CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-789

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

Sponsor: L. Perrigo Company

Approval Date: September 16, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-789

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-789

APPROVAL LETTER

ANDA 76-775 [2 mg (base), Regular]
76-776 [2 mg (base), Orange]
76-777 [2 mg (base), Mint]
76-778 [4 mg (base), Orange]
79-779 [4 mg (base), Mint]
76-789 [4 mg (base), Regular]

SEP 16 2004

L. Perrigo Company
Attention: Brian R. Schuster
515 Eastern Avenue
Allegan, MI 49010

Dear Sir:

This is in reference to your abbreviated new drug applications (ANDAs) dated June 30, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Nicotine Polacrilex Gum USP, 2 mg (base) (Regular, Orange, and Mint Flavored), and 4 mg (base) (Regular, Orange, and Mint Flavored).

Reference is also made to your amendments to each application dated January 20, February 6, March 16, March 29, May 20, June 17, June 28, August 13, and August 17, 2004.

We have completed the review of these abbreviated applications and have concluded that the drugs are safe and effective for over-the-counter (OTC) use as recommended in the submitted labeling. Accordingly, the applications are approved. The Division of Bioequivalence has determined your Nicotine Polacrilex Gum USP, 2 mg (base) (Regular, Orange, and Mint Flavored), and 4 mg (base) (Regular, Orange, and Mint Flavored), to be bioequivalent to the corresponding strength and flavor of the listed drug, Nicorette Gum, of GlaxoSmithKline. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your applications.

Under Section 506A of the Act, certain changes in the conditions described in these abbreviated applications require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for these abbreviated applications 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.

Sincerely yours,

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

9/16/04

cc: ANDA 76-775 (2 mg, Regular)
ANDA 76-776 (2 mg, Orange)
ANDA 76-777 (2 mg, Mint)
ANDA 76-778 (4 mg, Orange)
ANDA 79-779 (4 mg, Mint)
ANDA 76-789 (4 mg, Regular)
Division Files
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Approved Electronic Labeling Located at:

HFD-640/D.Skanchy/8/27/04
HFD-640/S.Rosencrance/8/27/04
HFD-617/T.Hinchliffe/8/27/04
HFD-613/M.Dillahunt/8/27/04
HFD-613/L.Golson/8/27/04

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F/T by TOH/8/27/04

APPROVAL

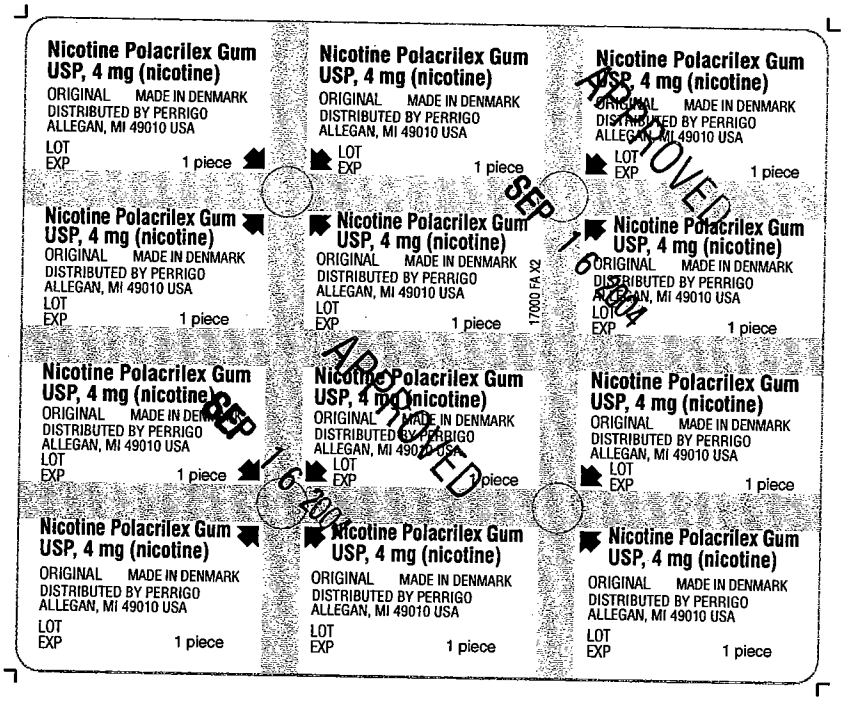
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-789

APPROVED LABELING

026.


Nicotine Polacrilex Gum
USP, 4 mg (nicotine)
ORIGINAL MADE IN DENMARK
DISTRIBUTED BY PERRIGO
ALLEGAN, MI 49010 USA
LOT
EXP
1 piece
APPROVED
SEP 16 2004
17000 FA X2

Drug Facts (continued)

- store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature]
- protect from light

Inactive ingredients acesulfame potassium, calcium carbonate, carnauba wax, D&C yellow #10, flavors, gum base, sodium bicarbonate, sodium carbonate, sorbitol, talc

Questions? If you have questions of a medical nature, please contact your pharmacist, doctor or health care professional.

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

BLISTER PACKAGED FOR YOUR PROTECTION. DO NOT USE IF INDIVIDUAL SEALS ARE BROKEN.

MADE IN DENMARK
DISTRIBUTED BY
PERRIGO®
ALLEGAN, MI 49010 U.S.A.

PRODUCTION QUALITY SAMPLE NOT FOR RESALE

48 PIECES, 4 mg EACH

Stop Smoking Aid

Original

REFILL

FOR THOSE WHO SMOKE 25 OR MORE CIGARETTES A DAY

If you smoke less than 25 cigarettes a day: use Nicotine Polacrilex Gum, 2 mg

APPROVED FEB 16 2004

Nicotine Polacrilex Gum, 4 mg (nicotine)

Theft surveillance tag area

17067 FA C3

Drug Facts

Active ingredient (in each chewing piece) — **Purpose**
Nicotine polacrilex, 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. ▶

Drug Facts (continued)

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

▲

Drug Facts (continued)

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 medication 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 or 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 Nicotine Polacrilex Gum, 2 mg ▶

Drug Facts (continued)

- **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 tingling 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 chewing piece contains:** calcium 97 mg and sodium 11 mg

▲

Drug Facts

Active ingredient (in each chewing piece) — **Purpose**

Nicotine polacrilex, 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 medication 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 or 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.

Drug Facts (continued)

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 Nicotine Polacrilex Gum, 2 mg
- **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 tingling 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 chewing piece contains:** calcium 97 mg and sodium 11 mg
- store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature]
- protect from light

Inactive ingredients

acesulfame potassium, calcium carbonate, carnauba wax, D&C yellow #10, flavors, gum base, sodium bicarbonate, sodium carbonate, sorbitol, talc

Questions?

If you have questions of a medical nature, please contact your pharmacist, doctor or health care professional.

MADE IN DENMARK

PERRIGO
DISTRIBUTED BY
ALLEGAN, MI 49010 U.S.A.

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

BLISTER PACKAGED FOR YOUR PROTECTION. DO NOT USE IF INDIVIDUAL SEALS ARE BROKEN.

Nicotine Polacrilex Gum, 4 mg (nicotine)
Stop Smoking Aid
Original

17008 FA C3

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 described in the enclosed User's Guide.

Push gum through foil — Peel backing starting at corner with loose edge — To remove the gum, tear off single unit

Nicotine Polacrilex Gum, 4 mg (nicotine)

APPROVED SEP 16 2004

Stop Smoking Aid

Original

STARTER KIT

Includes stop smoking plan with User's Guide and audio tape

FOR THOSE WHO SMOKE 25 OR MORE CIGARETTES A DAY

If you smoke less than 25 cigarettes a day: use Nicotine Polacrilex Gum, 2 mg

108 PIECES, 4 mg EACH

Nicotine Polacrilex Gum, 4 mg (nicotine)
Stop Smoking Aid
Original

Nicotine Polacrilex Gum, 4 mg (nicotine)
Stop Smoking Aid
Original

Theft surveillance tag area

Drug Facts

Active ingredient (in each chewing piece)	Purpose
Nicotine polacrilex, 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 medication 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 or 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. ▶

Drug Facts (continued)

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 Nicotine Polacrilex Gum, 2 mg
- **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 tingling 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, o.wkille 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 chewing piece contains:** calcium 97 mg and sodium 11 mg
- store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature]
- protect from light

Inactive ingredients acesulfame potassium, calcium carbonate, carnauba wax, D&C yellow #10, flavors, gum base, sodium bicarbonate, sodium carbonate, sorbitol, talc

Questions? If you have questions of a medical nature, please contact your pharmacist, doctor or health care professional.

MADE IN DENMARK
DISTRIBUTED BY
PERRIGO
ALLEGAN MI 49010 U.S.A.

17044 FA C3

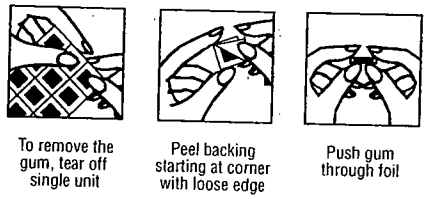
Nicotine Polacrilex Gum, 4 mg (nicotine)
Stop Smoking Aid
Original

BLISTER PACKAGED FOR YOUR PROTECTION. DO NOT USE IF INDIVIDUAL SEALS ARE BROKEN.

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

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 described in the enclosed User's Guide.



Push gum through foil | Peel backing starting at corner with loose edge | To remove the gum, tear off single unit

Nicotine Polacrilex Gum, 4 mg (nicotine)

APPROVED SEP 16 2004

Stop Smoking Aid

Original

REFILL

FOR THOSE WHO SMOKE 25 OR MORE CIGARETTES A DAY

If you smoke less than 25 cigarettes a day: use Nicotine Polacrilex Gum, 2 mg

168 PIECES, 4 mg EACH

Nicotine Polacrilex Gum, 4 mg (nicotine)
Stop Smoking Aid
Original

Nicotine Polacrilex Gum

2 mg and 4 mg User's Guide

How to Use
Nicotine Polacrilex Gum
To Help You
Quit Smoking.

- 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.

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 9.
3. You should continue to use Nicotine Polacrilex Gum as explained in this 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, pharmacist or health care professional.

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 inside the back cover of this User's Guide. 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

- 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 Nicotine Polacrilex Gum, 4 mg.

If you smoke less than 25 cigarettes a day, use Nicotine Polacrilex Gum, 2 mg. 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 this User's Guide:

STEP 1. (Weeks 1-6). 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 craving 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 starting on pages 7 and 9. Place the Step 1 sticker on this date.

STEP 2. (Weeks 7 to 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 10-12). 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 cassette tape, 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 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 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 9.
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.

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.

Place these stickers on your calendar:

At the Beginning of Week #1 (Quit Date)

At the Beginning of Week #7

Place these stickers on your calendar:

At the Beginning of Week #10

12 Weeks After Quit Date

The following chart lists the recommended usage 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.		

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 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 you 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.

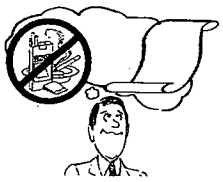
Right after Quitting:

- 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 your 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 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 or 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 4). 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 the first 8-10 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 to 2 hours	1 piece every 2 to 4 hours	1 piece every 4 to 8 hours

Made in Denmark

DISTRIBUTED BY PERRIGO® ALLEGAN, MI 49010 U.S.A.
www.perrigo.com
17008 FA J2

WALLET CARD

My most important reasons to quit smoking are:

_____

_____

_____

_____

_____

_____

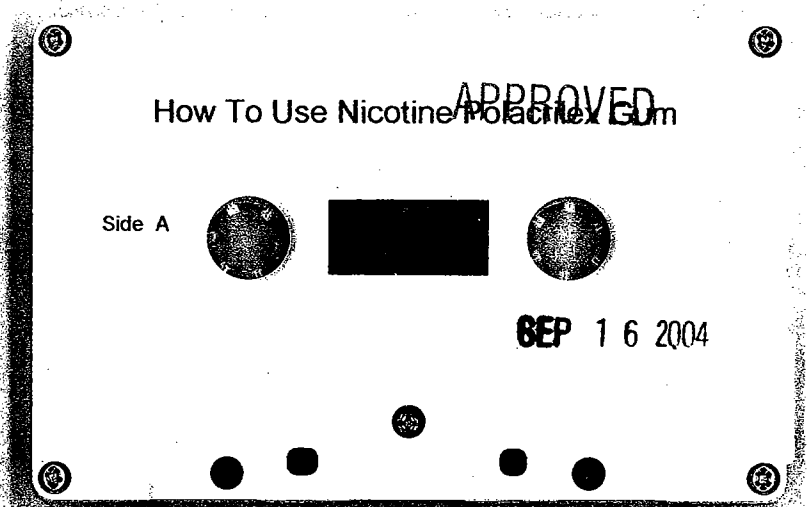
WALLET CARD

WHERE TO CALL FOR HELP:

American Lung Association
1-800-586-4872

American Cancer Society
1-800-227-2345

American Heart Association
1-800-242-8721



Nicotine Polacrilex Gum, 2 mg and 4 mg

APPROVED

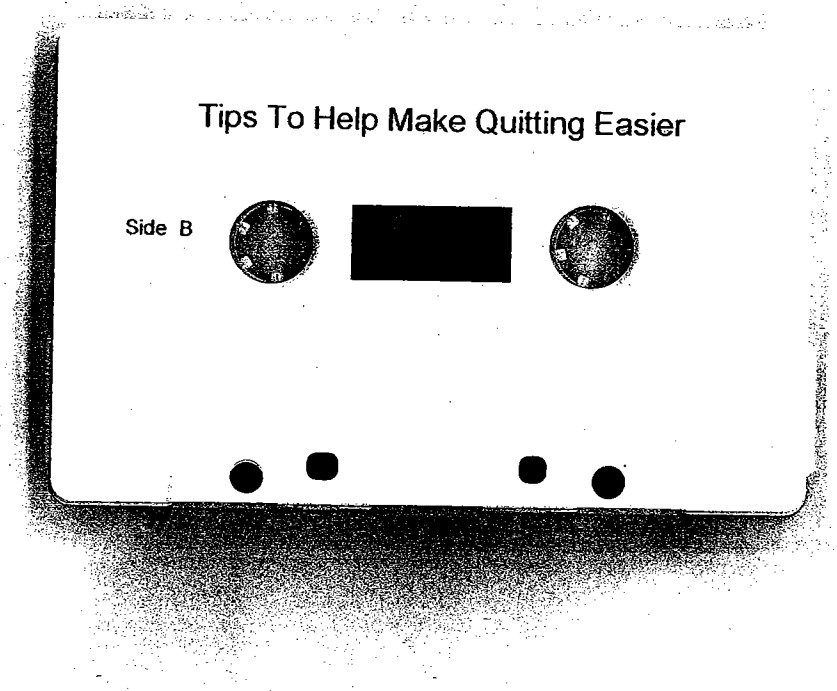
SEP 16 2004

Usage Instructions

- ▶ 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.

DISTRIBUTED BY
PERRIGO
ALLEGAN, MI 49010 U.S.A.

Nicotine Polacrilex Gum


Tips To Help Make Quitting Easier
Side B

Attachment 6

AUDIOTAPE SCRIPT

Final Printed Labeling

Nicotine Polacrilex Gum Audio Tape **August 13, 2004**
Side A, Section 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'll ever make. And one of the best.

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

The Nicotine Polacrilex Gum User's Guide and this audio tape 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're 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. It's serious medicine! 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 raps 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. Yamato'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: 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'm 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 nonsmoking 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 that 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 figure 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 family member, maybe even a co-worker, can provide moral support. Several national organizations offer support groups like this one - there's a list of their toll-free phone numbers on the back cover of the Nicotine Polacrilex Gum User' s Guide.

YM: So, the first step is to pick a Quit Date, and mark it in 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 park 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 chew, park, chew, park. Let's all repeat that.

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

LEADER: Pretty good, but let's get 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: 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: Yes it does. Again, the idea is to start with the recommended dosage, and to decrease it gradually, at a rate 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 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 your next support group, down the hall. In fact, it's just about to start. Good luck to you all!

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

(END OF SIDE A)

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

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

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

YAMATO: 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 down and out.) One of the things you will see as you go through your 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. I don't now because I haven't had a cigarette for a couple of hours while I'm in school here.

YAMATO: 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.

YAMATO: 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: 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!

YAMATO: 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's 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 Neary'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.

YAMATO: Yes, indeed it will. Perhaps you will decide not to go to Neary's for a week or so. But never lose sight of this: you want to give up smoking -- you don't want to give up your lifestyle. So sooner or later you will go back to Neary'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?

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

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

YAMATO: There is your answer. Your friend Maury joined a support group of people who were going through the same difficulties he was. And he avoided Neary'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.

YAMATO: 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 Neary's I have to go with my mind made up not to smoke -- and I have to keep reminding myself of my reasons?

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

OW: 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.

YAMATO: 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.

YAMATO: 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.

YAMATO: 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?

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

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

YAMATO: 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.

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

YW: Like this?

YAMATO: Yes, but you must relax. Try letting your 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.

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

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

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

YW: *(Breathes.)*

YAMATO: How does that feel?

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

YAMATO: 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?

YAMATO: 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.

YAMATO: 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, breathe a few times.)

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

OW: Me, too.

YAMATO: That is one of the keys to helping you resist smoking at those critical times. Find something to do that occupies your mind and your 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?

YAMATO: 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 are 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'm sure you will enjoy it.

(Music up. Plays to end of tape.)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-789

LABELING REVIEW(S)

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

ANDA Numbers: 76-775 (Original, 2mg)
76-776 (Orange, 2 mg)
76-777 (Mint, 2 mg)
76-778 (Orange, 4 mg)
76-779 (Mint, 4 mg)
76-789 (Original, 4 mg)

Date of Submission: June 30, 2003

Applicant's Name: L. Perrigo Company

Established Name: Nicotine Polacrilex Gum USP

Labeling Deficiencies:

1. GENERAL COMMENT

   a. Please note that the review was done using all labeling pieces for Nicorette®, including Carton, Blister, User's guide and Audiotape tape approved on August 9, 2002.

   b. Please provide a monitoring program to describe how you will report the findings of underage use of your nicotine product to FDA.

2. BLISTER

   Satisfactory in draft.

3. CARTON - Starter Kit (108 chewing pieces)
   Refill (168 chewing pieces)
   Refill (48 chewing pieces)

   a. Your original and mint flavor cartons use the same color for both flavors. We recommend using a different color for the original flavor.

   b. We encourage the inclusion of "USP" in association with your established name in your title,
   Nicotine Polacrilex Gum USP, 2 mg
   or
   Nicotine Polacrilex Gum USP, 4 mg

   c. Please include "nicotine" in parenthesis after the strength in your title.
   Nicotine Polacrilex Gum USP, 2mg (nicotine)
   or
   Nicotine Polacrilex Gum USP, 4mg (nicotine)

   d. Active ingredient, revise to read:
   Nicotine polacrilex.....2mg (nicotine).... Stop smoking aid
   or
   Nicotine polacrilex.....4mg (nicotine).... Stop smoking aid

   e. Inactive ingredient
   Your components and composition statement includes talc, however talc is not included in your labeling. Please revise/comment.

f. Other information
Revise the storage temperature statement to read "Store at 20 to 25° C (68 to 77°F)[see USP Controlled Room Temperature] - Protect from light.

g. Refill (48 chewing pieces)

i. Warnings-include this heading on the next column, above the paragraph beginning with "Smoking can .....known."

ii. Directions- include this heading on the next column, above the paragraph beginning with "If you smoke.....schedule."

4. User's guide

Satisfactory in draft.

5. Audiotape script

Side A, How to Use Nicotine Polacrilex Gum
(Please note the page numbers correspond to ANDA 76-776, however the comments apply to all applications.)

a. page 67, second paragraph, CROWD, revise to read: (VOICES: "Yeah!, Right! Way to go!")

b. page 67, fourth paragraph, revise to read; "The Nicotine Polacrilex Gum User's Guide and this audio..."

c. Page 67, fifth paragraph, CROWD, revise to read: (VOICE: "Yeah--you can do it")

d. Page 67, sixth paragraph, first sentence, revise to read, "Even though Nicotine Polacrilex Gum is easy..."

e. Page 68, seventh paragraph, LEADER, revise third line to read; " Okay, so let's begin."

f. Page 68, eighth paragraph, OW, revise to read; " I read it, yeah. It didn't take long..."

g. Page 68, last paragraph, LEADER, revise first line to read; "Sure. So the next question is:"

h. Page 69, second paragraph, LEADER, revise second sentence to read:, "..when you walk out of that building."

i. Page 69, third paragraph, OW, first sentence, revise to read; "Oh, I'm going to quit...."

j. Page 69, fourth paragraph, LEADER, revise last sentence to read;" How about you miss?"

k. Page 69, eleventh paragraph, OW, revise first sentence to read;"Oh I know, I know---it was.."

l. Page 70, first paragraph, LEADER, second sentence, revise to read:"One more time--and a one, and a two and a ....."

m. Page 70, fifth paragraph, LEADER, delete the fourth sentence, "Heavy smokers might need..."

n. Page 70, eighth paragraph, OW, revise first sentence to read: "Well now, the book....

o. Page 70, ninth paragraph, LEADER, revise first sentence to read; "Yes it does. Delete "oh" from third line.

p. Page 70, penultimate paragraph, LEADER, third line, revise to read; " used pieces of gum--enough ....."
fourth line, revise to read;..."And--also some foods..."

q. Page 70, last paragraph, YW, revise first sentence to read: "Gee, all I have to do..."

r. Page 71, second paragraph, LEADER, fourth line, revise to read: "...before they succeed. And there are some....willpower. And that's the subject...."

Side B, Tips to Help Make Quitting Easier

s. Page 72, fifth paragraph, YW, revise first sentence to read;" Oh. Well, I guess..."

t. Page 72, seventh paragraph, YW, revise first sentence to read;" Oh, no, I want to quit.."

u. Page 73, last paragraph, YAMATO, revise second sentence to read; "...smoking, they will probably...."

v. Page 74, ninth paragraph, STUDENTS: revise to read; "Huh? What? Hey, I do that all the time."

w. Page 75, fourth paragraph, YAMATO, revise second sentence to read; "Then let it all out slowly".

Prepare and submit 12 copies of final print for carton, blister and "User's guide", and two copies of the "Audiotape " (for each application) as an amendment to each of these unapproved applications.

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 your last submission with all differences annotated and explained.

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?			x
Is the strength and/or concentration of the product unsupported by the insert labeling?			x
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?			x
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	x		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			x
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.			x
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

FOR THE RECORD:

1. MODEL LABELING - NDA 18-612/S-031 (Nicorette® gum) approved on August 9, 2002 for the carton labeling. It appears that innovator's user's guide and audiotape were also last approved on August 9, 2002 (S-031). The SLR-026, approved August 24, 2001 is for the labeling format changes into the Drug Facts format for the both original and mint flavored gum.

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 inconsistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 131 (Volume 1.1). See comment under "Inactive ingredients".

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 [redacted]. Protect from light.

   The firm has been requested to revise storage temperature recommendation to: Store at 20 to 25° C (68 to 77°F)[see USP Controlled Room Temperature] - 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. All labeling pieces for the RLD, Nicorrette® were approved on August 9, 2002 per PM, Laura Shay. The labeling (faxed version) can be found in the file folder.

9. Fertin Pharma, Denmark is the contract manufacturer; .L. Perrigo is the distributor. (Vol 1.1, page 243)

Date of Review: 1/15/04 **Date of Submission:** 6/30/03

Primary Reviewer: Michelle Dillahunt **Date:** 2/6/04

Team Leader: Lillie Golson **Date:** 2/3/04

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cc:

ANDAs: 76-775, 76-776, 76-777, 76-778, 76--779, 76-789
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSNZ\PERRIGO\LTRS&REV\76775NA1.LABELING.doc
Review

3,1

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

ANDA Numbers: 76-775 (Original, 2mg)
76-776 (Orange, 2 mg)
76-777 (Mint, 2 mg)
76-778 (Orange, 4 mg)
76-779 (Mint, 4 mg)
76-789 (Original, 4 mg)

Date of Submission: March 29, 2004

Applicant's Name: L. Perrigo Company

Established Name: Nicotine Polacrilex Gum USP

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.

You should submit a detail 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. We acknowledge that you already have this element in place.

2. BLISTER

Please include "nicotine" in parenthesis after the strength; e.g.
Nicotine Polacrilex Gum USP, 2mg (nicotine)
or
Nicotine Polacrilex Gum USP, 4mg (nicotine)

Due to recent revisions in the labeling of the reference listed drug, Nicorette® Gum, approved June 18, 2004, please make the following revisions to your carton and user guide labeling;

3. CARTON

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

b. 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.

c. 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).

4. User's Guide

a. How To Reduce Your Nicotine Polacriliex Gum Usage

(1) First paragraph, second sentence, revise to read: "....will help you reduce your nicotine craving gradually as you reduce and then stop your use of nicotine polacrilex gum".

(2) First paragraph, last sentence, revise to read: "Here are some tips to help you cut back during each step and then stop using nicotine polacrilex gum:"

b. How To Reduce Your Nicotine Polacrilex Gum Usage, 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."

c. STOP USING NICOTINE POLACRILEX GUM AT THE END OF WEEK 12, revise this section 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

5. Audiotape script

Side A, How to Use Nicotine Polacrilex Gum
Page 4 out of 10, Leader, 11th paragraph, revise to read:"...that's weeks 10 through 12--you should be able to get along...."

Revise your blister labels, carton, user guide labeling and audiotape script and submit in final print.

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 your last submission with all differences annotated and explained.

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 27	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?			x
Is the strength and/or concentration of the product unsupported by the insert labeling?			x
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?			x
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			x
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.			x
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

FOR THE RECORD:

1. MODEL LABELING - NDA 18-612/S-035/S-037(Nicorette® gum) approved on June 18 and June 23, 2004. The SLR-026, approved August 24, 2001 is for the labeling format changes into the Drug Facts format for the both original and mint flavored gum.
   The audiotape was also last approved on August 9, 2002 (S-031).

The SLR-035 provides for removal of the CD/audio portion of the labeling, the RLD will include a statement indicating that free Audio/CD is available upon request. S-037 was used as the model labeling for the carton and 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 inconsistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 131 (Volume 1.1). See comment under "Inactive ingredients".

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)[see USP Controlled Room Temperature] - 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. All labeling pieces for the RLD, Nicorrette® was approved on August 9, 2002 per PM, Laura Shay. The labeling (faxed version) can be found in the file folder.

9. Packaging

Blister film: [redacted]
Blister foil: Peel-Push foil (child resistant) Contact layer: aluminum foil

10. The Audiotape and User's guide does not specify the flavors. We find this acceptable.

11. Per Chan Park, based on the internal discussion and in consultation with OTC, we decided that the carton labeling should read as follows in the Active ingredient section.

    Active Ingredient (in each chewing piece)
    Nicotine polacrilex ... x mg (Nicotine)

12. We decided that the sponsor should retain the term "(Nicotine)" after the expression of strength on the carton. This decision was made in association with the FTR#12 above. This is how we approved the original Nicotine polacrilex gum from Watson for the non flavor gum.

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13. Fertin Pharma, Denmark is the contract manufacturer; .L. Perrigo is the distributor. (Vol 1.1, page 243)

Date of Review: 6/28/04

Date of Submission: 3/29/04

Primary Reviewer: Michelle Dillahunt

Date: 7/6/04

Team Leader: Lillie Golson

Date: 7/8/04

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cc:

ANDAs: 76-775, 76-776, 76-777, 76-778, 76--779, 76-789
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSNZ\PERRIGO\LTRS&REV\76776NA2.LABELING.doc
Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: 76-789 Date of Submission: August 17, 2004

Applicant's Name: L. Perrigo Company

Established Name: Nicotine Polacrilex Gum USP, 4 mg (Regular)

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

CARTON LABELING - Starter Kit (108 chewing pieces)
Refill (168 and 48 chewing pieces)

Satisfactory in FPL as of August 17, 2004 submission (vol.4.1)

UNIT DOSE BLISTER LABEL

12 Blisters - Satisfactory in FPL as of August 17, 2004 submission (Vol.4.1)

USER'S GUIDE

Satisfactory in FPL as of Satisfactory in FPL as of August 17, 2004 submission (Vol.4.1)

Audio Tape (2 copies with the Tape sleeves)

Satisfactory in FPL as of March 29, 2004 submission (Vol. 3. 1)

BASIS OF APPROVAL:

Patent Data – 20-066

No	Expiration	Use Code	Use	File
		There are no unexpired patents		

Exclusivity Data - 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 20-066/S-019 (Nicorette® gum) approved on June 18, 2004 for the carton labeling. It appears that innovator's and audiotape was also last approved on August 9, 2002 (S-013).

NDA Number: 20-066

NDA Drug Name: Nicorette® Gum

NDA Firm: GlaxoSmith Kline

Date of Approval of NDA Insert and supplement #:
NDA 20-066/S-019, June 18, 2004
NDA 20-066/S-017, June 23, 2004
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

QUESTIONS/COMMENTS TO CHEMIST:

Question- David
Per Federal Register/Vol 69. No. 57 3/23/04 final rule, the firm must declare the amount of sodium and calcium on their labeling. The firm has stated that their product contains 97 mg calcium and 11 mg sodium. Is this an accurate statement?

Answer -
Dave Skanchy by email dated 9/7/04

The statement is accurate.

FOR THE RECORD

1. MODEL LABELING - NDA 20-066/S-017/S-019(Nicorette® gum) approved on June 18 and June 23, 2004.
The SLR-026, approved August 24, 2001 is for the labeling format changes into the Drug Facts format for the both original and mint flavored gum.
The audiotape was also last approved on August 9, 2002 (S-031).
The SLR-017 provides for removal of the CD/audio portion of the labeling and revisions to the carton and user's guide, the RLD will include a statement indicating that free Audio/CD is available upon request. S-019 was used as the model labeling for the carton.

   The above changes were made to the RLD's mint flavored gum, however the RLD only has one NDA number for the different flavors. Changes to the regular and orange flavor gums have not been revised yet. I emailed the PM in new drugs to see if she knew when the RLD would be making changes to the regular and orange flavored gums. She did not know but stated some changes were made to the FR publication and companies had 12 months after the date of the FR publication to comply (March 2004). It was decided that it would be OK for generics to make the changes since the changes are under one NDA. (see emails)

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 appearing on page 195 (Volume 1.1). See comment under "Inactive ingredients".

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)[see USP Controlled Room Temperature] - 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. Chan Parkl 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. All labeling pieces for the RLD, Nicorrette® was approved on August 9, 2002 per PM, Laura Shay. The labeling (faxed version) can be found in the file folder.

9. Packaging

Blister film: [redacted]
Blister foil: Peel-Push foil (child resistant) Contact layer: aluminum foil [redacted]

10. The Audiotape and User's guide does not specify the flavors. We find this acceptable.

11. Per Chan Park, based on the internal discussion and in consultation with OTC, we decided that the carton labeling should read as follows in the Active ingredient section.

Active Ingredient (in each chewing piece)
Nicotine polacrilex ... x mg (Nicotine)

12. We decided that the sponsor should retain the term "(Nicotine)" after the expression of strength on the carton. This decision was made in association with the FTR#12 above. This is how we approved the original Nicotine polacrilex gum from Watson for the non flavor gum.

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13. Fertin Pharma, Denmark is the contract manufacturer; .L. Perrigo is the distributor. (Vol 1.1, page 483)

14. Perrigo has submitted a marketing plan with elements that were required for the reference listed drug. It was decided that the marketing plan does not need to be consulted since it is similar to the reference listed drug's plan and Watson's plan was not consulted out.

Date of Review: 9/7/04 **Date of Submission: 8/17/04**

Primary Reviewer: Michelle Dillahunt **Date:** 9/14/04

Team Leader: Lillie Golson **Date:** 9/14/04

1

cc:

ANDAs: 76-789
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSNZ\PERRIGO\LTRS&REV\76789ap.LABELING.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-789

CHEMISTRY REVIEW(S)

#1

ANDA 76-789

Nicotine Polacrilex Gum USP
4 mg (Regular ———

L. Perrigo Company

David Skanchy

Office of Generic Drugs/Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-789

2. REVIEW #: 1

3. REVIEW DATE: November 18, 2003

4. REVIEWER: David Skanchy 12/17/2003

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	June 30, 2003
Amendment (telephone)	August 26, 2003

7. NAME & ADDRESS OF APPLICANT:

Name: L. Perrigo Company
Address: 515 Eastern Avenue
Allegan, Michigan
49010

Representative: Brian Schuster
Telephone: (269) 673-8451

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION:

The basis for this submission is the approved listed drug, Nicorette® 4 mg (Regular), the subject of NDA #20-066, held by GlaxoSmithKline. The referenced drug product has no unexpired patents or exclusivitiies. A Paragraph II Certification and Exclusivity Statement is provided on page 6.

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

11. DOSAGE FORM: Chewing Gum

12. STRENGTH/POTENCY: 4 mg

13. ROUTE OF ADMINISTRATION: Buccal

14. Rx/OTC DISPENSED: ___ Rx ___X_ OTC

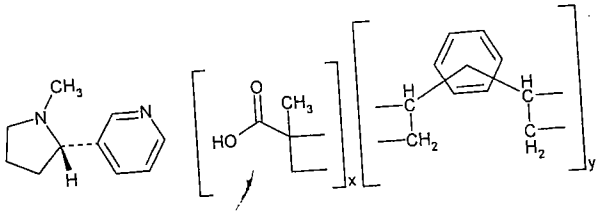
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X_Not a SPOTS product

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

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



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Inadequate	10/31/03	Reviewed by DSkanchy
	IV			4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	IV			4	N/A	N/A	
	IV			4	N/A	N/A	

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Pending		
Methods Validation	Not required		MDillahunt
Labeling	Pending		
Bioequivalence	Pending		
EA	Not Applicable (category exclusion)	10/23/03	NSadrieh
Pharm/tox consult	Acceptable		

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
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:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-789

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to minor deficiencies.

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

None.

II. Summary of Chemistry Assessments

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

Nicotine is a volatile strongly alkaline oily liquid. It is colorless when pure but becomes yellow when exposed to air, boiling point is 247°C. It is optically active containing a single chiral center and has an $[\alpha]_d$ of -139° to -151° . Nicotine is supplied ionically bound to Polacrilex Resin which contains —% nicotine. The resin is a weak cation exchange polymer made from vinylacrylate and divinyl benzene. The nicotine containing resin is blended with inactive ingredients such as Gum base, sorbitol(sweetener), sodium carbonate, sodium bicarbonate, ——— flavor, and acesulfame potassium to produce a sugar free chewing gum containing 4 mg of nicotine. The drug is delivered for buccal absorbtion by chewing a 1 gram dosage unit. The reference listed drug for this product is Nicorette® Gum 4 mg by GlaxoSmithKline (NDA 20-066).

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

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

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

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

C. Basis for Approvability or Not-Approval Recommendation

The information provided in the drug substance section of this ANDA does not ensure adequate control. The applicant referenced a Drug Master File No. ——— from ——— to support the manufacturing of the drug substance. This DMF was reviewed and found inadequate. The controls exerted over the manufacturing process for the drug product are not adequate. Blend uniformity testing is not a part of the in-process controls nor is an appropriate justification for the use of content uniformity data provided.

[redacted] may be necessary.

The stability commitments need modification and the bulk container needs to be described and stability data provided.

The bioequivalence review is pending. The labeling review, and establishment inspection are currently pending. The analytical methods will not need to be validated by a FDA laboratory according to the current policy.

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

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-640/DSkanchy/11/18/03;12/16/03 12/17/03
HFD-640/SRosencrance/12/16/03 12/17/03
HFD-617/THinchliffe/ 12/18/03

C. CC Block

ANDA 76-789 Original
ANDA 76-789 DUP

DIV FILE
Field Copy

APPEARS THIS WAY
ON ORIGINAL

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CHEMISTRY REVIEW #1

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Method validation of non-compendial methods is not required in accord with current Agency policy.

32. LABELING

The labeling review is pending.

Evaluation:

The CMC related information was reviewed as follows:

- The inactive ingredients section correctly lists the inactive components of the formulation. However, the ——— talc should also be listed.
- The active ingredient is satisfactorily listed as Nicotine Polacrilex, 4 mg.
- The storage statement under "other information" reads: "Store at ——— "; "protect from light". Any changes to this will be addressed by the labeling review.
- The name of the manufacturer and address are the same as presented in the submission.

Conclusion:

Not Satisfactory from chemistry's perspective.

Comment:

1. Please include talc as an inactive ingredient on the labeling.

33. ESTABLISHMENT INSPECTION

The establishment inspection request was submitted to the Office of Compliance. The overall evaluation is pending as of November 13, 2003.

34. BIOEQUIVALENCE

The Division of Bioequivalence (DBE) review is pending.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION

Categorical exclusion from the requirement to prepare an Environmental Assessment is requested (page 974).

Evaluation:

The drug product will not be administered at a higher dosage level or for a longer duration than were previously in effect. As per 21 CFR 25.31(a), the categorical exclusion should be granted.

Conclusion:
Satisfactory.

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CHEMISTRY REVIEW #1

3. The non-compendial analytical methods may be validated by the FDA laboratory.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

CHEMISTRY REVIEW

Chemistry Assessment Section

cc: ANDA 76-789 Original
ANDA 76-789 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/DSkanchy/11/18/2003;12/16/03 12/17/03
HFD-640/SRosencrance/12/16/03 12/17/03
HFD-617/THinchliffe/12/16/03 12/16/03

F/T by: EW 12/17/03

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TYPE OF LETTER: NOT APPROVABLE - Minor

APPEARS THIS WAY
ON ORIGINAL

#2

ANDA 76-789

Nicotine Polacrilex Gum USP
4 mg (Regular, ————)

L. Perrigo Company

David Skanchy

Office of Generic Drugs/Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-789

2. REVIEW #: 2

3. REVIEW DATE: July 30, 2004; August 20, 2004

4. REVIEWER: David Skanchy

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	June 30, 2003
Amendment (telephone)	August 26, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (telephone)	August 13, 2004
Amendment	June 28, 2004
Amendment	May 20, 2004
Amendment	March 16, 2004
Amendment	January 20, 2004

7. NAME & ADDRESS OF APPLICANT:

Name: L. Perrigo Company
Address: 515 Eastern
Allegan, Michigan
49010

Representative: Brian Schuster

Telephone: (269) 673-8451

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION:

The basis for this submission is the approved listed drug, Nicorette® 4 mg (Regular), the subject of NDA #20-066, held by GlaxoSmithKline. The referenced drug product has no unexpired patents or exclusivitiies. A Paragraph II Certification and Exclusivity Statement is provided on page 6.

10. PHARMACOL. CATEGORY:

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

11. DOSAGE FORM: Chewing Gum

12. STRENGTH/POTENCY: 4 mg

13. ROUTE OF ADMINISTRATION: Buccal

14. Rx/OTC DISPENSED: ___ Rx ___X__ OTC

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

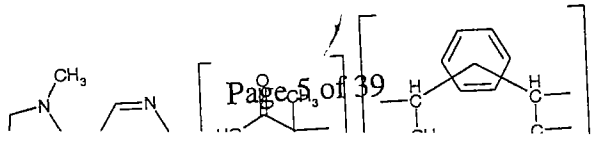
_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

Nicotine Polacrilex

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



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	5/14/04	Reviewed by SPatankar
	IV			4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	IV			4	N/A	N/A	
	IV			4	N/A	N/A	

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	~~Pending~~ Acceptable	9/1/04	THinchliffe
Methods Validation	Not required		
Labeling	~~Deficient~~ Acceptable 9/7/04	~~7/8/2004~~	MDillahunt
Bioequivalence	Acceptable	6/28/2004	MMakary
EA	Not Applicable (category exclusion)		
Pharm/tox consult	Acceptable	10/23/03	NSadrieh

9/1

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
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:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-789

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable.

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

None.

II. Summary of Chemistry Assessments

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

Nicotine is a volatile strongly alkaline oily liquid. It is colorless when pure but becomes yellow when exposed to air, boiling point is 247°C. It is optically active containing a single chiral center and has an $[\alpha]_d$ of -139° to -151° . Nicotine is supplied ionically bound to Polacrilex Resin which contains — % nicotine. The resin is a weak cation exchange polymer made from ~~vinylacrylate~~ methacrylic acid and divinyl benzene. The nicotine containing resin is blended with inactive ingredients such as Gum base, sorbitol(sweetener), sodium carbonate, sodium bicarbonate, ——— flavor, and acesulfame potassium to produce a sugar free chewing gum containing 4 mg of nicotine. The drug is delivered for buccal absorbtion by chewing a 1 gram dosage unit. The reference listed drug for this product is Nicorette® Gum 4 mg by GlaxoSmithKline (NDA 20-066).

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

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

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

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

C. Basis for Approvability or Not-Approval Recommendation

The information provided in the drug substance section of this ANDA ensures adequate control. The DMF for the drug substance was reviewed and found adequate. The controls exerted over the manufacturing process for the drug product are adequate. Blend uniformity testing is not a part of the routine in-process controls, but appropriate justification (including process validation data from one validation batch) for the use of content uniformity data is provided in the August 13, 2004 telephone amendment. The firm makes the post approval commitment to provide BUA data on additional batches in the first annual report.

The currently proposed acceptance criteria for the impurities in the drug product for the release and stability testing are adequate.

Labeling acceptable 9/1/04 RC

The bioequivalence review is acceptable. The labeling is currently deficient and awaiting a response. The establishment inspection is currently pending. The analytical methods will not need to be validated by a FDA laboratory according to the current policy.

The application is approvable pending satisfactory EER and labeling.

→ EER acceptable as of 9/1/04; labeling under review (appr. summary expected)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-640/DSkanchy/7/30/04; 8/20/04 9/7/04
HFD-640/SRosencrance/8/24/04 Concurrance 9/7/04
HFD-617/THinchliffe/9/2/04 9/2/04

C. CC Block

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ANDA 76-789 DUP
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CHEMISTRY REVIEW #2

- The storage statement under "other information" reads: "Store at———— —— "; "protect from light". Any changes to this will be addressed by the labeling review.
- The name of the manufacturer and address are the same as presented in the submission.

Conclusion:
Satisfactory from chemistry's perspective.

Comments from Review#1:

1. Please include talc as an inactive ingredient on the labeling.

Response: The firm indicates that they will include talc in the final version of the labeling.

33. ESTABLISHMENT INSPECTION

The establishment inspection request was submitted to the Office of Compliance. The overall evaluation is pending as of November 13, 2003.

34. BIOEQUIVALENCE

CR acceptable as of 9/1/04
MM 9/1/04

The Division of Bioequivalence (DBE) review is pending.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION

Categorical exclusion from the requirement to prepare an Environmental Assessment is requested (page 974).

Evaluation:
The drug product will not be administered at a higher dosage level or for a longer duration than were previously in effect. As per 21 CFR 25.31(a), the categorical exclusion should be granted.

Conclusion:
Satisfactory.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-789 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Nicotine Polacrilex Gum USP, 4 mg (Regular, Tutti Frutti Flavor)

N/A

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-789

BIOEQUIVALENCE REVIEW(S)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-789
Drug Product Name	Nicotine Polacrilex Gum USP (Regular)
Strength	4 mg
Applicant Name	L. Perrigo Company
Address	Allegan, MI
Submission Date(s)	June 30, 2003
Amendment Date(s)	February 6, 2004
Reviewer	Moheb H. Makary, Ph.D.
First Generic	No
File Location	V:\FIRMSNZ\PERRIGO\LTRS&REV\76789N0603.doc

I. Executive Summary

The application references GlaxoSmithKline's Nicorette® (nicotine Polacrilex), 4 mg gum (Regular), and includes one fasting bioequivalence (BE) study with a chew-out study component, one separate multi-dose chew-out study and dissolution data. The fasting BE study is a single-dose three-way crossover study using 24 male volunteers given a dose of 4 mg with a 30-minute chewing interval. The results of the pharmacokinetic (PK) parameters (point estimate, 90% CI) are: LAUCt of 98.1, 91.4-105.3%; LAUCi of 101.4, 94.0-109.4%; and LCmax of 99.7, 89.9-110.6%.

The multi-dose chew-out study combining the following three comparisons:

Perrigo's Nicotine Polacrilex Gum USP, 4 mg (Regular) vs. Nicorette® Gum, 4 mg (Regular)
Perrigo's Nicotine Polacrilex Gum USP, 4 mg (Mint) vs. Nicorette® Gum, 4 mg (Mint)
Perrigo's Nicotine Polacrilex Gum USP, 4 mg (Orange) vs. Nicorette® Gum, 4 mg (Orange)

A total of 14 male volunteers completed the clinical phase of the study. 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 and within ± 20%.

The Orange- and the Mint-flavored products are acceptable without in vivo PK studies, because they conform to the DBE recommendation to the firm which stated that "*If the only difference in formulation between 4 mg 'mint or orange flavored' gum and 4 mg 'regular' flavored gum is the flavor component, the firm may request a waiver for the 4 mg mint and orange flavored gum, provided the firm submits results of a chew-out study between its 4 mg mint and orange flavored gum and Nicorrete® 4 mg mint and orange flavored gum as well as the comparative results of the other in-vitro tests and assays*".

The in vitro comparative drug release testing is acceptable. However, the application is incomplete pending the firm's acceptance of the dissolution method and specifications.

II. Table of Contents

Historical Information: 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 (2mg 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. On 3-15-1999, the FDA had also approved Watson's 2 mg (74507) and 4 mg (74707) regular flavored gums.

III. Submission Summary

A. Drug Product Information

Test Product	Nicotine Polarcrilex Gum USP, 4 mg (Regular Flavor)
Reference Product	Nicorette® Gum, 4 mg (Regular Flavor)
RLD Manufacturer	GlaxoSmithKline
NDA No.	20-066
RLD Approval Date	12/23/98
Indication	Indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms

B. PK/PD 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^{R} Gum.
Food Effect	N/A
Tmax	~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	ANDA: 74-507 (Watson), 74-707 (Watson Labs.) Protocols: 94-001, 98-025, 00-018, 02-065 CD: 92-200, 93-479, 94-181, 95-221, 98-274, 99-014, 01-477, 02-460, 03-350, and 02-020 See Attachment-1.
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	yes	
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

D. Pre-Study Bioanalytical Method Validation

(Determination of Nicotine in Human Plasma)

	Parent
Analyte Name	Nicotine
Internal Standard	Nicotine-D3
Method description	Yes
QC range, ng/mL	0.474 to 31.5
Standard curve range, ng/mL	0.15 to 49.9
Limit of quantitation, ng/mL	0.15
Average recovery of Drug (%)	91.4-101.1
Average Recovery of Int. Std (%)	85.8-86.4
Intraday precision range (%)	3.7 to 13.8
Intraday accuracy range (%)	96.8 to 103.5
Interday precision range (%)	1.2 to 12.0
Interday accuracy range (%)	95.3 to 108.5
Bench-top stability (hrs)	4
Stock stability (days)	N/A
Processed stability (hrs)	65
Freeze-thaw stability (cycles)	4
Flash-freezing to -70 ^{0}C	Stable
Long-term storage stability at -10 ^{0}C (days)	70
Dilution integrity, x2 and x5	Yes
Specificity	Yes
SOPs submitted	Yes
Bioanalytical method is acceptable	Yes
20% Chromatograms included (Y/N)	Yes
Random or Serial Selection of Chromatograms	Yes

Pre-Study Bioanalytical Method Validation

Determination of Nicotine in Gum

	Parent
Analyte Name	Nicotine
Internal Standard	Antipyrine
Method description	Yes
QC range, ng/mL	31.8 to 318
Standard curve range, ng/mL	10 to 443
Limit of quantitation, ng/mL	10
Average recovery of Drug (%)	105.3-118.6
Average Recovery of Int. Std (%)	80.9-87.0
Intraday precision range (%)	3.3 to 13.3
Intraday accuracy range (%)	99.4 to 120.0
Interday precision range (%)	10.6 to 12.7
Interday accuracy range (%)	95.3 to 108.8
Bench-top stability (hrs)	25
Stock stability (days)	12
Processed stability (hrs)	65
Freeze-thaw stability (cycles)	1/2 cycle
Flash-freezing to -70 ^{0}C	Stable
Long-term storage stability at -10 ^{0}C (days)	41
Dilution integrity, x2 and x5	Yes
Specificity	Yes
SOPs submitted	Yes
Bioanalytical method is acceptable	Yes
20% Chromatograms included (Y/N)	Yes
Random or Serial Selection of Chromatograms	Yes

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	012162
Study Design	3-way cross-over
No. of subjects enrolled	29
No. of subjects completing	26
No. of subjects analyzed	26
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 29 Female: 0
Test product	A. Perrigo's nicotine polacrilex regular flavor chewing gum, 4 mg
Reference product	B. GlaxoSmithKline's Nicorette® 4 mg nicotine polacrilex regular flavor chewing gum. C. Aventis Pharma (Nicorrette^R) 4 mg nicotine polacrilex mint flavor chewing gum. (Aventis Pharma **Canada**)
Strength tested	4 mg
Dose	1 x 4 mg gum

Summary of Statistical Analysis		
Parameter	**Point Estimate**	**90% Confidence Interval**
LAUC0-t	0.981	91.4-105.3
LAUC∞	1.014	94.0-109.4
LCmax	0.997	89.9-110.6

Reanalysis of Study Samples Additional information in Appendix, Table 15				
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**
Incongruous Values Repeats	10	0.51	10	0.51
Lowest Standard Removed	67	3.4	58	3.0
Lost in processing	17	0.87	14	0.72
Diluted Concentration unreliable	4	0.20	4	0.2
Insufficient Sample available	2	0.1	0	0
Unacceptable Chromatography	1	0.05	1	0.05
Total	101	5.13	87	4.48

Did use of recalculated plasma concentration data change study outcome? No

There were no pharmacokinetic repeats. The analytical method and data are acceptable.

Comments on Fasting Study:
The firm conducted a three-way crossover study comparing the test product with the with the US (GlaxoSmithKline) and Canadian (Aventis Pharma) RLDs. The statistical analysis performed by the reviewer utilized all data. However, this review contains data for the test product comparison only with the US RLD.
The study is acceptable. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCt, AUCi and Cmax for nicotine. The reviewer's calculations are similar to those submitted by the firm.

2. Multiple-dose Chew-out Study

Study No.	AA01422
Study Design	Randomized multiple dose crossover study combining three separate comparisons (see below)of salivary dissolution of different flavors of nicotine gum.
Washout Period	First dose of each study period was separated by 24 Hrs.
No. of subjects enrolled	16
No. of subjects completing	14
No. of subjects analyzed	14
Subjects (Normal/Patients?)	Normal healthy smokers abstained from smoking for 1 hr prior to dosing and during each study period.
Sex(es) included (how many?)	Male 16 Female 0
Test and Reference Products	**Comparison 1** Test *(A1)*: Perrigo's Nicotine Polacrilex Gum, *Regular flavor*, 4 mg Reference *(B1)*: GSK's Nicorrete® Gum, *Regular flavor*, 4 mg **Comparison 2** Test *(A2)*: Perrigo's Nicotine Polacrilex Gum, *Mint flavor*, 4 mg Reference *(B2)*: GSK's Nicorrete® Gum, *Mint flavor*, 4 mg **Comparison 3** Test *(A3)*: Perrigo's Nicotine Polacrilex Gum, *Orange flavor*, 4 mg Reference (B3): GSK's Nicorrete® Gum, *Orange flavor*, 4 mg
Strength Tested	4 mg
Dose	Multiple 4 buccal doses of 4 mg gum
Chewing Intervals/Study Period	A practice session using a placebo gum was held prior to dosing. Each period had 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. Chewing gum pieces #1, 2, 3 and 4 were administered at 0, 1.5, 2.83 and 4 hours, respectively.

Ratios of Means (%) of Percentage of Nicotine Released

Formulation Comparison	Chewing Duration, Min.			
	5	10	20	30
Perrigo Regular (A1) Vs. GlaxoSmithKline Regular (B1)	113.2%	108.7%	108.0%	104.2%
Perrigo Mint (A2) Vs. GlaxoSmithKline Mint (B2)	104.6%	111.7%	122.3%	115.2%
Perrigo Orange (A3) Vs. GlaxoSmithKline Orange (B3)	111.0%	119.5%	111.9%	107.5%

Comments on Multiple-dose Chew-out Study:
After 30 minutes of chewing, the ratios of means of percentage of nicotine released for the test and reference formulations were comparable and within ± 20%. The study is acceptable.

Reanalysis of Study Samples Additional information in Appendix, Table 15				
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**
Above the Acceptable Range	8	2.22	8	2.22
Total	8	2.22	8	2.22

Did use of recalculated nicotine concentrations change study outcome? No

There were no pharmacokinetic repeats. The analytical method and data are acceptable.

F. Formulation

Location in appendix	Section B, Page 29
Inactive ingredients within IIG Limits (yes or no)	Yes
If no, list ingredients outside of limits	The ingredients in the —— —— flavor exceeding the — % level are all recognized at GRAS in 21CFR. The toxicology consult dated 10/23/03 found that the buccal route was essentially identical to the sublingual route and that the 3 mg limit for acesulfame potassium found in IIG for sublingual tablets exceeded the ——, proposed in this formulation.
If a tablet, is the product scored? (yes or no)	N/A
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test? (yes or no)	N/A
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	Firm (European Pharmacopoeia 2.9.25)
Medium	Buffer pH 7.4
Volume (mL)	20 mL of buffer into chewing chamber at 37°C.
EP Apparatus type	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.
Rotation (rpm)	60 cycles/min
Firm's proposed specifications	None
FDA-recommended method	
Medium:	Phosphate buffer at pH 7.4
Volume:	900 mL
USP Apparatus	I (Basket)
Rotation speed	100 rpm
Sampling times	1, 2, 3, 4, 5, 6, 7 and 8 hours
	This method is listed in the OGD data base. However, it has been found unsuitable for this drug product (see Watson application reviews)

Method is acceptable (yes or no) The firm's method is acceptable

H. Waiver Request(s)

The waivers of in vivo bioequivalence testing for Perrigo's Nicotine Polacrilex Gum, Mint flavor, 4 mg and Nicotine Polacrilex Gum, Orange flavor, 4 mg, are addressed in two separate ANDAs (76-779 and 76-778, respectively).

I. Deficiency Comment

The application is incomplete pending the firm's acceptance of the DBE's recommended dissolution testing method and specifications.

J. Recommendations

1. The single-dose fasting bioequivalence study conducted by L. Perrigo on its Nicotine Polacrilex 4 mg Gum, Regular Flavor, Lot #543697201, comparing it to Nicorette®, 4 mg Gum, Regular Flavor, manufactured by GlaxoSmithKline, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Perrigo's Nicotine Polacrilex 4 mg Gum, Regular Flavor is bioequivalent to Nicorette®, 4 mg Gum, Regular Flavor, manufactured by GlaxoSmithKline.

2. The multi-dose chew-out (drug-release) study conducted by L. Perrigo on its Nicotine Polacrilex Gum, Regular Flavor, 4 mg (lot #543697201), Nicotine Polacrilex Gum, Mint Flavor, 4 mg (lot #543697301) and Nicotine Polacrilex Gum, Orange Flavor, 4 mg (lot #5436397401), comparing them to Nicorette®, 4 mg Gum, Regular Flavor, Nicorette®, 4 mg Gum, Mint Flavor and Nicorette®, 4 mg Gum, Orange Flavor, respectively, manufactured by GlaxoSmithKline, is acceptable. The study demonstrates that the rates of nicotine released from Perrigo's Nicotine Polacrilex, 4 mg Gum, Regular Flavor, Nicotine Polacrilex Gum, Mint Flavor, 4 mg and Nicotine Polacrilex Gum, Orange Flavor, 4 mg, are similar to those of Nicorette®, 4 mg Gum, Regular Flavor, Nicorette®, 4 mg Gum, Mint Flavor and Nicorette®, 4 mg Gum, Orange Flavor, respectively, manufactured by GlaxoSmithKline.

3. The dissolution testing conducted by Perrigo on its Nicotine Polacrilex Gum USP, 4 mg, Regular Flavored, lot #543697201, is acceptable.

> The dissolution testing should be conducted in phosphate buffer pH 7.4 using European Pharmacopoeia (2.9.25) apparatus at 60 cycles / minute. The test products should meet the following tentative specification:

Not less than —% (Q) of labeled amount of nicotine in dosage form is dissolved in 30 minutes.

The application is incomplete pending the firm's acceptance the DBE's recommended dissolution testing method and specifications.

The firm should be informed of the above recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch IV

Gurjaipal Singh 5-17-04

GJP Singh, Ph.D
Division of Bioequivalence
Team Leader Review Branch II

for Barbara M Davit 5/17/04

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information	
Study Number	012162
Study Title	Comparative, Randomized 3-Way Crossover Bioavailability Study of Perrigo Regular Flavor Chewing Gum with Nicorette^{R} 4 mg Nicotine Polacrilex Regular Flavor and Mint Flavor Chewing Gum In Healthy Adult Males.
Clinical Site	[redacted]
Principal Investigator	Dr. [redacted]
Study/Dosing Dates	August 12, 2002 Period I August 19, 2002 Period II August 26, 2002 Period III
Analytical Site	[redacted]
Analytical Director	[redacted]
Analysis Dates	September 09 to November 22, 2002
Storage Period	42 days

Treatment ID	A	B	C
Test or Reference	Test	Reference	Reference
Product Name	Nicotine Polacrilex **Regular Flavor** Chewing Gum	Nicorette^{R} (Nicotine Polacrilex) **Regular Flavor** Chewing Gum	Nicorette^{R} (Nicotine Polacrilex) **Mint Flavor** Chewing Gum (**Canadian Reference Product**)
Manufacturer	L. Perrigo Company	GlaxoSmithKline	Aventis Pharma (Canada)
Batch/Lot No.	5436397201	CL770A	DC506A
Manufacture Date	June 11, 2002	N/A	N/A
Expiration Date	N/A	May 31, 2004	July 7, 2004
Strength	4 mg	4 mg	4 mg
Dosage Form	Chewing Gum	Chewing Gum	Chewing Gum
Batch Size	[redacted]	N/A	N/A
Production Batch Size	[redacted]	N/A	N/A
Potency	106.25%	105.5%	NR
Content Uniformity	111.5%	NR(not repoted)	NR
Formulation	See Appendix Section B		
Dose Administered	1x4 mg Gum	1x4 mg Gum	1x4 mg Gum
Route of Administration	Buccal	Buccal	Buccal

No. of Sequences	6
No. of Periods	3
No. of Treatments	3
No. of Groups	N/A
Washout Period	7 days
Randomization Scheme	ABC for subjects #3, 5, 7, 10, 19 BCA for subjects #12, 13, 16, 22, 26 CAB for subjects #1, 6, 21, 25, 27 ACB for subjects #2, 14, 17, 24, 29* BAC for subjects #9, 11, 15, 28, 30 CBA for subjects #4, 8, 18, 20, 23 *Subject was not included in the study
	A single oral dose of 4 mg nicotine polacrilex gum was given and chewed for a total of 30 minutes. The gum was chewed 3 times every 4 second. The rhythm of the chewing was provided by timer with an audible signal. The subjects were required to chew the gum 3 times on 1 side of the mouth and then move the gum to the other side of the mouth. Every four seconds the tone sounded, prompting the subject chew 3 times on the opposite side from the previous chew. The subjects were instructed to swallow at a verbal command given every 30 seconds. Subjects compliance was closely monitored with 1 observer for every 6 subjects.
Blood Sampling Times	0, 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.17, 1.33, 1.5, 1.67, 1.83, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 12, 16 and 24 hours after drug administration.
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	Blood samples were centrifuged under refrigeration, at 1500 g for 10 minutes at 4°C. The resulting plasma was transferred to appropriately labeled polypropylene screw-cap tubes and frozen at approximately -20°C pending assay.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hours pre-dose and 4 hours post-dose.
Length of Confinement	From at least 12 hours pre-dose to 24 hours post-dose
Safety Monitoring	Seated blood pressure and pulse rate were evaluated in the morning prior to dosing for each study period.

Table 1 Demographics of Study Subjects

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	100
Mean	26	Mean	75.5	18-40	100	Male	100	Afr. Amer.	0
SD	5	SD	7.1	41-64	0	Female	0	Hispanic	0
Range	18-38	Range	62-90	65-75	0			Asian	0
				>75	0			Others	0

Study Results

Table 2 Dropout Information

Subject No 9, 11 and 28

Reason Subject #9 withdrew himself from the study during period II.

Subject #11 did not check in for period II.

Subject #28 withdrew himself from the study during period I.

There was no data for subjects 20 and 25 since they were assayed 4 times and the batches were rejected. There was insufficient plasma left to repeat the samples from the two subjects.

Subjects # 20 and 25 were excluded from the statistical and pharmacokinetic analyses of the study since no reliable data could be obtained for the two subjects.

Replacement None

Was there a difference in side effects for the test versus the reference? No

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Hiccough	**0**	**6**
Burp	**30**	**34**
Headache	**1**	**1**
Cough	**15**	**22**
Dizzy	**0**	**1**
Nausea	**0**	**2**

Vomiting	0	1
Feel faint	1	1
Clearing of Throat	6	2
Burning in Throat	2	2
Tongue Burning	1	0
Total:	56	66

Comments: There were no serious adverse events reported in the study. All of the adverse events reported in the study were seen in the clinical studies for Nicorette^{R} (based on the PDR).

Was there a difference in protocol deviations for the test versus the reference? No

Table 3 Protocol Deviations

No significant deviations from the protocol were documented.

Table 4 Assay Validation – Within Study

	Parent								
QC Conc. (ng/mL)	0.414	13.8	34.5						
Inter day Precision (%CV)	14.7	5.9	6.9						
Inter day Accuracy (%)	103.6	98.6	100.9						
Cal. Standards Conc. (ng/mL)	0.138	0.276	0.46	0.92	4.6	9.2	18.4	36.8	46.0
Inter day Precision (%CV)	5.2	5.1	7.3	4.9	6.4	5.4	4.4	3.8	3.2
Inter day Accuracy (%)	110.9	107.2	102	94.5	95	97.9	98.9	98.9	102
Linearity Range (range of R^2 values)	0.995								

Chromatograms: Any interfering peaks? No

Table 5 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
DH 3.9	8-12-2002	Procedure for selection and reporting of Sample re-assay

Comments on repeat assays

- Did recalculation of plasma concentrations change the study outcome? No
- Does the reviewer agree with the outcome of the repeat assays? Yes
- In the reviewer's opinion, the repeats have no impact on the outcome of the study.

Comments on Within-Study Validation:

The analytical method and data for nicotine are acceptable.

Conclusion: Analytical method is acceptable.

Table 6 Arithmetic Mean Pharmacokinetic Parameters (Data Corrected for Non-Zero Pre-Dose Values)

Mean Nicotine plasma concentrations are presented in Table 9 and Figure 1

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	hr-ng/mL	36.50	30.7	36.39	23.9	1.00
AUC_{∞}	hr-ng/mL	41.78	29.1	39.47	26.3	1.05
C_{max}	ng/mL	9.795	20.9	9.83	21.1	0.996
T_{max}	hr	0.98		0.5		
$T_{1/2}$	hr	8.08		1.21		
kel	1/hr	0.106		0.69		

Table 7 Least Square Geometric Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	34.78	35.40	98.1	91.43-105.3
AUC_{∞}	39.18	38.64	101.4	94.0-109.4
C_{max}	9.76	9.79	99.7	89.9-110.62

Table 8 Additional Study Information

Root mean square error, AUC_{0-t}	0.145	
Root mean square error, AUC_{∞}	0.146	
Root mean square error, C_{max}	0.213	
mean ratio AUC_{0-t}/AUC_{∞}	T =0.87	R =0.92

Comments:

- kel and AUC_{∞} were determined for 22 subjects.
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr. All subject.
  Since the subjects in this study were considered heavy smokers (greater than 25 cigarettes per day), almost all subjects had non-zero pre-dose values. Some subjects had non-zero pre-dose concentrations greater than 5% of the corresponding Cmax value in the affected period (subjects #1, 5, 14, 16, 17, 18, 22, 26, 27, 30). After excluding these subjects from the statistical analyses the 90% CIs for LAUCt, LAUCi and LCmax remained within the acceptable 80-125% range (see Table below).

Parameter	T/R	90% CI
AUC0-t	103.8	96.4-111.7
AUC∞	103.4	92.8-115.2
Cmax	105.6	89.5-124.6

b. first scheduled post-dose sampling time as Tmax. None
c. first measurable drug concentration as Cmax. None

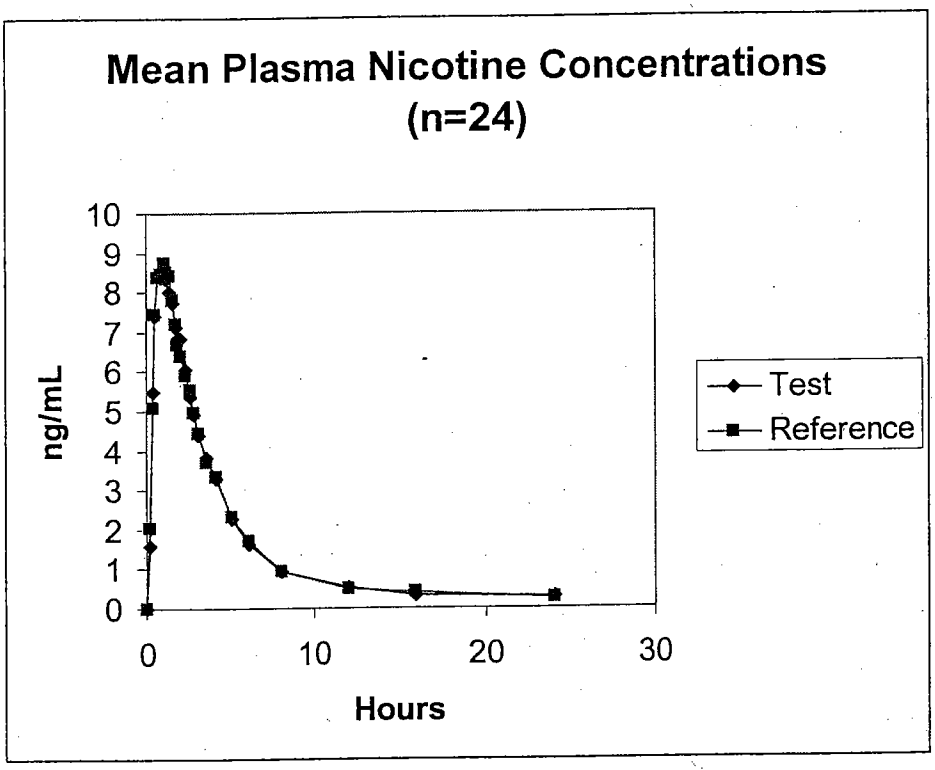
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes
- Were there statistically significant sequence or period effects? No
- Are the 90% confidence intervals for AUC0-t, AUC∞, Cmax within the acceptable limits of 80-125%. Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect. N/A

Conclusion: The single-dose fasting bioequivalence study is acceptable

Table 9 Mean Nicotine Plasma Concentrations (ng/mL), Single-Dose Fasting Bioequivalence Study

Time	Test (n=24)		Reference (n=24)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0	.	0	.	.
0.17	1.61	55.95	2.04	110.98	0.79
0.33	5.48	36.65	5.10	38.90	1.07
0.5	7.40	26.32	7.43	32.77	1.00
0.67	8.46	22.78	8.39	24.91	1.01
0.83	8.36	20.60	8.46	22.16	0.99
1	8.57	20.72	8.74	22.62	0.98
1.17	8.34	23.49	8.50	19.44	0.98
1.33	8.02	22.37	8.40	20.21	0.95
1.5	7.72	33.62	7.80	20.18	0.99
1.67	7.11	23.77	7.18	20.84	0.99
1.83	6.81	26.60	6.68	22.94	1.02
2	6.84	33.05	6.38	24.00	1.07
2.25	6.04	24.43	5.88	24.08	1.03
2.5	5.35	32.87	5.51	26.83	0.97
2.75	4.93	36.04	4.94	25.85	1.00
3	4.41	36.14	4.45	27.54	0.99
3.5	3.82	32.09	3.71	30.10	1.03
4	3.31	37.58	3.33	28.99	0.99
5	2.26	50.63	2.31	36.37	0.98
6	1.64	51.61	1.69	37.22	0.97
8	0.94	60.46	0.94	54.79	1.00
12	0.53	111.06	0.50	72.23	1.06
16	0.34	62.42	0.39	49.18	0.88
24	0.27	37.85	0.24	72.43	1.12

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



APPEARS THIS WAY
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2. Multiple-dose Chew-out Study

Study Information	
Study Number	AA01422
Study Title	Comparative, Randomized, Crossover Salivary Nicotine Dissolution Study of Perrigo and SmithKline Beecham Nicorette^{R} 4 mg Nicotine Polacrilex Chewing Gum In Healthy Adult Males.
Clinical Site	[redacted]
Principal Investigator	Dr. [redacted]
Study/Dosing Dates	September 2, 2002 Period I September 4, 2002 Period II September 6, 2002 Period III September 8, 2002 Period IV September 10, 2002 Period V September 12, 2002 Period VI
Analytical Site	[redacted]
Analytical Director	[redacted]
Analysis Dates	October 2 to October 8, 2002
Storage Period	36 days

Test and Reference Product Name	**Comparison 1** Perrigo's Nicotine Polacrilex **Regular Flavor** Chewing Gum [A1 (A)] vs. Nicorette^{R} (Nicotine Polacrilex) **Regular Flavor** Chewing Gum [B1 (B)]	**Comparison 2** Perrigo's Nicotine Polacrilex **Mint Flavor** Chewing Gum [A2 (C)] vs. Nicorette^{R} (Nicotine Polacrilex) **Mint Flavor** Chewing Gum [B2 (D)]	**Comparison 3** Perrigo's Nicotine Polacrilex **Orange Flavor** Chewing Gum [A3 (E)] vs. Nicorette^{R} (Nicotine Polacrilex) **Orange Flavor** Chewing Gum [B3 (F)]
Manufacturer Test	L. Perrigo	L. Perrigo	L. Perrigo
Manufacturer reference	GlaxoSmithKline	GlaxoSmithKline	GlaxoSmithKline
Batch/Lot No. Test	5436397201	5436397301	5436397401
Batch/Lot No. Reference	CL770A	DC565A	CL766A
Manufacture Date (Test)	June 11, 2002	June 11, 2002	June 11, 2002
Expiration Date (Ref)	May 31, 04	August 31, 04	Novembrt 20, 04
Strength	4 mg	4 mg	4 mg
Dosage Form	Chewing Gum	Chewing Gum	Chewing Gum
Batch Size	———	———	———
Potency Test	106.25%	102.0%	102.75%
Potency Reference	105.5%	106.5%	103.0%
Content Uniformity (Test)	111.5%	108.8%	107.5%
Formulation	See Appendix Section B		
Dose Administered	Multiple 4 buccal doses of 4 mg gum	Multiple 4 buccal doses of 4 mg gum	Multiple 4 buccal doses of 4 mg gum
Route of Administration	Buccal	Buccal	Buccal

No. of Sequences	2 A1B1A2B2A3B3 (1) and B1A1B2A2B3A3 (2)
No. of Periods	6
No. of Treatments	6
No. of Groups	N/A
Washout Period	One day
Randomization Scheme	A1B1A2B2A3B3 for subjects #2, 4, 6, 8, 10, 11, 14, 15, 17 and B1A1B2A2B3A3 for the rest of subjects.

Dose Administration

Each treatment period included a total 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. Subjects received 1 of 6 treatments according to the treatment schedule.

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

In each chewing session the gum was chewed 3 times every 4 second. The rhythm of the chewing was provided by timer with an audible signal. The subjects were required to chew the gum 3 times on 1 side of the mouth and then move the gum to the other side of the mouth. Every four seconds the tone sounded, prompting the subject chew 3 times on the opposite side from the previous chew. The subjects were instructed to swallow at a verbal command given every 30 seconds.

At the end of each chewing session chewed gum samples were collected for analysis of residual nicotine content.

Cud Storage

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 10

Length of Fasting

Subjects reported to the clinic on the morning prior to dosing and received a breakfast. Water and food were restricted 30 minutes prior to each chewing session.

Length of Confinement

Subjects reported to the clinic on the morning prior to each

dosing and were confined to the clinic during each study period.

Safety Monitoring Same as the fasting study

Data Analyses 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 Certificate of Analysis for the test and reference formulations

The percent of nicotine released from the test and reference formulations is calculated as follows:

$Percent_{Released} = 100 * Amount_{Released} / Amount_{Initial}$

Table 10 Demographics of Study Subjects

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	100
Mean	27	Mean	75.6	18-40	100	Male	100	Afr. Amer.	0
SD	5	SD	7	41-64	0	Female	0	Hispanic	0
Range	19-38	Range	63-87	65-75	0			Asian	0
				>75	0			Others	0

Study Results

Table 11 Dropout Information

Subject No 2 and 15

Reason Subject #2 failed to show up for dosing in period 4.

Subject #15 withdrew himself from the study for personal reasons prior to dosing in period 4.

As per protocol statistical analyses were performed on data from 16 subjects who completed at least 2 periods of the study.

Replacement None

Was there a difference in side effects for the test versus the reference? No

Table 12 Protocol Deviations

Comments: No significant deviations from the protocol were documented.

Table 13 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Burp	50	40
Clearing of Throat	1	2
Hiccough	30	18
Cough	84	75
Tired	0	1
Sneeze	1	0
Total:	166	136

Comment: There were no serious adverse events reported in the study. All of the adverse events reported in the study were seen in the clinical studies for Nicorette^{R} (based on the PDR).

Table 14 Assay Validation – Within Study

	Parent							
QC Conc. (ng/mL)	31.8	167	318					
Inter day Precision (%CV)	4.6	7.8	6.2					
Inter day Accuracy (% Accuracy)	88.4	105	111					
Cal. Standards Conc. (ng/mL)	10	20	44.3	70.6	88.6	176	353	443
Inter day Precision (%CV)	1.9	6.5	3.0	3.3	2.1	4.7	2.4	3.7
Inter day Accuracy (% Accuracy)	107	92	90.1	94.6	95.7	97.7	107.4	109.7
Linearity Range (range of R^2 values)	0.99							

Chromatograms: Any interfering peaks? No

Table 15 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
DH 3.9	8-12-2002	Procedure for selection and reporting of Sample re-assay

Comments on repeat assays

- Did recalculation of nicotine concentrations change the study outcome? No
- Does the reviewer agree with the outcome of the repeat assays? Yes
- The total number of repeats represents 2.2% of the overall number of samples for nicotine. In the reviewer's opinion, the repeats have no impact on the outcome of the study. The analytical method is acceptable.

Table 16 Arithmetic Means

Residual Amounts of Nicotine (mg) in Gum After Chewing for Indicated Duration

	Treatment A1 (A)				Treatment B1(B)			
	5 min	10 min	20 min	30 min	5 min	10 min	20 min	30 min
Mean	3.06	2.33	1.36	0.97	3.18	2.46	1.56	1.10
STD	0.42	0.56	0.38	0.33	0.19	0.23	0.42	0.35
%CV	13.86	23.96	27.55	33.53	5.93	9.41	26.64	32.19

Released Amounts of Nicotine (mg) After Chewing for Indicated Duration

	Treatment A1 (A)				Treatment B1(B)			
	5 min	10 min	20 min	30 min	5 min	10 min	20 min	30 min
Mean	1.19	1.92	2.89	3.28	1.04	1.76	2.66	3.12
STD	0.42	0.56	0.38	0.33	0.19	0.23	0.42	0.35
%CV	35.78	28.98	12.99	9.94	18.13	13.18	15.69	11.29

Percentage of Dose Released After Chewing a Gum for Indicated Duration

	Treatment A1 (A)				Treatment B1(B)				
	5 min	10 min	20 min	30 min	5 min	10 min	20 min	30 min	**T/R (30 min)**
Mean	27.92	45.27	67.95	77.14	24.66	41.66	62.94	74.03	**1.04**
STD	9.99	13.12	8.83	7.66	4.47	5.49	9.88	8.36	
%CV	35.78	28.98	12.99	9.94	18.12	13.18	15.69	11.29	

Residual Amounts of Nicotine (mg) in Gum After Chewing for Indicated Duration

	Treatment A2 (C)				Treatment B2(D)			
	5 min	10 min	20 min	30 min	5 min	10 min	20 min	30 min
Mean	3.0	2.2	1.4	0.9	3.18	2.52	1.96	1.40
STD	0.3	0.3	0.4	0.4	0.19	0.76	0.31	0.36
%CV	11.1	15.3	31.0	39.2	5.85	30.24	15.97	25.35

Released Amounts of Nicotine (mg) After Chewing for Indicated Duration

	Treatment A2 (C)				Treatment B2(D)			
	5 min	10 min	20 min	30 min	5 min	10 min	20 min	30 min
Mean	1.1	1.9	2.7	3.2	1.08	1.74	2.30	2.86
STD	0.3	0.3	0.4	0.4	0.19	0.76	0.31	0.36
%CV	30.6	18.3	15.9	11.5	17.18	43.95	13.56	12.43

Percentage of Dose Released After Chewing a Gum for Indicated Duration

	Treatment A2 (C)				Treatment B2(D)				
	5 min	10 min	20 min	30 min	5 min	10 min	20 min	30 min	**T/R (30 min)**
Mean	26.6	45.5	66.1	77.3	25.42	40.76	54.09	67.11	**1.15**
STD	8.1	8.3	10.5	8.9	4.37	17.91	7.33	8.34	
%CV	30.6	18.3	15.9	11.5	17.17	43.95	13.56	12.42	

Residual Amounts of Nicotine (mg) in Gum After Chewing for Indicated Duration

	Treatment A3 (E)				Treatment B3(F)			
	5 min	10 min	20 min	30 min	5 min	10 min	20 min	30 min
Mean	3.20	2.41	1.46	0.94	3.30	2.69	1.75	1.17
STD	0.28	0.42	0.49	0.41	0.28	0.32	0.49	0.52
%CV	8.78	17.40	33.15	42.94	8.60	11.94	28.01	44.74

Released Amounts of Nicotine (mg) After Chewing for Indicated Duration

	Treatment A3 (E)				Treatment B3(F)			
	5 min	10 min	20 min	30 min	5 min	10 min	20 min	30 min
Mean	0.91	1.70	2.65	3.17	0.82	1.43	2.37	2.95
STD	0.28	0.42	0.49	0.41	0.28	0.32	0.49	0.52
%CV	31.04	24.56	18.35	12.80	34.68	22.48	20.68	17.72

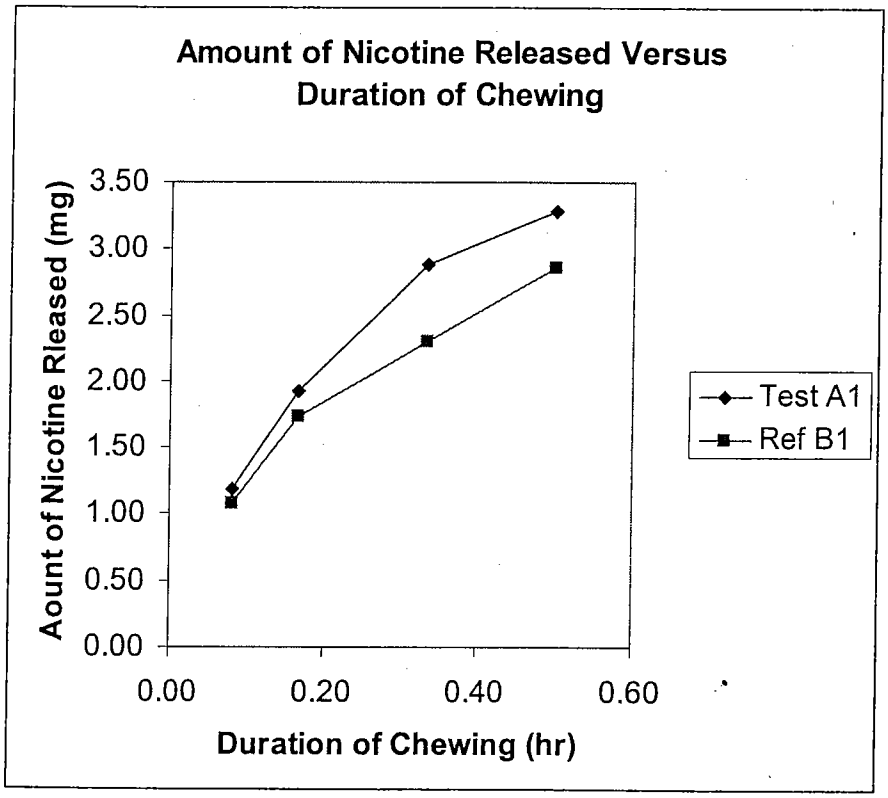
Percentage of Dose Released After Chewing a Gum for Indicated Duration

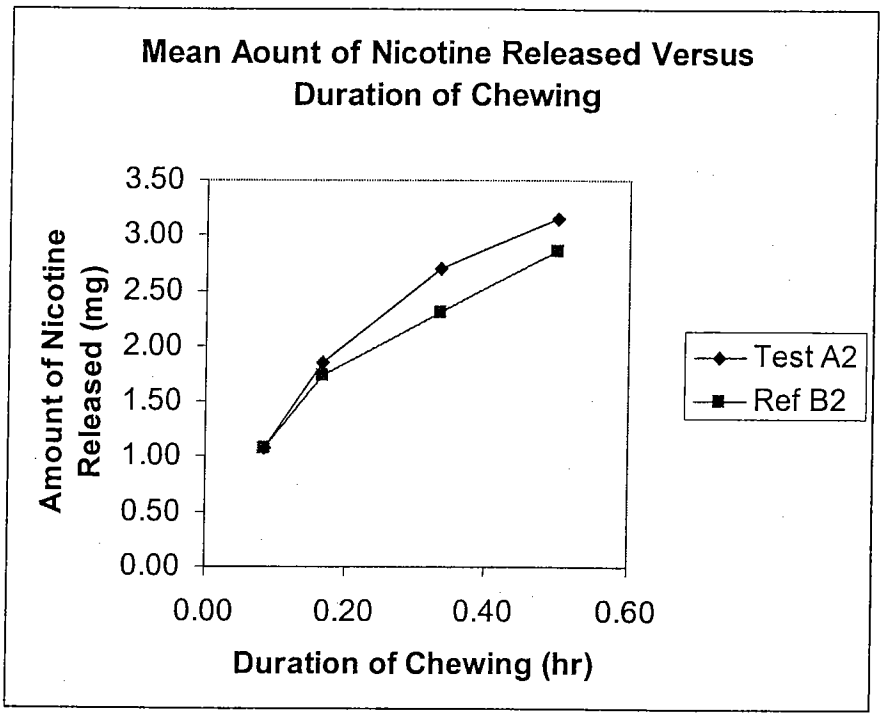
	Treatment A3 (E)				Treatment B3(F)				
	5 min	10 min	20 min	30 min	5 min	10 min	20 min	30 min	**T/R (30 min)**
Mean	22.05	41.47	64.36	77.03	19.87	34.69	57.53	71.64	**1.08**
STD	6.84	10.18	11.81	9.86	6.89	7.80	11.90	12.69	
%CV	31.04	24.56	18.35	12.80	34.68	22.48	20.68	17.72	

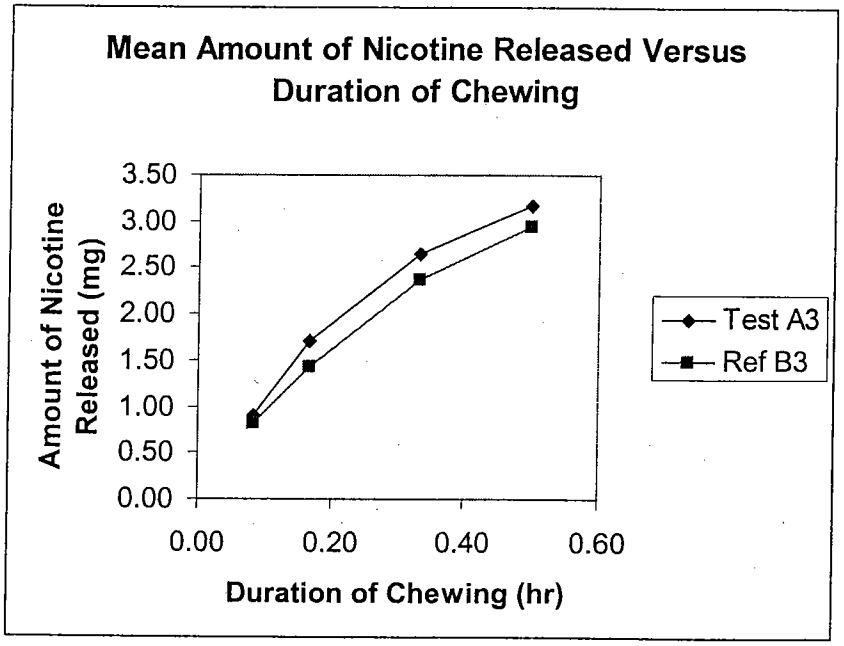
A1 (A) is Perrigo's Nicotine Polacrilex Regular Flavor Chewing Gum
B1 (B) is Nicorette^{R} (Nicotine Polacrilex) Regular Flavor Chewing Gum
A2 (C) is Perrigo's Nicotine Polacrilex Mint Flavor Chewing Gum
B2 (D) is Nicorette^{R} (Nicotine Polacrilex) Mint Flavor Chewing Gum
A3 (E) is Perrigo's Nicotine Polacrilex Orange Flavor Chewing Gum
B3 (F) is Nicorette^{R} (Nicotine Polacrilex) Orange Flavor Chewing Gum

Conclusion: The Test/Reference ratios for the percent nicotine released during the 30 minute chewing duration are 104.2%, 115.2% and 107.5% for Nicotine Polacrilex Regular Flavor, Nicotine Polacrilex Mint Flavor and Nicotine Polacrilex Orange Flavor, respectively. The ratios are within the acceptable $\pm$ 20% range.

Figure 2 Mean Amount of Nicotine Released




Mean Aount of Nicotine Released Versus Duration of Chewing
Amount of Nicotine Released (mg)
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0.00
0.20
0.40
0.60
Duration of Chewing (hr)
Test A2
Ref B2


Mean Amount of Nicotine Released Versus Duration of Chewing
Amount of Nicotine Released (mg)
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0.00
0.20
0.40
0.60
Duration of Chewing (hr)
Test A3
Ref B3

B. Formulation Data

Component	(Regular) mg/piece	(Mint) mg/piece	(Orange) mg/piece	
Nicotine Polacrilex USP (—% Nicotine) USP	*	*	*	
Acesulfame Potassium, Ph. Eur.***				
Pharmaceutical Gum Base				
Sorbitol, NF ****				
Calcium Carbonate USP****				
Sodium Carbonate NF				
Sodium Bicarbonate USP				
D&C Yellow #10				
Peppermint Flavor				
***				
Orange Flover				
Talc USP	N/A	N/A	N/A	
Carnauba Wax NF**				
Total Gum Piece Weight	1000.35 to 1000.45	1000.35 to 1000.45	1000.35 to 1000.45	

*Adjusted based on

**Used for , each unit dose contains

***Level found acceptable by pharmacology/toxicology consult on 10/23/03.

****Levels justified based on oral administration.

The ingredients in the flavor exceeding the —% level are all recognized at GRAS in 21CFR.

Peppermint flavor is used in the proposed drug products at a concentration of— % and has been cleared by OGD for use in a drug product for human use.

The toxicology consult dated 10/23/03 found that the buccal route was essentially identical to the sublingual route and that the 3 mg limit for acesulfame potassium found in IIG for sublingual tablets exceeded the proposed in this formulation. The toxicology consult also concluded that the components of the orange flavor are GRAS based on 21 CFR 172 and 182. was previously found acceptable at this level in a toxicology consult for a similar product (ANDA 76-569).

C. Dissolution Data

Sampling Time	Test Product, Strength 4 mg (Regular) Lot No. 5436-397201			Reference Product, Strength 4 mg (Regular) Lot No. CL770A		
	Mean	Range	%CV	Mean	Range	%CV
10	54		3.7	52		7.0
20	75		3.3	71		3.8
30	84		3.1	78		3.6

APPEARS THIS WAY
ON ORIGINAL

D. SAS Output

Study	Data	SAS Code	SAS Output
Fasting Study	 nicotine.prn	 nicotinecod.txt	 nicotineoutput.txt

APPEARS THIS WAY
ON ORIGINAL

E. Additional Attachments

History of Submissions

The DBE has reviewed several control documents and ANDA submissions on Nicotine Polacrilex Gum, 2 and 4 mg.

Control documents: #98-274[redacted]
#99-172[redacted]
#99-187[redacted]

Protocols: #94-001 by Circa Pharmaceuticals (1/3/94)
#98-025[redacted]
#00-018 by L. Perrigo (5/23/00)
#02-020 by L. Perrigo (5/6/02)

ANDA submissions: #74-507, original and amendments (12/14/95, 3/27/96, 9/21/01, 11/5/01 and 4/3/02) and 74-707 by Watson, original and amendments (7/6/95, 3/28/96, 11/20/98, 9/18/01, 9/21/01, 11/5/01 and 4/3/02). The amendments dated 9/18/01, 9/21/01, 11/5/01 and 4/3/02, submitted for mint and orange flavored gums, were found deficient by the DBE.

The relevant DBE recommendations, based on the above history, are as follows:

- Single dose two way cross over study on the 4 mg strength to establish in vivo bioequivalence of the generic formulation with the RLD (C #00-018, ANDA 74-707).
- Measurement of only the parent compound, nicotine in the BE study samples(C #00-018).
- Any adjustments to pharmacokinetic data using the residual nicotine levels analyzed from the gum cud is not acceptable. The DBE rejected a similar in vivo BE study because the bioequivalence determination was based upon dose adjusted data, i.e. the firm analyzed the chewed cuds from each dosed subject for residual nicotine and adjusted the pharmacokinetic parameters for each subject based on the fraction of the total nicotine delivered for rapid oral/buccal absorption in order to obtain an accurate pharmacokinetic profile (ANDA 74-707 supplements dated 9/18/01, 9/21/01, 11/5/01 and 4/3/02).
- The abuse liability testing is no longer requested (C #00-018).
- Multi dose crossover chew out studies on the 2 and 4 mg strengths to compare the in vivo nicotine release of the generic formulation to the RLD (ANDA 74-507, ANDA 74-707).
- Chew out studies with 9-14 subjects completing the study have been acceptable (ANDA 74-507 and 74-707).
- Sampling at several time points is recommended in the chew out studies to determine the nicotine release profiles from the test and reference formulations over time, i.e. after chewing the gum for 5, 10, 20 and 30 minutes (C #00-018, ANDA 74-507 and ANDA 74-707). The comment regarding the T/R ratios at earlier time points in the

chew out study "*however the clinical significance of the nicotine release pattern at the first 5-10 minutes during chew out study is unknown*" in the DBE review of ANDA 74-707 submission dated 11/20/98 is not supported by any clinical data or relevant reference.

- Waivers of in vivo bioequivalence testing may be requested for the 2 mg strength based on formulation proportionality and the in vitro drug release testing (C #98-274, ~~P #98-025~~, C #00-018, ANDA 74-507, ANDA 74-707).
- If the only difference in formulation between 4 mg 'mint or orange flavored' gum and 4 mg 'regular' flavored gum is the flavor component, the firm may request a waiver for the 4 mg mint and orange flavored gum, provided the firm submits results of a chew-out study between its 4 mg mint and orange flavored gum and Nicorrete® 4 mg mint and orange flavored gum as well as the comparative results of the other in-vitro tests and assays. Similar waivers may be requested for 2 mg mint and orange flavored gum based on results of a chew-out study between its 2 mg mint and orange flavored gum and Nicorrete® 2 mg mint and orange flavored gum as well as the comparative results of the other in-vitro tests and assays (C #00-018).

Redaction Error →

BIOEQUIVALENCE DEFICIENCY

ANDA: 76-789 APPLICANT: L. Perrigo Company

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

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

Please acknowledge that you have accepted the following dissolution method and specification:

The dissolution testing should be conducted in phosphate buffer pH 7.4 using European Pharmacopoeia (2.9.25) apparatus at 60 cycles / minute. The test products should meet the following tentative specification:

Not less than —% (Q) of labeled amount of nicotine in dosage form is dissolved in 30 minutes.

Sincerely yours,

for Barbara M Davit

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

CC: ANDA 76-789
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ M. makary

V:\FIRMSNZ\PERRIGO\LTRS&REV\76789N0603.doc
Printed in final on 5/12/2004

Endorsements: (Final with Dates)
HFD-658/ M. Makary MHM
HFD-658/ GJP Singh GJPS 5-17-04
HFD-650/B. Fabian-Fritsch
for HFD-650/ D. Conner BFD 5/17/04

BIOEQUIVALENCE – DEFICIENCY Submission Date: June 30, 2003

1. **FASTING STUDY** (STF) Strengths: 4 mg
Clinical: _____ Outcome: IC
Analytical: _____

2. **CHEW-OUT STUDY-MULTIDOSE** Strength: 4 mg
Clinical: _____ Outcome: IC
Analytical: _____

3. **Study Amendment (STA)** Strengths: 4 mg
February 6, 2004

Outcome: IC

Outcome Decisions: IC - Incomplete

CRO

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

3.1

ANDA # : 76-789 SPONSOR : Perrigo
DRUG AND DOSAGE FORM : Nicotine Polacrilex Gum (Regular)
STRENGTH(S) : 4 mg

TYPES OF STUDIES : Fasting study and Chew-out study multidose

CLINICAL STUDY SITE(S) : _____

ANALYTICAL SITE(S) : _____

STUDY SUMMARY : NA

DISSOLUTION : Perrigo accepts the dissolution method and tentative specification provided in the correspondence from Division of Bioequivalence dated May 25, 2004

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic NO New facility _____ For cause NO Other _____	Inspection requested: (date) Inspection completed: (date)	

Proposed Dissolution Method and Spec from Original Submission Acceptable Yes_____ No___X___
(If No, Project Manager (PM) should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Spec acknowledged by firm: Yes X

PROJECT MANAGER: Beth F. Ditsler DATE: 6/22/04

PRIMARY REVIEWER : Mohib Makhlouf BRANCH: IV

INITIAL : MBM DATE : 6/22/04

TEAM LEADER : Kuldeep Dhariwal BRANCH: IV

INITIAL : KDW DATE : 6/22/04

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm.D.

INITIAL : DPC DATE : 6/22/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-789

ADMINISTRATIVE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-775, 76-776, 76-777, 76-778, 76-779, ~~76-789~~ Applicant L. Perrigo Company
Drug Nicotine Polacrilex Gum, USP Strength(s) 2 mg & ~~4 mg~~ (Regular, Orange and Mint)

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

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

1. Martin Shimer
Chief, Reg. Support Branch
Date 3 Sept 2004 Initials MS
Date 9/16/04 Initials

Contains GDEA certification: Yes No
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes No
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes No
Was applicant sued w/in 45 days: Yes No
Has case been settled: Yes No
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes No
Type of Letter:
Comments: No patents/exclusivities ∴ eligible for Full Approval

Determ. of Involvement? Yes No
Pediatric Exclusivity System
RLD = NDA# 20-066
Date Checked N/A
Nothing Submitted
Written request issued
Study Submitted
Date settled:

2. Project Manager, TOM HINCHLIFFE Team 10 Date 9/2/04
Review Support Branch Initials
Date Initials

Original Rec'd date June 30, 2003 EER Status Pending ☒ Acceptable ☒ OAI ☐
Date Acceptable for Filing ~~June 30, 2004~~ 7/1/03 Date of EER Status 9/1/04
Patent Certification (type) I Date of Office Bio Review 6/22/04
Date Patent/Exclus.expires Date of Labeling Approv. Sum
Citizens' Petition/Legal Case Yes ☐ No ☒ Date of Sterility Assur. App. N/A
(If YES, attach email from PM to CP coord) Methods Val. Samples Pending Yes ☐ No ☒
First Generic Yes ☐ No ☒ MV Commitment Rcd. from Firm Yes ☐ No ☒
Acceptable Bio reviews tabbed Yes ☒ No ☐ Modified-release dosage form: Yes ☐ No ☒
Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

Previously reviewed and tentatively approved ☒ Date
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

3. David Read **(PP IVs Only)** Pre-MMA Language included
OGD Regulatory Counsel, Post-MMA Language Included
Comments: N/A
Date
Initials

4. Div. Dir./~~Deputy~~ Dir.
Chemistry Div. I II OR III
Comments:
Date 9/15/04
Initials RCM

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
N/A.

6. Vacant RLD: Nicorette Gum (Original) 4mg(base) Date_____
Deputy Dir., DLPS GlaxoSmithKline NDA 20-066(002) Initials_____

7. Peter Rickman Date 9/16/2004
Director, DLPS Initials_____
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments: Acceptable ES dated 9/1/04 (Verified 9/16/04) No O.A.Z. alerts noted Pharm/tox consult on certain inactive ingredients found acceptable Bioequivalence studies (single-dose, fasting, 4mg original regular flavor) found acceptable 9/1/04. Also multi-dose, chew-out (drug release) study found acceptable. Dissolution studies also found acceptable. Bio test sites have acceptable DSI inspectional histories. Office Level bio endorsed 9/22/04. FR found acceptable for approval 9/14/04. CMC found acceptable for approval 9/14/04. Methods validation was not requested. Per Request

8. Robert L. West Date 9/16/2004
Deputy Director, OGD Initials_____
Para.IV Patent Cert: Yes (No); Pending Legal Action: Yes (No); Petition: Yes No
Comments: There are no unexpired patents or exclusivity currently listed in the Orange Book for this drug product.

THIS ANDA IS RECOMMENDED for approval.

9. Gary Buehler Date 9/16/04
Director, OGD Initials GB
Comments:
First Generic Approval PD or Clinical for BE Special Scientific or Reg.Issue

10. Project Manager, Team 10 Tom Hinchliffe Date 9/16/04
Review Support Branch Initials TH
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
9 am Time notified of approval by phone 4pm Time approval letter faxed
FDA Notification:
9/16/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
9/16/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou8.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-789

CORRESPONDENCE

PERRIGO®

505(j)(2)(A)(i) OK
28-AUG-2003

ABBREVIATED NEW DRUG APPLICATION

June 30, 2003

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

Re: Abbreviated New Drug Application
Nicotine Polacrilex Gum USP, 4 mg (Regular)

Dear Mr. Buehler:

L. Perrigo Company is submitting for your review and approval an original Abbreviated New Drug Application (ANDA) for Nicotine Polacrilex Gum USP, 4 mg (Regular) pursuant to 505 (j) of the Federal Food, Drug, and Cosmetic Act. Perrigo's drug product is identical in strength, indications, active ingredient, route of administration, and dosage form to the reference listed drug, Nicorette®, distributed by GlaxoSmithKline under New Drug Application (NDA) 20-066.

Please note that Perrigo is submitting a total of six applications for Nicotine Polacrilex Gum USP, one application for each strength (2 mg and 4 mg) and flavor (Regular, Mint, and Orange). The Agency may find it beneficial to review these applications at the same time.

In support of this application, two bioequivalence studies were conducted for Perrigo by a contract research organization, _____.

The first study was an *in vivo* salivary nicotine dissolution study of:

- Perrigo Nicotine Polacrilex Gum USP, 4 mg (Regular) vs. Nicorette®, 4 mg (Regular)
- Perrigo Nicotine Polacrilex Gum USP, 4 mg (Mint) Nicorette®, 4 mg (Mint)
- Perrigo Nicotine Polacrilex Gum USP, 4 mg (Orange) vs. Nicorette®, 4 mg (Orange)

The second study was an *in vivo* study of Perrigo Nicotine Polacrilex Gum USP, 4 mg (Regular) vs. Nicorette®, 4 mg (Regular).

Both bioequivalence studies are being submitted with this application.

515 Eastern Avenue
Allegan, Michigan 49010

Exhibit batches were manufactured and packaged by a contract manufacturer, Fertin Pharma, Vejle, Denmark. Executed manufacturing and packaging records are provided in Section 12 of this application, In-Process Controls.

Batches for commercial distribution will be manufactured and packaged by Fertin Pharma, Vejle, Denmark. Master manufacturing and packaging records are provided in Section 11 of this application, Manufacturing and Processing Instructions. After the product has been manufactured and packaged at Fertin Pharma, it will be tested and released to Perrigo. Additional testing will be performed and the product will be released by Perrigo for secondary packaging. The product will then be released by Perrigo for commercial distribution.

This application is being provided as follows:

Archival Copy	Blue Binders	Sections 1 through 22	2 Binders
		Bioequivalence Study # 1	1 Binder
		Bioequivalence Study # 2	4 Binders
Technical Review Copy	Red Binders	Sections 1 through 22	2 Binders
Bioequivalence Review Copy	Orange Binders	Sections 1 through 7	1 Binder
		Bioequivalence Study # 1	1 Binder
		Bioequivalence Study # 2	4 Binders
	Padded Envelopes	Bioequivalence Studies Electronic Data	2 Diskettes
Methods Validation Package (2 copies)	Green Binders	Section 15	2 Binders

A true copy of the technical sections of this application is being provided to the Detroit District Field Office, including a copy of FDA Form 356h and a certification that the contents are a true copy of the application filed with the Office of Generic Drugs. This "field copy" is being provided in burgundy binders.

Please find attached an additional copy of this cover letter. Please stamp the date of receipt on the letter and return it to Perrigo in the attached self-addressed stamped envelope.

If you require additional information, please contact me by telephone at (269) 686-1920, by facsimile at (269) 673-7655, or at the address on the letterhead.

Respectfully submitted,

Mary E Short

Mary E. Short, RAC
ANDA Regulatory Affairs Project Manager

PERRIGO®

NEW CORRESP
NC

TELEPHONE
AMENDMENT

NAE MAS 05 Sept 2003

August 26, 2003

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

Via facsimile and Federal Express

Re: ANDA 76-789
Nicotine Polacrilex Gum USP, 4 mg (Regular)

Dear Mr. Buehler:

L. Perrigo Company submitted ANDA 76-789 on June 30, 2003.

In response to a telephone request from Martin Shimer, Project Manager, Regulatory Support Branch, regarding the inactive ingredients, L. Perrigo Company hereby commits to provide additional nonclinical pharmacology and toxicology information if the Agency requests it in the future.

A revised Form FDA 3454 (financial disclosure certification) may be found in Attachment 1. The form submitted with the original application was incomplete.

Respectfully submitted,

Mary E Short

Mary E. Short, RAC
ANDA Regulatory Affairs Project Manager

RECEIVED
AUG 27 2003
OGD/CDER

515 Eastern Avenue
Allegan, Michigan 49010
(269) 673-8451

ANDA 76-789

L. Perrigo Company
Attention: Brian R. Schuster
515 Eastern Avenue
Allegan, MI 49010

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated August 20, 2003 and your correspondence dated August 26, 2003.

NAME OF DRUG: Nicotine Polacrilex Gum USP, 4 mg (regular)

DATE OF APPLICATION: June 30, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 1, 2003

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Thomas Hinchliffe
Project Manager
(301) 827-5848

Sincerely yours,

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

ANDA 76-789
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/MShimer, Chief, RSB _____ date 28-AUG-2003
HFD-615/MShimer, CSO _____ date 26 August 2003
Word File V:Firmsnz/Perrigo/Ltrs&rev/76789.ack
F/T
ANDA Acknowledgment Letter!

Redacted 2 page(s)

of trade secret and/or

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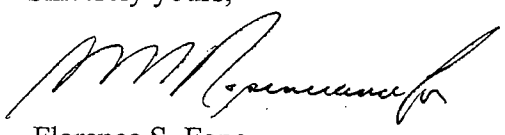
information from

12/19/2003 FDA FAX

3. The non-compendial analytical methods may be validated by the FDA laboratory.

Sincerely yours,



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

PERRIGO®

2.1

January 20, 2004

MINOR AMENDMENT– CHEMISTRY

Gary Buehler, Director
Office of Generic Drugs
CDER/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Via Federal Express

ORIG AMENDMENT
N/AM

Re: ANDA 76-789
Nicotine Polacrilex Gum USP, 4 mg (Regular)

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 76-789 for Nicotine Polacrilex Gum USP, 4 mg (Regular), filed on June 30, 2003. L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address deficiencies received from the Division of Chemistry II on December 19, 2003 (Attachment 1).

This communication is classified as a MINOR AMENDMENT as designated in the December 19, 2003, letter and is divided into the following sections:

- Chemistry Deficiencies/Responses
- Chemistry Comments/Responses

Chemistry Deficiencies/Responses

Deficiency 1

[redacted]

Response to Deficiency 1

[redacted]

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515 Eastern Avenue
Allegan, Michigan 49010
(269) 673-8451

Redacted 7 page(s)

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1/20/2004 PERRIGO LETTER

As required by 21 CFR 314.96(b), L. Perrigo Company certifies that a "field copy," which is a true copy of this amendment submitted to the FDA headquarters, has been submitted to the Detroit District Field Office.

Please contact me by telephone at (269) 686-1920, by fax at (269) 673-7655, or by mail at the address listed on this letterhead if you have any questions.

Respectfully submitted,

Mary E Short

Mary E. Short, RAC
Project Manager
ANDA Regulatory Affairs

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February 6, 2004

TELEPHONE AMENDMENT– BIOEQUIVALENCE

Gary Buehler, Director
Office of Generic Drugs
CDER/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB

Via Federal Express

Re: ANDA 76-789
Nicotine Polacrilex Gum USP, 4 mg (Regular)

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 76-789 for Nicotine Polacrilex Gum USP, 4 mg (Regular), filed on June 30, 2003. L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address telephone deficiencies received from Aaron Sigler, Pharm.D., Project Manager, Division of Bioequivalence, on January 30, 2004.

This communication is classified as a TELEPHONE AMENDMENT as designated in the January 30, 2004, voice mail message and is divided into the following sections:

- Deficiencies/Responses
- Additional Information

Deficiencies/Responses

Deficiency 1

Please provide the method and operation for *in vitro* comparative release referred to as the method described in the European Pharmacopoeia 2.9.25.

Response to Deficiency 1

European Pharmacopoeia 2.9.25 is provided in Attachment 1. The Fertin Pharma method that was used for *in vitro* comparative release is based on the method described in the European Pharmacopoeia 2.9.25 and is provided in Attachment 2. Validation of the HPLC method is included in Attachment 3.

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Deficiency 2

Please provide the potency for the test and references for all strengths.

Response to Deficiency 2

Please see Attachment 4 for a data summary of test and reference products used for the biostudies.

Deficiency 3

Please provide content uniformity and manufacturing dates for all test strengths.

Response to Deficiency 3

Please refer to the data summary included in Attachment 4.

Additional Information

Reported data for *in vitro* release (30 minute time point only) included a calculation error. All results for the 30 minute time point were too high because they were not properly corrected for the sample volume withdrawn at the 20 minute time point. Please see the "Calculations" section of the method in Attachment 2 for the equation for drug release at 30 minutes, including an explanation of the volume correction.

Affected data have been corrected. The *in vitro* comparative drug release data submitted in the original application should be replaced with the documents included in Attachment 5.

Please contact me by telephone at (269) 686-1920, by fax at (269) 673-7655, or by mail at the address listed on this letterhead if you have any questions.

Respectfully submitted,

Mary E Short

Mary E. Short, RAC
Project Manager
ANDA Regulatory Affairs

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2.1

March 16, 2004

AMENDMENT
TO
MINOR AMENDMENT –
CHEMISTRY
DATED
JANUARY 20, 2004

ORIG AMENDMENT
N/AM

Gary Buehler, Director
Office of Generic Drugs
CDER/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Via Federal Express

Re: ANDA 76-789
Nicotine Polacrilex Gum USP, 4 mg (Regular)

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 76-789 for Nicotine Polacrilex Gum USP, 4 mg (Regular), filed on June 30, 2003, and the Minor Amendment – Chemistry submitted to the application on January 20, 2004.

L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to correct an error in one of the documents that was included in the amendment dated January 20, 2004.

Please refer to the revised gum base certificate of analysis from Fertin Pharma on page 13 in Attachment 2 of the January 2004 amendment. This document was revised in response to deficiency number 1; however, limits for — were incorrect.

The certificate of analysis that was submitted in the January 2004 amendment should be replaced with the certificate of analysis included in this submission. Limits for — have been revised from ——— % to ——— %.

As required by 21 CFR 314.96(b), L. Perrigo Company certifies that a "field copy," which is a true copy of this amendment submitted to the FDA headquarters, has been submitted to the Detroit District Field Office.

Please contact me by telephone at (269) 686-1920, by fax at (269) 673-7655, or by mail at the address listed on this letterhead if you have any questions.

Respectfully submitted,

Mary E Short

Mary E. Short, RAC
Project Manager
ANDA Regulatory Affairs

RECEIVED
MAR 18 2004
OGD/CDER

515 Eastern Avenue
Allegan, Michigan 49010
(269) 673-8451

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March 29, 2004

LABELING AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
CDER/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Via Federal Express

Re: ANDA 76-789
Nicotine Polacrilex Gum USP, 4 mg (Regular)

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 76-789 for Nicotine Polacrilex Gum USP, 4 mg (Regular), filed on June 30, 2003. L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address labeling deficiencies received on February 4, 2004, from the Division of Labeling and Program Support (Attachment 1).

GENERAL COMMENT

Comment 1a

Please note that the review was done using all labeling pieces for Nicorette, including Carton, Blister, User's Guide, and Audiotape approved on August 9, 2002.

Response to Comment 1a

L. Perrigo Company acknowledges that Nicorette labeling approved on August 9, 2002, was utilized for the labeling review.

Comment 1b

Please provide a monitoring program to describe how you will report the findings of underage use of your nicotine product to FDA.

Response to Comment 1b

Perrigo commits to administer a postmarketing monitoring program for Perrigo Nicotine Polacrilex Gum USP, 4 mg (Regular). The purpose of the monitoring program is to identify usage of the product by minors and to report the findings to FDA.

515 Eastern Avenue
Allegan, Michigan 49010
(269) 673-8451

Please note that the labeling for this product clearly states:

- 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

The labeling also states "if you are under 18 years of age, ask a doctor before use." It is anticipated that smokers who are under the age of 18 will be using this product under a doctor's supervision.

Perrigo's Consumer Affairs department will be responsible for identifying usage of the products by minors utilizing its existing complaint management process. Written and oral complaints or inquiries (phone calls, letters, e-mails, faxes, information from a marketing/sales representative, etc.) that are received by Consumer Affairs will be entered into the Consumer Complaint Handling System (CCHS). If the report is an adverse drug experience, then the required information will be documented and reported to FDA in accordance with federal regulations. At the end of each annual reporting period, Consumer Affairs will analyze all data received and will determine how many reports of underage use were received during the reporting period. Consumer Affairs will provide this information to Regulatory Affairs.

Perrigo's Regulatory Affairs department will be responsible for submitting the findings of the monitoring program to FDA in the status report section of the annual report to this ANDA.

BLISTER

No deficiencies were received for blister labeling. Please see Attachment 2 for final printed labeling.

CARTON

Deficiency 3a

Your original and mint flavor cartons use the same color for both flavors. We recommend using a different color for the original flavor.

Response to Deficiency 3a

Labeling has been revised to change the color for the original flavor from green to blue.

Deficiency 3b

We encourage the inclusion of "USP" in association with your established name in your title.
Nicotine Polacrilex Gum USP, 2 mg
or
Nicotine Polacrilex Gum USP, 4 mg

Response to Deficiency 3b

Because use of "USP" is optional, Perrigo allows each of its store brand retailers to determine whether to use "USP" in the established name of the drug. Following approval of this application, labeling that includes "USP" may be submitted in the annual report.

Deficiency 3c

Please include "nicotine" in parentheses after the strength in your title.
Nicotine Polacrilex Gum USP, 2 mg (nicotine)
or
Nicotine Polacrilex Gum USP, 4 mg (nicotine)

Response to Deficiency 3c

Labeling has been revised as instructed.

Deficiency 3d

Active ingredient
Revise to read:
Nicotine polacrilex, 2 mg (nicotine).....Stop smoking aid
or
Nicotine polacrilex, 4 mg (nicotine).....Stop smoking aid

Response to Deficiency 3d

Labeling has been revised as instructed.

Deficiency 3e

Inactive ingredients
Your components and composition statement includes talc; however, talc is not included in your labeling. Please revise/comment.

Response to Deficiency 3e

Labeling has been revised to include talc in the inactive ingredients section.

Deficiency 3f

Other information
Revise the storage temperature statement to read "Store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature] – Protect from light.

Response to Deficiency 3f

The labeling has been revised so that the storage temperature statement reads as recommended. The statement "protect from light" appears as a separate bulleted statement for emphasis.

As discussed with Michelle Dillahunt, Labeling Reviewer, on March 18, 2004, the statement "[see USP Controlled Room Temperature]" may be omitted or revised to "excursions permitted to 15 – 30°C." If this minor labeling change is implemented, it will be submitted in the annual report.

Deficiency 3g

Refill (48 chewing pieces)

i. Warnings – include this heading on the next column, above the paragraph beginning with "Smoking can……..known."
ii. Directions – include this heading on the next column, above the paragraph beginning with "If you smoke…….schedule."

Response to Deficiency 3g

According to format and content requirements for over-the-counter (OTC) drug product labeling, the required order and flow of headings, subheadings, and information must be retained. The use of the same heading in two different columns is not in accordance with Drug Facts regulations and may cause consumer confusion.

Final printed labeling is provided in Attachment 3, along with a statement of labeling similarity, and a side-by-side comparison of proposed labeling vs. final printed labeling with all differences annotated and explained.

USER'S GUIDE

No deficiencies were received for the User's Guide. Please see Attachment 4 for final printed labeling.

AUDIOTAPE

All deficiencies received for the audiotape script have been addressed. The following items are provided in Attachment 5: final printed labeling, audiotape script (revised), statement of labeling similarity, and side-by-side comparison of proposed labeling vs. final printed labeling with all differences annotated and explained.

Please contact me by telephone at (269) 686-1920, by fax at (269) 673-7655, or by mail at the address listed on the letterhead if you have any questions.

Respectfully submitted,

Mary E Short

Mary E. Short, RAC
Project Manager
ANDA Regulatory Affairs

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ORIGINAL

May 20, 2004

CHEMISTRY
AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
CDER/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

Via Federal Express

Re: ANDA 76-789
Nicotine Polacrilex Gum USP, 4 mg (Regular)

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 76-789 for Nicotine Polacrilex Gum USP, 4 mg (Regular), filed on June 30, 2003, and the Chemistry Amendments submitted to the application on January 20, 2004, and March 16, 2004.

L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 per the request of the foreign inspection team to submit revised documentation in preparation for the inspection of two Danish firms: ——————— and Fertin Pharma A/S.

The drug substance specification that was submitted as pages 396 and 397 of the original submission has been revised and is included in Attachment 1, along with a summary of changes to the specification. Please note that the format has been updated and that other minor editorial changes have been made.

In addition, four pages of the Danish executed batch record were missing from the original submission. These four pages may be found in Attachment 2 and belong between pages 666 and 667 of the original submission. The English translation of these pages was included in the original submission (pages 712 to 715).

As required by 21 CFR 314.96(b), L. Perrigo Company certifies that a "field copy," which is a true copy of this amendment submitted to the FDA headquarters, has been submitted to the Detroit District Field Office.

Please contact me by telephone at (269) 686-1920, by fax at (269) 673-7655, or by mail at the address listed on this letterhead if you have any questions.

Respectfully submitted,

Mary E Short

Mary E. Short, RAC
Project Manager
ANDA Regulatory Affairs

RECEIVED
MAY 21 2004
OGD/CDER

515 Eastern Avenue
Allegan, Michigan 49010
(269) 673-8451

BIOEQUIVALENCY AMENDMENT

ANDA's 76-775 / 776 / 777 / 778 / 779 / 789

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)

MAY 25 2004

APPLICANT: L. Perrigo Company TEL: 269-573-8451

ATTN: Brian Schuster FAX: 269-673-7655

FROM: Steven Mazzella PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on June 30, 2003, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nicotine Polacrilex Gum USP (multiple flavors), 2 mg and 4 mg.

Reference is also made to your amendment(s) dated: .

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached three pages. 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:

MAY 25 2004

BIOEQUIVALENCE DEFICIENCY

ANDA Nos. 76-775, 76-776 and 76-777 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Nicotine Polacrilex Gum USP, 2 mg (Regular Flavor)
Nicotine Polacrilex Gum USP, 2 mg (Orange Flavor)
Nicotine Polacrilex Gum USP, 2 mg (Mint Flavor)

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

Please acknowledge that you have accepted the following dissolution method and specification:

> The dissolution testing should be conducted in phosphate buffer pH 7.4 using European Pharmacopoeia (2.9.25) apparatus at 60 cycles / minute. The test products should meet the following tentative specification:
>
> Not less than – % (Q) of labeled amount of nicotine in dosage form is dissolved in 30 minutes.

Sincerely yours,

for Barbara M Davit

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE DEFICIENCY

ANDA: 76-789 APPLICANT: L. Perrigo Company

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

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

Please acknowledge that you have accepted the following dissolution method and specification:

The dissolution testing should be conducted in phosphate buffer pH 7.4 using European Pharmacopoeia (2.9.25) apparatus at 60 cycles / minute. The test products should meet the following tentative specification:

Not less than ~~%~~ (Q) of labeled amount of nicotine in dosage form is dissolved in 30 minutes.

Sincerely yours,

Barbara M Davit

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE DEFICIENCY

ANDA: 76-778 APPLICANT: L. Perrigo Company
ANDA; 76-779

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

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

Please acknowledge that you have accepted the following dissolution method and specification:

The dissolution testing should be conducted in phosphate buffer pH 7.4 using European Pharmacopoeia (2.9.25) apparatus at 60 cycles / minute. The test products should meet the following tentative specification:

Not less than —% (Q) of labeled amount of nicotine in dosage form is dissolved in 30 minutes.

Sincerely yours,

for Barbara M Davit

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

PERRIGO®

June 17, 2004

BIOEQUIVALENCY AMENDMENT

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

ORIG AMENDMENT
N/A B

Via Federal Express

Re: ANDA 76-789
Nicotine Polacrilex Gum USP, 4 mg (Regular)

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 76-789 for Nicotine Polacrilex Gum USP, 4 mg (Regular), filed on June 30, 2003. On February 6, 2004, L. Perrigo Company submitted a Telephone Amendment to provide additional information that was requested by the Division of Bioequivalence on January 30, 2004.

This BIOEQUIVALENCY AMENDMENT is being submitted:

- to acknowledge that the Division of Bioequivalence has completed its review of this application
- to confirm acceptance of the dissolution method and tentative specification provided in correspondence from the Division of Bioequivalence dated May 25, 2004 (Attachment 1)

L. Perrigo Company acknowledges that the dissolution method and tentative specification are accepted for:

ANDA Number	Drug Product	Flavor
76-775	Nicotine Polacrilex Gum USP, 2 mg	Regular
76-776	Nicotine Polacrilex Gum USP, 2 mg	Orange
76-777	Nicotine Polacrilex Gum USP, 2 mg	Mint
76-778	Nicotine Polacrilex Gum USP, 4 mg	Orange
76-779	Nicotine Polacrilex Gum USP, 4 mg	Mint
76-789	Nicotine Polacrilex Gum USP, 4 mg	Regular

The dissolution method was submitted previously on February 6, 2004. All drug products listed above will meet the following tentative specification for *in vitro* release of nicotine: Not less than —% (Q) in 30 minutes.

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JUN 18 2004
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515 Eastern Avenue
Allegan, Michigan 49010
(269) 673-8451

A copy of this submission is being transmitted via facsimile to Beth Fritsch, Project Manager, Division of Bioequivalence.

If there are any questions, please contact me immediately at (269) 686-1920 or via facsimile at (269) 673-7655.

Respectfully submitted,

Mary E Short

Mary E. Short, RAC
Project Manager
ANDA Regulatory Affairs

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ORIGINAL 3.1

June 28, 2004

CHEMISTRY
AMENDMENT

ORIG AMENDMENT
N/AM

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

Via Federal Express

Re: ANDA 76-789
Nicotine Polacrilex Gum USP, 4 mg (Regular)

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 76-789 for Nicotine Polacrilex Gum USP, 4 mg (Regular), filed on June 30, 2003. On December 19, 2003, a deficiency letter was received from the Division of Chemistry. On January 20, 2004, Perrigo submitted a Minor Amendment – Chemistry in response to these deficiencies. Two additional chemistry amendments were submitted on March 16, 2004, and May 20, 2004.

An inspection of the Fertin Pharma drug product manufacturing and packaging facilities was conducted by FDA's foreign inspection team May 27, 2004 through June 3, 2004. No inspectional observations were issued.

This CHEMISTRY AMENDMENT is being submitted in order to provide:

- a revised finished product specification in response to a deficiency identified by the Division of Bioequivalence in correspondence dated May 25, 2004 (Attachment 1)
- additional information on dissolution testing
- additional information on blend uniformity reviewed by the foreign inspection team
- additional revised documentation

This submission should be reviewed at the same time as the following submissions:

- Minor Amendment – Chemistry (January 20, 2004)
- Amendment to Minor Amendment – Chemistry
  Dated January 20, 2004 (March 16, 2004)
- Chemistry Amendment (May 20, 2004)

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JUN 29 2004
OGD / CDER

515 Eastern Avenue
Allegan, Michigan 49010
(269) 673-8451

Response to Deficiency from the Division of Bioequivalence

The Division of Bioequivalence has completed its review of this application and has identified a deficiency in the finished product specification. Dissolution testing, previously not included in the specification, is now required.

An amendment was submitted to the Division of Bioequivalence on June 17, 2004, to confirm acceptance of the dissolution method and tentative specification provided in the correspondence dated May 25, 2004.

The finished product specification has been revised to include the requirement for dissolution testing of every batch with tentative acceptance criteria of not less than —% (Q) of label claim in 30 minutes. Please see Attachment 2 for the revised finished product specification.

European Pharmacopoeia pharmaceutical technical procedure 2.9.25 is the basis for the dissolution method and is provided in Attachment 3. The Fertin Pharma method for operation of the customized dissolution apparatus, analysis of the samples, and calculation of the results may be found in Attachment 4. The method has been validated. Please see Attachment 5 for the validation report.

Please note that these documents were thoroughly reviewed during the inspection of the Fertin Pharma laboratory facilities, and the FDA chemist was provided with a demonstration of the customized dissolution apparatus by one of the operators.

Additional Information on Dissolution Testing

Ten batches of drug product (six biostudy batches and four additional batches) were evaluated for the effects of time, temperature, and humidity on dissolution test results. Based on data from these stability studies (Attachment 6), it can be concluded that there is no correlation between the drug release profile and stability storage conditions. Therefore, we believe that it is not necessary to add the requirement for dissolution testing to the stability specification.

Justification for the inclusion of dissolution testing only on the finished product specification is as follows:

1. The European Pharmacopoeia procedure is not sufficiently discriminatory to detect minor variations in drug release of Nicotine Polacrilex Gum USP when samples are analyzed in the stability program.
2. There are no USP monographs which require use of a "chewing machine" as a dissolution apparatus. Also, a "chewing machine" is not included in the general chapter for dissolution (USP <711>).
3. Dissolution is not a required test for Nicotine Polacrilex Gum USP.
4. Dissolution using the "chewing machine" is labor intensive and does not provide useful data.

Furthermore, *in vitro* release testing of medicated gum is a fairly new standard method in the European Pharmacopoeia; therefore, no calibrator is available. There are no accepted protocols to handle potential situations where gum may adhere to the apparatus jaws during dissolution. Current dissolution protocols allow tolerances to handle physical phenomena which may affect dissolution, e.g., the use of wire to prevent the sticking of a caplet to the bottom of a vessel, the use of enzymes to prevent cross-linking, etc.

Additional Information on Blend Uniformity

In addition to the initial deficiency response regarding blend uniformity, and in order to assist the foreign inspection team in understanding the manufacturing process, two documents were prepared by Fertin Pharma. Please see Attachment 7 for a report summarizing the justification for omission of blend uniformity testing. Please see Attachment 8 for a simplified description of the manufacturing process accompanied by color photos.

Additional Revised Documentation

The manufacturing summary submitted in Section 11 of the original submission has been revised and is included in Attachment 9.
The revisions are as follows:

- ———————————————————
  The affected page of the manufacturing order was submitted in the January 2004 amendment.
- In-process testing for ———————————————————
  ———————— A report for the justification for the establishment of weight limits may be found in Attachment 10. The revised manufacturing order will be submitted in the first annual report.
- Because bulk stability data are not yet available, product will be packaged immediately following completion of the manufacturing process, until such time that bulk stability data are available. Data will be submitted in the first annual report.

The analytical method for nicotine content in the drug product has been revised to ———————— and therefore improve efficiency. The revised method, HPLC 52, *Nicotine in Medical Chewing Gum*, may be found in Attachment 11. A report on the optimization of the method is included in Attachment 12.

The analytical method for ——— content in the drug substance has been revised based on comments received from the FDA chemist. The revised method, RA HPLC 01, *Quantitative Determination of*——————————— and a summary of changes may be found in Attachment 13.

The specification for Sorbitol NF was revised in order to comply with current compendial requirements that were effective on April 1, 2004, and is included in Attachment 14.

If you have any questions, please contact me immediately at (269) 686-1920 or via facsimile at (269) 673-7655.

In accordance with 21 CFR 314.94(d)(5), L. Perrigo Company certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Detroit District Office.

Respectfully submitted,

Mary E Short

Mary E. Short, RAC
Project Manager
ANDA Regulatory Affairs

PERRIGO®

August 13, 2004

TELEPHONE AMENDMENT

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

ORIG AMENDMENT

N/AM

Via facsimile and Federal Express

Re: ANDA 76-789
Nicotine Polacrilex Gum USP, 4 mg (Regular)

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 76-789 for Nicotine Polacrilex Gum USP, 4 mg (Regular), filed on June 30, 2003. Further reference is made to the chemistry amendments submitted on January 20, 2004; March 16, 2004; May 20, 2004; and June 28, 2004.

L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address deficiencies received from the Division of Chemistry on July 28, 2004, during a teleconference with Thomas Hinchliffe, Project Manager, and David Skanchy, Chemistry Reviewer. This communication is classified as a TELEPHONE AMENDMENT.

Deficiency 1

Submit blend uniformity data from at least one validation batch and provide a postapproval commitment to submit additional data.

Response to Deficiency 1

Process validation is currently being conducted in the new Fertin Pharma manufacturing facility according to the plan as outlined in the amendment to this ANDA dated January 20, 2004.

For the first process validation batch, acceptance criteria for blend uniformity were met and data are presented in Attachment 1.

Perrigo hereby commits to submit blend uniformity data from additional process validation batches in the first annual report.

Deficiency 2

Tighten the limit for total impurities from —% to —%.

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Response to Deficiency 2

We have reviewed the test data for all test batches of the drug product and have confirmed that the proposed limit will be acceptable.

Finished product specification (revised) may be found in Attachment 2. Stability specification (revised) may be found in Attachment 3.

Deficiency 3

Add the test for *in vitro* drug release to the stability specification.

Response to Deficiency 3

The test for *in vitro* drug release has been added to the stability specification at the end of shelf life only, as agreed during the July 28, 2004, teleconference. Please refer to Attachment 3 for the revised stability specification.

Deficiency 4

Provide a postapproval commitment to submit stability data for the bulk storage container.

Response to Deficiency 4

Perrigo hereby commits to submit stability data in the first annual report for drug product stored in the bulk storage container.

Additional Information

All available room temperature stability data are included in Attachment 4.

If you have any questions or require additional information, please contact me immediately at (269) 686-1920 or via facsimile at (269) 673-7655.

In accordance with 21 CFR 314.94(d)(5), L. Perrigo Company certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Detroit District Office.

Respectfully submitted,

Mary E Short

Mary E. Short, RAC
Project Manager
ANDA Regulatory Affairs

PERRIGO®

August 17, 2004

LABELING
AMENDMENT

ORIG AMENDMENT
N/AF

Gary Buehler, Director
Office of Generic Drugs
CDER/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Via Federal Express

Re: ANDA 76-789
Nicotine Polacrilex Gum USP, 4 mg (Regular)

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 76-789 for Nicotine Polacrilex Gum USP, 4 mg (Regular), filed on June 30, 2003. L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address labeling deficiencies received on July 8, 2004, from the Division of Labeling and Program Support (Attachment 1).

GENERAL COMMENT

Labeling Deficiency 1

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.

You should submit a detail 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.

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

- Provisions for child-resistant packaging. We acknowledge that you already have this element in place.

Response to Labeling Deficiency 1

A detailed Marketing and Surveillance Plan may be found in Attachment 2.

BLISTER

Labeling Deficiency 2

Please include "nicotine" in parenthesis after the strength: e.g.

Nicotine Polacrilex Gum USP, 2mg (nicotine)
or
Nicotine Polacrilex Gum USP, 4mg (nicotine)

Response to Labeling Deficiency 2

Labeling has been revised as instructed.

Final printed labeling is included in Attachment 3.

CARTON

Labeling Deficiency 3a

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

Labeling Deficiency 3b

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.

Labeling Deficiency 3c

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).

Response to Labeling Deficiencies 3a, 3b, and 3c

Labeling has been revised as instructed due to recent revisions in the labeling of the reference listed drug, Nicorette® Gum, approved on June 18, 2004.

Final printed labeling is included in Attachment 4.

USER'S GUIDE

Labeling Deficiency 4a

How To Reduce Your Nicotine Polacrilex Gum Usage

First paragraph, second sentence, revise to read: " ...will help you reduce your nicotine craving gradually as you reduce and then stop your use of nicotine polacrilex gum".

First paragraph, last sentence, revise to read; "Here are some tips to help you cut back during each step and then stop using nicotine polacrilex gum:"

Labeling Deficiency 4b

How To Reduce Your Nicotine Polacrilex Gum Usage, 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."

Labeling Deficiency 4c

STOP USING NICOTINE POLACRILEX GUM AT THE END OF WEEK 12, revise this section 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

Response to Labeling Deficiencies 4a, 4b, and 4c

Labeling has been revised as instructed due to recent revisions in the labeling of the reference listed drug, Nicorette® Gum, approved on June 18, 2004.

Final printed labeling is included in Attachment 5.

AUDIOTAPE SCRIPT

Labeling Deficiency 5

Side A, How to Use Nicotine Polacrilex Gum
Page 4 out of 10, Leader, 11th paragraph, revise to read:
". . .that's weeks 10 through 12--you should be able to get along... "

Response to Labeling Deficiency 5

Labeling has been revised as instructed.

Final printed labeling is included in Attachment 6.

Statement of labeling similarity may be found in Attachment 7. Side-by-side comparison of labeling (current submission vs. previous submission) may be found in Attachment 8.

If you have any questions or require additional information, please contact me immediately at (269) 686-1920.

Respectfully submitted,

Mary E Short

Mary E. Short, RAC
Project Manager
ANDA Regulatory Affairs