CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 077850

Name: Nicotine Polacrilex Gum USP, 4 mg (base) (Original Flavor)

Sponsor: IVAX Pharmaceuticals Inc.

Approval Date: February 18, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077850

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077850

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-850

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 August 23, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Nicotine Polacrilex Gum USP, 4 mg (base) (Original Flavor).

Reference is also made to your amendments dated January 1, and September 11, 2006; April 26, 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, 4 mg (base) (Original Flavor) to be bioequivalent to the reference listed drug, Nicorette Gum, 4 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 77-850***".

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 02:21:58 PM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077850

LABELING


NDC 0172-6731-00
NICOTINE POLACRILEX GUM USP
4 mg (nicotine)
Original
1 piece
KEEP OUT OF REACH OF CHILDREN
Mfd for: Ivax Pharmaceuticals, Inc.
Miami, FL 33137 01/08A
Made in U uguay
Lot:
Exp.

Drug Facts

Active ingredient (in each chewing piece)	***Purpose***
Nicotine polacrilex (equal to 4 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 8.44 mg
- Store at 20°-25°C (68°-77°F) • Protect from light

Inactive Ingredients corn starch, D&C yellow #10, gum base, noncrystallizing sorbitol solution, peppermint oil, sodium bicarbonate, sodium carbonate, 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).

Made in Uruguay

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

0108A

NICOTINE POLACRILEX GUM USP

For those who smoke 25 **or more** cigarettes a day

If you smoke less than 25 cigarettes a day: use nicotine polacrilex gum USP 2 mg

108 pieces, 4 mg each

Free Audio CD upon request. See inside.

IVAX Pharmaceuticals, Inc. NDC 0172-6731-27

Compare to the active ingredient in Nicorette®*

NICOTINE POLACRILEX GUM USP

Original

4 mg

(nicotine)

Stop Smoking Aid

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.

To remove the gum, tear off single unit.

Peel off backing starting at corner with loose edge.

Push gum through foil.

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

NICOTINE POLACRILEX GUM USP

4 mg

(nicotine)

Original

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.

NICOTINE POLACRILEX GUM USP

4 mg

(nicotine)

Original

PLACE ANTI-THEFT STICKER HERE

THEFT SURVEILLANCE TAG AREA

EAS Tagged

3 0172-6731-27 9

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

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 077850

LABELING REVIEWS

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

ANDA Numbers: 77-850 Date of Submission: August 23, 2005

Applicant's Name: Ivax Pharmaceuticals, Inc.

Established Name: Nicotine Polacrilex Gum USP, 4 mg

Labeling Deficiencies:

1. GENERAL COMMENT

The reference listed drug manufacturer of Nicorette®, provides initiatives to safeguard against the potential abuse or misuse of this product. Initiatives are also in place to safeguard against inappropriate sales to minors in compliance with the labeled sales restrictions. It is important that you have a similar program in place to ensure that adequate precautions will be taken to provide for the safe marketing of your products.

Please submit a detailed marketing and surveillance plan designed to ensure that retailers and distributors of your products will only sell them to persons 18 years of age or older. This plan should include at a minimum:

- One or more mechanisms, in addition to the proposed labeling, for ensuring that these products will not be sold to people less than 18 years of age, i.e. a mechanism that will require proof of lawful age at the time of purchase, and that the product cannot be sold from a vending machine or in any other manner or form that would allow a person to obtain the product without first presenting proof of lawful age.

- One or more mechanisms for identifying and reporting on use by people less than 18 years of age.

- Your commitment not to market trial or sample packages of nicotine polacrilex gum.

- Provisions for child-resistant packaging.

2. BLISTER

Add "NDC" to appear before "0172-6731-00". See 21 CFR 201.35.

3. CARTON- 108s

Information Panel

a. Active ingredient, revise to read;
"Nicotine polacrilex (equal to 4 mg nicotine)…Stop smoking aid"

b. Ask a doctor before use if you have, include the following as the first bullet
• a sodium-restricted diet

c. Directions, last bullet, revise to read: "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.

d. Other information, include a statement declaring the amount of sodium and calcium in your product to be in accordance with the final rule of March 24, 2004 (69 FR 13717).

Principal Display Panel

e. The reference listed drug includes a statement "Free Audio CD upon request". Please revise

accordingly.

4. User's Guide

a. GENERAL

Please ensure that your user's guide is in a format of a booklet to be in accordance with the reference listed drug.

b. Keys to Success

(1) Number 2, delete '[redacted (b) (4)]" and include page number as seen in the reference listed drug's user's guide.

(2) Number 4, delete [redacted (b) (4)] and include page number as seen in the reference listed drug's user's guide.

(3) Add the following as number 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)

c. SOME IMPORTANT WARNINGS

Ask a doctor before use if you have, include the following as the first bullet
• a sodium-restricted diet

d. [redacted (b) (4)]

e. HOW TO USE NICOTINE POLACRILEX GUM

(1) Number 2, delete '[redacted (b) (4)]" and include page numbers as seen in the reference listed drug's user's guide.

(2) Number 5, revise to read;"PARK" the nicotine polacrilex gum piece…"

(3) Number 7, revise to read; "PARK" the nicotine polacrilex gum piece…"

f. HOW TO REDUCE YOUR NICOTINE POLACRILEX GUM USAGE

(1) First paragraph, revise second and third sentences as follows; " …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."

(2) Add the following as the last bullet; " 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."

g. STOP USING NICOTINE POLACRILEX GUM AT THE END OF WEEK 12. Revise as follows;

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

h. QUESTIONS AND ANSWERS
(1) Number 3, second sentence, delete (b) (4) and include include page number as seen in the reference listed drug's user's guide.

i. Include wallet card and stickers as seen in the reference listed drug's user's guide.

5. CD audio script

a. Page 3, sixth paragraph, LEADER, last sentence, change (b) (4) to "user's guide".

b. Page 4, 8th paragraph, OW, add the following as the second sentence;
And the book also includes calendar stickers to mark week seven <u>now,</u> so we'll be reminded when to start decreasing the amount we use.

c. Page 6, 8th paragraph, (b) (4), penultimate sentence, change " (b) (4) to "user's guide".

d. Page 7, fifth paragraph, (b) (4), first sentence, delete (b) (4).

Please revise your blister labels, carton, user guide labeling and CD script and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA. Also, submit two copies of the CD for your application.

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://www.fda.gov/cder/cdernew/listserv.html

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 the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

FOR THE RECORD:

1. MODEL LABELING - NDA 20-066/S-024 (4 mg)(Nicorette® gum) , approved on May 4, 2006. This supplement provides for a new package size of 20s. This model was used for the carton labeling.

   The audiotape/CD was also last approved on August 9, 2002 (NDA 20-(b) (4)/S-013).

   NDA 20-(b) (4)/S-017 was approved on June 23, 2004. This supplement provides for removal of the CD/audio portion of the labeling, the RLD includes a statement indicating that free "Audio/CD is available upon request. See inside"

   NDA 20-(b) (4)/S-023, approved on December 2, 2005 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

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 appears 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, 100s
   ANDA - 108s

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

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	

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
11/15/2006 04:50:45 PM
MEDICAL OFFICER

Lillie Golson
11/16/2006 12:57:02 PM
MEDICAL OFFICER

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

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.

---

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:**

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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

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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

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*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 Pages 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 074650

CHEMISTRY REVIEWS

ANDA 77-850

Nicotine Polacrilex Gum USP, 4 mg (Original Flavor)

IVAX Pharmaceuticals, Inc.

Barbara O. Scott

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 77-850

2. REVIEW #: 1

3. REVIEW DATE: February 2, 2006

4. REVIEWER: Barbara O. Scott

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
none	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	August 23, 2005

7. NAME & ADDRESS OF APPLICANT:

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

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

8. DRUG PRODUCT NAME/CODE/TYPE:

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

Executive Summary Section

9. LEGAL BASIS FOR SUBMISSION:

The legal basis for this submission is Nicorette® gum that is made by GlaxoSmithKline and was approved-NDA #20-066. The reference listed drug has no unexpired exclusivity and no unexpired patents for this product according to the 'Orange Book.'

Ivax Pharmaceuticals Inc. intends to market its generic version of Nicotine Polacrilex Gum USP, 4 mg as soon as approval is granted to this application.

10. PHARMACOLOGICAL CATEGORY:

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

11. DOSAGE FORM: Chewing Gum

12. STRENGTH/POTENCY: 4 mg

13. ROUTE OF ADMINISTRATION: Buccal

14. Rx/OTC DISPENSED: ___ Rx __X__ OTC

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

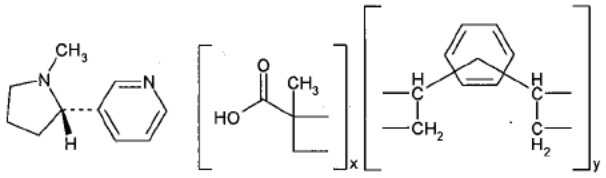
_____SPOTS product – Form Completed

__X__Not a SPOTS product

Executive Summary Section

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

Name: Nicotine Polacrilex 20% (Resin)
Molecular Formula: $C_{10}H_{14}N_2(C_{18}H_{22}O_4)_n$
Molecular Weight: N/A
Structural Formula:



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)

Letters of authorization are provided for DMF #s: (b) (4)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

Executive Summary Section

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Pending	11/17/2005	
Methods Validation	Not required		
Labeling	Pending		
Bioequivalence	Pending		
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

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 77-850

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is 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)

The drug substance is Nicotine Polacrilex USP and consists of nicotine bound ionically to a weak carboxylic cation-exchange resin prepared from methacrylic acid and divinylbenzene.

The drug product consists of the nicotine containing resin blended with the following inactive ingredients: chewing gum base, sodium bicarbonate, sodium carbonate, sorbitol solution NF, peppermint oil, coloring and starch. The drug product is delivered for buccal absorption by chewing 1 dosage unit. The reference listed drug for this product is Nicorette® Gum 4 mg by GlaxoSmithKline (NDA 20-066).

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

Nicotine Polacrilex gum works as a temporary aid to combat the physical and mental craving that occurs when trying to quit smoking. The gum, when chewed properly and in the schedule provided in the insert, provides the patient with a smoke-free source of nicotine that gets absorbed into the blood. This helps the physical craving for nicotine and allows for the gradual weening of the body's need for it.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The application is not approvable due to deficiencies in the following areas: substance control, lack of proper debarment certification, manufacturing and processing, and stability OOS.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-640/B.Scott/ B. Scott 2/8/06
HFD-640/NYa/ 2/8/2006
HFD-617/THinchliffe/ 2/8/06

C. CC Block

ANDA 77-850 Original
ANDA 77-850 DUP
DIV FILE
Field Copy

18 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: 77-850 APPLICANT: IVAX

DRUG PRODUCT: Nicotine Polacrilex Gum USP, 4 mg (Original Flavor)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please correct [redacted] (b) (4)

2. Terms like 'complies or meets requirements' for a result when a numerical value can be obtained for a specific test are unacceptable. Please revise all Ivax [redacted] (b) (4) raw material COA's to provide actual data for tests where numerical values are in the specification.

3. Please provide cGMP certifications for [redacted] (b) (4) and [redacted] (b) (4)

4. Please provide a brief written manufacturing summary of the steps involved in the manufacture of the drug product.

5. Please provide a Blank Batch Record for the cartoning process performed at [redacted] (b) (4)

6. Please establish tests and acceptance criteria for dissolution and moisture in your drug product stability specification.

7. Please lower [redacted] (b) (4) The results for the RLD and your drug product do not justify [redacted] (b) (4)

8. The data show that under controlled room temperature conditions, the 9 month data point for the impurity [redacted] (b) (4) whereas the RLD is acceptable. Please provide an explanation. In addition, please provide all available room temperature and intermediate stability data in your next amendment.

Chemistry Assessment Section

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

1. The labeling portion of your application is currently under review. The Division of Labeling and Program Support will notify you under separate cover of all labeling deficiencies.

2. The bio-equivalence review is pending. The Division of Bioequivalence will notify you under separate cover of all deficiencies.

3. Pease commit to bringing the drug substance specification table and COA in line with the USP monograph once the addition of Residual Solvents becomes official in January of 2007.

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 77-850 Original
ANDA 77-850 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/BScott/2/2/06 BScott 2/3/06
HFD-640/NYa/2/6/06 2/8/2006
HFD-617/THinchliffe/2/6/06 2/9/06

F/T by rad2/7/06

TYPE OF LETTER: NOT APPROVABLE – Minor

ANDA 77-850

Nicotine Polacrilex Gum USP, 4 mg (Original Flavor)

IVAX Pharmaceuticals, Inc.

Barbara O. Scott **(updated by D. 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 77-850

2. REVIEW #: 2

3. REVIEW DATE: June 7, 2007

4. REVIEWER: Barbara O. Scott (updated by D. Skanchy)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	August 23, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (gratuitous)	February 2, 2006
Amendment (response)	October 3, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	IVAX Pharmaceuticals Inc.
Address:	125 Wells Avenue Congers, New York 10920
Representative:	Patricia Jaworski
Telephone:	(845)267-2444 ext. 200 or 201
Fax:	(845)268-0117

8. DRUG PRODUCT NAME/CODE/TYPE:

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

Executive Summary Section

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

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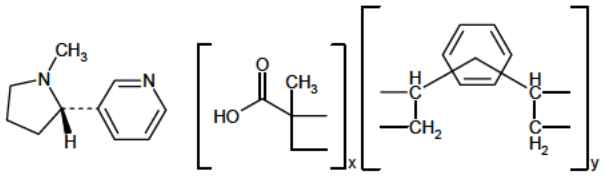
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: Nicotine Polacrilex 20% (Resin)
Molecular Formula: $C_{10}H_{14}N_2(C_{18}H_{22}O_4)_n$
Molecular Weight: N/A
Structural Formula:

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 (b) (4)	1	Adequate	9/15/05	Reviewed by DSkanchy
	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)

Letters of authorization are provided for DMF #s: (b) (4) and (b) (4).

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	2/9/2006	OC
Methods Validation	Not required		

Executive Summary Section

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Labeling	Deficient	11/15/2006	M. Dillahunt
Bioequivalence	Pending		E. Stier
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

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 77-850

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is approvable for CMC. *DBE review and acceptable labeling are pending. Application will be closed out for CMC.*

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)

The drug substance is Nicotine Polacrilex USP and consists of nicotine bound ionically to a weak carboxylic cation-exchange resin prepared from methacrylic acid and divinylbenzene.

The drug product consists of the nicotine containing resin blended with the following inactive ingredients: chewing gum base, sodium bicarbonate, sodium carbonate, sorbitol solution NF, peppermint oil, coloring and starch. The drug product is delivered for buccal absorption by chewing 1 dosage unit. The reference listed drug for this product is Nicorette® Gum 4 mg by GlaxoSmithKline (NDA 20-066).

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

Nicotine Polacrilex gum works as a temporary aid to combat the physical and mental craving that occurs when trying to quit smoking. The gum, when chewed properly and in the schedule provided in the insert, provides the patient with a smoke-free source of nicotine that gets absorbed into the blood. This helps the physical craving for nicotine and allows for the gradual weening of the body's need for it.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable for CMC. *DBE review and acceptable labeling are pending.*

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-640/B.Scott (D. Skanchy for)/
HFD-640/NYa/
HFD-617/THinchliffe/

C. CC Block

ANDA 77-850 Original
ANDA 77-850 DUP
DIV FILE
Field Copy

20 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: 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 on or about November 16, 2006 under separate cover. We also note that Division of Bioequivalence (DBE) deficiencies were issued on or about September 6, 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 77-850 Original
ANDA 77-850 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/BScott (D. Skanchy for)/
HFD-640/NYa/
HFD-617/THinchliffe/10/2/07

F/T by

TYPE OF LETTER: Not Approvable (Minor)

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 02:20:03 PM
CHEMIST
for Barbara Scott

Thomas Hinchliffe
10/3/2007 08:59:49 AM
CSO

Naiqi Ya
10/5/2007 02:08:28 PM
CHEMIST

Chemistry Assessment Section

ANDA 77-850

Nicotine Polacrilex Gum USP, 4 mg (Original Flavor)

IVAX Pharmaceuticals, Inc.

Barbara O. Scott (updated by D. 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 77-850

2. REVIEW #: 3

3. REVIEW DATE: January 02, 2008

4. REVIEWER: Barbara O. Scott (updated by D. Skanchy)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	August 23, 2005
Amendment (gratuitous)	February 2, 2006
Amendment (response)	October 3, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	November 13, 2007

7. NAME & ADDRESS OF APPLICANT:

Name: 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:

Chemistry Assessment Section

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

9. LEGAL BASIS FOR SUBMISSION:

The legal basis for this submission is Nicorette® gum that is made by GlaxoSmithKline and was approved-NDA #20-066. The reference listed drug has no unexpired exclusivity and no unexpired patents for this product according to the 'Orange Book.'

Ivax Pharmaceuticals Inc. intends to market its generic version of Nicotine Polacrilex Gum USP, 4 mg as soon as approval is granted to this application.

10. PHARMACOLOGICAL CATEGORY:

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

11. DOSAGE FORM: Chewing Gum

12. STRENGTH/POTENCY: 4 mg

13. ROUTE OF ADMINISTRATION: Buccal

14. Rx/OTC DISPENSED: ___ Rx __X__ OTC

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

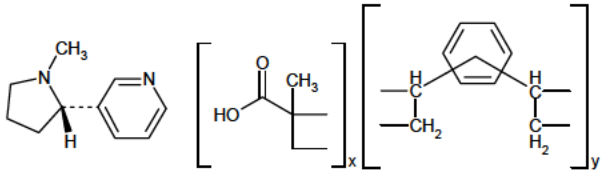
_____SPOTS product – Form Completed

__X__Not a SPOTS product

Chemistry Assessment Section

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

Name: Nicotine Polacrilex 20% (Resin)
Molecular Formula: $C_{10}H_{14}N_2(C_{18}H_{22}O_4)_n$
Molecular Weight: N/A
Structural Formula:



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)

Letters of authorization are provided for DMF #s: (b) (4) and (b) (4).

B. Other Documents:

Chemistry Assessment Section

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	2/9/2006	OC
Methods Validation	Not required		
Labeling	***Pending***		
Bioequivalence	***Pending***		
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

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 77-850

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is approvable for CMC. *DBE review and acceptable labeling 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)

The drug substance is Nicotine Polacrilex USP and consists of nicotine bound ionically to a weak carboxylic cation-exchange resin prepared from methacrylic acid and divinylbenzene.

The drug product consists of the nicotine containing resin blended with the following inactive ingredients: chewing gum base, sodium bicarbonate, sodium carbonate, sorbitol solution NF, peppermint oil, coloring and starch. The drug product is delivered for buccal absorption by chewing 1 dosage unit. The reference listed drug for this product is Nicorette® Gum 4 mg by GlaxoSmithKline (NDA 20-066).

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

Nicotine Polacrilex gum works as a temporary aid to combat the physical and mental craving that occurs when trying to quit smoking. The gum, when chewed properly and in the schedule provided in the insert, provides the patient with a smoke-free source of nicotine that gets absorbed into the blood. This helps the physical craving for nicotine and allows for the gradual weening of the body's need for it.

Chemistry Assessment Section

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable for CMC. A*cceptable labeling is pending.*

III. Administrative

Endorsement Block

HFD-640/D.Skanchy/
HFD-640/NYa/
HFD-617/THinchliffe/

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Chemistry Assessment Section

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. However, this application is still pending a satisfactory Labeling review. We note that Labeling deficiencies were issued on or about November 16, 2006 under separate cover. Do not respond to this deficiency until you have responded to the issues raised in the Labeling communication. 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 77-850 Original
ANDA 77-850 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/D.Skanchy/1/22/08
HFD-640/NYa/1/22/08
HFD-617/THinchliffe/1/22/08

F/T by

TYPE OF LETTER: Approval -- Minor due 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 10:15:04 AM
CHEMIST

Thomas Hinchliffe
1/22/2008 11:46:13 AM
CSO

Naiqi Ya
1/22/2008 02:48:56 PM
CHEMIST

Chemistry Assessment Section

ANDA 77-850

Nicotine Polacrilex Gum USP, 4 mg (Original Flavor)

IVAX Pharmaceuticals, Inc.

David Skanchy
(note B. Scott reviewed previous cycle, CR#3)

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 77-850

2. REVIEW #: 4

3. REVIEW DATE: January 02, 2009

4. REVIEWER: D. Skanchy (B. Scott reviewed previous cycle, CR#3)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	August 23, 2005
Amendment (gratuitous)	February 2, 2006
Amendment (response)	October 3, 2006
Amendment	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:

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

Chemistry Assessment Section

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 legal basis for this submission is Nicorette® gum that is made by GlaxoSmithKline and was approved-NDA #20-066. The reference listed drug has no unexpired exclusivity and no unexpired patents for this product according to the 'Orange Book.'

Ivax Pharmaceuticals Inc. intends to market its generic version of Nicotine Polacrilex Gum USP, 4 mg as soon as approval is granted to this application.

10. PHARMACOLOGICAL CATEGORY:

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

11. DOSAGE FORM: Chewing Gum

12. STRENGTH/POTENCY: 4 mg

13. ROUTE OF ADMINISTRATION: Buccal

14. Rx/OTC DISPENSED: ___ Rx __X__ OTC

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

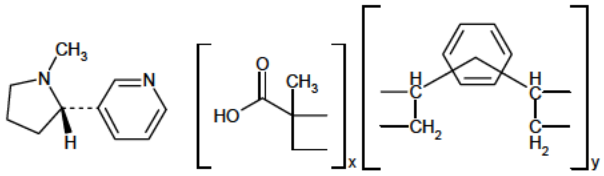
_____SPOTS product – Form Completed

__X__Not a SPOTS product

Chemistry Assessment Section

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

Name: Nicotine Polacrilex 20% (Resin)
Molecular Formula: $C_{10}H_{14}N_2(C_{18}H_{22}O_4)_n$
Molecular Weight: N/A
Structural Formula:



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	

*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)

Chemistry Assessment Section

Letters of authorization are provided for DMF #s: (b) (4) and (b) (4).

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	2/9/2006;01/31/2008	OC
Methods Validation	Not required		
Labeling	Acceptable	12/19/2008	M. Dillahunt
Bioequivalence	Acceptable	11/06/2007	A. Zigler
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

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 77-850

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is approvable for CMC.

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)

The drug substance is Nicotine Polacrilex USP and consists of nicotine bound ionically to a weak carboxylic cation-exchange resin prepared from methacrylic acid and divinylbenzene.

The drug product consists of the nicotine containing resin blended with the following inactive ingredients: chewing gum base, sodium bicarbonate, sodium carbonate, sorbitol solution NF, peppermint oil, coloring and starch. The drug product is delivered for buccal absorption by chewing 1 dosage unit. The reference listed drug for this product is Nicorette® Gum 4 mg by GlaxoSmithKline (NDA 20-066).

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

Nicotine Polacrilex gum works as a temporary aid to combat the physical and mental craving that occurs when trying to quit smoking. The gum, when chewed properly and in the schedule provided in the insert, provides the patient with a smoke-free source of nicotine that gets absorbed into the blood. This helps the physical craving for nicotine and allows for the gradual weening of the body's need for it.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable for CMC.

Chemistry Assessment Section

III. Administrative

Endorsement Block

HFD-640/D.Skanchy/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: 77-850 APPLICANT: IVAX

DRUG PRODUCT: Nicotine Polacrilex Gum USP, 4 mg (Original Flavor)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

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 07:37:33 AM
CHEMIST

Naiqi Ya
2/18/2009 01:43:59 PM
CHEMIST

Thomas Hinchliffe
2/18/2009 01:45:51 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077850

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-850
Drug Product Name	Nicotine Polacrilex Gum
Strength	4 mg
Applicant Name and Address	Ivax Pharmaceuticals, Inc., Congers, NY
Contact	Pat Jaworksi, 845-267-2444 (phone) and 845-268-0117 (fax)
Submission Date(s)	August 23, 2005
Amendment Date(s)	01-13-06(WC), 09-11-06 (New dissolution data)
Reviewer	Ethan M. Stier, Ph.D., R.Ph.
First Generic	No
DSI	**THE ANALTYICAL STUDIES WERE CONDUCTED AT** (b) (4)

I. Executive Summary

This application references Nicorette® Gum (original flavor) and includes one fasting bioequivalence (BE) study and one multiple dose chew-out study. The fasting study is a single-dose two-way crossover study using 16 male and 18 female normal healthy volunteers (in two groups) given a dose of 4 mg. The reviewer found a statistically significant grp*trt effect ($p<0.1$) for LCmax and analyzed the groups separately for that parameter. The reviewer calculated results (point estimate, 90% CI) of the fasting BE study for pooled data are LAUCt of **108, 103.34-113.76%**; LAUCi of **1.09, 103.76-113.97%**; and LCmax of 102, 96.43-107.94%. The results (point estimate, 90% CI) of the fasting BE study for group I are LAUCt of 104, 98.28-110.11%; LAUCi of 1.05, 99.41-111.23%; and LCmax of **95, 88.61-102.92%**. The results (point estimate, 90% CI) of the fasting BE study for group II are LAUCt of 114, 105.00-123.74%; LAUCi of 1.13, 103.88-122.35%; and LCmax of **111, 102.24-119.45%**. *NOTE: As per the current DBE practice, under certain appropriate conditions (see ANDAs 40620, 40760, 65451, 77828, and* (b) (4) *an ANOVA is performed on pooled data even though there is a significant grp*trt effect on a PK parameter.* The part analytical testing was done at the (b) (4) during the suspect period of (b) (4). **However the OGD has decided that the firm does not need to conduct a third party audit of the BE study. The fasting study is acceptable and the only deficiency is that the firm has not yet acknowledged the dissolution method and specification.**

The multidose chew-out study is a two-way crossover study using 7 male and 7 female normal healthy volunteers given a dose of 4 mg. Each treatment period included a total of 4 chewing sessions of different durations: 30, 20, 10, and 5 minutes. The residual amount of nicotine in the chewed gum cuds was assayed. The amount of released nicotine was calculated. After 30 minutes of chewing, the ratios of means of percentage of nicotine released for the test and reference formulations were comparable. The T/R ratio at 30 minutes was 1.103. The multidose chew-out study is acceptable. Since the analytical testing was done at the (b) (4) after the suspect period of (b) (4) the third party audit of the study is not needed.

The firm conducted in-vitro dissolution testing using two different methods, which both used the (b) (4) apparatus. The major difference between the two methods was the medium (0.1% Sodium Lauryl Sulfate vs. phosphate buffer at pH 7.4). The DBE has previously found the method using 0.1% SLS to be acceptable for the 2 mg Nicotine Polacrilex Gum submitted by IVAX under 76-880. Therefore, the firm will be requested to acknowledge the FDA recommended method and data driven specification.

No waivers were requested.

The application is incomplete pending firm's acceptance of the FDA dissolution testing method and specification.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Nicotine Polacrilex Gum USP
Reference Product	Nicorette®
RLD Manufacturer	GlaxoSmithKline
NDA No.	18-612
RLD Approval Date	2/9/96 (Regular), 12/23/98 (Mint), 12/25/00 (Orange)
Indication	Stop smoking aid that reduces withdrawal symptoms, including nicotine craving.

B. PK Information

Bioavailability	1.8-3.2 mg nicotine was systemically available and 3.1-3.7 mg of residual nicotine was extracted from the chewed piece after 30 minutes of paced chewing of a single piece of 4 mg Nicorette® Gum.
Food Effect	N/A
T_{max}	~1 Hr. for nicotine polacrilex lozenge
Metabolism	Nicotine is extensively metabolized to a number of metabolites, all of which are less active than the parent compound. Cotinine is the major metabolite, and is formed by a two-step process, via CYP450 enzyme (CYP2A6) and aldehyde oxidase.
Excretion	Nicotine and its metabolites are excreted almost exclusively in the urine, ~5% of the dose as nicotine and 10% as cotinine in 24 hrs.
Half-life	Approximately 6 hours

Relevant OGD or DBE History

This is an OTC product. The brand name product, Nicorette®, gum is available in six varieties viz. three flavors (regular, mint and orange) and two strengths (2 mg and 4 mg) in each flavor. The brand name products were approved under 2 separate NDAs. The NDA 18612 is for the 2 mg strengths (regular, mint and orange) and the NDA 20066 is for the 4 mg strengths.

DBE has received ANDAs 76-775 (Perrigo), 76-776 (Perrigo), 76-777 (Perrigo), 76-789 (Perrigo), 74-507 (Watson), 74-707 (Watson), 77-656 (Novartis), and (b) (4)) and 76-880 (IVAX – application for 2 mg strength) .

DBE has received protocols: 99-172, 99-187, 94-001, 98-025, 00-018, 02-065

The DBE accepted following dissolution methods for nicotine polacrilex gum: method A (ANDAs 76-778, 76-779, 76-789, L. Perrigo) and Method B:

Method A

Source of Method: European Pharmacopoeia 2.9.25
Medium: Phosphate buffer pH 7.4
Volume: 20 mL of buffer into chewing chamber at 37 ^{o}C
Rotation: 60 cycles/min
Specifications (tentative): NLT (b) (4)(Q) of the labeled amount of nicotine in dosage form is dissolved in 30 minutes.
Machine: A machine is used to simulate gum chewing. Each piece of gum is placed in a small chamber at 37°C containing 20 mL "saliva" (chewing buffer). Two horizontal pistons "chew" the gum at a constant speed. A "tongue" (vertical piston) ensures that that the gum remains in the correct place.

Method B
Medium: 0.1% SLS
Volume: 40 mL at 37 °C
Rotation: 40 stroke/min
Specifications (tentative): NLT (b) (4) (Q) of the labeled amount of nicotine in dosage form is dissolved in 30 minutes.
Machine: (b) (4)

The DBE currently recommends the following for this drug product (based on review of control 05-343):

a. A single-dose, two-way crossover fasting *in-vivo* bioequivalence study comparing Nicotine Polacrilex Gum Regular Flavor, 4 mg, to the RLD, Nicorette® (Nicotine Polacrilex) Gum, 4 mg, with a 30 minute chewing interval during each period.

b. Instead of a multi-dose, crossover chew-out study, a comparative dissolution testing with a chewing machine is necessary on all six chewing gums (see number 3 below).

2. Only the parent compound, nicotine, in plasma needs to be measured. The firm should not adjust the pharmacokinetic data using the residual nicotine levels analyzed from the gum cud.

3. A comparative dissolution testing for all strengths of the test and reference products should be conducted. Currently, there is no USP dissolution testing method for nicotine polacrilex gum. Therefore, the firm should develop a dissolution method that correlates well with the *in-vivo* nicotine release profile based on the time points (5, 10, 20, and 30 minutes) used in the chew-out studies. The firm should consult the European Pharmacopoeia (2.9.25) for information about dissolution testing of nicotine polacrilex gum products.

4. Nicotine Polacrilex Gum, 2 mg and 4 mg (mint and orange flavored), may be considered for a waiver of *in-vivo* bioequivalence testing based on (1) an acceptable bioequivalence study on the 4 mg strength (regular flavor), (2) acceptable dissolution testing with chewing machine of all strengths and flavors, (3) proportional similarity in the formulations of all strengths and flavors and (4) the only difference in the formulation between the flavored and regular gum is the flavor component.

5. Please use smokers in the study. You may submit a protocol for review by the DBE prior to initiating studies.

Agency Guidance None
Drug Specific Issues (if any) None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	2, (1 BE and 1 multi-dose chew-out studies)
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	1
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

D. Pre-Study Bioanalytical Method Validation

Table 3. Bioanalytical Method Validation for Nicotine in Gum Cuds for study AA21387/CUN

Report location		Volume page
Analyte		Nicotine (b) (4)
Internal Standard (I.S.)		
Method description		High performance liquid chromatographic mass spectrometric method
Limit of quantitation (Solution) (ng/mL)		10.0 ng/mL
Limit of quantitation (Gum Cuds) (ng/mL)		0.100 mg/gum
Average recovery of drug (Gum Cuds) (%)	Low	118.6%
	High	105.3%
Average recovery of I.S. (%)		83.6%
Standard curve concentrations (Solution) (ng/mL)		10.0 ng/mL to 443 ng/mL
Standard curve concentrations (Gum Cuds) (ng/mL)		0.100 mg/gum to 4.50 mg/gum
QC concentrations (Solution) (ng/mL)	LLOQ	9.90 ng/mL
	Low	31.8 ng/mL
	Med	159 ng/mL
	High	318 ng/mL
QC Intraday precision range (Solution) (%)		2.5% to 7.5%
QC Intraday accuracy range (Solution) (%)		81.8% to 106.9%
QC Interday precision range (Solution) (%)		10.6% to 12.7%
QC Interday accuracy range (Solution) (%)		95.3% to 108.8%
Bench-top stability (Gum Cuds) (hrs)		25.0 hours at ambient temperature
Stock stability (days)		415 days at 45.1 mg/mL in 0.02% Acetic Acid at -20°C
Process sample integrity (Solution) (hrs)		29.0 hours at ambient temperature
Process sample integrity (re-injection) (Solution) (hrs)		75.0 hours at ambient temperature
Process sample integrity (re-injection) (Gum Cuds) (hrs)		136 hours at ambient temperature
Freeze-thaw stability (Gum Cuds) (cycles)		1 cycles at -20°C
Long-term storage stability (Solution) (days)		45 days at ambient temperature and 5°C 366 days in 0.02% Acetic Acid at -20°C
Long-term storage stability (Gum Cuds) (days)		91 days at -20°C
Selectivity (Gum Cuds)		No interfering peaks noted in placebo gum not chewed

Table 3. Bioanalytical Method Validation for Nicotine in Human Plasma for study AA21388/CTC

Report location		Volume page
Analyte		Nicotine
Internal Standard (I.S.)		(b) (4)
Method description		High performance liquid chromatographic mass spectrometric method
Limit of quantitation (ng/mL)		0.167 ng/mL
Average recovery of drug (%)	Low	101.1%
	Med	93.9%
	High	91.4%
	High (40.1 ng/mL)	93.1%
Average recovery of I.S. (at 5.40 ng/mL) (%)		86.4%
Average recovery of I.S. (at 11.0 ng/mL) (%)		85.8%
Standard curve concentrations (ng/mL)		0.167 ng/mL to 55.5 ng/mL
QC concentrations (ng/mL)	LLOQ	0.166 ng/mL
	Low	0.498 ng/mL
	Medium-Low	3.32 ng/mL
	Medium-High	16.6 ng/mL
	High	41.6 ng/mL
QC Intraday precision range (%)		1.5% to 12.1%
QC Intraday accuracy range (%)		0.0% to 12.7%
QC Interday precision range (%)		3.0% to 8.7%
QC Interday accuracy range (%)		1.0% to 9.6%
Bench-top stability (hrs)		58.0 hours at ambient temperature
Stock stability (days)		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
Process sample integrity (hrs)		120 hours at ambient temperature
Freeze-thaw stability (cycles)		4 cycles at -20°C
Long-term storage stability (days)		815 days at -20°C
Dilution Integrity		up to 149 ng/mL
Selectivity		Interfering peaks were noted in all sources

Reviewer's Comments:
Acceptable

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	AA21388
Study Design	Two-way crossover, randomized, single-dose
No. of subjects enrolled	40
No. of subjects completing	34
No. of subjects analyzed	31
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many completed?)	Male: 16 Female: 18
Test product	Nicotine Polacrilex Chewing Gum (Original Flavor)
Reference product	Nicorette® (Original Flavor)
Strength tested	4 mg
Dose	1 x 4 mg

Reviewer's Calculations for Pooled Data

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	36.71	33.85	1.08	103.34	113.76
LAUCI	38.59	35.49	1.09	103.76	113.97
LCMAX	10.00	9.80	1.02	96.43	107.94

Reviewer's Calculation for Group I

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	37.73	36.27	1.04	98.28	110.11
LAUCI	40.11	38.14	1.05	99.41	111.23
LCMAX	10.27	10.76	0.95	88.61	102.92

Results for Group II

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	35.86	31.46	1.14	105.00	123.74
LAUCI	37.11	32.92	1.13	103.88	122.35
LCMAX	9.81	8.87	1.11	102.24	119.45

Table 8. Reanalysis of Study Samples (Unadjusted Nicotine)

AA21388 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
Lowest Standard Removed	32	32	2.48	2.48	32	32	2.48	2.48
Lost in Processing	0	2	0.00	0.16	0	2	0.00	0.16
Total	32	34	2.48	2.64	32	34	2.48	2.64

Did use of recalculated plasma concentration data change study outcome? No. There were no pharmacokinetic repeats.

2. Multi-Dose Chew-Out Study

Study Summary, Chew-out Study	
Study No.	AA21387
Study Design	Two-way crossover, open-label, randomized, multiple-dose
No. of subjects enrolled	14
No. of subjects completing	14
No. of subjects analyzed	12 as per protocol
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male 7 Female 7
Test product	Nicotine Polacrilex Gum (Original Flavor)
Reference product	Nicorette® (Original Flavor)
Strength tested	4 mg
Dose	4 x 4 mg (per period)

Summary of Statistical Analysis, Chew-out Study				
Comparison	**Chewing Duration, Min**			
	5	10	20	30
IVAX Nicotine Polacrilex Mint vs. GSK Nicorette® Mint (T/R)	1.288299	1.185868	1.15621	1.103347

Reanalysis of Study Samples, Chew-out Study Additional information in Appendix, Table 17								
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**
n/a								

Total								

Did use of recalculated plasma concentration data change study outcome? There were no repeats.

F. Formulation

Location in appendix	SectionIV.B, Page 29
Are inactive ingredients within IIG limits?	No
If no, list ingredients outside of limits	-
If a tablet, is the product scored?	NA
If yes, which strengths are scored?	
Is scoring of RLD the same as test?	NA
Is the formulation acceptable?	Yes
If not acceptable, why?	-

Reviewer's Note: See Formulation Data for detailed comments

G. In Vitro Dissolution

Apparatus	(b) (4)
Manufacturer	
Medium	0.1% Sodium Lauryl Sulfate
Volume (mL)	40 mL
Temp.	37 ^{0}C
Chewing Frequency	40 Strokes/min.
Stroke Length	5 mm
Rotation Angle	20 ^{0} (5 mm)
Gap between Jaws	1.6 mm
Compression	6 Bar (84 psi)
FDA Recommended Specification	NLT (b) (4) (Q) in 30 minutes

H. Waiver Request(s)

Strengths for which waivers are requested	None
Regulation cited	NA
Proportional to strength tested in vivo?	NA
Is dissolution acceptable?	NA
Waivers granted?	NA
If not then why?	

I. Deficiency Comments

1. The firm should acknowledge the FDA recommended method and data driven specification.

J. Recommendations

1. The bioequivalence study conducted under fasting conditions by IVAX Pharmaceuticals, Inc. on its nicotine polacrilex 4 mg gum (original flavor), lot US20201B040001 comparing it to Nicorette® 4 mg gum (original flavor), lot EF080A manufactured by GlaxoSmithKline is acceptable.

2. The multi-dose chew-out study conducted by IVAX Pharmaceuticals, Inc. on its nicotine polacrilex 4 mg gum (original flavor), lot US20201B040001 comparing it to Nicorette® 4 mg gum (original flavor), lot EF080A manufactured by GlaxoSmithKline is acceptable.

3. The dissolution testing conducted by the firm is acceptable. The firm should acknowledge the following FDA recommended method and data driven specification:

Apparatus Manufacturer	(b) (4)
Medium	0.1% Sodium Lauryl Sulfate
Volume (mL)	40 mL
Temp.	37 ^{0}C
Chewing Frequency	40 Strokes/min.
Stroke Length	5 mm
Rotation Angle	20 ^{0} (5 mm)
Gap between Jaws	1.6 mm
Compression	6 Bar (84 psi)
FDA Recommended Specification	NLT (b) (4) (Q) in 30 minutes

4. The Division of Chemistry may note that the test product uses (b) (4)

5. The ANDA is incomplete pending firm's acceptance of dissolution testing method and specification.

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	AA021388
Study Title	Comparative, Randomized, 2-Way Crossover Fasting BE study of IVAX and GlaxoSmithKline (Nicorette®) 4 mg Nicotine Polacrilex Chewing Gum in Healthy Adult Volunteers
Clinical Site	MDS Pharma Services, Lincoln, NE, USA
Principal Investigator	Alan S. Marion, M.D.
Study/Dosing Dates	Period I: 09-29-04 (group 1) Period I: 11-10-04 (group 2) Period II: 10-06-04 (group 1) Period II: 11-17-04 (group 2)
Analytical Site	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	12-15-04 to 02-07-05
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	130 days

Treatment ID	**Test**	**Reference**
Test or Reference	A	B
Product Name	Nicotine Polacrilex Chewing Gum (original)	Nicorette® (original)
Manufacturer	IVAX Pharmaceuticals, Inc.	GlaxoSmithKline
Batch/Lot No.	US20201B040001	EF080A
Manufacture Date	08/17/04	n/a
Expiration Date	n/a	11/2005
Strength	4 mg	4 mg
Dosage Form	Chewing Gum	Chewing Gum
Batch Size	(b) (4)	NA
Production Batch Size	(b) (4)	NA
Potency	102	106
Content Uniformity (mean, %CV)	102.1 (1.8)	106.1 (0.9)
Formulation	See Appendix Section B	
Dose Administered	1x4 mg	1x4 mg
Route of Administration	Buccal	
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 (36 hours prior to dosing), 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.	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2 (Gr 1= 17 subjects and Gr 2 = 14 subjects)
Washout Period	7 days
Randomization Scheme	See section 16.1.7
Blood Sampling Times	0, 0.0833, 0.167, 0.333, 0.5, 0.67, 0.833, 1, 1.25, 1.5, 2, 3, 6, 9, 12, 16, 24 h
Blood Volume Collected/Sample	17 x 10 ml
Blood Sample Processing/Storage	Samples were collected in Vacutainers containing EDTA, placed in ice baths prior to centrifugation, and were centrifuged as soon as possible under refrigerated conditions. Samples were stored at -20^{o}C until assayed.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	Overnight fast and at least 4 hours thereafter.
Length of Confinement	At least 36 hours before dosing and until after the 24-hour sampling
Safety Monitoring	Blood pressure and heart rate was measured before dosing in each period. In addition, at check-in and at random times throughout the study, expired carbon monoxide levels were measured. Subjects with CO levels greater than 12 ppm in the morning prior to dosing were excluded.

Comments on Study Design:
The study design is acceptable.

b) Clinical Results

Table 1 Demographics of Study Subjects

Table 6. Demographic Profile of Subjects Completing the Bioequivalence Study

	Study # AA21387		Study # AA21388	
	Test Product (N=14)	Reference Product (N=14)	Test Product (N=34)	Reference Product (N=34)
Age (Years)				
Mean±SD	27.2±9.5	27.2±9.5	27.0±8.7	27.0±8.7
Range	20-54	20-54	19-55	19-55
Age Groups				
18-39	13 (92.9%)	13 (92.9%)	31 (91.2%)	31 (91.2%)
40-64	1 (7.1%)	1 (7.1%)	3 (8.8%)	3 (8.8%)
Sex				
Female	7 (50%)	7 (50%)	18 (52.9%)	18 (52.9%)
Male	7 (50%)	7 (50%)	16 (47.1%)	16 (47.1%)
Race				
American indian			1 (2.9%)	1 (2.9%)
Black			3 (8.8%)	3 (8.8%)
Caucasian	13 (92.9%)	13 (92.9%)	30 (88.2%)	30 (88.2%)
European/middle eastern	1 (7.1%)	1 (7.1%)		
Frame				
Large	5 (35.7%)	5 (35.7%)	7 (20.6%)	7 (20.6%)
Medium	8 (57.1%)	8 (57.1%)	26 (76.5%)	26 (76.5%)
Small	1 (7.1%)	1 (7.1%)	1 (2.9%)	1 (2.9%)
Weight (kg)				
Mean±SD	72.4±11.8	72.4±11.8	71.6±7.2	71.6±7.2
Range	54.9-90.7	54.9-90.7	54.9-91.6	54.9-91.6
Height (cm)				
Mean±SD	176.7±8.4	176.7±8.4	173.3±8.2	173.3±8.2
Range	165-193	165-193	160-185	160-185
Elbow Breadth (cm)				
Mean±SD	7.0±0.6	7.0±0.6	6.8±0.4	6.8±0.4
Range	5.9-8.0	5.9-8.0	5.7-7.6	5.7-7.6

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
13	Unable to draw blood	1	No
19	Personal reasons	1	No
22	Adverse event (hematoma)	1	No
25	Personal reason	2	No
29	Failed to check in for labwork	2	No
31	Personal reason	2	No

Table 3 Study Adverse Events

Table 7. Incidence of Adverse Events
N=Number of Subjects Reporting the Event (% of Subjects Dosed)

Adverse Event (Classified according to MedDRA Version 8.0)	Study # AA21387		Study # AA21388	
System Organ Class Preferred Term	Test	Reference	Test	Reference
Number of Subjects Dosed	14 (100%)	14 (100%)	38 (100%)	37 (100%)
Number of Subjects With Adverse Events	12 (85.7%)	10 (71.4%)	23 (60.5%)	21 (56.8%)
Number of Subjects Without Adverse Events	2 (14.3%)	4 (28.6%)	15 (39.5%)	16 (43.2%)
Gastrointestinal disorders	10 (71.4%)	7 (50.0%)	12 (31.6%)	16 (43.2%)
Nausea	3 (21.4%)	1 (7.1%)	10 (26.3%)	11 (29.7%)
Dyspepsia	7 (50.0%)	6 (42.9%)	3 (7.9%)	4 (10.8%)
Eructation	1 (7.1%)	1 (7.1%)	2 (5.3%)	7 (18.9%)
Flatulence	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Retching	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Vomiting	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Respiratory, thoracic and mediastinal disorders	8 (57.1%)	6 (42.9%)	10 (26.3%)	9 (24.3%)
Throat irritation	8 (57.1%)	5 (35.7%)	3 (7.9%)	3 (8.1%)
Hiccups	2 (14.3%)	1 (7.1%)	9 (23.7%)	6 (16.2%)
Increased upper airway secretion	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Pharyngolaryngeal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Nervous system disorders	1 (7.1%)	2 (14.3%)	12 (31.6%)	9 (24.3%)
Dizziness	0 (0.0%)	0 (0.0%)	10 (26.3%)	7 (18.9%)
Headache	1 (7.1%)	1 (7.1%)	2 (5.3%)	2 (5.4%)
Hypoaesthesia	0 (0.0%)	0 (0.0%)	2 (5.3%)	0 (0.0%)
Dysgeusia	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)
Somnolence	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
General disorders and administration site conditions	0 (0.0%)	0 (0.0%)	2 (5.3%)	3 (8.1%)
Fatigue	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (2.7%)
Chest pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Feeling hot	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)

Table 4 Protocol Deviations

Type	#s
Sampling time deviation	80
No blood collected at 0.667 h during Period I (Sub. 21)	1
Subject 23 had BMI of 19% as opposed to 15% specified in protocol	1
Subjects 21 and 24 did not have blood collected at one hour of period I	1
Subject 24 vital signs were out of range, but subject was enrolled	1
Subject 39 took Robitussin within 7 days prior to study	1

Comments on Dropouts/Adverse Events/Protocol Deviations: There were six dropouts. The number of adverse events experienced by the treatment groups was comparable.

Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Nicotine								
QC Conc. (ng/mL)	0.498		3.32		16.6		41.6		
Inter day Precision (%CV)	6.3		3.6		3.4		3.1		
Inter day Accuracy (%)	105.6		101.2		101.8		100.7		
Cal. Standards Conc. (ng/mL)	0.167	0.333	0.555	1.11	5.55	11.1	22.2	44.4	55.5
Inter day Precision (%CV)	6.0	6.0	6.9	4.7	2.6	1.8	2.6	2.3	1.5
Inter day Accuracy (%)	111.4	103.6	93.5	96.4	96.8	99.1	100.0	100.0	100.5
Linearity Range (range of R^2 values)	0.9985-0.9999								

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Random

Comments on Chromatograms: Acceptable

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
GL-Bio-10603-00	Jul 29, 2004	Reporting of Data Generated from the Analysis of Biological Matrices and the Reassay of Samples

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did use of recalculated plasma concentrations change the study outcome?	No. There were no pk repeats.
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	n/a

Summary/Conclusions, Study Assays: Acceptable

c) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters (Data without correction for baseline)

Mean plasma concentrations are presented in Table 11 and Figure 1
Means presented for pooled data only

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	39.51	38.37	18.52	92.80	36.09	35.79	19.47	73.48	1.09
AUCI	ng hr/mL	41.09	39.27	20.09	97.43	37.83	35.53	20.17	76.63	1.09
CMAX	ng/mL	10.48	29.45	6.39	20.60	10.23	26.55	7.06	16.40	1.02
TMAX	hr	0.83	.	0.50	2.04	0.83	.	0.35	1.25	1.00
KE	hr-1	0.20	44.43	0.08	0.47	0.18	48.17	0.05	0.43	1.10
THALF	hr	4.15	41.92	1.47	8.31	4.82	53.54	1.60	12.65	0.86

Table 9 Geometric Means and 90% Confidence Intervals

Group Not in Model

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	**36.65**	**33.82**	**1.08**	**103.31**	**113.70**
LAUCI	**38.55**	**35.45**	**1.09**	**103.76**	**113.94**
LCMAX	10.00	9.80	1.02	96.43	107.94

Group I

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	37.59	36.15	1.04	98.26	110.02
LAUCI	39.97	38.02	1.05	99.41	111.19
LCMAX	**10.27**	**10.76**	**0.95**	**88.61**	**102.92**

Group II

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	35.90	31.50	1.14	104.98	123.69
LAUCI	37.14	32.96	1.13	103.86	122.30
LCMAX	**9.81**	**8.87**	**1.11**	**102.24**	**119.45**

Table 10 Additional Study Information (2 groups pooled)

Root mean square error, AUC_{0-t}	0.1059
Root mean square error, AUC_{∞}	0.1033
Root mean square error, C_{max}	0.1245
K_{el} and AUC_{∞} determined for how many subjects?	30 for test and 31 for reference
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	37
-first measurable drug concentration as C_{max}	0
Were the subjects dosed as more than one group?	Yes

Comments on Pharmacokinetic and Statistical Analysis:

The design for the fasting BE study is a two-way, crossover study in healthy male and female subjects (n=31). Subjects were dosed in two groups (Group 1: n=17; Group 2: n=14). At a =0.10, the reviewer found a statistically significant ($p<0.1$) result for LCmax. The calculated LCmax for both Group I and II pass the 80-125% confidence interval.

Note: The firm took three pre-dose samples 5, 10, and 15 minutes. The reviewer used the 5 minute pre-dose sample as the zero hour timepoint for their calculations.

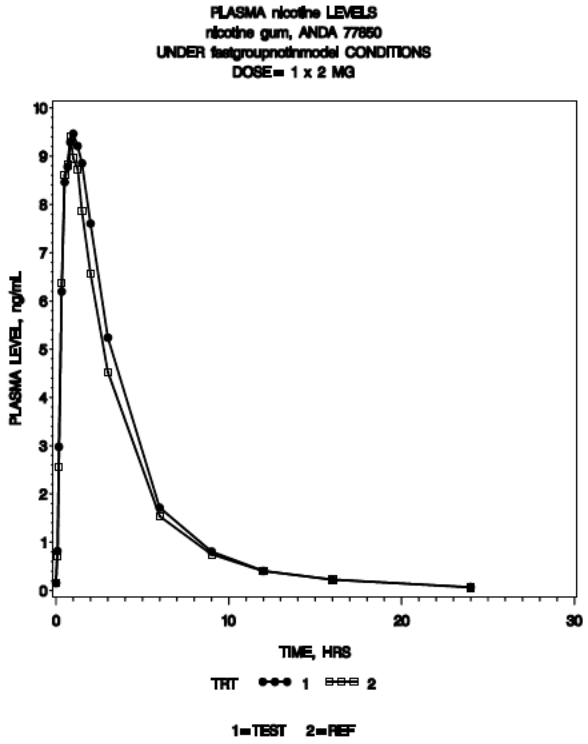
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The single-dose fasting bioequivalence study is acceptable.

Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=31)		Reference (n=31)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.15	93.42	0.16	98.75	0.96
0.08	0.81	107.85	0.71	51.70	1.14
0.17	2.98	66.54	2.57	47.99	1.16
0.33	6.19	34.28	6.37	30.91	0.97
0.50	8.46	33.13	8.61	29.76	0.98
0.67	8.78	33.86	8.82	26.01	1.00
0.83	9.29	31.77	9.40	28.40	0.99
1.00	9.46	32.11	8.95	29.18	1.06
1.25	9.21	30.92	8.73	31.45	1.05
1.50	8.85	31.99	7.86	32.33	1.13
2.00	7.60	31.73	6.56	29.46	1.16
3.00	5.24	37.02	4.53	35.11	1.16
6.00	1.71	48.62	1.54	46.40	1.12
9.00	0.81	61.99	0.75	55.41	1.08
12.00	0.40	83.40	0.40	68.26	1.02
16.00	0.22	97.67	0.23	86.84	0.97
24.00	0.07	190.65	0.06	178.06	1.13

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



2. Multiple dose chew-out Study

a) Study Design

Study Information	
Study Number	AA021387
Study Title	Comparative, Randomized, 2-Way Crossover Salivary Dissolution Study of IVAX and GlaxoSmithKline (Nicorette®) 4 mg Nicotine Polacrilex Chewing Gum in Healthy Adult Volunteers
Clinical Site	MDS Pharma Services, Lincoln, NE, USA
Principal Investigator	Alan S. Marion, M.D.
Study/Dosing Dates	Period I: 12-11-04 Period II: 12-12-04
Analytical Site	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	02-18-05 to 02-24-05
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	74 days

Treatment ID	**Test**	**Reference**
Test or Reference	A	B
Product Name	Nicotine Polacrilex Chewing Gum (original)	Nicorette® (original)
Manufacturer	IVAX Pharmaceuticals, Inc.	GlaxoSmithKline
Batch/Lot No.	US20201B040001	EF080A
Manufacture Date	08/17/04	n/a
Expiration Date	n/a	11/2005
Strength	4 mg	4 mg
Dosage Form	Chewing Gum	Chewing Gum
Batch Size	(b) (4)	NA
Production Batch Size	(b) (4)	NA
Potency	102	106
Content Uniformity	102.1 (1.8)	106.1 (0.9)
Formulation	See Appendix Section B	
Dose Administered	Multiple 4 buccal doses of 4 mg gum	Multiple 4 buccal doses of 4 mg gum
Route of Administration	Buccal	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Chewing Session Schedule	Each treatment period included a total of 4 chewing sessions of different durations: 30, 20, 10, and 5 minutes. The first chewing session was 30 minutes and subsequent sessions were of decreasing duration. Each chewing session was separated by one hour. Time of administration / Chewing duration Gum Piece #1 Hour 0 30 minutes Gum Piece #2 Hour 1, 30 minutes 20 minutes Gum Piece #3 Hour 2, minutes 50 10 minutes Gum Piece #4 Hour 4, minutes 0 5 minutes
Washout Period	At least 1 day from the first dose in each period
Randomization Scheme	See Section 16.1.7
Sample Processing/Storage	At the end of each chewing session, the chewed cuds were collected and stored at -20^{o}C for analysis of residual nicotine content.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See **Table 12**
Length of Fasting before Meal	Subjects received a light breakfast approximately 1.5 hours prior to the first chewing session. A full lunch was served to subjects following completion of the fourth chewing session, prior to release from the clinic.
Length of Confinement	Subjects were admitted to the study unit at least 4 hours prior to the scheduled dose in periods 1 and 2. They remained in the unit until completion of the last chewing session (approx. 8 hours) in each period.
Safety Monitoring	Yes
Data Analysis	The amount of nicotine released from the gum was calculated as follows: $Amount_{released} = Amount_{initial} – Amount_{Residual}$ Where $Amount_{initial}$ = content of nicotine listed in the assay for test and reference formulations The percent of nicotine released from the test and reference formulation is calculated as follows: $Percent_{released} = 100*Amount_{released} / Amount_{Initial}$

Comments on Study Design: Acceptable.

b) Clinical Results

Table 12 Demographics of Study Subjects

Table 6. Demographic Profile of Subjects Completing the Bioequivalence Study

	Study # AA21387		Study # AA21388	
	Test Product (N=14)	Reference Product (N=14)	Test Product (N=34)	Reference Product (N=34)
Age (Years)				
Mean±SD	27.2±9.5	27.2±9.5	27.0±8.7	27.0±8.7
Range	20-54	20-54	19-55	19-55
Age Groups				
18-39	13 (92.9%)	13 (92.9%)	31 (91.2%)	31 (91.2%)
40-64	1 (7.1%)	1 (7.1%)	3 (8.8%)	3 (8.8%)
Sex				
Female	7 (50%)	7 (50%)	18 (52.9%)	18 (52.9%)
Male	7 (50%)	7 (50%)	16 (47.1%)	16 (47.1%)
Race				
American indian			1 (2.9%)	1 (2.9%)
Black			3 (8.8%)	3 (8.8%)
Caucasian	13 (92.9%)	13 (92.9%)	30 (88.2%)	30 (88.2%)
European/middle eastern	1 (7.1%)	1 (7.1%)		
Frame				
Large	5 (35.7%)	5 (35.7%)	7 (20.6%)	7 (20.6%)
Medium	8 (57.1%)	8 (57.1%)	26 (76.5%)	26 (76.5%)
Small	1 (7.1%)	1 (7.1%)	1 (2.9%)	1 (2.9%)
Weight (kg)				
Mean±SD	72.4±11.8	72.4±11.8	71.6±7.2	71.6±7.2
Range	54.9-90.7	54.9-90.7	54.9-91.6	54.9-91.6
Height (cm)				
Mean±SD	176.7±8.4	176.7±8.4	173.3±8.2	173.3±8.2
Range	165-193	165-193	160-185	160-185
Elbow Breadth (cm)				
Mean±SD	7.0±0.6	7.0±0.6	6.8±0.4	6.8±0.4
Range	5.9-8.0	5.9-8.0	5.7-7.6	5.7-7.6

Table 13 Dropout Information

Subject No	Reason	Period	Replaced?
NONE			

Table 14 Study Adverse Events

Table 7. Incidence of Adverse Events
N=Number of Subjects Reporting the Event (% of Subjects Dosed)

Adverse Event (Classified according to MedDRA Version 8.0)	Study # AA21387		Study # AA21388	
System Organ Class Preferred Term	Test	Reference	Test	Reference
Number of Subjects Dosed	14 (100%)	14 (100%)	38 (100%)	37 (100%)
Number of Subjects With Adverse Events	12 (85.7%)	10 (71.4%)	23 (60.5%)	21 (56.8%)
Number of Subjects Without Adverse Events	2 (14.3%)	4 (28.6%)	15 (39.5%)	16 (43.2%)
Gastrointestinal disorders	10 (71.4%)	7 (50.0%)	12 (31.6%)	16 (43.2%)
Nausea	3 (21.4%)	1 (7.1%)	10 (26.3%)	11 (29.7%)
Dyspepsia	7 (50.0%)	6 (42.9%)	3 (7.9%)	4 (10.8%)
Eructation	1 (7.1%)	1 (7.1%)	2 (5.3%)	7 (18.9%)
Flatulence	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Retching	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Vomiting	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Respiratory, thoracic and mediastinal disorders	8 (57.1%)	6 (42.9%)	10 (26.3%)	9 (24.3%)
Throat irritation	8 (57.1%)	5 (35.7%)	3 (7.9%)	3 (8.1%)
Hiccups	2 (14.3%)	1 (7.1%)	9 (23.7%)	6 (16.2%)
Increased upper airway secretion	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Pharyngolaryngeal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Nervous system disorders	1 (7.1%)	2 (14.3%)	12 (31.6%)	9 (24.3%)
Dizziness	0 (0.0%)	0 (0.0%)	10 (26.3%)	7 (18.9%)
Headache	1 (7.1%)	1 (7.1%)	2 (5.3%)	2 (5.4%)
Hypoesthesia	0 (0.0%)	0 (0.0%)	2 (5.3%)	0 (0.0%)
Dysgeusia	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)
Somnolence	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
General disorders and administration site conditions	0 (0.0%)	0 (0.0%)	2 (5.3%)	3 (8.1%)
Fatigue	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (2.7%)
Chest pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Feeling hot	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)

Table 15 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
The Principal Investigator had signed the delegation of authority form on December 16, 2004 four days after completion of the study. However, all associates who had worked in the study had been appropriately trained.	-	-

Comments on Adverse Events/Protocol Deviations: There were no dropouts.

c) Bioanalytical Results

Table 16 Assay Quality Control – Within Study

	Parent							
QC Conc. (ng/mL)			31.8			150		318
Inter day Precision (%CV)			7.3			5.9		5.3
Inter day Accuracy (%)			100.6			104.4		100.6
Cal. Standards Conc. (ng /mL)	9.90	19.8	44.1	75.6	89.7	180	349	411
Inter day Precision (%CV)	*	*	*	*	*	*	*	*
Inter day Accuracy (%)	100.8	96.0	102.3	105.1	101.7	101.7	98.3	94.3
Linearity Range (range of R^2 values)	0.9966-0.9990							

*** Firm reported as "Not Statistically Valid", as all samples were assayed in 2 days.**

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Random

Comments on Chromatograms: Acceptable

Table 17 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
N/a		

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	n/a
Did use of recalculated plasma concentrations change the study outcome?	n/a there were no repeats
Does the reviewer agree with the outcome of the repeat assays?	n/a
If no, reason for disagreement	

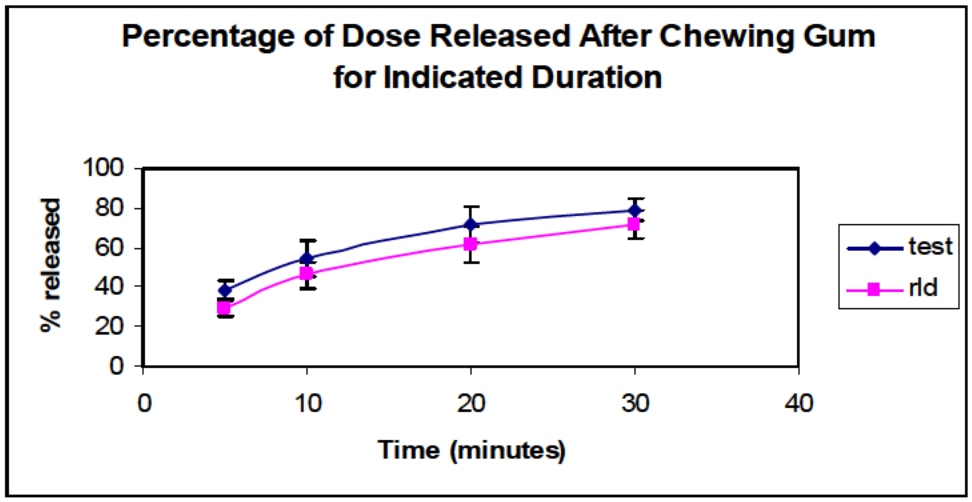
Summary/Conclusions, Study Assays:
Acceptable

Table 19 Arithmetic Means

Percentage of Dose Released After Chewing a Gum for Indicated Duration

	Nicotine Polacrilex Gum				Nicorette®			
	5 min	10 min	20 min	30 min	5 min	10 min	20 min	30 min
Mean	38.36478	54.61871	71.53105	79.15881	29.77941	46.05801	61.86683	71.74428
±SD	4.68291	8.796804	8.869353	5.525757	4.516363	6.968922	9.052931	6.640819
%CV	12.20627	16.10584	12.3993	6.980597	15.16606	15.13075	14.63293	9.256235

T/R (at 30 min) = 1.103



Summary/Conclusions, Multi-dose Chew-out Study:

The Test/Reference ratio for the percent nicotine released during the 30 minute chewing duration was 1.103 for Nicotine Polacrilex Gum. This is within the acceptable limits of 0.80-1.25 ratio. The study is acceptable. Note: the reviewer used potency values of nicotine per gum piece to calculate percent of nicotine released for the chew-out study. The reviewer's values are reported in the above table.

B. Formulation Data

Component/Grade	Role	Mg/piece	% w/w	Per ANDA Batch #US20201B040001 and Production Batch (b) (4) (g)
Nicotine Polacrilex USP (20% Nicotine)	Active	(b) (4)		
Chewing Gum Base**/Food Grade	Chewing gum			
Sodium Bicarbonate, USP	(b) (4)			
Sodium Carbonate, NF[c]				
D&C Yellow #10				
Sorbitol, NF[a]				
Sorbitol solution, USP (noncrystallizing)[b]				
Peppermint Oil, NF [d]				
Starch NF#				
Total	-			

a. Level of Sorbitol being proposed (b) (4) than the level previously approved for use in a buccal drug product as per IIG. Pharm/Tox data provided.
b. Level of Sorbitol Solution being proposed (b) (4) than the level previously approved for use in a buccal drug product as per the IIG. Pharm/Tox data provided.
c. Level of Sodium Bicarbonate being proposed (b) (4) than the previous amount previously approved for use in a buccal drug product as per the IIG. Pharm/Tox data provided.
d. Level of Peppermint Oil being proposed (b) (4) than previously approved for use in a buccal drug product as per the IIG. Pharm/Tox data provided.

1. The following statement is taken from the reg. support review: "The Inactive Ingredients listed below were used at the same levels or lower in Ivax's ANDA # 76-880 (Nicotine Polacrilex Gum USP, 2 mg). A Pharm/Tox consult was sent out for each of the Inactive Ingredients that were used at a level greater than what has been previously approved for use in a buccal drug product. See attached documents in jacket. I also spoke to Dr. David Skanchy who reviewed ANDA # 76-880 and he stated that since there are not a lot of buccal products on the market, some of the inactive ingredients used in buccal products are usually justified based on levels being used in oral drug products especially if the inactive ingredient is known to have poor absorption through the buccal mucosa. He also stated that if the formulation for the 4 mg strength (current ANDA) is the same as the formulation for the 2 mg strength then there shouldn't be a problem since the ANDA for the 2 mg strength has already been reviewed and the issues with the inactive ingredients addressed (10/20/05). "

2. The following statement is taken from the chemistry review regarding chemistry "There is [redacted] of nicotine polacrilex, USP used in the formulation. The RLD also contains a [redacted] This is acceptable.".

3. The following data is taken from the review for the 2 mg strength of Ivax's Nicotine gum regarding the mint flavor "The ANDA refers to the drug product as being "original" flavored. However, the labeling on the package cover states "peppermint flavor", and the formulation contains peppermint oil. The reviewer discussed with the chemistry reviewer the amendment submitted by the firm on March 4, 2004 regarding whether the peppermint oil in the formulation creates a "mint" flavor. The firm states that the flavor profile in the ANDA formulation is intended to mimic the innovator's "original" flavor. The use of peppermint oil in the firm's 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. The chemistry reviewer agrees with the firm's statement (See attachment). The test product is not considered mint flavor by the Division of Chemistry."

Reviewer's Comments: The formulation is acceptable.

C. Dissolution Data

Reviewer's Comments:

1) The firm originally submitted dissolution data using method A listed below. The firm was requested to conduct dissolution testing using method B. The main difference between the two methods was the medium: 0.1% Sodium Lauryl Sulfate (method A) vs. Phosphate Buffer at pH 7.4 (B). Even though both methods provide acceptable data, in consultation with our dissolution focal point, we will recommend the method A (0.1% SLS) for the sake of consistency with Ivax's 2 mg original flavor gum (ANDA 76-880).

2) The DBE has typically recommended using the [redacted] chewing apparatus. However the [redacted] apparatus is not commercially/readily available. According to the review of Ivax's submission for the 2 mg strength of this product (ANDA 76-880):

   "Typically for chewing gum dosage forms, DBE has recommended the [redacted] chewing gum apparatus", however, the [redacted] apparatus is not commercially/readily available. The [redacted] shares many similarities with typical chewing gum dissolution apparatuses (e.g. [redacted] Apparatus type: A machine is used to simulate gum chewing. Each piece of gum is placed in a small chamber at 37oC 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 [redacted] is sufficiently adequate in performing dissolution testing on nicotine polacrilex chewing gum."

3) The firm's data for method A demonstrate the product passes at the S1 level for the data driven specification NLT (b) (4) (Q) in 30 minutes.
4) **The firm should acknowledge that it will use Method A with a specification of NLT (b) (4) (Q) in 30 minutes.**

Method A:

Apparatus:	(b) (4)
Manufacturer:	
Medium:	0.1% Sodium lauryl sulfate
Volume :	40 mL
Temperature:	37 ^{0}C
Chewing Frequency:	40 Strokes/min.
Stroke length:	5 mm
Rotation angle	20 ^{0} (5 mm)
Gap between jaws:	1.6 mm
Compression:	6 Bar (84 psi)
Sampling time:	5, 10, 20, 30 45 minutes
specification	NLT (b) (4) (Q) in 30 minutes.

Dissolution Data using Method A:

Table 4. Summary of In Vitro Dissolution Study

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)					Study report Location
					5 min	10 min	20 min	30 min	45 min	
Dissolution study report # Re/9-Rev.0 (June 2005)	Nicotine Polacrilex Gum, 4 mg , Lot # US20201B040001	4 mg Chewing Gum	Chewing Gum Dissolution Apparatus: DRT-01 Rotation Angle: 20° Frequency: 40 strokes/minute Dissolution Medium: 0.1% Sodium Lauryl Sulfate (SLS) Volume: 40 mL.	12	33 (b) (4)	64 (b) (4)	86 (b) (4)	93 (b) (4)	97 (b) (4)	Vol.1, Section VI, 5.
Dissolution study report # Re/9-Rev.0 (June 2005)	Nicorette® 4 mg Gum, Lot # FD003	4 mg Chewing Gum	Chewing Gum Dissolution Apparatus: DRT-01 Rotation Angle: 20° Frequency: 40 strokes/minute Dissolution Medium: 0.1% Sodium Lauryl Sulfate (SLS) Volume: 40 mL.	12	52 (b) (4)	80 (b) (4)	91 (b) (4)	95 (b) (4)	97 (b) (4)	Vol.1, Section VI, 5.

Dissolution Data using Method B:

Apparatus	(b) (4)
Manufacturer	
Medium	Phosphate buffer at pH 7.4
Volume (mL)	20 and 40 mL
Temp.	37 ^{0}C
Chewing Frequency	20, 40 and 60 Strokes/min.
Stroke Length	5 mm
Rotation Angle	20 ^{0} (5 mm)
Gap between Jaws	1.6 mm
Compression	6 Bar (84 psi)

20 STK/MIN

Nicotine Polacrilex Gum USP, **4mg** Batch #US **20201B040001**(NPG* USP 4mg) - Exp. Date : 08/06
Nicorette 4mg Batch **GC125A** Exp. date: 08/07

	%Nicotine dissolved at 20 stk/20mL		%Nicotine dissolved at 20 stk/40mL	
	mean of 12 units		mean of 12 units	
Time (min)	NPG* USP 4mg	Niwrette 4mg	NPG* USP 4mg	Nicorette 4mg
5	16	30	15	29
10	30	57	29	55
20	50	74	52	73
30	61	80	64	80
45	70	84	72	84
60	75	87	78	86
120	84		86	

*NPG=Nicotine Polacrilex Gum

40 STK/MIN

Comparative study :

Nicotine Polacrilex Gum USP, 4mg Batch #US **20201B040001**(NPG* USP 4mg) - Exp. Date : 08/06
Nicorette 4mg Batch **GC125A** Exp. date: 08/07

	%Nicotine dissolved at 40stk/20mL		%Nicotine dissolved at 40stk/40mL	
	mean of 12 units		mean of 12 units	
Time (min)	NPG* USP 4mg	Nicorette 4mg	NPG* USP 4mg	Nicorette 4mg
5	18	38	23	41
10	31	63	41	66
20	48	77	59	79
30	59	82	67	84
45	67	84	73	87
60	73		78	
90	80		83	
120	84		87	

*NPG=Nicotine Polacrilex Gum

50 STK/MIN

Nicotine Polacrilex Gum USP, 4mg Batch #US 20201B040001(NPG* USP 4mg) - Exp. Date : 08/06

Nicorette 4mg Batch GC125A Exp. date: 08/07

	% Nicotine dissolved 50stk/20ml.		% Nicotine dissolved at 50stk/40ml.	
	mean of 12 units		mean of 12 units	
Time (min)	NPG* USP 4mg	Nicorette 4mg	NPG* USP 4mg	Nicorette 4mg
5	25	42	24	43
10	47	68	48	70
20	67	82	68	83
30	78	87	78	87
45	85	90	85	90

*NPG=Nicotine Polacrilex Gum

D. **Consult Reviews** None

E. SAS Output

FASTING STUDY DATA

(b) (4)

[redacted]

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

(b) (4)

[redacted]

F. **Additional Attachments:**

The fasting BE study in this ANDA needed a third party audit. The OGD has decided not to request the audit for the following reasons.

1. There is an acceptable fasting BE study on the 2 mg strength.

2. The multi-dose human chew-out study and dissolution testing with chewing machine for both strengths are acceptable.
3. Majority of analysis [16 days (a suspect period) vs. 38 days (a non-suspect period)] was done in non- suspect period.
4. Only subjects 1 to 5 were run in the suspect period (till December 31, 2004) and remaining 6 to 40 were analyzed in a non-suspect period.
5. ANOVA on subject 6 to 40 showed acceptable 90% CI for all 3 PK parameter (see the table below).

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	35.89	32.79	1.09	103.85	115.34
LAUCI	37.35	34.42	1.09	103.03	114.32
LCMAX	9.68	9.43	1.03	96.85	108.88

BIOEQUIVALENCE DEFICIENCY

ANDA: 77-850 APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Nicotine Polacrilex Chewing Gum, 4 mg

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

Please provide a statement of your acceptance of the following dissolution method and specification:

Apparatus:	(b) (4)
Manufacturer:	
Medium:	0.1% Sodium lauryl sulfate
Volume :	40 mL
Temperature:	37°C
Chewing Frequency:	40 Strokes/min.
Stroke length:	5 mm
Rotation angle 20 0	(5 mm)
Gap between jaws:	1.6 mm
Compression:	6 Bar (84 psi)
Sampling time:	5, 10, 20, 30 45 minutes
Specification:	NLT (b) (4) (Q) in 30 minutes

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

CC: ANDA 77-850

BIOEQUIVALENCE - DEFICIENCIES Submission Date:

1. **FASTING STUDY** (STF) Strengths: 4 mg
   Clinical: MDS Pharma Services, Lincoln, NE, USA **Outcome: IC**
   Analytical: (b) (4)

2. **CHEW-OUT STUDY-MULTIDOSE** Strengths: 4 mg
   Clinical: MDS Pharma Services, Lincoln, NE, USA **Outcome: IC**
   Analytical: (b) (4)

3. **Study Amendment** 01-13-06 Strengths: 4 mg
   Outcome: WC-IC

4. **Study Amendment** 09-11-06 Strengths: 4 mg
   Outcome: IC

Outcome Decisions:
IC: incomplete

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

/s/

Ethan Stier
8/22/2007 03:43:47 PM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
8/22/2007 03:45:10 PM
BIOPHARMACEUTICS

Barbara Davit
8/22/2007 05:04:00 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	77-850
Drug Product Name	Nicotine Polacrilex Gum
Strength	4 mg
Applicant Name	Teva Pharmaceuticals
Submission Date	September 27, 2007
Reviewer	Aaron Sigler, Pharm.D.

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.

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/s/

Aaron Sigler
11/6/2007 11:17:23 AM
BIOPHARMACEUTICS

Lizzie Sanchez
11/6/2007 01:53:46 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077850

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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, 4 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, 4 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 4 mg, NDA held by Glaxo SmithKline)
- Draft Labeling (Four paper copies each in the archival [blue] binder, chemistry review [red] binder and the pharmacokinetic and bioavailability review [orange] binder. There is 1 (one) CD-ROM containing the electronic files as required by the FDA Final Rule "Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format" located in the archival binder, Volume 1, Section V. The format of the CD-ROM conforms to the Guidance for Industry "Providing Regulatory Submissions in Electronic Format – ANDAs" dated June 2002. The approximate size of the CD-ROM is 4.5 megabytes. IVAX has verified that the CD-ROM is virus-free using Norton Symantec Anti-Virus software, version 8.1.0.825 Corporate Edition.
- Certification of Financial Interests and Arrangements of Clinical Investigators (Form FDA 3454)
- *In Vivo* Bioequivalence Studies (Fasted and Salivary Dissolution):

  Protocol No. AA21388: A Comparative Randomized, Single-Dose, Two-Way Crossover Bioavailability Study of Nicotine Polacrilex Gum 4 mg in Healthy Adult Volunteers under Fasting Conditions

  Protocol No. AA21387: A Comparative Randomized, Two-Way Salivary Dissolution Crossover Bioavailability Study of Nicotine Polacrilex Gum 4 mg in Healthy Adult Volunteers.

The Diskettes are included in the front covers of the pharmacokinetic and bioavailability review (orange) binders: Volumes 2 of 11 and 9 of 11, respectively.

- 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, 4 mg. Section VI of this application contains comparative analytical data for IVAX's Nicotine Polacrilex Gum USP, 4 mg, versus the innovator's 4 mg strength.

The archival copy of this application consists of 13 volumes. The chemistry review copy consists of three (3) volumes. The pharmacokinetic and bioavailability review copy consists of eleven (11) volumes.

The exhibit batch for this application was manufactured and packaged for IVAX Pharmaceuticals, Inc., by Laboratorios Haymann S.A located in Montevideo, Uruguay. Secondary packaging may be conducted at (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 (845) 267-2444, extension 201 or 200.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Director, Regulatory Affairs

cc: District Office

PJ/amh

IVAX

Archival

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

OCT 2 1 2005

Via Facsimile:
Kwadwo Awuah, Project Manager, Regulatory Support, 301-443-3847

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

TELEPHONE AMENDMENT

Re: ANDA # 77-850 Nicotine Polacrilex Gum USP, 4 mg

Dear Mr. Buehler:

Reference is made to IVAX Pharmaceuticals, Inc.'s Abbreviated New Drug Application dated August 23, 2005 and to the Agency's telephone communications of October 20-21, 2005. Per our October 20th telephone conversation with the Agency, we are providing in **Exhibit 1** a revised Debarment Certification to replace the one included with the ANDA submission which contained an inadvertent reference to the 2 mg strength. IVAX apologizes for the inconvenience that this may have caused in the review of this application.

Additionally, per our October 21st telephone conversation with the Agency, we are providing an original signed Field Copy Certification in **Exhibit 2**.

IVAX Pharmaceuticals, Inc. has made a concerted effort to ensure that this submission 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

RECEIVED
OCT 2 4 2005
OGD/CDER

IVAX Pharmaceuticals, Inc.
Regulatory Affairs Department
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Telephone: 845-267-2444
www.IVAXPharmaceuticals.com

ORIG AMENDMENT
N/AB

Via Facsimile: (301) 594-0181
Kerrie Suh, FDA

Via Federal Express

JAN 13 2006

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 – BIOEQUIVALENCY

Re: ANDA # 77-850 Nicotine Polacrilex Gum USP, 4 mg

Dear Mr. Buehler:

Reference is made to IVAX Pharmaceuticals, Inc.'s Abbreviated New Drug Application (ANDA) dated August 23, 2005 and to the Agency's telephone communication of January 4, 2006. Pursuant to the Agency's January 4th telephone request, please find below the Agency's comments in bold followed by IVAX's response in plain text:

1. **Please provide details of the *in-vitro* dissolution method used in the study, including design and technical details of the apparatus (b) (4) SOP for inter and intra variability.**

Response:
Dissolution testing of Nicotine Polacrilex Gum has taken two schemes: *in-vivo* chewing, with subsequent testing of the residual gum 'cud' know as a "chew-out" study and *in-vitro* testing using mechanical apparatus designed to simulate mastication.

Based on the Agency's chemistry comments to pending **ANDA 77-880** for Nicotine Polacrilex Gum USP, **2 mg**, dated April 6, 2004, (b) (4) selected the use of the (b) (4) (b) (4) dissolution apparatus, which is the apparatus referred to in the Kvist literature article, "Apparatus for studying *in-vitro* drug release from medicated chewing gums" (International J. of Pharmaceutics 189 (1999) pp 57-65). This device consists of two vertically opposed surfaces contained in a thermostatted glass test 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. In addition to the Agency's comments referred to above, this apparatus was selected primarily based upon: its availability from a commercial supplier (b) (4) and the ready availability of replacement components, service, technical assistance and economic factors. (b) (4) currently has a one cell version of the device. Additional testing capabilities (6- cell device) can be added as sample requirements dictate. (b) (4) has had the opportunity to conduct *in- vitro* dissolution testing using only the (b) (4) device (Note that an *in-vivo* 'chew-out' study was also included in the Bioequivalence Study included in the ANDA application, please refer to *Salivary Dissolution Study*, Protocol # AA21387).

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JAN 17 2006
OGD / CDER

The method has been optimized using the variable parameters for the apparatus: chewing rate (vertical number of strokes per minute), angle of rotation of the upper surface during the 'chew' event, distance of the gap between upper and lower surfaces during the 'chew', bath temperature and dissolution medium. Method parameters are described in [redacted] (b) (4) Analytical Method [redacted] (b) (4) (please refer to section XV, Volume 3, page 67, in the original ANDA). Analysis of dissolution samples is conducted by HPLC with UV detection of Nicotine.

For design and technical details of the apparatus [redacted] (b) (4) we provide the following:

- **Exhibit 1** – Operating Manual for Chewing Apparatus [redacted] (b) (4)
- **Exhibit 2** – Documents:
  - Instrument Qualification: Dissolution Tester for Chewing [redacted] (b) (4)
  - Installation Qualification: Dissolution Tester for Chewing
  - Operation Qualification: Dissolution Tester for Chewing [redacted] (b) (4)

Regarding the inter and intra variability, please refer to the Analytical Method Validation Report: Dissolution of Nicotine Polacrilex Gum USP, 4 mg, located in Section XV, Volume 3 pages 473-508 of the ANDA, which includes typical intra and intermediate precision data. The results obtained from validation confirmed that the Analytical Method [redacted] (b) (4) for dissolution is specific, accurate, precise, linear, and robust for the evaluation of dissolution of Nicotine Polacrilex USP, 4 mg.

2. Please provide details of other methods of dissolution conditions tested and the results of such tests including individual data.

Response:
Please be advised that [redacted] (b) (4) has not employed or developed any *in-vitro* dissolution method, other than the one already presented in the original application. Other devices designed to simulate mastication are not readily available from commercial laboratory suppliers and would require custom manufacture with associated costs and technological issues.

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.

Dottie Titi

for: Patricia Jaworski
Director, Regulatory Affairs

PJ/amh

Archive

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 77-850 Nicotine Polacrilex Gum USP, 4 mg

Dear Mr. Buehler:

Reference is made to IVAX Pharmaceuticals, Inc.'s pending Abbreviated New Drug Application for Nicotine Polacrilex Gum USP, 4 mg, dated August 23, 2005.

Pursuant to 21 CFR Part 314.96 Ivax is amending its application by withdrawing [redacted] (b) (4) [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

RECEIVED
FEB 0 3 2006
OGD / CDER

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

September 11, 2006

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-AB

BIOEQUIVALENCY AMENDMENT

Re: ANDA 77-850 Nicotine Polacrilex Gum USP, 4 mg

Dear Mr. Buehler:

Reference is made to IVAX Pharmaceuticals' pending Abbreviated New Drug Application (ANDA) for Nicotine Polacrilex Gum USP, 4 mg and to the Agency's correspondence dated February 27, 2006 (copy provided in Reference). Pursuant to 21 CFR 314.96, we are amending our application by responding to the deficiencies cited in your letter.

In response to the Agency's comment, we submit the following (your comment in bold text, followed by our response in plain text):

1. **Please conduct additional comparative dissolution testing using the apparatus and experimental conditions as follows:**

Apparatus:	(b) (4)
Manufacturer:	
Medium:	**Phosphate buffer at pH 7.4**
Volumes:	**20 and 40 mL**
Temperature:	**37°C**
Chewing Frequency:	**20, 40 and 60 Strokes/min**
Stroke length:	**5 mm**
Rotation angle	**20° (5 mm)**
Gap between jaws:	**1.6 mm**
Compression:	**6 Bar (84 psi)**
Sampling time:	**10, 20, 30 and 45 minutes or until (b) (4) f the drug is released**
Units:	**12 gums each**

Response:
IVAX is providing in **Exhibit 1** additional comparative dissolution testing results using the apparatus and experimental conditions recommended by the FDA above as follows:

- A dissolution profile of our product and the reference listed drug for 12 test units, with 20 mL and 40 mL buffers at 20, 40, and 50 strokes per minute. Please note that the high-end chewing frequency used for testing was 50 strokes per minute instead of the 60 strokes per minute recommended by the Agency, due to the limitations of the testing apparatus (the (b) (4) has a maximum strokes per minute capacity of only 56 strokes per minute).

- A comparative study between our product and the reference listed drug comparing the mean of 12 test units.

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

October 3, 2006

ORIG AMENDMENT
N-AM

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 77-850 Nicotine Polacrilex Gum USP, 4 mg

Dear Mr. Buehler:

Reference is made to IVAX Pharmaceuticals Inc.'s Abbreviated New Drug Application for Nicotine Polacrilex Gum USP, 4 mg, submitted August 23, 2005. Further reference is made to the Agency's correspondence of February 8, 2006 (copy provided in Reference). Pursuant to 21 CFR 314.96 and 21 CFR 314.120, IVAX is amending its 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 correct** [redacted (b) (4)]

Response
We have corrected [redacted (b) (4)] and are providing the corrected copy in **Exhibit 1**.

2. **Terms like 'complies or meets requirements' for a result when a numerical value can be obtained for a specific test are unacceptable. Please revise all Ivax/** [redacted (b) (4)] **raw material COA's to provide actual data for tests where numerical values are in the specification.**

Response
We have revised all IVAX's and [redacted (b) (4)] raw materials Certificates of Analysis to provide actual data for tests where numerical values are in the specification. We are providing the revised certificates of analysis in **Exhibit 2**.

3. Please provide cGMP certifications for [redacted] and [redacted]

Response
At this time we are withdrawing [redacted] as a contract test laboratory for packaging components. [redacted] was not used for any essential testing in this application. IVAX has already withdrawn [redacted] as a contract test laboratory for raw materials in its Gratuitous Amendment dated January 31, 2006.

4. Please provide a brief written manufacturing summary of the steps involved in the manufacture of the drug product.

Response
We are providing a brief written manufacturing summary of the steps involved in the manufacture of the drug product in **Exhibit 3**.

5. Please provide a Blank Batch Record for the cartoning process performed at [redacted]

Response
Please note that although we have not yet implemented secondary packaging for this product, IVAX acknowledges the Agency's request and commits to provide a Blank Batch Record for the cartoning process performed at the [redacted] in an amendment or post-approval as appropriate before marketing.

6. Please establish tests and acceptance criteria for dissolution and moisture in your drug product stability specification.

Response
We have established tests and acceptance criteria for dissolution and moisture in our drug product stability specifications as follows:

Test	**Limits**		
Water	NMT [redacted]		
Dissolution	t=5 min:	Average [redacted]	
	t=30 min: Q = [redacted]	S1	Each unit ≥ Q + [redacted]
		S2	Average (12 units: S1+S2) ≥ Q No unit < Q – [redacted]
		S3	Average (24 units: S1+S2+S3) ≥ Q Not more than 2 units < Q – [redacted] No unit < Q – [redacted]

Reflecting these specifications we are providing the revised submission batch and post approval stability protocols with stability specifications in **Exhibit 4**.

7. **Please lower** [redacted] (b) (4)

[redacted] (b) (4)

Response
IVAX acknowledges the Agency's request to [redacted] (b) (4)

[redacted] (b) (4)

- [redacted] (b) (4)
-

8. [redacted]

Response

[redacted] (b) (4)

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

1. The labeling portion of your application is currently under review. The Division of Labeling and Program Support will notify you under separate cover of all labeling deficiencies.

Response
IVAX acknowledges that the labeling portion of our application is currently under review and that the Division of Labeling and Program Support will notify IVAX under separate cover of all labeling deficiencies.

2. **The bio-equivalence review is pending. The Division of Bioequivalence will notify you under separate cover of all deficiencies.**

Response
IVAX acknowledges the in-vivo portion of our bioequivalence is pending review and that the Division of Bioequivalence will notify us under separate cover of all deficiencies. IVAX also acknowledges the Agency's comments of February 27, 2006 regarding our in-vitro dissolution testing and will respond under separate cover.

3. **Pease commit to bringing the drug substance specification table and COA in line with the USP monograph once the addition of Residual Solvents becomes official in January of 2007.**

Response
IVAX commits to bringing the drug substance specification table and Certificate of Analysis in line with the USP monograph once the addition of Residual Solvents becomes official in January of 2007.

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.

(b) (6)

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Director, Regulatory Affairs

PJ/amh

Telephone Fax

ANDA 77-850

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301 827 7885

TO: Ivax Pharmaceuticals, Inc.

TEL: 845-267-2444

ATTN: Patricia Jaworski

FAX: 845-268-0117

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, USP, 4 mg.

Pages (including cover): 5

SPECIAL INSTRUCTIONS:

Labeling Comments

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

ANDA Numbers: 77-850 Date of Submission: August 23, 2005

Applicant's Name: Ivax Pharmaceuticals, Inc.

Established Name: Nicotine Polacrilex Gum USP, 4 mg

Labeling Deficiencies:

1. GENERAL COMMENT

The reference listed drug manufacturer of Nicorette®, provides initiatives to safeguard against the potential abuse or misuse of this product. Initiatives are also in place to safeguard against inappropriate sales to minors in compliance with the labeled sales restrictions. It is important that you have a similar program in place to ensure that adequate precautions will be taken to provide for the safe marketing of your products.

Please submit a detailed marketing and surveillance plan designed to ensure that retailers and distributors of your products will only sell them to persons 18 years of age or older. This plan should include at a minimum:

- One or more mechanisms, in addition to the proposed labeling, for ensuring that these products will not be sold to people less than 18 years of age, i.e. a mechanism that will require proof of lawful age at the time of purchase, and that the product cannot be sold from a vending machine or in any other manner or form that would allow a person to obtain the product without first presenting proof of lawful age.

- One or more mechanisms for identifying and reporting on use by people less than 18 years of age.

- Your commitment not to market trial or sample packages of nicotine polacrilex gum.

- Provisions for child-resistant packaging.

2. BLISTER

Add "NDC" to appear before "0172-6731-00". See 21 CFR 201.35.

3. CARTON- 108s

Information Panel

a. Active ingredient, revise to read;
"Nicotine polacrilex (equal to 4 mg nicotine)…Stop smoking aid"

b. Ask a doctor before use if you have, include the following as the first bullet
• a sodium-restricted diet

c. Directions, last bullet, revise to read: "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.

d. Other information, include a statement declaring the amount of sodium and calcium in your product to be in accordance with the final rule of March 24, 2004 (69 FR 13717).

Principal Display Panel

e. The reference listed drug includes a statement "Free Audio CD upon request". Please revise

accordingly.

4. User's Guide

a. GENERAL

Please ensure that your user's guide is in a format of a booklet to be in accordance with the reference listed drug.

b. Keys to Success

(1) Number 2, delete "See Usage Schedule Chart" and include page number as seen in the reference listed drug's user's guide.

(2) Number 4, delete "See Where to Get Help" and include page number as seen in the reference listed drug's user's guide.

(3) Add the following as number 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)

c. SOME IMPORTANT WARNINGS

Ask a doctor before use if you have, include the following as the first bullet
• a sodium-restricted diet

d. LET'S GET STARTED, Step 1, first paragraph, last sentence, delete "in the User's Guide" and include page numbers as seen in the reference listed drug's user's guide.

e. HOW TO USE NICOTINE POLACRILEX GUM

(1) Number 2, delete "in your User's Guide" and include page numbers as seen in the reference listed drug's user's guide.

(2) Number 5, revise to read;"PARK" the nicotine polacrilex gum piece…"

(3) Number 7, revise to read; "PARK" the nicotine polacrilex gum piece…"

f. HOW TO REDUCE YOUR NICOTINE POLACRILEX GUM USAGE

(1) First paragraph, revise second and third sentences as follows; " …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."

(2) Add the following as the last bullet; " 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."

g. STOP USING NICOTINE POLACRILEX GUM AT THE END OF WEEK 12. Revise as follows;

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

h. QUESTIONS AND ANSWERS
(1) Number 3, second sentence, delete "(see Some Important Warnings)" and include include page number as seen in the reference listed drug's user's guide.

i. Include wallet card and stickers as seen in the reference listed drug's user's guide.

5. CD audio script

a. Page 3, sixth paragraph, LEADER, last sentence, change "kit" to "user's guide".

b. Page 4, 8th paragraph, OW, add the following as the second sentence;
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.

c. Page 6, 8th paragraph, (b) (4) penultimate sentence, change "kit" to "user's guide".

d. Page 7, fifth paragraph, (b) (4) first sentence, delete "few".

Please revise your blister labels, carton, user guide labeling and CD script and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA. Also, submit two copies of the CD for your application.

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://www.fda.gov/cder/cdernew/listserv.html

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 the enclosed copy of the reference listed drug's 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
11/16/2006 12:56:13 PM
Lillie Golson for Wm. Peter Rickman

Archival

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

April 26, 2007

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

XA -

NEW CORRESPONDENCE
NOTIFICATION OF ADDRESS CHANGE

Re: ANDA 77-850 Nicotine Polacrilex Chewing Gum USP, 4 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.
An indirect 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 USP, 4 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, Laboratorios Haymann SA, Uruguay, for the finished drug product Nicotine Polacrilex Chewing Gum USP, 4 mg. Also, please note that IVAX is now an indirect 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.
An indirect wholly-owned subsidiary of TEVA Pharmaceuticals, USA

RECEIVED
APR 27 2007
OGD / CDER

Patricia Jaworski
Director, Regulatory Affairs

PJ/zt

BIOEQUIVALENCY AMENDMENT

ANDA 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: 845-267-2444 x201

ATTN: Patricia Jaworski

FAX: 845-268-0117

FROM: Keri Suh

PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on August 23, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nicotine Polacrilex Gum USP, 4 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **one** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all 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. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCY

ANDA: 77-850 APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Nicotine Polacrilex Chewing Gum, 4 mg

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

Please provide a statement of your acceptance of the following dissolution method and specification:

Apparatus:	(b) (4)
Manufacturer:	
Medium:	0.1% Sodium lauryl sulfate
Volume :	40 mL
Temperature:	37°C
Chewing Frequency:	40 Strokes/min.
Stroke length:	5 mm
Rotation angle 20 0	(5 mm)
Gap between jaws:	1.6 mm
Compression:	6 Bar (84 psi)
Sampling time:	5, 10, 20, 30 45 minutes
Specification:	NLT (b) (4) (Q) in 30 minutes

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

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

/s/

Barbara Davit
9/6/2007 05:54:11 PM
Signing for Dale P Conner

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

ORIG AMENDMENT

N/AB

September 27, 2007

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 77-850 Nicotine Polacrilex Chewing Gum USP, 4 mg

Dear Mr. Buehler:

Reference is made to IVAX Pharmaceuticals, Inc.'s pending Abbreviated New Drug Application (ANDA) for Nicotine Polacrilex Chewing Gum USP, 4 mg and to the Agency's bioequivalency comments dated September 6, 2007 (copy provided in **Reference**). Further reference is made to the telephone communication on September 14, 2007 between Keri Suh, FDA Project Manager, Dr. Ethan Stier, FDA reviewer, and (b) (6) of IVAX, during which IVAX requested clarification on the sampling time requirement listed in the dissolution specifications for the finished product. Based on the conversation, it was concluded that the sampling time was inadvertently included in the dissolution specifications provided in the deficiency letter.

We are amending our application by responding to the deficiency cited in your letter.

Comment:

Please provide a statement of your acceptance of the following dissolution method and specification:

RECEIVED

OCT - 1 2007

OGD

Apparatus:	(b) (4)
Manufacturer:	
Medium:	**0.1% Sodium lauryl sulfate**
Volume:	**40 mL**
Temperature:	**37°C**
Chewing Frequency:	**40 Strokes/min.**
Stroke length:	**5 mm**
Rotation angle:	**20° (5 mm)**
Gap between jaws:	**1.6 mm**
Compression:	**6 Bar (84 psi)**
Sampling Time:	**5, 10, 15, 20, 30, 45 minutes**
Specification:	**NLT (b) (4) Q) in 30 minutes**

Response:

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

Apparatus:	(b) (4)
Manufacturer:	
Medium:	**0.1% Sodium lauryl sulfate**
Volume:	**40 mL**
Temperature:	**37°C**
Chewing Frequency:	**40 Strokes/min.**
Stroke length:	**5 mm**
Rotation angle:	**20° (5 mm)**
Gap between jaws:	**1.6 mm**
Compression:	**6 Bar (84 psi)**
Specification:	**NLT (b) (4) Q) in 30 minutes**

As a result of the telephone conversation mentioned above, the sampling time requirement was removed from the dissolution specifications as it was inadvertently included in the deficiency letter.

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

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 77-850
Nicotine Polacrilex Chewing Gum USP, 4 mg

Dear Mr. Buehler:

Reference is made to IVAX Pharmaceuticals, Inc.'s pending Abbreviated New Drug Application (ANDA) for Nicotine Polacrilex Chewing Gum USP, 4 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 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.

Response:
IVAX acknowledges the Agency's following comments:

- Currently no Chemistry, Manufacturing, and Controls (CMC) deficiencies to report at this time.
- Labeling deficiency letter dated November 16, 2006.
- DBE's correspondence dated September 6, 2007.

RECEIVED

NOV 14 2007

OGD

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. The specification of *NLT* [redacted] *(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes* was adopted for the 4 mg strength, ANDA 77-850, which concurs with the specification set for the 2 mg strength, ANDA 76-880. Subsequently, IVAX has revised the following documentation to reflect the DBE's recommendations for dissolution.

- 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 77-850

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 August 23, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nicotine Polacrilex Gum USP, 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: 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. However, this application is still pending a satisfactory Labeling review. We note that Labeling deficiencies were issued on or about November 16, 2006 under separate cover. Do not respond to this deficiency until you have responded to the issues raised in the Labeling communication. 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 02:51:59 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 77-850 – Nicotine Polacrilex Gum. 4 mg

Dear Mr. Buehler:

Reference is made to IVAX Pharmaceuticals' Abbreviated New Drug Application for Nicotine Polacrilex Gum USP, 4 mg. Further reference is made to the Agency facsimile correspondence issued on or about November 16, 2006 (resent July 11, 2007) 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. Additional reference is made to the October 5, 2007 Chemistry facsimile correspondence which advised that labeling was still pending and that once amended, a minor Chemistry Amendment be submitted concurrently with this Labeling Amendment to re-open review of the ANDA.. Please refer to **Reference.**

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**.

At the Agency's request, two (2) discs of the CD text are being provided 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

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 77-850
Nicotine Polacrilex Gum, 4 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, 4 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 the 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 th (b) (4) (b) (4)

Response:

Isopropanol residual solvent results for a lot of (b) (4) (b) (4)

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) 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
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

ORIG AMENDMENT

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

TELEPHONE AMENDMENT - CHEMISTRY

RE: ANDA 77-850
Nicotine Polacrilex Gum, 4 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, 4 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

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-850 ApplicantIVAX Pharmaceuticals, Inc.
Drug Nicotine Polacrilex Gum USP, 4 mg (Original Flavor) Strength(s)_____

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date2/9/2009 Date2/18/09
Chief, Reg. Support Branch InitialsSTM Initialsrlw
Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD =Nicorette NDA#20-066
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 8/23/2005, BOS=Nicorette NDA 20-066. PI certification provided . ANDA ack for filing 8/24/2005 (LO dated 10/25/2005). 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_____ Date2/9/09
Initials_____ InitialsTOH

Original Rec'd dateAugust 24, 2005 EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for FilingAugust 24, 2005 Date of EER Status 1/31/2008
Patent Certification (type)_____ Date of Office Bio Review 11/6/2007
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: August 23, 2005

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 listed in the current "Orange Book" for this 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 OTC drug product.

7. Vacant Date_____ Deputy Dir., DLPS
Initials_____
RLD = Nicorette Chewing Gum 4 mg (base)
GlaxoSmithKline NDA 20-066

8. Peter Rickman Date2/18/09
Director, DLPS Initialsrlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐No ☐;Petition: Yes☐ No☐ Comments:Bioequivalence studies (fasting and multiple-dose chew out study) found acceptable. lso found acceptable. Analytical testing performed at (b) (4) facility post January 2000 to December 2004 suspect period. Thus, bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 8/22/07 and 11/6/07.

Final-printed labeling (FPL) found acceptable for approval 12/19/08.

CMC found acceptable for approval (Chemistry Review #4).

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 currently listed in the "Orange Book" for this drug product.

This ANDa is recommended for approval (OTC).

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 TOH
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
3pmTime notified of approval by phone 3pmTime approval letter faxed

FDA Notification:

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 020066 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

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
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 02:24:44 PM