack, NJ 07601

Patricia Jaworski
Director, Regulatory Affairs

Direct Dial: (215) 293-6150
Direct Fax: (201) 489-1403
pat.jaworski@tevausa.com

March 19, 2007

XA

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE
NOTIFICATION OF ADDRESS CHANGE

Re: ANDA 76-880 Nicotine Polacrilex Chewing Gum, 2 mg

Dear Mr. Buehler:

IVAX Pharmaceuticals, Inc. [IVAX] is writing to advise the Agency that the Regulatory Affairs Department has moved its offices from Congers, New York to Hackensack, New Jersey.

New Address for Regulatory Affairs:
IVAX Pharmaceuticals, Inc.
A wholly-owned subsidiary of TEVA Pharmaceuticals, USA
Two University Plaza, Suite 220
Hackensack, NJ 07601

Contact Information for Regulatory Affairs:
Phone: 215-293-6150 or 215-293-6151
FAX: 201-489-1403

Effective immediately please send all correspondence related to IVAX's Abbreviated New Drug Application for Nicotine Polacrilex Chewing Gum, 2 mg to our new mailing address. Please note that this change of address does not affect any of the manufacturing or packaging operations performed at our contract manufacturer, (b) (4) for the finished drug product Nicotine Polacrilex Chewing Gum, 2 mg. Also, please note that IVAX is now a wholly-owned subsidiary of TEVA Pharmaceuticals USA.

IVAX Pharmaceuticals has made a concerted effort to ensure that this correspondence contains all of the information that the Office of Generic Drugs may require. Should you have any questions or require additional information, please contact our office at your convenience.

Sincerely,
IVAX PHARMACEUTICALS, INC.
A Wholly-owned Subsidiary of TEVA Pharmaceuticals, USA

Patricia Jaworski
Director, Regulatory Affairs

MAR 21 2007
OGD / CDER

PJ/zt

TEVA PHARMACEUTICALS USA
Two University Plaza, Suite 220
Hackensack, NJ 07601

Patricia Jaworski
Director, Regulatory Affairs

Direct Dial: (215) 293-6150
Direct Fax: (201) 489-1403
pat.jaworski@tevausa.com

ORIG AMENDMENT

N-000-AC

June 19, 2007

Via Federal Express

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT - CHEMISTRY

Re: ANDA 76-880 Nicotine Polacrilex Chewing Gum USP, 2 mg

Dear Mr. Buehler:

Reference is made to a telephone conversation with Thomas Hinchliffe of the FDA on June 19, 2007, during which IVAX was advised that an FDA Chemistry Deficiency Letter was sent to IVAX on September 01, 2006. IVAX did not have this correspondence on file. The deficiency was retransmitted to IVAX on June 19, 2007 (copy provided in **Reference**). IVAX is amending its application by addressing the Agency's comment cited in the letter.

Comment
We note in a June 2005 deficiency letter issued by the Division of Bioequivalence (DBE) that a new bioequivalence study was requested. To date your response to the DBE letter has not been received and the current review cycle must now be closed. Please submit a Chemistry Amendment to re-open review of this ANDA when you submit your response to the DBE letter.

Response
IVAX confirms that, at the Agency's recommendation, a new bioequivalence study was performed and submitted to the Agency on March 16, 2007. A copy of the Bioequivalency Amendment cover letter is included as **Exhibit 1**.

IVAX Pharmaceuticals, Inc. has made a concerted effort to ensure that this application contains all of the information that the Office of Generic Drugs may require. Should you have any questions, or require additional information, please contact our office at your convenience at (215) 293-6150 or (215) 293-6151.

Sincerely,

IVAX PHARMACEUTICALS, INC.
Wholly owned subsidiary of TEVA Pharmaceutical USA

Patricia Jaworski
Sr. Director, Regulatory Affairs

PJ/zt

TEVA PHARMACEUTICALS USA

FACSIMILE TRANSMITTAL SHEET

To: Dave Skanchy	**From:** Patricia Jaworski
FAX NUMBER: 301-443-3839	**Date:** July 6, 2007
COMPANY:	**TOTAL NO. OF PAGES INCLUDING COVER:** 4
PHONE NUMBER:	**SENDER'S REFERENCE NUMBER:** ANDA 76-880
Re: Telephone Amendment - Chemistry	**YOUR REFERENCE NUMBER:**

☐ URGENT X FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

NOTES/COMMENTS:

TWO UNIVERSITY PLAZA • SUITE 220 • HACKENSACK, NJ 07601
PHONE: 215-293-6150 • FAX: 201-489-1403

TEVA PHARMACEUTICALS USA
Two University Plaza, Suite 220
Hackensack, NJ 07601

Patricia Jaworski
Director, Regulatory Affairs

Direct Dial: (215) 293-6150
Direct Fax: (201) 489-1403
pat.jaworski@tevausa.com

Via facsimile to: Dave Skanchy at 301-443-3839

July 06, 2007

Via Federal Express

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT - CHEMISTRY

Re: ANDA 76-880 Nicotine Polacrilex Chewing Gum USP, 2 mg

Dear Mr. Buehler:

Reference is made to a telephone conversation with Dave Skanchy of the FDA on July 06, 2007, during which IVAX was advised to amend the June 19, 2007 Chemistry - Major Amendment, with clarification on bioequivalence amendment status.

On April 20, 2007, IVAX received a deficiency letter from the Division of Bioequivalence in reference to the new bioequivalence study submitted on March 16, 2007. IVAX responded to these comments in a Bioequivalency Amendment submitted May 16, 2007.

IVAX Pharmaceuticals, Inc. has made a concerted effort to ensure that this application contains all of the information that the Office of Generic Drugs may require. Should you have any questions, or require additional information, please contact our office at your convenience at (215) 293-6150 or (215) 293-6151.

Sincerely,

IVAX PHARMACEUTICALS, INC.
Wholly owned subsidiary of TEVA Pharmaceutical USA

Patricia Jaworski
Sr. Director, Regulatory Affairs

PJ/zt

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
IVAX Pharmaceuticals, Inc. A wholly owned subsidiary of Teva Pharmaceuticals USA	7/06/07
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(215) 293-6150 or (215) 293-6151	(201) 489-1403
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* Two University Plaza, Suite 220 Hackensack, New Jersey 07601	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 76-880

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Nicotine Polacrilex Gum, USP	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
1-Methyl-2-(3-pyridyl)pyrrolidine, 2-propenoic acid, 2-methyl-, polymer with divinylbenzene, Methacrylic acid polymer with divinylbenzene	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Chewing gum	2 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

top smoking aid; Reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking.

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Nicorette® Holder of Approved Application GlaxoSmithKline

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Telephone Amendment response to the FDA's telephone communication of July 6, 2007

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☒ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

N/A

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☒	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Telephone Amendment response to provide clarification on the bioequivalence amendment status.

CERTIFICATION

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

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Patricia Jaworski, Sr. Director, Regulatory Affairs	7/06/07

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Two University Plaza, Suite 220, Hackensack, New Jersey 07601	(215) 293-6150 or 215-293-6151

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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

TEVA PHARMACEUTICALS USA
Two University Plaza, Suite 220
Hackensack, NJ 07601

Patricia Jaworski
Sr. Director, Regulatory Affairs

Direct Dial: (215) 293-6150
Direct Fax: (201) 489-1403
pat.jaworski@tevausa.com

Via Federal Express

September 27, 2007

ORIG AMENDMENT
WJ AB

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCY AMENDMENT

Re: ANDA 76-880 Nicotine Polacrilex Chewing Gum USP, 2 mg

Dear Mr. Buehler:

Reference is made to IVAX Pharmaceuticals, Inc.'s pending Abbreviated New Drug Application (ANDA) for Nicotine Polacrilex Chewing Gum USP, 2 mg. Further reference is made to the Agency's bioequivalency comments dated July 27, 2007 (copy provided in **Reference**). We are amending our application by responding to the deficiency cited in your letter.

Comment:

You did not propose a dissolution specification. The dissolution testing should be conducted as follows:

Apparatus:	(b) (4)
Medium:	**0.1% SLS**
Volume:	**40 mL**
Gap:	**1.6 mm**
Twist Angle:	**20°**
Speed:	**40 strokes/min**

The test products should meet the following specification:

Not less than (b) (4) (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

With your response to the above deficiency, please indicate if you accept the above dissolution method and specification.

RECEIVED
OCT 01 2007
OGD

Response:

IVAX acknowledges and accepts the FDA-recommended dissolution method and specifications, as follows:

Apparatus:	(b) (4)
Medium:	**0.1% SLS**
Volume:	**40 mL**
Gap:	**1.6 mm**
Twist Angle:	**20°**
Speed:	**40 strokes/min**
Specification:	**NLT (b) (4) (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes**

Accordingly, IVAX will revise the Finished Product Release and Stability Specifications to include the Division of Bioequivalence recommendations for dissolution. The revised specifications will be provided to the Agency in a separate cover letter as an Unsolicited Chemistry Amendment.

IVAX Pharmaceuticals, Inc. has made a concerted effort to ensure that this application contains all of the information that the Office of Generic Drugs may require. Should you have any questions, or require additional information, please contact our office at your convenience at (215) 293-6150 or (215) 293-6151.

Sincerely,

IVAX PHARMACEUTICALS, INC.
An indirect, wholly owned subsidiary of Teva Pharmaceuticals USA

Patricia Jaworski
Sr. Director, Regulatory Affairs

Enclosures

PJ/gm

MINOR AMENDMENT

ANDA 76-880 & 77-850

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: IVAX Pharmaceuticals, Inc TEL: 215-293-6150

ATTN: Patricia Jaworski, Director, Regulatory Affairs FAX: 201-489-1403

FROM: Thomas Hinchliffe PROJECT MANAGER: (301) 827-5771

Dear Madam:

This facsimile is in reference to your abbreviated new drug applications dated October 23, 2003 and August 23, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nicotine Polacrilex Gum USP, 2 mg and 4 mg.

Reference is also made to your amendment dated June 19, 2007 and July 6, 2007 (76-880); and February 2, 2006 and October 3, 2006 (77-850)

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing

You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

In an effort to improve document flow and availability to review staff, please submit your response in electronic PDF format, with a signed cover letter and 356h form.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-880 APPLICANT: IVAX

DRUG PRODUCT: Nicotine Polacrilex Gum USP, 2 mg (Original Flavor)

Please note that there are currently no Chemistry, Manufacturing, and Controls (CMC) deficiencies to communicate at this time. This application, however, is still pending satisfactory Bioequivalence and Labeling reviews. We note that Labeling issues were communicated to you on or about July 10, 2007 by telephone. We also note that Division of Bioequivalence (DBE) deficiencies were issued to you on or about July 27, 2007 under separate cover. When you respond to the issues raised in the Labeling and DBE communications, please submit a MINOR Chemistry amendment to re-open review of this ANDA.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-850 APPLICANT: IVAX

DRUG PRODUCT: Nicotine Polacrilex Gum USP, 4 mg (Original Flavor)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

Please note that there are currently no Chemistry, Manufacturing, and Controls (CMC) deficiencies to communicate at this time. This application, however, is still pending satisfactory Bioequivalence and Labeling reviews. We note that Labeling deficiencies were issued to you on or about November 16, 2006 under separate cover. We also note that Division of Bioequivalence (DBE) deficiencies were issued to you on or about September 6, 2007 under separate cover. When you respond to the issues raised in the Labeling and DBE communications, please submit a MINOR Chemistry amendment to re-open review of this ANDA.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Naiqi Ya
10/5/2007 02:45:15 PM
for Florence S. Fang

TEVA PHARMACEUTICALS USA
Two University Plaza, Suite 220
Hackensack, NJ 07601

Patricia Jaworski
Sr. Director, Regulatory Affairs

Direct Dial: (215) 293-6150
Direct Fax: (201) 489-1403
pat.jaworski@tevausa.com

Via Federal Express

November 13, 2007

ORIG AMENDMENT

N/AM

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT – CHEMISTRY

Re: ANDA 76-880
Nicotine Polacrilex Chewing Gum USP, 2 mg

Dear Mr. Buehler:

Reference is made to IVAX Pharmaceuticals, Inc.'s pending Abbreviated New Drug Application (ANDA) for Nicotine Polacrilex Chewing Gum USP, 2 mg and to the Agency's correspondence dated October 5, 2007 (copy provided in **Reference**). In response to the Agency's comments, we are submitting a Minor Amendment to re-open the review of this ANDA.

Comment:
Please note that there are currently no Chemistry, Manufacturing, and Controls (CMC) deficiencies to communicate at this time. This application, however, is still pending satisfactory Bioequivalence and Labeling reviews. We note that Labeling issues were communicated to you on or about July 10, 2007 by telephone. We also note that Division of Bioequivalence (DBE) deficiencies were issued to you on or about July 27, 2007 under separate cover. When you respond to the issues raised in the Labeling and DBE communications, please submit a MINOR Chemistry amendment to re-open review of this ANDA.

Response:
IVAX acknowledges the Agency's following comments:

- Currently no Chemistry, Manufacturing, and Controls (CMC) deficiencies to report at this time.
- Labeling telephone communication dated July 10, 2007.
- DBE's correspondence dated July 27, 2007.

Please note that the labeling issues will be addressed and submitted to the Agency under a separate cover.

In response to the Division of Bioequivalence recommendations, IVAX Pharmaceuticals submitted a Bioequivalence Amendment dated September 27, 2007 to accept the FDA-recommended dissolution method and specifications. Subsequently, IVAX has revised the following documentation to reflect the DBE's dissolution recommendations. Specifically, a dissolution specification of *NLT* (b) (4) *(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes* was adopted.

- Finished Product Specifications provided in **Exhibit 1**.
- Analytical Method for Finished Product Study provided in **Exhibit 2**.
- Stability Protocol provided in **Exhibit 3**.
- Analytical Method for Stability Study provided in **Exhibit 4**.

IVAX Pharmaceuticals, Inc., has made a concerted effort to ensure that this application contains all of the information that the Office of Generic Drugs may require. Should you have any questions, or require additional information, please contact our office at your convenience at (215)293-6150 or (215)293-6151.

Sincerely,

IVAX PHARMACEUTICALS, INC.
An indirect, wholly owned subsidiary of Teva Pharmaceuticals USA

Patricia Jaworski
Sr. Director, Regulatory Affairs

Enclosures

PJ/gm

MINOR AMENDMENT

ANDA 76-880

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: IVAX Pharmaceuticals, Inc TEL: 215-293-6150

ATTN: Patricia Jaworski, Director, Regulatory Affairs FAX: 201-489-1403

FROM: Thomas Hinchliffe PROJECT MANAGER: (240) 276-8536

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated October 23, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nicotine Polacrilex Gum USP, 2 mg and 4 mg.

Reference is also made to your amendment dated November 13, 2007.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (**2** pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-880 APPLICANT: IVAX

DRUG PRODUCT: Nicotine Polacrilex Gum USP, 2 mg (Original Flavor)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

There are currently no Chemistry, Manufacturing, and Controls (CMC) deficiencies to communicate at this time. However, this application is still pending a satisfactory Labeling review. We note that Labeling comments were communicated to you on or about July 10, 2007 by telephone and you have still failed to respond. Do not respond to this communication until you have responded to the issues raised in the Labeling communications. Please submit a MINOR Chemistry amendment to re-open review of this ANDA.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Naiqi Ya
1/22/2008 02:50:53 PM
for Florence S. Fang

September 12, 2008

Via Federal Express

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

Re: ANDA 76-880 – Nicotine Polacrilex Gum, 2 mg

Dear Mr. Buehler:

Reference is made to IVAX Pharmaceuticals' Abbreviated New Drug Application for Nicotine Polacrilex Gum USP, 2 mg. Further reference is made to a March 4, 2004 Agency facsimile correspondence in which IVAX was asked to revise its product labeling and provide a monitoring program to describe how IVAX will report findings of underage use to the FDA. Further reference is made to the Agency's July 6, 2007 Chemistry telephone communication noting labeling comments were still outstanding. Additional reference is made to the Agency's January 22, 2008 Chemistry facsimile correspondence which advised that labeling was still pending. The minor Chemistry Amendment is being submitted concurrently with this Labeling Amendment under separate cover and a copy of that cover letter is being provided herein. Please refer to **Reference.** It should be noted, IVAX has submitted the 4 mg strength as a separate submission (ANDA 77-850).

IVAX has revised all labeling components in final print to be in accord with the Agency's requests. In addition, IVAX has provided a marketing plan which we feel adequately addresses the Agency's concern regarding underage use. Please refer to **Exhibit 1**.

IVAX also has provided two (2) discs of the CD text in **Exhibit 2**.

To facilitate review of our submission, we have provided a side-by-side comparison of the labeling proposed in this amendment versus our previously submitted labeling, with all differences annotated and explained. The labeling portion of this submission is provided in electronic format, on one (1) CD ROM, using approximately 6 megabytes. Please refer to **Exhibit 3** of the Archival copy. IVAX has verified that the CD-ROM is virus-free using Trend Micro™ OfficeScan™, version 7.3.

The minor Chemistry amendment (copy of letter in **Reference**) was submitted under separate cover on September 12, 2008.

IVAX Pharmaceuticals, Inc. has made a concerted effort to ensure that this correspondence contains all of the information required by the Office of Generic Drugs. Should you have any questions, or require additional information, please contact our office at your convenience at (215) 293-6150 or (215) 293-6151.

Sincerely,

IVAX Pharmaceuticals, Inc.
An indirect, wholly owned subsidiary of TEVA Pharmaceuticals USA

Patricia Jaworski
Sr. Director, Regulatory Affairs

PJ/jaf

TEVA PHARMACEUTICALS USA
Two University Plaza, Suite 220
Hackensack, NJ 07601

Patricia Jaworski
Sr. Director, Regulatory Affairs

Direct Dial: (215) 293-6150
Direct Fax: (201) 489-1403
pat.jaworski@tevausa.com

October 13, 2008

Ms. Irma Rivera
Field Copy – International Submissions
Food and Drug Administration
5600 Fishers Lane
Room 1364
Rockville, MD 20857

TELEPHONE AMENDMENT - CHEMISTRY

Re: ANDA 76-880
Nicotine Polacrilex Gum, 2 mg

Dear Ms. Rivera:

In accordance with 21 CFR 314.96 (b) regarding submission of a field copy of an amendment to an unapproved application, we are forwarding a true copy of the submission referenced above. A certification statement affirming that the enclosed is a **true copy** is included with this letter.

Sincerely,

IVAX Pharmaceuticals, Inc.
An indirect, wholly-owned subsidiary of TEVA Pharmaceuticals, USA

Patricia Jaworski
Sr. Director, Regulatory Affairs

PJ/rh

enclosures

TEVA PHARMACEUTICALS USA
Two University Plaza, Suite 220
Hackensack, NJ 07601

Patricia Jaworski
Sr. Director, Regulatory Affairs

Direct Dial: (215) 293-6150
Direct Fax: (201) 489-1403
pat.jaworski@tevausa.com

Facsimile to Project Manager, Tom Hinchcliffe at 240-276-8582

Electronic copy: CD-ROM included with Archival copy

Hard Copy via Federal Express

October 13, 2008

Mr. Gary Buehler, Director
Office of Generic Drugs
Center of drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT - CHEMISTRY

Re: ANDA 76-880
Nicotine Polacrilex Gum, 2 mg

Dear Mr. Buehler:

IVAX Pharmaceuticals Inc., an indirect, wholly owned subsidiary of Teva Pharmaceuticals USA is submitting a telephone amendment for the above-referenced ANDA for Nicotine Polacrilex Gum, 2 mg in response to the Office of Generic Drugs correspondence dated October 3, 2008 (see **Reference**), in which the Agency discussed Chemistry minor deficiencies pertaining to USP <467>.

We are amending our application with the following (OGD's comments are in bold text, followed by our response in plain text):

Comment:

1. **Please provide a commitment to update the USP<467> information upon a change in supplier or method of manufacture for any of the formulation components.**

Response:

IVAX commits that any future changes in suppliers or method of manufacture for formulation components, which affect residual solvent amounts, will require an update to the USP <467> information for this product.

Comment:

2. Please update your finished product specifications and Certificate of Analysis format to include a statement that the product complies with USP <467> requirements

Response:

IVAX Pharmaceutical's Minor Amendment on September 12, 2008 included updated residual solvents information for the drug substance, all excipients and finished product for Nicotine Polacrilex Gum, 2 mg in compliance with the USP <467> initiative of July 1, 2008. These finished product specifications and analysis report with residual solvents <467> test stating that product meets "**Option 2, no testing is required**" is supplied again in **Exhibit 1** for the reviewer's convenience.

Comment:

3. Please provide data from a representative lot of the (b) (4) [redacted] (b) (4) [redacted]

Response:

(b) (4) [redacted]

Additionally, information for the current Form FDA 356h Section I, Attachment A (see **Exhibit 3**) has been included with this submission for IVAX Affiliate Companies/Alternate Testing Sites. This updated information removes the former (b) (4) [redacted] facility from the application and provides the current contact information for the US Agent for Active Drug Substance Manufacturer.

A copy of this telephone amendment is provided in electronic format on one (1) CD-ROM, using approximately 3 megabytes (please refer to the Archival copy). IVAX has verified that the CD-ROM is virus-free using Trend Micro™ OfficeScan™, Engine 8.710.1002 Version 7.3.

IVAX Pharmaceuticals, Inc. has made a concerted effort to ensure that this correspondence contains all the information requested by the Office of Generic Drugs. Should you have any questions or require additional information, please contact our office at your convenience at (215) 293-6150 or 6151.

Sincerely,

IVAX PHARMACEUTICALS, INC.
An indirect, wholly owned subsidiary of Teva Pharmaceuticals USA

Patricia Jaworski
for Senior Director, Regulatory Affairs

PJ/rh

TEVA PHARMACEUTICALS USA
Two University Plaza, Suite 220
Hackensack, NJ 07601

Patricia Jaworski
Sr. Director, Regulatory Affairs

Direct Dial: (215) 293-6150
Direct Fax: (201) 489-1403
pat.jaworski@tevausa.com

Facsimile: Dave Skanchy 240-276-8582

Hard Copy: via Federal Express

October 31, 2008

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N AM

TELEPHONE AMENDMENT - CHEMISTRY

RE: ANDA 76-880
Nicotine Polacrilex Gum, 2 mg

Dear Mr. Buehler:

Reference is made to recent telephone correspondences with the chemistry reviewer, Dave Skanchy on October 24, 2008 and October 29, 2008, regarding calcium content in Nicotine Polacrilex Gum, 2 mg. As per Mr. Skanchy's request, a copy of the manufacturer's declaration including the amount of calcium per unit (61 mg) for this product is attached.

Should you have any questions, please do not hesitate to contact me by telephone at (215) 293-6150 or (215) 293-6151, or via facsimile at (201)489-1403.

Sincerely,

IVAX Pharmaceuticals, Inc.
An indirect, wholly owned subsidiary of TEVA Pharmaceuticals USA

Patricia Jaworski
Sr. Director, Regulatory Affairs

PJ/rh
Enclosure

RECEIVED
NOV 03 2008
OGD

Telephone Fax

ANDAs 77-850 (4mg, original)
76-880 (2 mg, peppermint)

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240 276 8991

TO: Ivax Pharmaceuticals, Inc.

TEL: 215-293-6150

ATTN: Patricia Jaworksi

FAX: 215-489-1403

FROM: Michelle Dillahunt

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nicotine Polacrilex Gum.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Numbers: 77-850 (4 mg, original)
76-880 (2 mg, peppermint)

Date of Submission: September 12, 2008

Applicant's Name: Ivax Pharmaceuticals, Inc.

Established Name: Nicotine Polacrilex Gum, USP

Labeling Deficiencies:

1. CARTON

Please include on your labeling the amount of calcium contained in your gum. (See 21 CFR 201.70)

2. User's Guide

Please relocate the stickers to be placed on your calendar to appear at the end of the User's Guide.

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. 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

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your previous labeling with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Lillie Golson
11/3/2008 05:50:17 PM
Lillie Golson for Wm. Peter Rickman

November 13, 2008

Via Federal Express

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

Re: ANDA 76-880 – Nicotine Polacrilex Gum, 2 mg

Dear Mr. Buehler:

Reference is made to IVAX Pharmaceuticals' Abbreviated New Drug Application for Nicotine Polacrilex Gum USP, 2 mg. Further reference is made to a November 4, 2008 Agency facsimile correspondence in which IVAX was asked to revise its product labeling. Please refer to **Reference.** It should be noted, IVAX has submitted the 4 mg strength as a separate submission (ANDA 77-850).

IVAX has revised the carton labeling to include the calcium content of its gum and has relocated the calendar stickers in its user's guide. These labeling components are being provided electronically in final print to be in accord with the Agency's requests.

To facilitate review of our submission, we have provided a side-by-side comparison of the labeling proposed in this amendment versus our previously submitted labeling, with all differences annotated and explained. The labeling portion of this submission is provided in electronic format, on one (1) CD ROM, using approximately 6 megabytes. Please refer to **Exhibit 1** of the Archival copy. IVAX has verified that the CD-ROM is virus-free using Trend Micro™ OfficeScan™, version 7.3.

IVAX Pharmaceuticals, Inc. has made a concerted effort to ensure that this correspondence contains all of the information required by the Office of Generic Drugs. Should you have any questions, or require additional information, please contact our office at your convenience at (215) 293-6150 or (215) 293-6151.

Sincerely,

IVAX Pharmaceuticals, Inc.
An indirect, wholly owned subsidiary of TEVA Pharmaceuticals USA

Patricia Jaworski
Sr. Director, Regulatory Affairs

PJ/jaf

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-880 Applicant IVAX Pharmaceuticals, Inc.
Drug Nicotine Polacrilex Gum USP 2 mg (Original Flavor) Strength(s)_____

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer** Chief, Reg. Support Branch	Date 2/9/2009 Initials STM	Date 2/18/09 Initials rlw

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = Nicorette NDA# 18-612
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked N/A
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval
Comments: ANDA submitted on 10/23/2003, BOS=Nicorette NDA 18-612. PI certification provided . ANDA ack for filing 10/27/2003 (LO dated 12/22/2003). No patents or exclusivities covering the RLD. Therefore, this ANDA is eligible for Full Approval

2. Project Manager, Thomas Hinchliffe Team 10 Review Support Branch	Date 1/30/09 Initials TOH	Date 2/9/09 Initials toh

Original Rec'd date October 27, 2003 EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for Filing October 27, 2003 Date of EER Status 1/31/2008
Patent Certification (type)_____ Date of Office Bio Review 10/30/2007
Date Patent/Exclus.expires Date of Labeling Approv. Sum 12/19/2008
Citizens' Petition/Legal Case Yes ☐ No ☒ Labeling Acceptable Email Rec'd Yes ☒ No ☐
(If YES, attach email from PM to CP coord) Labeling Acceptable Email filed Yes ☒ No ☐
First Generic Yes ☐ No ☒ Date of Sterility Assur. App. NA
Priority Approval Yes ☐ No ☒ Methods Val. Samples Pending Yes ☐ No ☐
(If yes, prepare Draft Press Release, Email it to Cecelia Parise) MV Commitment Rcd. from Firm Yes ☒ No ☐
Acceptable Bio reviews tabbed Yes ☐ No ☒ Modified-release dosage form: Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐ Interim Dissol. Specs in AP Ltr: Yes ☐
Suitability Petition/Pediatric Waiver Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments: DATE OF APPLICATION: October 23, 2003

3. Labeling Endorsement

Reviewer: Labeling Team Leader:

Date2/3/09 Date2/3/09

Name/InitialsMD Name/InitialsLDG

Comments:

From: Golson, Lillie D
Sent: Tuesday, February 03, 2009 11:49 AM
To: Hinchliffe, Thomas; Golson, Lillie D
Subject: FW: 77-850 and 76-880 AP endorsement needed

Hi Tom,

From a labeling standpoint, these applications are acceptable for approval. Please endorse the AP routing forms on behalf of Michelle and me.

Thanks

Lillie

From: Dillahunt, Michelle
Sent: Tuesday, February 03, 2009 11:36 AM
To: Golson, Lillie D
Subject: FW: 77-850 and 76-880 AP endorsement needed

Labeling acceptable.

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 2/18/09
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments:N/A. There are no patents currently listed in the "Orange Book" for this OTC drug product.

5. Div. Dir./Deputy Dir. Date2/11/09
Chemistry Div. II Initials FF

Comments:cmc ok.

6. Frank Holcombe **First Generics Only** Date2/18/09
Assoc. Dir. For Chemistry Initials rlw/for Comments: (First generic drug review)
N/A. Multiple ANDAs have been approved for this drug product.

7. Vacant Date_____ Deputy Dir., DLPS
Initials_____
RLD = Nicorette Chewing Gum 2 mg (base)
GlaxoSmithkline NDA 18-612

8. Peter Rickman Date2/18/09
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐No ☐;Petition: Yes☐ No☐ Comments:Bioequivalence studies (fasting and multiple-dose chew out). Multiple-dose chew out study found acceptable. DSI inspection requested for both the analytical (b) (4)) and study test sites (MDS Pharma Services, Belfast, Northern Ireland). New fasting study requested of IVAX based upon DSI findings. New fasting sutdy submitted by IVAX on March 16, 2007. Fasting BE study found acceptable 7/13/07. In-vitro dissolution testing found acceptable 10/30/07. Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 7/13/07 and 10/30/07.

Final-printed labeling (FPL) found acceptable for approval 12/19/08, as endorsed 2/3/09 (above).

CMC found acceptable for approval (Chemistry Review #6).

OR

8. Robert L. West Date 2/18/09
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments:Acceptable EES dated 1/31/08 (Verified 2/18/09). No "OAI" Alerts noted.

There are no patents or exclusivity listed in the current "Orange Book" for this drug product. This ANDA is recommended for approval.

9. Gary Buehler Date 2/18/09
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Thomas Hinchliffe Team 10 Date2/18/09
Review Support Branch Initials TOH1
_____Date PETS checked for first generic drug (just prior to notification to firm)

(b) (4)

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 018612 Product 002 in the OB_OTC list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

Division of Labeling and Program Support

Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through January, 2009

Patent and Generic Drug Product Data Last Updated: February 17, 2009

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

/s/

Thomas Hinchliffe
2/18/2009 02:24:29 PM