CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 79-038

Name: Nicotine Polacrilex Gum USP, 4 mg (base) (Coated, Fruit)

Sponsor: Watson Laboratories, Inc.

Approval Date: July 8, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-038

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-038

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 79-038

Watson Laboratories, Inc.
Attention: Aibin You
Manager, Regulatory Affairs
P.O. Box 30
33 Ralph Avenue
Copiague, NY 11726-0030

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated June 1, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Nicotine Polacrilex Gum USP, 4 mg (base) (Coated, Fruit).

Reference is also made to your amendments dated September 19, November 16, and December 17, 2007; April 9, May 2, May 9, June 25, July 3, August 11, August 14, and September 19, 2008; and January 16, May 22, June 10, July 1, and July 2, 2009.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for over-the-counter (OTC) use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Nicotine Polacrilex Gum USP, 4 mg (base) (Coated, Fruit) to be therapeutically equivalent to the reference listed drug, Nicorette Gum, 4 mg (base) (Coated, Fruit Chill), of GlaxoSmithKline. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

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

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

Robert L. West
7/8/2009 11:05:41 AM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-038

LABELING

Watson Blister Back

Nicotine Polacrilex Gum USP, 4 mg (nicotine) COATED FRUIT 1 piece Manufactured by: Watson Laboratories, Inc. Copiague, NY 11726 LOT # EXP	**Nicotine Polacrilex Gum USP, 4 mg** (nicotine) COATED FRUIT 1 piece Manufactured by: Watson Laboratories, Inc. Copiague, NY 11726 LOT # EXP	**Nicotine Polacrilex Gum USP, 4 mg** (nicotine) COATED FRUIT 1 piece Manufactured by: Watson Laboratories, Inc. Copiague, NY 11726 LOT # EXP	**Nicotine Polacrilex Gum USP, 4 mg** (nicotine) COATED FRUIT 1 piece Manufactured by: Watson Laboratories, Inc. Copiague, NY 11726 LOT # EXP	**Nicotine Polacrilex Gum USP, 4 mg** (nicotine) COATED FRUIT 1 piece Manufactured by: Watson Laboratories, Inc. Copiague, NY 11726 LOT # EXP

Keep out of reach of children

Nicotine Polacrilex Gum USP, 4 mg (nicotine) COATED FRUIT 1 piece Manufactured by: Watson Laboratories, Inc. Copiague, NY 11726 LOT # EXP	**Nicotine Polacrilex Gum USP, 4 mg** (nicotine) COATED FRUIT 1 piece Manufactured by: Watson Laboratories, Inc. Copiague, NY 11726 LOT # EXP	**Nicotine Polacrilex Gum USP, 4 mg** (nicotine) COATED FRUIT 1 piece Manufactured by: Watson Laboratories, Inc. Copiague, NY 11726 LOT # EXP	**Nicotine Polacrilex Gum USP, 4 mg** (nicotine) COATED FRUIT 1 piece Manufactured by: Watson Laboratories, Inc. Copiague, NY 11726 LOT # EXP	**Nicotine Polacrilex Gum USP, 4 mg** (nicotine) COATED FRUIT 1 piece Manufactured by: Watson Laboratories, Inc. Copiague, NY 11726 LOT # EXP

Varnish Omit

Theft surveillance tag area

C41MC0457-0.0 gdfng57

Drug Facts (continued)

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 your first cigarette more than 30 minutes after waking up,** use 2 mg nicotine gum
- **If you smoke your first cigarette within 30 minutes of waking up,** use 4 mg nicotine gum according to the following 12 week schedule:

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

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

Other information

- **each piece contains:** calcium 115 mg, sodium 8 mg
- store at 20 - 25˚C (68 - 77˚F) • protect from light

Inactive ingredients acacia, acesulfame potassium, carnauba wax, D&C yellow #10 lake, FD&C blue #2 lake, FD&C red #40, FD&C yellow #6 lake, flavors, gum base, magnesium oxide, sodium bicarbonate, sodium carbonate, sucralose, talc, titanium dioxide and xylitol.

This product is not affiliated with GlaxoSmithKline Consumer Healthcare, L.P.

14147-01 R1 5/09

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■ 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.

Blister packaged for your protection.
Do not use if individual seals are open or torn.

Push gum through foil.

Peel off backing starting at corner with loose edge.

To remove the gum, tear off single unit.

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 **full** 12 weeks.
3. **Use Long Enough** – Use Nicotine Polacrilex Gum for the **full** 12 weeks.
4. **Use with a support program** as directed in the enclosed User's Guide.

Drug Facts (continued)

Questions or comments?
Call 1-877-440-7867 8 AM-8 PM EST, Monday-Friday

Manufactured by
Watson Laboratories, Inc.
Copiague, NY 11726
For Rugby Laboratories, Inc.
Duluth, GA 30097

Made in the USA

Rugby®
NDC 0536-3387-37

COMPARE TO THE ACTIVE INGREDIENT IN NICORETTE® FRUIT CHILL™ COATED GUM*

SUGAR FREE
NICOTINE Polacrilex GUM
USP, 4 mg (nicotine)

4 mg
COATED FRUIT

STOP SMOKING AID

FREE AUDIO CD Upon Request. See Inside.

FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE WITHIN 30 MINUTES OF WAKING UP.
If you smoke your first cigarette MORE THAN 30 MINUTES after waking up, use Nicotine Polacrilex Gum USP, 2 mg

40 coated chewing pieces

*Nicorette® is a registered trademark of GlaxoSmithKline Consumer Healthcare, L.P.

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 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

TO INCREASE YOUR SUCCESS IN QUITTING:

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

To remove the gum, tear off single unit.

Peel off backing starting at corner with loose edge.

Push gum through foil.

NDC 0536-3387-01

Rugby®

COMPARE TO THE ACTIVE INGREDIENT IN NICORETTE® FRUIT CHILL™ COATED GUM*

SUGAR FREE

NICOTINE Polacrilex GUM

USP, 4 mg (nicotine)

STOP SMOKING AID

4 mg

FREE AUDIO CD Upon Request. See Inside.

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

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

100 coated chewing pieces

COATED FRUIT

*Nicorette® is a registered trademark of GlaxoSmithKline Consumer Healthcare, L.P.

Rugby®

SUGAR FREE

NICOTINE Polacrilex GUM USP, 4 mg (nicotine)

4 mg

STOP SMOKING AID

100 coated chewing pieces

Varnish Omit

Blister packaged for your protection. **Do not use if individual seals are open or torn.**

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

SUGAR FREE

NICOTINE Polacrilex GUM

USP, 4 mg (nicotine)

STOP SMOKING AID

100 coated chewing pieces

Theft surveillance tag area

1414G-01 R1 5/09

This product is not affiliated with GlaxoSmithKline Consumer Healthcare, L.P.
Manufactured by Watson Laboratories, Inc., Copiague, NY 11726
For Rugby Laboratories, Inc., Duluth, GA 30097

Made in the USA

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 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.

Drug Facts (continued)

Directions

- **If you are under 18 years of age, ask a doctor before use**
- before using this product, read the enclosed Users Guide for complete directions and other important information
- stop smoking completely when you begin using the gum
- **If you smoke your first cigarette more than 30 minutes after waking up,** use 2 mg nicotine gum
- **If you smoke your first cigarette within 30 minutes of waking up,** use 4 mg nicotine gum according to the following 12 week schedule:

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

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

Other information

- **each piece contains:** calcium 115 mg, sodium 8 mg
- store at 20 - 25°C (68 - 77°F) • protect from light

Inactive ingredients

acacia, acesulfame potassium, carnauba wax, D&C yellow #10 lake, FD&C blue #2 lake, FD&C red #40, FD&C yellow #6 lake, flavors, gum base, magnesium oxide, sodium bicarbonate, sodium carbonate, sucralose, talc, titanium dioxide and xylitol.

Questions or comments?

Call 1-877-440-7867 8 AM-8 PM EST, Monday-Friday

Watson User's Guide

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

Nicotine Polacrilex Gum Usage Instructions

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 ***"HOW TO REDUCE YOUR NICOTINE POLACRILEX GUM USAGE."***)
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 Heading **"WHERE TO GET HELP."**)
5. If you have trouble using **Nicotine Polacrilex Gum**, ask your doctor or pharmacist or call Watson at 1-877-440-7867 weekdays (8 AM-8 PM EST).
6. To request a free audio CD containing tips to help make quitting easier, call the toll free number listed above. (ONE CD PER CUSTOMER)

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** (pronounced "nik-ah-teen poh-lah-cry'-lex 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** included on the top of the page 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** included on the top of the page 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

- a sodium-restricted diet.
- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes.

Ask a doctor or pharmacist before use if you are

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

Stop use and ask a doctor if

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

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

LET'S GET STARTED.

Becoming a non-smoker starts today. First, check that you bought the right starting dose. **If you smoke your first cigarette within 30 minutes of waking up,** use 4 mg nicotine gum. **If you smoke your first cigarette more than 30 minutes after waking up,** use 2 mg nicotine gum. Next, read through the entire User's Guide carefully. Then, set your personalized quitting schedule. Take out a calendar that you can use to track your progress, and identify four dates, using the stickers attached to this User's Guide:

STEP 1. (Weeks 1 to 6). Your quit date (and the day you'll start using Nicotine Polacrilex Gum). Choose your quit date (it should be soon). This is the day you will quit smoking cigarettes entirely and begin using **Nicotine Polacrilex Gum** to satisfy your cravings for nicotine. For the first six weeks, you'll use a piece of **Nicotine Polacrilex Gum** every hour or two. Be sure to follow the directions. (See Heading **"HOW TO USE NICOTINE POLACRILEX GUM"**.) 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 to 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's sugar-free chewing pieces provide nicotine to your system - they work as a temporary aid to help you quit smoking by reducing nicotine withdrawal symptoms. **Nicotine Polacrilex Gum** provides a lower level of nicotine to your blood than cigarettes, and allows you to gradually do away with your body's need for nicotine.

Because **Nicotine Polacrilex Gum** does not contain the tar or carbon monoxide of cigarette smoke, it does not have the same health dangers as tobacco. However, it still delivers nicotine, the addictive part of cigarette smoke. Nicotine can cause side effects such as headache, nausea, upset stomach, and dizziness.

HOW TO USE NICOTINE POLACRILEX GUM.

If you are under 18 years of age, ask a doctor before use. Before you can use **Nicotine Polacrilex Gum** correctly, you have to practice! That sounds silly, but it isn't. **Nicotine Polacrilex Gum isn't like ordinary chewing gum.** It's a medicine, and must be chewed a certain way to work right. Chewed like ordinary gum, **Nicotine Polacrilex Gum** won't work well and can cause side effects. An overdose can occur if you chew more than one piece of **Nicotine Polacrilex Gum** at the same time, or if you chew many pieces one after another. Read all the following instructions before using **Nicotine Polacrilex Gum**. Refer to them often to make sure you're using **Nicotine Polacrilex Gum** correctly. If you chew too fast, or do not chew correctly, you may get hiccups, heartburn, or other stomach problems. Don't eat or drink for 15 minutes before using **Nicotine Polacrilex Gum,** or while chewing a piece. The effectiveness of **Nicotine Polacrilex Gum** may be reduced by some foods and drinks, such as coffee, juices, wine or soft drinks.

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

The following chart 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.		

To improve your chances of quitting, use at least 9 pieces of **Nicotine Polacrilex Gum** a day. If you experience strong or frequent cravings you may use a second piece within the hour. However, do not continuously use one piece after another, since this may cause you hiccups, heartburn, nausea or other side effects.

HOW TO REDUCE YOUR NICOTINE POLACRILEX GUM USAGE.

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

Watson User's Guide

- After a while, start chewing each **Nicotine Polacrilex Gum** piece for only 10 to 15 minutes, instead of half an hour. Then, gradually begin to reduce the number of pieces used.
- Or, try chewing each piece for longer than half an hour, but reduce the number of pieces you use each day.
- Substitute ordinary chewing gum for some of the **Nicotine Polacrilex Gum** pieces you would normally use. Increase the number of pieces of ordinary gum as you cut back on the **Nicotine Polacrilex Gum** pieces.
- Check how well you've reduced your daily usage of **Nicotine Polacrilex Gum** in weeks 10 to 12. You should only be using about 3 to 5 pieces a day. Get ready to stop.

STOP USING NICOTINE POLACRILEX GUM AT THE END OF WEEK 12.

The following tips may help you with stopping **Nicotine Polacrilex Gum** at the end of 12 weeks.

- Set a stop date.
- Use the same number of pieces of confectionery gum or mints as you were using **Nicotine Polacrilex Gum** per day. At the times when you have an urge to use **Nicotine Polacrilex Gum**, use a strong flavored gum or mint such as cinnamon or peppermint.
- Reduce the number of pieces of gum or mints you use by one piece per day until you do not need to use any gum or mints.

Talk to your doctor if you:

- Still feel the need to use **Nicotine Polacrilex Gum** at the end of week 12.
- Start using **Nicotine Polacrilex Gum** again after stopping.
- Start smoking again.

TIPS TO MAKE QUITTING EASIER.

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

On Your Quit Date:

- Ask your family, friends and co-workers to support you in your efforts to stop smoking.
- Throw away all your cigarettes, matches, lighters, ashtrays, etc.
- Keep busy on your quit day. Exercise. Go to a movie. Take a walk. Get together with friends.
- Figure out how much money you'll save by not smoking. Most ex-smokers can save more than $1,000 a year.
- Write down what you will do with the money you save.
- Know your high risk situations and plan ahead how you will deal with them.
- Keep **Nicotine Polacrilex Gum** near your bed, so you'll be prepared for any nicotine cravings when you wake up in the morning.
- Visit your dentist and have your teeth cleaned to get rid of the tobacco stains.

Right after Quitting:

- During the first few days after you've stopped smoking, spend as much time as possible at places where smoking is not allowed.
- Drink large quantities of water and fruit juices.
- Try to avoid alcohol, coffee and other beverages you associate with smoking.
- Remember that temporary urges to smoke will pass, even if you don't smoke a cigarette.
- Keep your hands busy with something like a pencil or a paper clip.
- Find other activities which help you relax without cigarettes.
- Swim, jog, take a walk, play basketball.
- Don't worry too much about gaining weight. Watch what you eat, take time for daily exercise, and change your eating habits if you need to.
- Laughter helps. Watch or read something funny.

WHAT TO EXPECT.

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

After a Week or Two.

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

After a Month.

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

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

What to do About Relapse.

What should you do if you slip and start smoking again? The answer is simple. A lapse of one or two or even a few cigarettes has not spoiled your efforts! Discard your cigarettes, forgive yourself and try again.

If you start smoking again, keep your box of **Nicotine Polacrilex Gum** for your next quit attempt.

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

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

WHEN THE STRUGGLE IS OVER.

Once you've stopped smoking, take a second and pat yourself on 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 new life as a non-smoker.

QUESTIONS & ANSWERS.

1. ***How will I feel when I stop smoking and start using Nicotine Polacrilex Gum?***

You'll need to prepare yourself for some nicotine withdrawal symptoms. These begin almost immediately after you stop smoking, and are usually at their worst during the first three 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 Heading **"SOME IMPORTANT WARNINGS"**). 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 12 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 1 piece every 1 to 2 hours	**weeks 7 to 9** 1 piece every 2 to 4 hours	**weeks 10 to 12** 1 piece every 4 to 8 hours

Watson Laboratories, Inc. 13841-03 R3 5/09

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Watson User's Guide Spanish

Goma de mascar con nicotina polacrilex USP, 2 mg y 4 mg (nicotina)

Goma de mascar con nicotina polacrilex
Instrucciones de uso

CÓMO USAR LA GOMA DE MASCAR CON NICOTINA POLACRILEX PARA AYUDARLE A DEJAR DE FUMAR

- **PROHIBIDA la venta a menores de 18 años.**
- **Se requiere prueba de edad.**
- **Prohibida la venta en máquinas expendedoras o en cualquier fuente donde no pueda verificarse la prueba de edad.**

CLAVES PARA EL ÉXITO.

1. Para que la **Goma de mascar con nicotina polacrilex** le ayude, usted debe realmente desear dejar de fumar.
2. Puede aumentar en gran medida sus probabilidades de éxito usando, por lo menos 9 a 12 gomas de mascar por día cuando comience a usar la **Goma de mascar con nicotina polacrilex**. (Consulte ***"CÓMO REDUCIR EL USO DE LA GOMA DE MASCAR CON NICOTINA POLACRILEX"***).
3. Debe continuar usando la **Goma de mascar con nicotina polacrilex** durante 12 semanas completas, tal como se explica en esta Guía del Usuario.
4. **La Goma de mascar con nicotina polacrilex** funciona mejor cuando se la usa junto con un programa de apoyo. (Consulte la sección **"DÓNDE OBTENER AYUDA"**).
5. Si tiene problemas con el uso de la **Goma de mascar con nicotina polacrilex**, consulte a su médico o farmacéutico, o comuníquese con Watson, llamando al 1-877-440-7867 los días de semana (de 8 a. m. a 8 p. m., hora estándar del Este).
6. Para pedir un CD de audio gratuito con consejos para que dejar de fumar sea más fácil, llame al número gratuito mencionado más abajo. (UN CD POR CLIENTE).

FINALMENTE SE DECIDIÓ A DEJAR DE FUMAR.

¡Felicitaciones!
Su decisión de dejar de fumar es una decisión importante. Es por eso que ha tomado la decisión correcta al elegir la **Goma de mascar con nicotina polacrilex**.

Sus propias probabilidades de dejar de fumar dependen de cuánto desea dejar de fumar, qué grado de adicción al tabaco tiene y en qué medida cumple con un programa para dejar de fumar similar al que se incluye con la **Goma de mascar con nicotina polacrilex**.

¡DEJAR DE FUMAR ES DIFÍCIL!

Si ha intentado dejar de fumar antes y no lo ha logrado, ¡no se desanime! Dejar de fumar no es fácil. Lleva tiempo, y la mayoría de las personas hacen algunos intentos antes de lograrlo. Lo importante es intentarlo nuevamente hasta lograrlo. Esta Guía del usuario le brindará apoyo mientras usted se convierte en no fumador. Aquí encontrará respuestas a preguntas comunes acerca de la **Goma de mascar con nicotina polacrilex** y le dará consejos para ayudarle a dejar de fumar; por lo tanto, deberá consultarla a menudo.

DÓNDE OBTENER AYUDA.

Tiene más probabilidades de dejar de fumar si usa la **Goma de mascar con nicotina polacrilex** junto con un programa de apoyo que le ayude a dejar el hábito de fumar. Es posible que en su área existan grupos de apoyo para personas que intentan dejar de fumar. Para obtener más información, llame a su oficina local de la Asociación Americana del Pulmón (American Lung Association), la Sociedad Americana del Cáncer (American Cancer Society) o la Asociación Americana del Corazón (American Heart Association). Los números gratuitos están impresos en la **Tarjeta tamaño billetera** incluida en la parte superior de esta Guía del Usuario.

Si nota que no puede dejar de fumar o si comienza a fumar nuevamente después de usar la **Goma de mascar con nicotina polacrilex**, recuerde que no se deja esta adicción de la noche a la mañana. Quizás desee hablar con un profesional de cuidados de la salud que pueda ayudarle a mejorar sus probabilidades de dejar de fumar la próxima vez que lo intente con la **Goma de mascar con nicotina polacrilex** o con otro método.

ORGANICÉMONOS.

Es posible que su razón para dejar de fumar sea una combinación de preocupaciones acerca de la salud, el efecto que pueda causar el cigarrillo en su aspecto físico y la presión por parte de su familia y amigos para que deje de fumar. O bien, quizás está preocupado acerca del efecto peligroso del humo de segunda mano en sus seres queridos.

Todas estas son buenas razones. Probablemente, usted tenga otras. Decida cuáles son sus razones más importantes y anótelas en la **Tarjeta tamaño billetera** incluida en la parte superior de esta Guía del Usuario. Lleve esta tarjeta con usted. En los momentos difíciles, cuando desee fumar, la tarjeta le recordará por qué está intentando dejar de fumar.

LO QUE DEBERÁ ENFRENTAR.

El cigarrillo es adictivo de dos maneras. Su necesidad de nicotina se ha vuelto una necesidad tanto física como mental. Para dejar de fumar, debe superar ambas adicciones. Entonces, mientras la **Goma de mascar con nicotina polacrilex** reducirá la adicción física del cuerpo a la nicotina, usted debe desear dejar de fumar para superar la dependencia mental al cigarrillo. Una vez que haya tomado la decisión de dejar de fumar, es hora de comenzar. Pero primero, hay algunas advertencias importantes que debe tener en cuenta.

ALGUNAS ADVERTENCIAS IMPORTANTES.

Este producto es únicamente para las personas que desean dejar de fumar.

Si está embarazada o amamantando, use este medicamento únicamente si se lo indica un proveedor de cuidados de la salud. El cigarrillo puede perjudicar seriamente a su hijo. Intente dejar de fumar sin usar ningún medicamento de reemplazo de la nicotina. Se cree que este medicamento es más seguro que fumar. No obstante, se desconocen todos los riesgos de este medicamento para su hijo.

No use el producto si:

- sigue fumando, mastica tabaco, usa rapé, o usa un parche de nicotina u otros productos que contengan nicotina.

Consulte a un médico antes de usar este producto si:

- Realiza una dieta restringida en sodio.
- Tiene una enfermedad cardíaca, tuvo un ataque cardíaco reciente o tiene latidos cardíacos irregulares. La nicotina puede aumentar su frecuencia cardíaca.
- Tiene presión arterial alta no controlada con medicamentos. La nicotina puede aumentar su presión arterial.
- Tiene una úlcera estomacal o diabetes.

Consulte a un médico o farmacéutico antes de usar el producto si está:

- usando un fármaco sin nicotina para dejar de fumar.
- tomando un medicamento con receta para la depresión o el asma. Es posible que deba ajustarse la dosis de su receta.

Deje de usar el producto y consulte a su médico si tiene:

- problemas en la boca, los dientes o la mandíbula.
- tiene latidos cardíacos irregulares o palpitaciones.
- síntomas de sobredosis de nicotina, como náuseas, vómitos, mareos, diarrea, debilidad y latidos cardíacos rápidos.

Mantenga el producto fuera del alcance de los niños y las mascotas. Las gomas de mascar con nicotina pueden tener suficiente nicotina como para ser perjudiciales para los niños y las mascotas. Envuelva las gomas de mascar usadas en papel y arrójelas a la basura. En caso de sobredosis, obtenga ayuda médica de inmediato o comuníquese con un Centro de Control de Intoxicaciones.

EMPECEMOS.

Comience hoy mismo a convertirse en no fumador. Primero, verifique que haya comprado la dosis inicial correcta. **Si fuma su primer cigarrillo en el término de los 30 minutos de haberse levantado,** use goma de mascar con nicotina de 4 mg. **Si fuma su primer cigarrillo después de más de 30 minutos de haberse levantado,** use goma de mascar con nicotina de 2 mg. Luego, lea atentamente la Guía del Usuario completa. A continuación, establezca su cronograma personalizado para dejar de fumar. Tenga a mano un calendario que pueda usar para hacer un seguimiento de sus avances e identifique cuatro fechas usando las etiquetas adhesivas proporcionadas con esta Guía del Usuario:

PASO 1. (Semanas 1 a 6). La fecha en la que dejará de fumar (y el día en que comenzará a usar la Goma de mascar con nicotina polacrilex). Elija la fecha en la que dejará de fumar (debe ser pronto). Este es el día en que dejará de fumar cigarrillos por completo y comenzará a usar la **Goma de mascar con nicotina polacrilex** para satisfacer sus ansias de consumir nicotina. Durante las primeras seis semanas, usará una **Goma de mascar con nicotina polacrilex** cada una o dos horas. Asegúrese de seguir las instrucciones. (Consulte la sección **"CÓMO USAR LA GOMA DE MASCAR CON NICOTINA POLACRILEX"**). Coloque la etiqueta adhesiva correspondiente al Paso 1 en esta fecha.

PASO 2. (Semanas 7 a 9). El día en que comenzará a reducir su uso de la Goma de mascar con nicotina polacrilex. Al cabo de seis semanas, comenzará gradualmente a reducir su uso de la **Goma de mascar con nicotina polacrilex** a una goma de mascar cada dos a cuatro horas. Coloque la etiqueta adhesiva correspondiente al Paso 2 en esta fecha (el primer día de la semana siete).

PASO 3. (Semanas 10 a 12). El día en que reducirá aún más su uso de la Goma de mascar con nicotina polacrilex. Nueve semanas después de comenzar a usar la **Goma de mascar con nicotina polacrilex**, reducirá aún más su ingesta de nicotina usando una goma de mascar cada cuatro a ocho horas. Coloque la etiqueta adhesiva correspondiente al Paso 3 en esta fecha (el primer día de la semana diez). Durante las próximas tres semanas, usará una **Goma de mascar con nicotina polacrilex** cada cuatro a ocho horas.

Fin del tratamiento: el día en que completará la terapia con Goma de mascar con nicotina polacrilex. La **Goma de mascar con nicotina polacrilex** no debe usarse durante más de doce semanas. Identifique la fecha trece semanas después de la fecha que eligió en el Paso 1 y coloque la etiqueta adhesiva que dice "EX FUMADOR" en su calendario.

ANTICÍPESE.

Debido a que fumar es una adicción, no es fácil dejar de fumar. Incluso después de haber dejado los cigarrillos, sentirá un fuerte impulso de fumar. Anticípese AHORA a esos momentos, para no ser derrotado en un momento de debilidad. Estos consejos pueden ayudarle:

- Tenga a la mano los números de teléfono de amigos y familiares que le brindan apoyo.
- Mantenga un registro de su proceso para dejar de fumar. Haga un seguimiento de la cantidad de **Gomas de mascar con nicotina polacrilex** que usa por día y si siente ansias de consumir cigarrillos. En caso de una recaída, deje de fumar inmediatamente y retome el programa de **Goma de mascar con nicotina polacrilex** para intentar dejar de fumar.
- Arme un kit de emergencia que incluya elementos que le ayuden a alejar su mente de los impulsos ocasionales de fumar. Incluya goma de mascar con sabor a canela o caramelos de limón para tener en la boca, una cinta de casete relajante y algo para jugar con sus manos, como una piedra suave, una banda elástica o pelotitas metálicas.
- Resérvese algunas pequeñas recompensas, como una revista nueva o un certificado de regalo de su tienda favorita, que se dará a usted mismo después de superar los obstáculos difíciles.
- Piense ahora en esos momentos en los que siente más ganas de consumir un cigarrillo y luego planifique qué otra cosa puede hacer en lugar de fumar. Por ejemplo, puede planificar una pausa para tomar un café en un lugar nuevo o salir a caminar inmediatamente después de la cena, de modo tal de evitar la tentación de fumar.

CÓMO ACTÚA LA GOMA DE MASCAR CON NICOTINA POLACRILEX.

La **Goma de mascar con nicotina polacrilex** sin azúcar le proporciona nicotina a su sistema: actúa como una ayuda temporal para ayudarle a dejar de fumar reduciendo los síntomas de abstinencia de la nicotina. La **Goma de mascar con nicotina polacrilex** proporciona a la sangre un nivel de nicotina inferior que los cigarrillos y le permite deshacerse gradualmente de la necesidad del cuerpo de consumir nicotina.

Debido a que la **Goma de mascar con nicotina polacrilex** no contiene ni el alquitrán ni el monóxido de carbono del humo del cigarrillo, no representa el mismo riesgo para la salud que el tabaco. Sin embargo, de todos modos proporciona nicotina, la parte adictiva del humo del cigarrillo. La nicotina puede provocar efectos secundarios tales como dolor de cabeza, náuseas, malestar estomacal y mareos.

CÓMO USAR LA GOMA DE MASCAR CON NICOTINA POLACRILEX.

Si es menor de 18 años, consulte a un médico antes de usar este producto. Antes de que pueda usar la **Goma de mascar con nicotina polacrilex** en forma correcta, ¡tiene que practicar! Puede parecerle una tontería, pero no lo es. La **Goma de mascar con nicotina polacrilex no es una goma de mascar común.** Es un medicamento, y debe masticarse de una manera determinada para que funcione correctamente. Si se la mastica como una goma de mascar común, la **Goma de mascar con nicotina polacrilex** no funcionará bien y puede provocar efectos secundarios. Puede producirse una sobredosis si mastica más de una **Goma de mascar con nicotina polacrilex** al mismo tiempo o si mastica muchas gomas de mascar una después de otra. Lea las siguientes instrucciones antes de usar la **Goma de mascar con nicotina polacrilex**. Consúltelas a menudo para asegurarse de estar usando la **Goma de mascar con nicotina polacrilex** correctamente. Si mastica demasiado rápido, o no mastica correctamente, puede provocar hipo, acidez estomacal u otros problemas estomacales. No coma ni beba nada durante 15 minutos antes de usar la **Goma de mascar con nicotina polacrilex** ni mientras la mastica. La efectividad de la **Goma de mascar con nicotina polacrilex** puede verse reducida debido a determinados alimentos y bebidas, tales como café, jugos, vino o refrescos.

1. Deje de fumar por completo antes de comenzar a usar la **Goma de mascar con nicotina polacrilex**.
2. Para reducir las ansias y otros síntomas de abstinencia, use la **Goma de mascar con nicotina polacrilex** de acuerdo con el cronograma de dosis. **(Consulte el Cronograma de uso recomendado.)**
3. Mastique cada **Goma de mascar con nicotina polacrilex** muy lentamente varias veces.
4. Deje de masticar cuando note un sabor picante o un pequeño cosquilleo en la boca. (Esto generalmente sucede después de masticar 15 veces, aunque puede variar de una persona a otra).
5. COLOQUE la **Goma de mascar con nicotina polacrilex** entre la mejilla y las encías y déjela allí.
6. Una vez que el sabor picante o el cosquilleo hayan prácticamente desaparecido (al cabo de alrededor de un minuto), comience nuevamente a masticar un poco más lentamente. Cuando vuelva a sentir el sabor o el cosquilleo, deje de masticar nuevamente.
7. Coloque la **Goma de mascar con nicotina polacrilex** nuevamente entre la mejilla y las encías (en otro lugar de la boca).
8. Repita los Pasos 3 a 7 (masticar, masticar, colocar entre la mejilla y las encías) hasta que desaparezca la mayor parte de la nicotina de la **Goma de mascar con nicotina polacrilex** (esto generalmente sucede al cabo de alrededor de una hora; no volverá a sentir el sabor picante ni el cosquilleo).
9. Envuelva en un papel la **Goma de mascar con nicotina polacrilex** usada y arrójela a la basura.

Watson User's Guide Spanish

El cuadro que aparece a continuación incluye el cronograma de uso recomendado de la Goma de mascar con nicotina polacrilex:

Semanas 1 a 6	Semanas 7 a 9	Semanas 10 a 12
1 goma de mascar cada 1 a 2 horas	1 goma de mascar cada 2 a 4 horas	1 goma de mascar cada 4 a 8 horas
NO USE MÁS DE 24 GOMAS DE MASCAR POR DÍA.		

Para mejorar sus probabilidades de dejar de fumar, use, al menos, 9 **Gomas de mascar con nicotina polacrilex** por día. Si siente ansias fuertes o frecuentes, puede usar una segunda goma de mascar en el término de 1 hora. Sin embargo, no debe usar continuamente una goma de mascar después de otra, dado que esto puede provocar hipo, acidez estomacal, náuseas u otros efectos secundarios.

CÓMO REDUCIR SU USO DE LA GOMA DE MASCAR CON NICOTINA POLACRILEX.

Al usar la **Goma de mascar con nicotina polacrilex**, la meta es reducir lentamente su dependencia de la nicotina. El cronograma de uso de la **Goma de mascar con nicotina polacrilex** le ayudará a reducir gradualmente sus ansias de consumir nicotina a medida que usted reduce el uso de la goma de mascar con nicotina polacrilex y luego deja de usarla. A continuación se incluyen algunos consejos para ayudarle a reducir en cada paso el uso de la **Goma de mascar con nicotina polacrilex** y luego dejar de usarla.

- Después de un tiempo, comience a masticar cada **Goma de mascar con nicotina polacrilex** solamente durante 10 a 15 minutos, en lugar de media hora. Luego, comience gradualmente a reducir la cantidad de gomas de mascar que usa.
- O, intente masticar cada goma de mascar durante más de media hora, pero reduzca la cantidad de gomas de mascar que usa por día.
- Sustituya algunas de las **Goma de mascar con nicotina polacrilex** que usaría normalmente por goma de mascar común. Aumente la cantidad de gomas de mascar comunes mientras reduce la cantidad de **Gomas de mascar con nicotina polacrilex**.
- Verifique cuán bien ha reducido su uso diario de **Gomas de mascar con nicotina polacrilex** en las semanas 10 a 12. Sólo deberá usar alrededor de 3 a 5 gomas de mascar por día. Prepárese para dejar de usar el producto.

DEJE DE USAR LA GOMA DE MASCAR CON NICOTINA POLACRILEX AL FINAL DE LA SEMANA 12.

Los siguientes consejos pueden ayudarle a dejar de usar la **Goma de mascar con nicotina polacrilex** al final de la semana 12.

- Establezca una fecha para dejar de usar el producto.
- Use la misma cantidad de gomas de mascar dulces o mentas que las **Gomas de mascar con nicotina polacrilex** que usaba cada día.
- Cuando sienta ganas de usar las **Goma de mascar con nicotina polacrilex**, use una goma de mascar o una menta con sabor fuerte, como canela o menta piperita.
- Reduzca la cantidad de gomas de mascar o mentas que usa a una por día hasta que ya no necesite más usar gomas de mascar o mentas.

Hable con su médico si:

- Aún siente la necesidad de usar la **Goma de mascar con nicotina polacrilex** al final de la semana 12.
- Comienza a usar la **Goma de mascar con nicotina polacrilex** nuevamente después haber dejado de usarla.
- Comienza a fumar nuevamente.

CONSEJOS PARA QUE DEJAR DE FUMAR SEA MÁS FÁCIL.

Dentro de las primeras semanas de haber dejado de fumar, es posible que se sienta tentado a fumar por placer, especialmente después de realizar una tarea difícil o en una fiesta o un bar. A continuación, se incluyen algunos consejos para ayudarle a superar las primeras etapas importantes del proceso de convertirse en no fumador.

La fecha en la que dejará de fumar:

- Pídale a su familia, amigos y compañeros de trabajo que apoyen sus esfuerzos para dejar de fumar.
- Arroje a la basura todos sus cigarrillos, cerillas, encendedores, ceniceros, etc.
- Manténgase ocupado el día en que dejará de fumar. Haga ejercicio. Vaya al cine. Salga a caminar. Reúnase con amigos.
- Calcule cuánto dinero ahorrará al dejar de fumar. La mayoría de los ex fumadores pueden ahorrar más de $1,000 por año.
- Anote lo que hará con el dinero que ahorre.
- Conozca sus situaciones de alto riesgo y anticipe cómo las enfrentará.
- Tenga **Goma de mascar con nicotina polacrilex** cerca de su cama, de modo tal de estar preparado ante cualquier ansia de consumir nicotina cuando se despierta por la mañana.
- Visite a su dentista y hágase una limpieza dental para quitar las manchas de tabaco.

Immediatamente después de dejar de fumar:

- Durante los primeros días después de dejar de fumar, pase todo el tiempo posible en lugares en los que no esté permitido fumar.
- Beba abundante cantidad de agua y jugos de frutas.
- Trate de evitar beber alcohol, café y otras bebidas que asocie con el hábito de fumar.
- Recuerde que los impulsos temporales de fumar cesarán, incluso si no fuma un cigarrillo.
- Mantenga las manos ocupadas con algo, como un lápiz o un sujetapapeles. Busque otras actividades que le ayuden a relajarse sin el cigarrillo.
- Nade, trote, salga a caminar, juegue al basquetbol.
- No se preocupe demasiado si aumenta de peso. Controle lo que come, tómese el tiempo para hacer ejercicio diariamente y cambie sus hábitos alimenticios, si es necesario.
- Reírse ayuda. Vea o lea algo divertido.

QUÉ DEBE ESPERAR.

Su cuerpo ahora está comenzando a recobrar el equilibrio. Durante los primeros días después de dejar de fumar, es posible que se sienta tenso y nervioso y que tenga dificultades para concentrarse. Es posible que experimente dolores de cabeza, se sienta mareado y algo decaído, se sienta sudoroso o tenga malestar estomacal. Incluso, es posible que al principio tenga dificultades para dormir. Estos son síntomas típicos de abstinencia que desaparecerán con el tiempo. Su tos de fumador empeorará antes de mejorar. Pero no se preocupe, es un buen signo. La tos ayuda a despejar los depósitos de alquitrán de los pulmones.

Después de una o dos semanas.

A esta altura, seguramente se sentirá más seguro de poder manejar esos impulsos de fumar. Muchos de sus síntomas de abstinencia han desaparecido a esta altura, y seguramente notará algunos signos positivos: tose menos, respira mejor y tiene un mejor sentido del gusto y del olfato, para citar algunos.

Después de un mes.

Probablemente ahora sienta con menor frecuencia el impulso de fumar. Sin embargo, los impulsos aún pueden presentarse y cuando se presentan, es probable que sean fuertes y que aparezcan sin motivo alguno. No permita que lo sorprendan con la guardia baja. Anticípese a estos momentos difíciles.

Concéntrese en las razones por las que los no fumadores son más atractivos que los fumadores. Es menos probable que se les arrugue la piel. Sus dientes son más blancos y limpios. Su aliento es más fresco. Su cabello y ropa huelen mejor. Esa tos que parece hacer que incluso una risa suene más como un traqueteo pertenece al pasado. Sus hijos y otras personas que les rodean están más saludables también.

Qué hacer en caso de una recaída.

¿Qué debe hacer si recae y comienza nuevamente a fumar? La respuesta es simple. ¡Un desliz de uno o dos, o incluso varios cigarrillos, no han arruinado sus esfuerzos! Deseche sus cigarrillos, perdónese e inténtelo otra vez.

Si comienza a fumar nuevamente, conserve su caja de **Goma de mascar con nicotina polacrilex** para su próximo intento de dejar de fumar.

Si ha comenzado a fumar en forma regular nuevamente, no se desanime. Las investigaciones indican que lo mejor que puede hacer es intentarlo nuevamente. Lo importante es que aprenda de su último intento.

- Acepte que ha tenido una recaída, pero no se considere un fracasado.
- Intente identificar el "factor desencadenante" que hizo que tuviera una recaída y prepare un plan mejor para enfrentar este problema la próxima vez.
- Hable positivamente con usted mismo: dígase que ha aprendido algo a partir de esta experiencia.
- Asegúrese de haber usado correctamente la **Goma de mascar con nicotina polacrilex**, durante todo el período de 12 semanas para reducir sus ansias de consumir nicotina.
- Recuerde que con la práctica se obtienen buenos resultados y dejar de fumar no es la excepción.

CUANDO FINALIZA LA LUCHA.

Una vez que haya dejado de fumar, tómese un segundo y felicítese. Ahora, hágalo nuevamente. Se lo merece.

Recuerde ahora por qué decidió dejar de fumar en primer lugar. Revise su lista de razones. Léalas nuevamente. Y sonría.

Ahora, piense en todo el dinero que está ahorrando y lo que hará con él. Todos los lugares para no fumadores a los que puede ir y lo que puede hacer allí. Todos los años que posiblemente haya sumado a su vida y lo que hará con ellos. Recuerde que es posible que la tentación no haya desaparecido para siempre. Sin embargo, la parte más difícil quedó atrás; entonces, mire hacia adelante con una actitud positiva y disfrute de su nueva vida como no fumador.

PREGUNTAS Y RESPUESTAS.

1. ***¿Cómo me sentiré cuando deje de fumar y comience a usar la Goma de mascar con nicotina polacrilex?***

Deberá prepararse para experimentar algunos síntomas de abstinencia de la nicotina. Estos comienzan prácticamente apenas deja de fumar y, por lo general, son más intensos durante los primeros tres o cuatro días. Comprenda que es posible que experimente cualquiera de los siguientes síntomas:

- ansias de consumir cigarrillos;
- ansiedad, irritabilidad, intranquilidad, cambios en el estado de ánimo, nerviosismo;
- somnolencia;
- dificultad para concentrarse;
- aumento del apetito y de peso;
- dolores de cabeza, dolor muscular, constipación, fatiga.

La **Goma de mascar con nicotina polacrilex** puede ayudarle a aliviar los síntomas de abstinencia tales como irritabilidad y nerviosismo, así como las ansias de consumir nicotina que usted solía calmar fumando un cigarrillo.

2. ***La Goma de mascar con nicotina polacrilex, ¿simplemente sustituye una forma de nicotina por otra?***

Es cierto que la Goma de mascar con nicotina polacrilex contiene nicotina. El objetivo de la **Goma de mascar con nicotina polacrilex** es proporcionarle suficiente nicotina para ayudarle a controlar los síntomas de abstinencia físicos, de manera tal que usted pueda enfrentar los aspectos mentales relacionados con el hecho de dejar de fumar. Durante el programa de 12 semanas, usted reducirá gradualmente su ingesta de nicotina cambiando a una menor cantidad de gomas de mascar por día. Recuerde, no use las **Gomas de mascar con nicotina polacrilex** junto con parches de nicotina ni otros productos que contengan nicotina.

3. ***¿Puede perjudicarme el uso de Goma de mascar con nicotina polacrilex?***

Para la mayoría de los adultos, la cantidad de nicotina presente en la goma de mascar es menor que la que tiene el cigarrillo. Algunas personas serán susceptibles incluso a esta cantidad de nicotina y no deben usar este producto sin el asesoramiento de su médico (Consulte la sección **"ALGUNAS ADVERTENCIAS IMPORTANTES"**). Dado que la **Goma de mascar con nicotina polacrilex** es un producto basado en la goma de mascar, masticarlo puede producir el aflojamiento de las obturaciones dentarias y agravar otros problemas bucales, dentales y mandibulares. La **Goma de mascar con nicotina polacrilex** también puede provocar hipo, acidez estomacal y otros problemas estomacales, especialmente si se la mastica demasiado rápido o si no se la mastica correctamente.

4. ***¿Aumentaré de peso?***

Muchas personas tienden a aumentar algunas libras durante las primeras 8 a 10 semanas después de dejar de fumar. Este es un pequeño precio que deben pagar a cambio de los grandes logros que obtendrán para su salud y atractivo en general. Si continúa aumentado de peso después de los primeros dos meses, intente analizar qué es lo que está haciendo de manera diferente. Reduzca su ingesta de grasa, elija refrigerios saludables y aumente su actividad física para quemar las calorías adicionales.

5. ***¿Es la Goma de mascar con nicotina polacrilex más costosa que fumar?***

El costo total de la **Goma de mascar con nicotina** polacrilex durante el programa de 12 semanas es prácticamente equivalente a lo que gastaría en cigarrillos una persona que fuma un paquete y medio de cigarrillos por día durante el mismo período. Por otra parte, el uso de la **Goma de mascar con nicotina polacrilex** es sólo un costo a corto plazo, mientras que el costo de fumar es un costo a largo plazo, debido a los problemas de salud que provoca el hábito de fumar.

6. ***¿Qué hago si tengo una recaída?***

Deseche sus cigarrillos, perdónese y vuelva a encaminarse. No se considere un fracaso ni se castigue. De hecho, las personas que han intentado dejar de fumar anteriormente tienen más probabilidades de lograrlo la próxima vez. **¡MUCHA SUERTE!**

Cronograma de dosis recomendado para el uso de la Goma de mascar con nicotina polacrilex:

PASO 1	PASO 2	PASO 3
semanas 1 a 6 1 goma de mascar cada 1 a 2 horas	**semanas 7 a 9** 1 goma de mascar cada 2 a 4 horas	**semanas 10 a 12** 1 goma de mascar cada 4 a 8 horas

Watson Stickers

Watson User's Guide

WALLET CARD • TARJETA TAMAÑO BILLETERA

My most important reasons to quit smoking are:
Mis razones más importantes para dejar de fumar son:

_____

_____

_____

_____

_____

_____

Please be sure to keep this card with you.
Asegúrese de llevar con usted esta tarjeta.

WHERE TO CALL FOR HELP:
(DÓNDE LLAMAR PARA OBTENER AYUDA:)

American Heart Association **(1-800-242-8721)**
(Asociación Americana del Corazón)

American Lung Association **(1-800-586-4872)**
(Asociación Americana del Pulmón)

(American Cancer Society **(1-800-227-2345)**
(Sociedad Americana del Cáncer)

Watson Laboratories, Inc.

ATTACHMENT 3

CD Script (English and Spanish Versions)

English Version

Nicotine Polacrilex Gum CD

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 CD are designed to help make it as easy as possible to break the habit. But keep in mind that this program won't work unless you'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 man. 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.

OW: 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. Dinesh'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.

OW: 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?

OM: 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?

OM: 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.

YM: 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?

OW: 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?

OM: 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, sir?

YM: My cousin is visiting this weekend. I figure I'll be so busy showing him around, I won't have time to think about wanting to smoke! And if I am tempted to slip, he 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.

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

LEADER: Right. Now, we have to learn how to use Nicotine Polacrilex Gum.

OW: 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.

OM: 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!

OW: 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.

YW: 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 to12. 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.

OM: 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 that you feel comfortable with. Then, for the last three weeks --that's weeks 10 through 12 --you should be able to get along with a piece every 4 to 8 hours. At the end of the 12 weeks you shouldn't need Nicotine Polacrilex Gum any longer.

YM: 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.

YM: Gee, all I have to do is use Nicotine Polacrilex Gum the right way and I can kick my smoking habit?

YW: 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).

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

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

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

DINESH: 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, sir.

YM: 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 aftershave, 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.

DINESH: 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.

DINESH: 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.

OM: 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.

OW: Yeah, well my husband is the one who started bugging me. He 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!

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

OW: 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 girlfriends hang out there. They all smoke so it's going to be tough for me not to.

DINESH: 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 <u>don't</u> 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.

OW: How do I do that?

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

OW: Yeah, Mary. She used to smoke more than anybody there. But I guess she got worried about her health, so she quit. I think she joined some kind of group. She didn't show up at Neary's for a couple of weeks, but she's back to being a regular.

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

OW: Yeah, I guess that might work.

DINESH: 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.

OW: 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?

DINESH: 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.

OM: 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.

DINESH: An excellent thought.

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

DINESH: 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.

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

DINESH: 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.

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

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

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

DINESH: 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 man, you will assist me demonstrating.

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

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

YM: Like this?

DINESH: 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?

YM: Pretty good.

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

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

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

YM: *(Breathes).*

DINESH: How does that feel?

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

DINESH: 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.

YM: Like walking on the beach?

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

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

DINESH: 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.)

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

OM: Me, too.

DINESH: 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.

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

DINESH: 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.)

13655-12 R3 9/05

Spanish Version

Following this page, 1 page withheld in full - (b)(4)

PAGE 1

Goma de mascar con nicotina polacrilex
Ayuda para dejar de fumar

Disco compacto

Watson Laboratories, Inc.
13655-12 R3 9/05

CÓMO USAR LA GOMA DE MASCAR CON NICOTINA POLACRILEX PARA AYUDARLE A DEJAR DE FUMAR

PROHIBIDA la venta a menores de 18 años.
Se requiere prueba de edad.
Prohibida la venta en máquinas expendedoras o en cualquier fuente donde no pueda verificarse la prueba de edad.

PAGE 2

Goma de mascar con nicotina polacrilex USP,
2 mg y 4 mg (nicotina)

AYUDA PARA DEJAR DE FUMAR

DISCO COMPACTO
Instrucciones para el uso de la Goma de mascar con nicotina polacrilex

CÓMO USAR LA GOMA DE MASCAR CON NICOTINA POLACRILEX PARA AYUDARLE A DEJAR DE FUMAR
PROHIBIDA la venta a menores de 18 años.
Se requiere prueba de edad.
Prohibida la venta en máquinas expendedoras o en cualquier fuente donde no pueda verificarse la prueba de edad.

Watson Laboratories, Inc. 13655-12 R3 9/05

CD de la Goma de mascar con nicotina polacrilex

SFX: Sound of various voices from happy crowd.

ANNCR: ¡Felicitaciones por su decisión de convertirse en no fumador! Esta es una de las decisiones más importantes que tomará en su vida. Y una de las mejores.

(VOICES: "¡Sí! ¡Es cierto! ¡Bien hecho!")

La Guía del usuario de la Goma de mascar con nicotina polacrilex y este CD están diseñados para ayudarle a que dejar el hábito de fumar sea lo más fácil posible. Pero tenga en cuenta que este programa no funcionará a menos que usted esté realmente comprometido a convertirse en no fumador. Quizás usted ya lo intentó y no lo logró. Si así fue, no se sienta desanimado. Recuerde que muchas personas lo intentan varias veces antes de lograrlo. En esta oportunidad, la Goma de mascar con nicotina polacrilex le ayudará a aliviar los síntomas físicos que sentirá al dejar de fumar, a fin de que esté mejor preparado para manejar el aspecto mental.

(VOICE: "¡Sí, usted puede hacerlo!")

Si bien la Goma de mascar con nicotina polacrilex es fácil de usar, no se la usa como las gomas de mascar comunes. ¡Es un medicamento en serio! Como cualquier medicamento, debe usarlo únicamente según las instrucciones. Más adelante, nos referiremos a las instrucciones, pero también es necesario que sepa que hay algunas personas que no deben usar la Goma de mascar con nicotina polacrilex ni ningún producto que contenga nicotina sin antes consultar a su médico. Por ejemplo, las mujeres que están embarazadas o amamantando.

Las personas que tengan antecedentes de problemas del corazón, presión arterial alta que no se pueda controlar con medicamentos, que tomen insulina para la diabetes o que tengan una úlcera estomacal deberán primero obtener asesoramiento médico. Dejar de fumar también puede afectar la manera en que el cuerpo reacciona frente a algunos otros medicamentos que quizás esté tomando para el asma o la depresión; por lo tanto, verifique con su médico si algunos de estos es su caso.

Asegúrese de leer la Guía del usuario que se incluye en este kit para obtener otra información importante acerca del uso de la Goma de mascar con nicotina polacrilex.

Si bien la Goma de mascar con nicotina polacrilex contiene nicotina, no contiene ninguna de las miles de sustancias químicas nocivas presentes en el humo del cigarrillo. Y está diseñada para alejarlo de la nicotina para siempre.

Support group. Adults. Group leader is authoritative but pleasant man. 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: Muy bien, hagamos silencio ahora, estamos listos para comenzar. Este grupo de apoyo se trata de cómo usar la Goma de mascar con nicotina polacrilex para ayudarles a dejar de fumar.

OW: ¿Pero quién necesita un grupo de apoyo? Es una goma de mascar. Se mastica. En ese caso, también deberíamos tomar una clase sobre cómo respirar.

LEADER: Cómo respirar es el grupo del Sr. Dinesh, al final del corredor. Estarán en ese grupo más adelante. Pero este grupo está primero porque la Goma de mascar con nicotina polacrilex no es una goma de mascar común. Hay que usarla correctamente o no funcionará de la manera que se supone que debe hacerlo.

OW: ¡Eh!, masticar goma de mascar es cosa de niños.

LEADER: Pero masticar la Goma de mascar con nicotina polacrilex no lo es. Es únicamente para las personas que tienen, al menos, 18 años y que realmente desean dejar de fumar. Las personas más jóvenes deben hablar antes con un médico.

Bien, entonces comencemos. Antes que nada, ¿alguien leyó la Guía del usuario de la Goma de mascar con nicotina polacrilex?

OM: Sí, yo la leí. No me llevó mucho tiempo, y me aclaró mucho todo el proceso para dejar de fumar.

LEADER: Exacto. No hay nada misterioso ni complicado acerca de este proceso. Hay una manera correcta de hacerlo, y la única manera de asegurarse de que logrará los resultados deseados es usar la Goma de mascar con nicotina polacrilex de la manera que se supone se debe usar.

Ahora, ¿quién recuerda la primera instrucción de todas?

OM: Comprar la Goma de mascar con nicotina polacrilex.

LEADER: En realidad, hay un paso anterior. Antes de usar la Goma de mascar con nicotina polalicrex, deben dejar de fumar, y por completo. Esto es importante. Y no deben masticar tabaco ni tampoco usar rapé o parches de nicotina.

Comienzan a usar la Goma de mascar con nicotina polacrilex el mismo día en que dejan de fumar y, en ningún momento, fuman y usan la Goma de mascar con nicotina

polacrilex a la vez. Esto podría provocarles una sobredosis de nicotina, que es algo bastante fuerte. Los resultados pueden hacer que se sienta mal.

YM: Lo sé. A veces, si fumo dos o tres cigarrillos seguidos, por ejemplo, cuando estoy nervioso, me mareo.

LEADER: Seguro. Entonces, la siguiente pregunta es: ¿cuándo dejarán de fumar? ¿Ya todos han escogido una Fecha en la que dejarán de fumar?

OW: Yo lo hice. Debo asistir a un seminario el lunes en un edificio en el que no está permitido fumar. Creo que si la Goma de mascar con nicotina polacrilex me ayuda a superar el primer día, será más fácil a partir de entonces.

LEADER: No es una mala idea. Sólo debe tener cuidado porque cuando salga de ese edificio, sentirá un fuerte deseo de fumar y debe estar preparada para enfrentarlo. La Guía del usuario de la Goma de mascar con nicotina polacrilex incluye una lista de consejos para manejar esas tentaciones. ¿Alguien más?

OM: Eh, voy a dejar de fumar lo antes posible. Después de tomar las clases de hoy voy a dejar de fumar. Ya marqué el día de mañana en mi calendario.

LEADER: Muy bien. Elijan una fecha y cumplan con ella. ¿Y usted señor?

YM: Mi primo vendrá a visitarme durante el fin de semana. ¡Creo que estaré tan ocupado llevándolo a todas partes que no tendré tiempo para pensar en tener ganas de fumar! Y si estoy tentado a hacerlo, puede convencerme para que no lo haga.

LEADER: En realidad, es una buena idea tener a alguien que les dé apoyo cuando lo necesiten. Un amigo o un familiar, incluso un compañero de trabajo, pueden brindarle apoyo moral. Varias organizaciones nacionales ofrecen grupos de apoyo como este; hay una lista de sus números de teléfono gratuitos en la contratapa de la Guía del usuario de Goma de mascar con nicotina polacrilex.

YW: Entonces, el primer paso es elegir una fecha en la que dejarán de fumar y marcarla en nuestro calendario.

LEADER: Exacto. Ahora bien, debemos aprender a usar la Goma de mascar con nicotina polacrilex.

OW: ¿Cuál es el problema con esto?

LEADER: Bueno, como dije anteriormente, la Goma de mascar con nicotina polacrilex no es una goma de mascar común, por lo tanto, no se la debe masticar de la manera en que uno está acostumbrado a hacerlo. La principal diferencia es que contiene nicotina, que se libera al masticarla. La idea es masticarla de modo tal que libere la nicotina gradualmente: ni demasiado rápido, ni demasiado lento.

OM: Ah, sí, ya sé, estaba en el libro. Hay que masticar hasta que uno tenga una sensación de cosquilleo en la boca. Luego hay que colocarla entre la mejilla y las encías y la sensación de cosquilleo desaparece. Hay que mantenerla allí hasta dejar de sentir el cosquilleo.

LEADER: Nuevamente, correcto. Primero, la mastica; y después la coloca entre la mejilla y las encías. Luego la mastica; y después la coloca entre la mejilla y las encías. Deben hacerlo hasta que el gusto picante desaparezca. Hay que masticarla alrededor de 15 veces para que comience el cosquilleo, y tarda aproximadamente un minuto en desaparecer. Entonces, el método es masticar, colocar entre la mejilla y las encías, masticar, colocar entre la mejilla y las encías. Repitamos todos juntos.

CLASS: (not quite together): masticar, colocar entre la mejilla y las encías, masticar, colocar entre la mejilla y las encías, masticar, colocar entre la mejilla y las encías....

LEADER: Bastante bien, pero hagámoslo todos juntos un poco mejor. Una vez más: a la una, a las dos y a las...

CLASS (in unison): masticar, colocar entre la mejilla y las encías, masticar, colocar entre la mejilla y las encías, masticar, colocar entre la mejilla y las encías, masticar....

LEADER: Muy bien, ¡estuvo fantástico!

OW: Entonces, ¿cuándo usamos este producto? ¿Después de las comidas? ¿Cuándo?

LEADER: La cantidad recomendada es una goma de mascar cada una o dos horas mientras se está despierto durante las primeras seis semanas. Esto es entre 8 y 16 gomas de mascar por día. Tendrán la mayor probabilidad de no consumir cigarrillos si usan, por lo menos, 9 gomas de mascar por día. Si experimentan ansias de fumar fuertes o frecuentes, pueden usar una segunda goma de mascar dentro de la hora. Sin embargo, no usen continuamente una goma de mascar después de otra, ya que esto puede provocarles hipo, acidez estomacal, náuseas y otros efectos secundarios.

YW: ¿Es decir, que si comienzo con 16 gomas de mascar por día, debo usar 16 gomas de mascar por día durante seis semanas?

LEADER: No. La idea es reducir gradualmente la necesidad del cuerpo de consumir nicotina. Por lo tanto, si comienzan con 16 gomas de mascar por día, traten de reducir la cantidad a 14 gomas de mascar después de la primera semana. Después de la siguiente semana, quizás puedan reducir la cantidad a 12. Sería ideal que pudieran llegar a entre 8 y 10 gomas de mascar por día al final de las primeras seis semanas.

OM: Ahora, bien. El libro dice que hay que usar una goma de mascar cada dos a cuatro horas durante las semanas siete a nueve. Además, el libro incluye etiquetas para marcar

ahora en el calendario la semana siete, de manera tal que recordemos cuándo comenzar a reducir la cantidad de goma de mascar que usamos.

LEADER: Así es. Nuevamente, la idea es comenzar con la dosis recomendada y reducirla gradualmente, a un ritmo con el que se sientan cómodos. Luego, durante las últimas tres semanas, esto sería de la semana 10 a la 12, deberían poder manejarse con una goma de mascar cada 4 a 8 horas. Al final de las 12 semanas, no deberían sentir más la necesidad de consumir la Goma de mascar con nicotina polacrilex.

YM: Parece bastante fácil. ¿Hay algo más que debamos saber?

LEADER: Sí, si hay niños o mascotas en su hogar, asegúrense de descartar en forma segura las Gomas de mascar con nicotina polacrilex usadas. Envuelvan las gomas de mascar usadas en papel y arrójenlas a la basura. Quedará algo de nicotina en las gomas de mascar usadas, lo suficiente para ser perjudiciales para los niños o los animales pequeños.

Además, algunos alimentos y bebidas pueden hacer que la Goma de mascar con nicotina polacrilex sea menos efectiva, por lo tanto, no deben comer ni beber nada durante 15 minutos antes de usar una goma de mascar. Y no deben beber nada mientras mastiquen. Si lo hacen, la Goma de mascar con nicotina polacrilex no funcionará bien.

YM: Increíble, ¿todo lo que debo hacer es usar la Goma de mascar con nicotina polacrilex de la manera correcta y podré deshacerme de mi hábito de fumar?

YW: Debe haber algo más que eso.

LEADER: En realidad, sí. Si bien la Goma de mascar con nicotina polacrilex ayuda con el aspecto físico de la adicción a los cigarrillos, no puede manejar el aspecto mental. Para muchas personas, la adicción mental es la parte más difícil de combatir.

Pero no entren en pánico, porque muchas personas lo intentan varias veces antes de lograrlo. Y existen algunas técnicas bastante efectivas para manejar la adicción mental y aumentar su fuerza de voluntad.

Y ese es tema de su próximo grupo de apoyo, al final del corredor. De hecho, está a punto de comenzar. ¡Mucha suerte para todos!

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

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

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

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

DINESH: Buenas tardes. Veo que están todos algo callados. Eso se debe a la música. Es cierto que la música tranquila favorece un estado mental tranquilo y relajado. (Music down and out). Una de las cosas que podrán advertir a medida que avancen con el programa para terminar con su hábito de fumar es que la relajación es importante para aliviar el estrés mental que posiblemente sientan.

Pero antes de que se relajen demasiado, me gustaría que cada uno de ustedes me diga cuál es la razón más importante que tienen para dejar de fumar. Comencemos por usted, señor.

YM: Eh, bueno, creo que deseo dejar de fumar porque no quiero oler a cigarrillo todo el tiempo. Me pongo esta loción para después de afeitar costosa pero aún así huelo a cigarrillo. En este momento no huelo a cigarrillo porque no he fumado durante un par de horas mientras estoy aquí en la clase.

DINESH: Las cosas tendrán un mejor olor para usted después de haber dejado de fumar por un tiempo. Las cosas tendrán un mejor olor y sabor. Pero, probablemente esta no es su razón más importante para dejar de fumar.

YM: Oh, no, fundamentalmente deseo dejar de fumar porque creo que será mucho mejor para mi salud. En este momento hago ejercicio o juego un poco al basquetbol y me agito con bastante facilidad.

DINESH: Esa es la mejor razón de todas. Todos han leído muchos informes que relacionan al hábito de fumar con algunas enfermedades y problemas de salud graves. Apenas dejan de fumar, su riesgo de contraer estas enfermedades comienza a disminuir.

OM: También dejo de fumar por mi salud. Pero además, tengo a mi sobrina y sus dos hijos que viven conmigo y no creo que vivir en una casa de fumador sea bueno para ellos. Entonces, creo que lo estoy haciendo por todos nosotros.

OW: Sí, mi marido es el que empezó a insistirme. Me hace salir al porche trasero cada vez que deseo fumar, y eso no es divertido cuando hay mal tiempo. Así que estoy tratando de dejar de fumar. Es decir, sé que dejar de fumar será bueno para mí si puedo lograrlo. Y sé que me hará ahorrar algo de dinero. Además, ¡es posible que incluso encuentre un poco de paz y tranquilidad!

DINESH: ¡Excelente! Las razones que todos ustedes han dado son muy importantes. Es bueno repasarlas en su mente cuando sientan la necesidad de fumar. Tengan presente todas las razones por las que decidieron dejar de fumar. Incluso puede anotarlas y leerlas todos los días. De hecho, incluso hay una tarjeta tamaño billetera en su Guía del usuario con espacio para que haga justamente esto. Cuando necesite ayuda para superar el impulso, puede sacarla y leer lo que anotó.

OW: Sé que voy a tener un problema. Paso mucho tiempo en Neary's, eh, un bar de mi vecindario, porque mis amigas suelen ir allí. Todas fuman, por lo que va a ser difícil para mí no hacerlo.

DINESH: Sí, ya lo creo. Quizás deba optar por no ir a Neary's durante una semana o más. Pero no pierda esto de vista: usted desea dejar de fumar, no desea cambiar de estilo de vida. De modo tal que tarde o temprano regresará a Neary's. Cuando lo haga, debe hacerlo dentro de un marco mental que le permita resistir la tentación que la rodeará.

OW: ¿Cómo lo hago?

DINESH: Veamos si podemos encontrar una respuesta. ¿Tiene en Neary's alguna amiga que haya dejado de fumar?

OW: Sí, Mary. Solía fumar más que cualquiera allí. Pero creo que se preocupó por su salud y entonces dejó de fumar. Creo que se unió a algún tipo de grupo. No apareció por Neary's durante un par de semanas, pero ahora comenzó nuevamente a ser una cliente habitual.

DINESH: Allí tiene su respuesta. Su amiga Mary se unió a un grupo de apoyo de personas que atravesaban las mismas dificultades que ella. Y evitó ir a Neary's durante un tiempo porque sabía que la tentación de fumar iba a ser imposible de resistir. Sin embargo, al cabo de un tiempo, conquistó su adicción lo suficiente como para regresar y encontrarse con sus amigas.

OW: Sí, creo que eso puede funcionar.

DINESH: Recuerden que las primeras semanas son las más difíciles, y es en ese momento cuando deben evitar la tentación, si es posible. Después de ese período, el aspecto mental de su dependencia del cigarrillo comenzará a estar bajo control, y podrán retomar algunas de las actividades que quizás abandonaron durante un tiempo. Pronto, podrán sentirse orgullosos de su capacidad de sentirse cómodos en situaciones en las que otras personas están fumando.

OW: Entonces, ¿cuando me sienta preparada para regresar a Neary's debo hacerlo decidida a no fumar, y debo tener presente todo el tiempo mis razones para no hacerlo?

DINESH: Exactamente. Si ustedes dicen a sus amigos que están dejando de fumar, probablemente estarán contentos de ayudarle a mantener su decisión, si consideran que ustedes son honestos.

OM: Creo que encontraré mucho apoyo con sólo mirar a los niños. Si recuerdo que lo estoy haciendo por ellos, será más fácil que si solamente lo estuviera haciendo por mí.

DINESH: Una excelente manera de pensar.

YM: En mi caso, creo que es más bien un hábito que cualquier otra cosa. Con frecuencia, advierto que estoy fumando y ni siquiera recuerdo en qué momento busqué el cigarrillo y lo encendí.

DINESH: Eso les sucede a la mayoría de los fumadores. Si no hay cigarrillos a su alcance, no podrán fumar automáticamente sin pensarlo. Es por eso que la mayoría de las personas que desean dejar de fumar arrojan a la basura sus cigarrillos, encendedores y ceniceros.

YM: Bueno, en realidad, me gusta fumar. Supongo que me da placer, aunque haga que mi ropa tenga olor.

DINESH: Ese es el principal obstáculo que hay que superar. Los fumadores sienten placer al fumar. No al fumar cada cigarrillo, ya que muchos de ellos sólo son parte del hábito. Aunque ese primer cigarrillo de la mañana es placentero. Y un cigarrillo con el café o después de una comida es placentero para muchas personas. Quizás la mejor manera de enfrentar esto es encontrar un placer sustituto que funcione para ti. Busca alguna actividad que sea placentera y que no se lleve bien con el hábito de fumar.

YW: Yo fumo cuando me pongo nerviosa. ¿Hay algo que pueda hacer para esto?

DINESH: Sí, existen técnicas que puedes usar para que te ayuden a relajarte. Por ejemplo, la respiración.

STUDENTS: ¿Cómo? ¿Qué? Eh, lo hago todo el tiempo.

DINESH: Sabía que esto les sorprendería. No hablo de la respiración común, el tipo de respiración que hacemos inconscientemente. Hablo de la respiración profunda y relajante, el tipo de respiración en la que uno concentra toda su atención. Quizás, joven, puedas ayudarme a demostrarlo.

YM: Pero no sé nada de eso.

DINESH: No importa. Es realmente muy sencillo. Lo primero que hay que hacer es sentarse derecho, pero sin tensionarse.

YM: ¿Así?

DINESH: Sí, pero debes relajarte. Intenta dejar que los brazos cuelguen relajadamente. Sacúdelos un poco para relajar los músculos. Asegúrate de que los músculos de las piernas y de la espalda también estén relajados. Mueve la cabeza en círculos un poco para relajar el cuello. ¿Cómo se siente?

YM: Bastante bien.

DINESH: Bien. Ahora, exhala y luego inspira lentamente tan profundo como puedas.

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

DINESH: Ahora, mantén la respiración durante unos segundos. Luego exhala lentamente. Espera un segundo y vuelve a inspirar profundamente.

YM: *(Breathes).*

DINESH: ¿Cómo se siente?

YM: Impresionante, nunca pensé que podría sentirme así sólo por respirar.

DINESH: Es increíble, ¿no? Ahora, para asegurar que esa respiración profunda realmente te relaje, cierra los ojos e imagina un lugar que te parezca muy placentero y reconfortante.

YM: ¿Como caminar en la playa?

DINESH: Si ese lugar te hace sentir bien, sí.

YW: Pensaré en eso. Salvo que me gusta caminar en el bosque.

DINESH: Ahora, intentémoslo todos. Siéntense derechos pero relajados. Inspiren lenta y profundamente y piensen en algo que los tranquilice.

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

OW: Hombre, nunca pensé que podría sentir tanto placer sólo por respirar.

OM: Yo tampoco.

DINESH: Esa es una de las claves para ayudarles a resistir la tentación de fumar en esos momentos críticos. Busquen algo para hacer que ocupe la mente y el cuerpo por completo. Esto puede ayudarles a no pensar en fumar. Su rutina puede ser tan simple como este ejercicio de respiración, pero lo importante es encontrar alguna actividad fácil de hacer que sea la correcta para ustedes.

YW: Eso es genial. ¿Hay algo más para ayudarnos a resistir la tentación?

DINESH: Fundamentalmente, cualquier cosa que les ayude a relajarse. Como dije al comienzo de la clase, la música reconfortante y tranquila es una buena ayuda para relajarse. Si están en su hogar y sienten la necesidad de fumar, intenten poner algo de música suave. Siéntense en una silla cómoda, relajen los músculos, respiren profundamente y déjense flotar.

Están comenzando un proceso que no será fácil. Sin embargo, si usan la Goma de mascar con nicotina polacrilex correctamente, tal como se explica en la Guía del usuario, y si recuerdan estos consejos para ayudarles a superar los obstáculos mentales, podrán aumentar en gran medida sus probabilidades de éxito.

Ahora, vamos a dedicar el resto del tiempo a practicar la relajación muscular y la respiración profunda, y a pensar en imágenes mentales tranquilas y reconfortantes. Pónganse cómodos; pondré algo de música para ayudarles a eliminar de sus mentes cualquier pensamiento relacionado con fumar. Estoy seguro de que lo disfrutarán.

(Music up. Plays to end.)

13655-12 R3 9/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-038

LABELING REVIEWS

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

ANDA Numbers: 79-216 (Cinnamon,Coated,2 mg)
79-044 (Fruit, Coated,2 mg)
79-219(Cinnamon, Coated,4 mg)
79-038 (Fruit, Coated,4 mg)

Date of Submissions: June 1, June 5, September 4 and 6, 2007, June 25 and July 3, 2008

Applicant's Name: Watson Laboratories, Inc.

Established Name: Nicotine Polacrilex Gum USP

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

1. BLISTER - 2 x 5

   2 mg (Cinnamon) - Satisfactory in FPL as of the September 6, 2007 submission.
   2 mg (Fruit) - Satisfactory in FPL as of the June 5, 2007 submission.

   4mg (Cinnamon) -Satisfactory in FPL as of the September 4, 2007 submission.
   4 mg (Fruit) - Satisfactory in FPL as of the June 1, 2007 submission.

2. CARTON- 40s, 100s (b) (4)

   2 mg (Cinnamon) - Satisfactory in FPL as of the July 3, 2008 submission.
   2 mg (Fruit) - Satisfactory in FPL as of the July 3, 2008 submission.

   4mg (Cinnamon) -Satisfactory in FPL as of the July 3, 2008 submission.
   4 mg (Fruit) - Satisfactory in FPL as of the July 3, 2008 submission.

3. USER'S GUIDE

   Satisfactory in FPL as of the July 3, 2008 submission.

4. Audio CD

   Satisfactory in FPL as of the June 25, 2008 submission.

5. CD audio script

   Satisfactory in FPL as of the June 25, 2008 submission.

6. Marketing and Surveillance Plan

   Satisfactory in FPL as of the June 25, 2008 submission.

Revisions needed post approval:

Blisters- differentiate your strengths by boxing, shadowing or some other means.

BASIS OF APPROVAL:

Patent Data –18-612 and 20-066

No	Expiration	Use Code	Use	File
		There are no unexpired patents		

Exclusivity Data - 18-612 and 20-066

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

Was this approval based upon a petition? No

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

NDA Number: 18-612 and 20-066

NDA Drug Name: Nicorette® Gum

NDA Firm: GlaxoSmith Kline

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

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

Was this approval based upon an OGD labeling guidance? No

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

NOTE TO CHEMIST

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.
Please confirm that the following amounts of calcium and sodium listed on the labeling are correct:
79-216 (Cinnamon (Coated),2 mg) - 115 mg calcium and 11 mg sodium
79-044 (Fruit, (Coated),2 mg) - 115 mg calcium and 8 mg sodium
79-219(Cinnamon (Coated),4 mg) -115 mg calcium and 11 mg sodium
79-038 (Fruit, (Coated),4 mg) - 115 mg calcium and 8 mg sodium

---

From: Skanchy, David
Sent: Thursday, August 14, 2008 5:10 PM
To: Dillahunt, Michelle
Subject: RE: Calcium in the gums

The amendment just came. The calcium levels (115 mg) are correct.

From: Skanchy, David
Sent: Wednesday, July 30, 2008 9:59 AM
To: Dillahunt, Michelle
Subject: RE: Nicotine applications

Michelle,

The amounts for sodium are correct. For calcium the firm will have to provide their calculation since the sources are not easily discernable from the component list. I'll have them fax it in and get back to you ASAP.

Dave S.

FOR THE RECORD:
1. MODEL LABELING - NDA 18-612/S-050 (2 mg); NDA 20-066/S-031 (4 mg) (Nicorette® gum) approved on June 13, 2008. This supplement provides for a new cinnamon flavor. The audiotape/CD was also last approved on August 9, 2002 (S-031). NDA 18-612/S-035 (2 mg); NDA 20-066/S-017 (4 mg), approved June 23, 2004 was used as the model labeling for the user's guide.

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

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

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

   Watson has verified that their amounts of calcium and sodium are correct in their June 25, 2008

amendment.

5. PATENTS/EXCLUSIVITIES

None

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

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

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

8. Packaging -

Fill Size	Component Description	Manufacturer	DMF No.
Ten 2 mg gum pieces/blister pack	Blister film: (b) (4) Resin: (b) (4) film Or Blister film: (b) (4) Resin: (b) (4) film	(b) (4) (b) (4)	(b) (4) (b) (4)
	Blister foil: (b) (4) Contact layer: aluminum foil (b) (4)	(b) (4)	(b) (4)
Bulk Package	Material: (b) (4)	(b) (4)	N/A

9. Package sizes:

RLD - 20s, 40s, 50s, 110s and 170s

ANDA - 40s, 100s (b) (4)

10. Watson submitted a waiver request to delete the printing from the gum. It was decided that the waiver would be granted since Perrigo's approved products do not have imprints on them and no waiver was submitted. See emails below:

From: Golson, Lillie D
Sent: Tuesday, January 15, 2008 12:40 PM
To: Dillahunt, Michelle
Subject: RE: Coated Nicotine gums: imprinting issue
Thanks. Go ahead and let it go based on the fact that we approved Perrigo's product w/o the imprinting. Include this email in you FTR.

From: Dillahunt, Michelle
Sent: Tuesday, January 15, 2008 12:30 PM
To: Golson, Lillie D
Subject: FW: Coated Nicotine gums: imprinting issue
See the chemist email below
From: Skanchy, David

Sent: Tue 1/15/2008 9:23 AM
To: Dillahunt, Michelle
Cc: Hinchliffe, Thomas
Subject: Coated Nicotine gums: imprinting issue

Michelle,

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

Dave S.

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

*These ANDA's were originally the uncoated mint gum. Supplement 5 reformulated to the coated mint gum and the original uncoated (b) (4) became the subject of a new ANDA. Approval date is for the coated formulation in Supplement 5.

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

11. The AudioCD and User's guide do not specify the flavors

12. Manufacturer
    Watson Laboratories, Inc.
    Copiague, New York 11726

13. Description

    2mg Gum: Pink square biconvex coated polished mottled gum pieces.

    4mg Gum: Red square biconvex coated polished mottled gum pieces.

14. The firm has provided a certification of translation stating that the translation from English to Spanish for Watson's user's guide and information script for CD is accurate in their 6/25/08 submission.

Date of Review: July 28, 2008 **Date of Submissions:** June 1, June 5, September 4 and 6, 2007
June 25 and July 3, 2008

Primary Reviewer: Michelle Dillahunt Date:

Team Leader: Lillie Golson **Date:**

---

cc:
ANDAs: 79216, 79219,79038, 79044
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSNZ\WATSON\LTRS&REV\792167921979038790 44AP1 LABELINGrev.doc
Review

Following this page, 27 pages withheld in full - (b)(4) draft labeling

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

/s/

Michelle Dillahunt
8/15/2008 05:51:18 AM
LABELING REVIEWER

Lillie Golson
8/15/2008 03:53:01 PM
LABELING REVIEWER

APPROVAL SUMMARY

(Supersedes the approval summary for the June 1, June 5, September 4 and 6, 2007, June 25 and July 3, 2008 submissions)

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

ANDA Numbers: 79-216 (Cinnamon,Coated,2 mg)
79-044 (Fruit, Coated,2 mg)
79-219(Cinnamon, Coated,4 mg)
79-038 (Fruit, Coated,4 mg)

Date of Submission: May 22, 2009

Applicant's Name: Watson Laboratories, Inc.

Established Name: Nicotine Polacrilex Gum USP

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

1. BLISTER - 2 x 5

   2 mg (Cinnamon) - Satisfactory in FPL as of the September 6, 2007 submission.
   2 mg (Fruit) - Satisfactory in FPL as of the June 5, 2007 submission.

   4mg (Cinnamon) -Satisfactory in FPL as of the September 4, 2007 submission.
   4 mg (Fruit) - Satisfactory in FPL as of the June 1, 2007 submission.

2. CARTON- 40s, 100s

   2 mg (Cinnamon) - Satisfactory in FPL as of the May 22, 2009 submission.
   2 mg (Fruit) - Satisfactory in FPL as of the May 22, 2009 submission.

   4mg (Cinnamon) -Satisfactory in FPL as of the May 22, 2009 submission.
   4 mg (Fruit) - Satisfactory in FPL as of the May 22, 2009 submission.

3. USER'S GUIDE

   Satisfactory in FPL as of the May 22, 2009 submission.

4. Audio CD

   Satisfactory in FPL as of the June 25, 2008 submission.

5. CD audio script

   Satisfactory in FPL as of the June 25, 2008 submission.

6. Marketing and Surveillance Plan

   Satisfactory in FPL as of the June 25, 2008 submission.

Revisions needed post approval:

Blisters- differentiate your strengths by boxing, shadowing or some other means.

Carton- 40s- increase the prominence of the strength.

Carton 40s, 100s- include a statement indicating the strength per each piece of gum as seen in the reference listed drug's product.

BASIS OF APPROVAL:

Patent Data –18-612 and 20-066

No	Expiration	Use Code	Use	File
		There are no unexpired patents		

Exclusivity Data - 18-612 and 20-066

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

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: NDA 18-612/S-052 (2 mg); NDA 20-066/S-033 (4 mg) (Nicorette® gum) approved on May 6, 2009.
It appears that the innovator's audiotape was also last approved on August 9, 2002 (S-013). See FTR

NDA Number: 18-612 and 20-066

NDA Drug Name: Nicorette® Gum

NDA Firm: GlaxoSmith Kline

Date of Approval of NDA Insert and supplement #:
NDA 18-612/S-052 (2 mg); NDA 20-066/S-033 (4 mg) approved on May 6, 2009.

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

Was this approval based upon an OGD labeling guidance? No

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

NOTE TO CHEMIST

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.
Please confirm that the following amounts of calcium and sodium listed on the labeling are correct:
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Michelle,

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Dave S.

FOR THE RECORD:

1. MODEL LABELING - NDA 18-612/S-050 (2 mg); NDA 20-066/S-031 (4 mg) (Nicorette® gum) approved on May 6, 2009. This supplement provides for a new dosing regimen. The audiotape/CD was also last approved on August 9, 2002 (S-031).

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.

   Watson has verified that their amounts of calcium and sodium are correct in their June 25, 2008 amendment.

5. PATENTS/EXCLUSIVITIES

   None

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

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8. Packaging -

Fill Size	Component Description	Manufacturer	DMF No.
Ten 2 mg gum pieces/blister pack	Blister film: (b) (4) Resin: (b) (4) film Or Blister film: (b) (4) Resin: (b) (4) film	(b) (4)	(b) (4)
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Bulk Package	Material: (b) (4) (b) (4)	(b) (4)	N/A

9. Package sizes:

RLD - 20s, 40s, 50s, 110s and 170s

ANDA - 40s, 100s

6/10/09 new correspondence, Watson provided a statement that they will not market the (b) (4) (b) (4)

10. Watson submitted a waiver request to delete the printing from the gum. It was decided that the waiver would be granted since Perrigo's approved products do not have imprints on them and no waiver was submitted. See emails below:

From: Golson, Lillie D
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78-967 Perrigo 2 mg (coated, orange) CMC AP w/TL, Bio and labeling pending No No
78-968 Perrigo 4 mg (coated, orange) CMC AP w/TL, Bio and labeling pending No No
78-697 Watson 4 mg (coated, orange) CMC deficient, Bio and labeling pending Yes Yes
78-699 Watson 2 mg (coated, orange) CMC deficient, Bio and labeling pending Yes Yes
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79-044 Watson 2 mg (coated, fruit) Not yet reviewed Not known, but probably Not known
79-216 Watson 2 mg (coated, cinnamon) Not yet reviewed Not known, but probably Not known
79-219 Watson 4 mg (coated, cinnamon) Not yet reviewed Not known, but probably Not known

*These ANDA's were originally the uncoated mint gum. Supplement 5 reformulated to the coated mint gum and the original uncoated (b) (4) became the subject of a new ANDA. Approval date is for the coated formulation in Supplement 5.

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

11. The AudioCD and User's guide do not specify the flavors

12. Manufacturer
    Watson Laboratories, Inc.
    Copiague, New York 11726

13. Description

    2mg Gum: Pink square biconvex coated polished mottled gum pieces.

    4mg Gum: Red square biconvex coated polished mottled gum pieces.

6-10-09 new correspondence

14. The firm has provided a certification of translation stating that the translation from English to Spanish for Watson's user's guide and information script for CD is accurate in their 6/10/09 submission.

Date of Review: June 9, 2009 **Date of Submission: May 22 and June 10, 2009**

Primary Reviewer: Michelle Dillahunt **Date:**

Team Leader: Lillie Golson **Date:**

cc:
ANDAs: 79216, 79219,79038, 79044
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSNZ\WATSON\LTRS&REV\792167921979038790 44AP1 LABELINGrev.doc
Review

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

/s/

Michelle Dillahunt
6/22/2009 10:56:04 AM
LABELING REVIEWER

Lillie Golson
6/22/2009 11:59:53 AM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-038

CHEMISTRY REVIEWS

CHEMISTRY REVIEW

ANDA 79-038

Nicotine Polacrilex *Coated* Gum USP, 4 mg (Fruit)

Watson Laboratories, Inc.

David Skanchy
Office of Generic Drugs/Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. ANDA 79-038

2. REVIEW #: 1

3. REVIEW DATE: 7/02/2009

4. REVIEWER: David Skanchy

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	6/01/2007
Amendment (tele)	4/09/2008
Amendment (grat.)	5/09/2008
Amendment (tele, USP<467>)	8/11/2008
Amendment (tele)	8/14/2008
Amendment (tele, Clin/tox info)	9/19/2008
Amendment (tele, Clin/tox info)	1/16/2009
Amendment (tele)	7/01/2009
Amendment (tele)	7/02/2009

7. NAME & ADDRESS OF APPLICANT:

Name: Watson Laboratories, Inc.

Chemistry Review Data Sheet

P.O. Box 30
Address: 33 Ralph Ave.
Copiague, New York 11726-0030

Telephone: 631-693-8038

Fax: 631-693-8896

8. DRUG PRODUCT NAME/CODE/TYPE:

(a) Proprietary Name: N/A
(b) Non-Proprietary Name (USAN): Nicotine Polacrilex Gum, Coated (Fruit)

9. LEGAL BASIS FOR SUBMISSION:
The basis for this submission is the approved listed drug, Nicorette® Fruit Chill™ 4 mg, the subject of NDA #20-066, held by GlaxoSmithKline, Consumer Healthcare, L.P. The referenced drug product has no unexpired patents or exclusivities. A Paragraph I and II Certification and Exclusivity Statement are provided.

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 product

_____SPOTS product – Form Completed

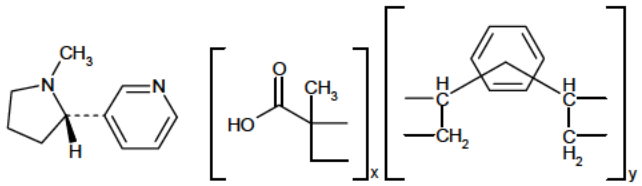
__X___Not a SPOTS product

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

Nicotine Polacrilex

Chemistry Review Data Sheet

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



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	01/25/2008	Adequate per review by DSkanchy
	IV			4			
	III			4			
	III			4			
	III			4			
	IV			4			
	IV			4			
	I			4			

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

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

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ANDA CMC review	79-044	sister application for 2 mg strength
ANDA CMC review	78-697	Similar coated mint
ANDA CMC review	78-699	Similar coated mint

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	ACCEPTABLE	12/15/2008	OC
Methods Validation	Not required		
Labeling	ACCEPTABLE	6/22/2009	M. Dillahunt
Bioequivalence	ACCEPTABLE	5/07/2008	A. Sigler
EA	N/A		
Radiopharmaceutical	N/A		
Toxicology consult	ACCEPTABLE	2/21/2008	ONDP
OGD Clinical Review Team consult	ACCEPTABLE	5/05/2009	N. Chang

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:

The Chemistry Review for ANDA 79-038

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval is recommended. ***Note that the firm provides a Post Approval Commitment to provide*** [redacted]

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

N/A

II. Summary of Chemistry Assessments

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

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 [redacted] nicotine. The resin is a weak cation exchange polymer made from [redacted] The nicotine containing resin is [redacted] with inactive ingredients such [redacted]. The drug is delivered for buccal absorbtion by chewing a 1272 mg dosage unit. *The formulation in the submission is similar to the uncoated mint formulation approved in ANDA 76-569. The firm takes the same basic gum* [redacted] *and then applies a* [redacted] *flavor coating. The only difference in the composition of the gum* [redacted] *is the use of sucralose and acesulfame potassium. Otherwise they are qualitatively and quantitatively identical.*

The manufacturer of the drug substance, Polacrilex Resin [redacted] Nicotine, is [redacted] (DMF # [redacted] A two-year expiration dating 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 and works as a temporary aid to help in quitting smoking by reducing nicotine withdraw symptoms. Nicotine Polacrilex Gum provides a lower level of nicotine to the blood stream than cigarettes, and allows people to gradually do away with the body's need for nicotine. The recommended usage schedule and instructions on gradually decreasing the use of nicotine polacrilex gum are provided in the User's Guide.

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable from a chemistry perspective. All other disciplines and consults are acceptable.

III. Administrative

Endorsement Block

HFD-640/DSkanchy/7/02/09
HFD-643/NYa/7/02/09
HFD-617/THinchliffe/7/02/09

Following this page, 62 pages withheld in full - (b)(4)

R2 Information on Components

The firm provides vendor statements of compliance with (b) (4) (b) (4) requirements for the excipients used.

R3 Methods Validation Package

Provided. No FDA validation of the methods is requested per current policy.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

The labeling review is acceptable.

Evaluation:

This is an OTC drug. There is no labeling insert. The ingredients listed on the carton have been reviewed by chemistry and found satisfactory. The labeling review is acceptable.

Note that the firm has been granted a waiver for the printing requirement on individual pieces for ANDA's 78-697 and 78-699 (coated, mint). They intend for the waiver to apply to all of the coated gum flavors under review. *The firm submitted a waiver request to this ANDA for the sake of completeness in the 4/09/2008 amendment. The request was approved by labeling.*

Conclusion:
Satisfactory from chemistry's perspective.

B. Environmental Assessment Or Claim Of Categorical Exclusion

Categorical exclusion from the requirement to prepare an Environmental Assessment is requested.

Evaluation:
The drug product has the same indications and usage as the reference listed drug and 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.

III. List Of Deficiencies To Be Communicated

N/A-Application is approvable from CMC perspective.

<u>Attachment #1:</u> CHEMISTRY COMMENTS PROVIDED TO THE APPLICANT for Telephone Amendment (faxed 3/31/2008, response received 4/09/2008)

ANDA: 79-038 APPLICANT: Watson Laboratories

DRUG PRODUCT: Nicotine Polacrilex Gum USP 2 mg (Coated, Fruit)

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

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

4. Please submit the waiver request for the printing requirements on the individual gum pieces to this ANDA. We note a similar waiver was provided for your coated mint applications.

5. Please provide any available updated stability data for the exhibit batch.

<u>Attachment #2.</u> CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT for T-con (faxed 6/18/2008 for ANDAs 78-697/699, the firm was told to supply the same information requested in that fax for this ANDA in 7/01/2008 by telephone; response received 8/11/2008)

ANDA: 79-038 APPLICANT: Watson Laboratories

DRUG PRODUCT: Nicotine Polacrilex Gum USP 2 mg and 4 mg (Coated, Mint)

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

Please note that if the above referenced ANDA's receive approval prior to July 01, 2008 then the information requested below can be provided in the first Annual Report.

Please note that the new USP<467> chapter on residual solvents is effective on July 01, 2008. You therefore must meet the new requirements prior to approval of this ANDA. In order to comply with the new USP<467> requirements please provide the information listed below in your response. Reference is also made to the Office of Generic Drug's communication entitled "Residual Solvents Acceptability Letter" posted on the OGD website. The letter is available at the following link: (http://www.fda.gov/cder/ogd/#New).

We note that you have already provided residual solvent information for your API compliant with the new USP<467>. We also note (b) (4) **in the drug product specification. Please provide the following additional information on all of the excipients used in the formulation.**

1. (b) (4)

2.

- (b) (4)
- [redacted]

Acceptable

Attachment #3: CHEMISTRY COMMENTS PROVIDED TO THE APPLICANT for Telephone Amendment (faxed 6/25/2009; responses received July 01 and 02, 2009)

ANDAs: 79-038; 79-044 APPLICANT: Watson Laboratories

DRUG PRODUCT: Nicotine Polacrilex Gum USP 2 mg and 4 mg (Coated, Fruit)

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

1. (b) (4)

2. We note that you have added the requested compliance statement for USP<467> Residual Solvents to your drug product release specifications. In an effort to harmonize these statements we now have more specific guidance on the format of the statement. Please submit a revised drug product specification with a USP<467> statement meeting the following criteria:

    a. The statement should appear as a line item test, similar in format to all of the other required tests listed on the specification (footnoted statements are no longer acceptable).
    b. The statement should indicate compliance according to (b) (4) consistent with the data and calculations you provided.

3. Please update the (b) (4) specification and test protocol in the following manner.

    a. (b) (4)

b. [redacted] (b) (4)

Appears this way on original

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

/s/

David Skanchy
7/8/2009 09:39:48 AM
CHEMIST

Bing Wu
7/8/2009 12:56:38 PM
CHEMIST

Simon Eng
7/8/2009 02:36:27 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-038

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	79-038 and 79-044		
Drug Product Name	Nicotine Polacrilex Gum (Coated Fruit)		
Strength(s)	4 mg and 2 mg		
Applicant Name	Watson Laboratories, Inc.		
Address	33 Ralph Avenue, Copiague, New York 11726		
Applicant's Point of Contact	Beverly Bailey		
Contact's Telephone Number	(631) 693-8038		
Contact's Fax Number	(631) 693-8896		
Original Submission Date(s)	June 1, 2007 (4 mg) & June 5, 2007 (2 mg)		
Submission Date(s) of Amendment(s) Under Review	December 17, 2007 (Mastication Results Using Watson's Method)		
Reviewer	Patrick Nwakama, Pharm.D.		
Study Number (s)	R06-1613	R06-1613	R06-1612
Study Type (s)	Fasting	Single-dose Chew out	Multi-dose Chew out
Strength (s)	4 mg	4 mg	4 mg & 2 mg
Clinical Site	PRACS Institute, Ltd.		
Clinical Site Address	4801 Amber Valley Parkway, Fargo, North Dakota		
Analytical Site	(b) (4) Nicotine in Plasma)	PRACS Institute, Ltd. (Nicotine in Gum)	
Analytical Site Address	(b) (4)	Fargo, North Dakota	
OUTCOME DECISION	**INCOMPLETE**		

1 EXECUTIVE SUMMARY

The application (ANDA 79-038 for 4 mg and ANDA 79-044 for 2 mg) references GlaxoSmithKline's Nicorette® Fruit Chill™ (Nicotine Polacrilex) 2 mg and 4 mg Fruit flavored gums, and includes one fasting bioequivalence (BE) study on the 4 mg gum with chew-out study component and two four-way crossover multi-dose chew-out studies (2 and 4 mg strengths). The fasting BE study is a single-dose two-way crossover study in healthy adult smokers (n=46) administered a dose of 4 mg with a 30-minute chewing interval. The results of the fasting BE study are summarized in the table below.

Fasted Bioequivalence Study, Study #: R06-1613 (N=46)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*h/mL)	27.66	31.81	86.96	83.37	90.69
AUC∞ (ng*h/mL)	29.75	33.95	87.63	84.27	91.12
Cmax (ng/mL)	8.29	9.78	84.78	80.95	88.79

The fasting bioequivalence (nicotine in plasma) study is acceptable.

In the chew-out component of the fasting BE study, residual nicotine levels in expectorated cuds are compared (Test vs. Reference). The results (point estimate and 90% CI) of the percent of nicotine released during 30 minute chewing duration are 0.94 and 92.2 – 94.8%, respectively. The comparative multi-dose chew-out studies on test and reference products for 2 and 4 mg strengths were conducted on 19 subjects. Test vs. reference ratios for 2 and 4 mg strengths were 1.00 and 1.01, respectively. Data for chew-out studies (component of the fasting BE study on the 4 mg strength and the multi-dose chew-out studies on the 2 mg and 4 mg strengths) are acceptable. The chew-out studies were provided for informational purpose only.

The in vitro dissolution testing using Phosphate Buffer pH 7.4 + 0.1% SLS is acceptable. The firm has proposed a dissolution specification of NLT (b) (4) (Q) in 30 minutes. However, based on the data submitted, the DBE recommends an alternative specification of NLT (b) (4) (Q) in 30 minutes) for the test product. The firm is requested to acknowledge the DBE-recommended specification.

The re-integration bioanalytical issue involving PRACS does not affect the outcome of this application since the PK study was conducted at a different analytical lab, (b) (4).

The application is incomplete pending the firm's acknowledgement of DBE-recommended dissolution specification.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Nicotine Polacrilex Coated Gum (Fruit Flavor), 4 mg
Reference Product	Nicorette® 4 mg Gum
RLD Manufacturer	GlaxoSmithKline
NDA No.	20-066
RLD Approval Date	February 9, 1996
Indication	Indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms

3.2 PK/PD Information

Bioavailability	Oral BA of nicotine is ~25-30%
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 2 hours
Drug Specific Issues (if any)	None

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	1, fasting study and 2 Multi-dose Chew out Studies

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	4 mg
	Subjects:	Normal healthy males and females, (smoking) general population
	Additional Comments:	N/A

2.	**Type of study:**	Multi-dose Chew out
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	2 mg and 4 mg

	Subjects:	Normal healthy males and females, (smoking) general population
	Additional Comments:	N/A

Analytes to measure (in plasma/serum/blood):	Nicotine
Bioequivalence based on:	(90% CI)
Waiver request of in-vivo testing:	2 mg
Source of most recent recommendations:	Control Document # 06-0591, 4/28/06, (b) (4)
Summary of OGD or DBE History (for details, see Appendix 4.4):	Several Nicotine Gum ANDAs (77658 & 77656, Novartis; 76775, 76776, 76777, 76778, 76779, 76789, 78547, 78325, 78546, & 78326, Perrigo; and 74507, 76568 & 74707, Watson) are currently on the market. The DBE currently recommends the following for this drug product (based on review of control 06-0591): 1. A single-dose, two-way crossover fasting *in-vivo* bioequivalence study comparing Nicotine Polacrilex Gum Regular Flavor, 4 mg, to the RLD Nicorette® (Nicotine Polacrilex) Gum, 4 mg, with a 30 minute chewing interval during each period, AND, 2. Please conduct comparative dissolution testing for all strengths of the test and reference products. Currently, there is no USP dissolution testing method for nicotine polacrilex gum. Therefore, please develop a dissolution method that correlates well with the *in-vivo* nicotine release profile based on the time points (5, 10, 20, and 30 minutes) used in the chew-out studies. Please use the dissolution method described in the European Pharmacopoeia (2.9.25) 3. A multi-dose, crossover chew-out study comparing Nicotine Polacrilex Gum Regular Flavor, 2 mg and 4 mg to evaluate the *in-vivo* nicotine release of the generic formulations to the RLD, is not needed if the dissolution method described in (2) above can be developed. If the dissolution method cannot be developed, the multi-dose, crossover chew-out study will be requested. If you are conducting the chew-out study, please determine the nicotine release profiles over time (i.e. after chewing the gum) by sampling at several time points, 5, 10, 20, and 30 minutes. 4. Please measure only the parent compound, nicotine, in plasma. Please do not adjust the pharmacokinetic data using the residual nicotine levels analyzed from the gum cud. 5. Nicotine Polacrilex Gum, 2 mg and 4 mg (mint and orange flavored), may be considered for a waiver of *in-vivo* bioequivalence testing based on (1) an acceptable bioequivalence study on the 4 mg strength (regular flavor), (2) acceptable dissolution testing of all strengths and flavors, (3) proportional similarity in the formulations of all strengths and flavors and (4) the only difference in the formulation between the flavored and regular gum is the flavor component. 6. Please use smokers in the study. You may submit a protocol for review prior to initiating the studies.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose Chew out	Yes	1
Multi-dose Chew out	Yes	2 (2 mg and 4 mg)
Single-dose fed	No	0
Steady-state	No	0
In vitro dissolution	Yes	2
Waiver requests	Yes	1
BCS Waivers	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	No	0

3.5 Pre-Study Bioanalytical Method Validation - Plasma

Information Requested	Nicotine (Plasma)
Bioanalytical method validation report location	Module 5.3.1.4 (b) (4) Report Page #s: Appendix C, Pages C1-C129
Analyte	Nicotine
Internal standard (IS)	(b) (4)
Method description	Nicotine was isolated from the plasma samples by liquid liquid extraction and detected by LC-MS/MS techniques.
Limit of quantitation	0.500 ng/mL
% recovery (and %CV) at each concentration tested	99.9%
Average recovery of IS (%)	99.3%
Standard curve concentrations (ng/mL)	0.500, 1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 75.0, and 100 ng/mL
QC concentrations (ng/mL)	0.500, 1.00, 7.50, and 75.0 ng/mL
QC Intraday precision range (%)	0.991 to 6.33%
QC Intraday accuracy range (%)	91.77 to 101.59%
QC Interday precision range (%)	1.50 to 7.3%
QC Interday accuracy range (%)	94.6 to 102.8%
Bench-top stability (hrs)	12 hours at room temperature
Stock stability (days)	Analyte: 3227 days at -20°C in methanol, IS: 121 days at -20°C in methanol, IS 121 days at -20°C in acetonitrile
Processed stability (hrs)	101.5 hours at room temperature
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	50 days at -20°C
Dilution integrity	7.50 ng/mL diluted 2-fold, 250 ng/mL diluted 5-fold
Selectivity	No interfering peaks noted in blank plasma samples that were more than 14.6% of the response of the lowest standard curve concentration.

SOPs submitted	Yes
Bioanalytical method is acceptable	Yes

Bioanalytical Method Validation – Chewed Gum

Information Requested	**Nicotine in Chewed Gum**
Bioanalytical method validation report location	Module 5.3.1.4, PRACS Report Page #s: Section 16.6
Analyte	Nicotine
Internal standard (IS)	(b) (4)
Method description	Liquid-liquid extraction Nicotine is extracted from the gum samples with a mixture of (b) (4) and (b) (4) mixed for 30 min. Then aliquot of the aqueous layers is diluted with water and injected on LC/MS/MS. Details of the procedure can be found in AP number 165.2
Limit of quantitation	100.00 µg/unit
Average recovery of drug (%)	95.3%
Average recovery of IS (%)	105.4%
Standard curve concentrations (µg/units)	100.00, 200.00, 500.00, 1000.00, 2250.00, 3150.00, 3870.00, 4500.00
QC concentrations (µg/units)	300.00, 2000.00, 3500.00
QC Intraday precision range (%)	1.27 – 2.11
QC Intraday accuracy range (%)	88.72 – 94.30
QC Interday precision range (%)	2.30 – 6.71
QC Interday accuracy range (%)	89.11 – 94.76
Bench-top stability (hrs)	50:11 hours:minutes @ room temperature
Stock stability (days)	144:02 hours:minutes @ room temperature
Processed stability (hrs)	117:06 hours:minutes @ room temperature
Freeze-thaw stability (cycles)	4 cycles
Long-term storage stability (days)	235 days @ -20ºC
Dilution integrity	No dilution integrity test needed
Selectivity	No interference detected
Uniformity of Unchewed Gum - accuracy range (%)	94.8 – 106.7
Homogeneity of Chewed Gum	0.90%
Homogeneity of Unchewed Gum	0.37%

Comments on the Pre-Study Method Validation: Acceptable.

3.6 In Vivo Studies

Table 1a. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (units/mL)	T_{max} (hr)	AUC_{0-t} (units)	AUC_{∞} (units)	T½ (hr)	K_{el} (hr-1)	
R06-1613 (b) (4) #: AEII)	A pharmacokinetic study of Watson 4 mg nicotine polacrilex coated gum, fruit flavor and GlaxoSmithKline (Nicorette® Fruit Chill™) 4 mg nicotine polacrilex gum in healthy adult smokers	Open, randomized, two-way crossover, single 4 mg dose	Test: Nicotine Polacrilex Coated Gum, Fruit Flavor, 4 mg Transmucosal [Lot No. RD1407] Reference: Nicorette® Fruit Chill™, 4 mg (Nicotine Polacrilex Coated Gum) Transmucosal [Lot No. HA935A]	46 (32/14) Healthy Smoking Volunteers 27.22 yr (18 - 45 yr)	8.63 (27.91)	0.97 (0.33 - 1.5)	28.74 (27.47)	30.82 (26.53)	2.15 (19.60)	0.3341 (19.42)	Module 5.3.1.2, Table 2.1, Statistics Report page 25
					10.03 (21.68)	0.92 (0.5 - 1.25)	32.85 (24.05)	34.94 (22.94)	2.12 (15.45)	0.3343 (15.07)	Module 5.3.1.2, Table 2.2, Statistics Report page 27

Table 1b Summary of Salivary Dissolution (Multi-dose Chew-out) Study – Initial Amount

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects[1] No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (+/- SD) Percent Released, Based on Initial Amount[1]						Study Report Location
					5 minutes	8 minutes	12 minutes	16 minutes	22 minutes	30 minutes	
R06-1612	Comparative, randomized, 4 period, 2 sequence, crossover salivary dissolution study of Watson nicotine polacrilex coated gum, fruit flavor (2 mg and 4 mg) and GlaxoSmithKline (Nicorette® Fruit Chill™) nicotine polacrilex gum (2 mg and 4 mg) in healthy adult smokers	Open, randomized, four-way crossover, multiple 2 and 4 mg doses	Test 1 (A): Nicotine Polacrilex Coated Gum, Fruit Flavor, 4 mg, Transmucosal [Lot No. RD1407]	Treatments (A and B): 20 (15/5) Healthy Volunteers 26.95 yr (18 - 44 yr)	20.71 ± 6.36	35.39 ± 6.49	49.77 ± 7.17	59.07 ± 6.52	70.64 ± 6.79	79.82 ± 5.52	**Module 5.3.1.2:** Table 4.1, Statistics Report page 18
			Reference 1 (B): Nicorette® Fruit Chill™, 4 mg (Nicotine Polacrilex Coated Gum), Transmucosal [Lot No. HA935A]		16.69 ± 6.14	31.93 ± 8.03	46.49 ± 7.79	56.65 ± 8.58	67.91 ± 7.81	78.69 ± 6.97	Table 4.2, Statistics Report page 19
			Test 2 (C): Nicotine Polacrilex Coated Gum, Fruit Flavor, 2 mg, Transmucosal [Lot No. RD1408]	Treatments (C and D): 19 (14/5) Healthy Volunteers 26.26 yr (18 - 44 yr)	19.09 ± 3.34	29.15 ± 4.07	41.47 ± 5.06	51.91 ± 7.16	63.18 ± 6.66	73.15 ± 6.33	Table 4.3, Statistics Report page 20
			Reference 2 (D): Nicorette® Fruit Chill™, 2 mg (Nicotine Polacrilex Coated Gum) Transmucosal [Lot No. HA925A]		17.01 ± 4.93	28.06 ± 5.85	40.90 ± 5.60	52.58 ± 7.85	63.33 ± 9.13	72.82 ± 8.58	Table 4.4, Statistics Report page 21

Table 1c Summary of Salivary Dissolution Study – Labeled Claim

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects[1] No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (+/- SD) Percent Released, Based on Label Claim Amount[1]						Study Report Location
					5 minutes	8 minutes	12 minutes	16 minutes	22 minutes	30 minutes	
R06-1612	Comparative, randomized, 4 period, 2 sequence, crossover salivary dissolution study of Watson nicotine polacrilex coated gum, fruit flavor (2 mg and 4 mg) and GlaxoSmithKline (Nicorette® Fruit Chill™) nicotine polacrilex gum (2 mg and 4 mg) in healthy adult smokers	Open, randomized, four-way crossover, single 2 and 4 mg dose	Test 1 (A): Nicotine Polacrilex Coated Gum, Fruit Flavor, 4 mg, Transmucosal [Lot No. RD1407] Reference 1 (B): Nicorette® Fruit Chill™, 4 mg (Nicotine Polacrilex Coated Gum), Transmucosal [Lot No. HA935A] Test 2 (C): Nicotine Polacrilex Coated Gum, Fruit Flavor, 2 mg, Transmucosal [Lot No. RD1408] Reference 2 (D): Nicorette® Fruit Chill™, 2 mg (Nicotine Polacrilex Coated Gum), Transmucosal [Lot No. HA925A]	Treatments (A and B): 20 (15/5) Healthy Volunteers 26.95 yr (18 - 44 yr) Treatments (C and D): 19 (14/5) Healthy Volunteers 26.26 yr (18 - 44 yr)	20.09 ± 6.17	34.33 ± 6.30	48.28 ± 6.95	57.30 ± 6.33	68.52 ± 6.58	77.42 ± 5.36	**Module 5.3.1.2:** Table 3.1, Statistics Report page 14
					17.41 ± 6.40	33.30 ± 8.38	48.49 ± 8.12	59.09 ± 8.95	70.83 ± 8.14	82.08 ± 7.26	Table 3.2, Statistics Report page 15
					19.16 ± 3.35	29.27 ± 4.09	41.64 ± 5.08	52.12 ± 7.19	63.43 ± 6.68	73.45 ± 6.36	Table 3.3, Statistics Report page 16
					17.36 ± 5.03	28.65 ± 5.97	41.76 ± 5.72	53.69 ± 8.02	64.66 ± 9.32	74.35 ± 8.76	Table 3.4, Statistics Report page 16

Table 2a Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Nicotine Polacrilex Coated Gum, Fruit Flavor Dose (1 x 4 mg) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data					
Fasted Bioequivalence Study, Study #: R06-1613 N=46					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*h/mL)	27.66	31.81	86.96	83.37	90.69
AUC∞ (ng*h/mL)	29.75	33.95	87.63	84.27	91.12
Cmax (ng/mL)	8.29	9.78	84.78	80.95	88.79

Table 2b Statistical Summary for Percent Nicotine Released from Nicotine Gum in Single-dose Chew out Study –Reviewer Calculated.

Drug name: Nicotine Dose: 4 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals		
Residual Nicotine in Cud – Component of Fasting PK Study, Study No. R06-1613		
Parameter	**Point Estimate**	**90% Confidence Interval**
Percent Nicotine Release		
Ln Percent Nicotine Release	0.94	92.2 – 94.9

Table 2c Statistical Summary for Percent Nicotine Released from Nicotine Gum in Multi-dose Chew out Study –Reviewer Calculated.

Chewing Duration (minutes)	Test (Watson's 4 mg) (RD1407)		Reference (Nicorette® 4mg) (HA935A)		T/R
	Mean	%CV	Mean	%CV	
5	20.71	30.73	16.69	36.77	1.24
8	35.39	18.35	31.93	25.15	1.11
12	49.77	14.40	46.49	16.76	1.07
16	59.07	11.04	56.65	15.14	1.04
22	70.64	9.61	67.91	11.50	1.04
30	79.82	6.92	78.69	8.85	**1.01**

Chewing Duration (minutes)	Test (Watson's 2 mg) (RD1408)		Reference (Nicorette® 2mg) (HA925A)		T/R
	Mean	%CV	Mean	%CV	
5	19.09	17.49	17.01	28.98	1.12
8	29.15	13.97	28.06	20.85	1.04
12	41.47	12.19	40.90	13.70	1.01
16	51.91	13.79	52.58	14.93	0.99
22	63.18	10.54	63.33	14.41	0.99
30	73.15	8.66	72.82	11.78	**1.00**

Table 3. Reanalysis of Study Samples

Pharmacokinetic Study, Study No. R06-1613 Additional information in Module 5.3.1.2, (b) (4) Report, Tab les 2-1 and 2-2 (pages 70 and 72)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Reason A - Unacceptable Internal Standard	35	5	3.84	0.55	35	5	3.84	0.55
Reason B- Extraction Error	2	0	0.22	0.0	2	0	0.22	0.0
Total	37	5	4.06	0.55	37	5	4.06	0.55

Reanalysis of Study Samples – Chewed Gum in Pharmacokinetic Study

Pharmacokinetic Study, Study #: R06-1613 (Chewed Gum Pieces) Additional information in Module 5.3.1.2, PRACS Report, Section 6.7 (page 10)								
Reason for Reanalysis	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis[5]			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test N=25[2]	Reference N=25[2]	Test N=25[2]	Reference N=25[2]	Test N=25[2]	Reference N=25[2]	Test N=25[2]	Reference N=25[2]
	n[3]	n[3]	%[4]	%[4]	n[3]	n[3]	%[4]	%[4]
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Number of Samples Reanalyzed	0.0	0.0	0.0	0.0	-	-	-	-

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout the table
[2] N = Number of samples analyzed for each treatment
[3] n = Number of samples repeated
[4] % = percentage of assays repeated (i.e. 100*(n/N)%)
[5] Reported values that are different from the original value

Reanalysis of Study Samples – Chewed Gum

Salivary Dissolution Study, Study #: R06-1612 Additional information in Module 5.3.1.2, PRACS Report, Section 6.7 (page 10)								
Reason for Reanalysis	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis[5]			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test 1 (A) N=120[2]	Reference 1 (B) N=120[2]	Test 1 (A) N=120[2]	Reference 1 (B) N=120[2]	Test 1 (A) N=120[2]	Reference 1 (B) N=120[2]	Test 1 (A) N=120[2]	Reference 1 (B) N=120[2]
	n[3]	n[3]	%[4]	%[4]	n[3]	n[3]	%[4]	%[4]
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Number of Samples Reanalyzed	0.0	0.0	0.0	0.0	-	-	-	-

Salivary Dissolution Study, Study #: R06-1612 Additional information in Module 5.3.1.2, PRACS Report, Section 6.7 (page 10)								
Reason for Reanalysis	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test 2 (C) N=114	Reference 2 (D) N=114	Test 2 (C) N=114	Reference 2 (D) N=114	Test 2 (C) N=114	Reference 2 (D) N=114	Test 2 (C) N=114	Reference 2 (D) N=114
	n	n	%	%	n	n	%	%
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Number of Samples Reanalyzed	0.0	0.0	0.0	0.0	-	-	-	-

Did use of recalculated plasma concentration data change study outcome? Not Applicable

Comments from the Reviewer: No pharmacokinetic repeats.

3.7 Formulation

Location in appendix	Section 4.2, Page 44
If a tablet, is the RLD scored?	Not Applicable
If a tablet, is the test product biobatch scored	Not Applicable
Is the formulation acceptable?	Acceptable
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	N/A
Source of Method (USP, FDA or Firm)	Firm
Medium	Phosphate Buffer (0.05M) pH 7.4 **OR** Phosphate Buffer (0.0125M) pH 7.4+ 0.1% SLS
Volume (mL)	20 mL
USP Apparatus type	(b) (4) Mastication Device
Chewing Frequency:	50 chews/minute
Jaw Distance:	1.2 mm
Rotational Jaw Angle:	20°
DBE-recommended specifications	Not less tha (b) (4) (Q) in 30 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N/A
Is method acceptable?	**Yes**
If not then why?	N/A

F2 metric, biostudy strengths compared to other strength(s) Phosphate Buffer (0.05M)			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**
4 mg	2 mg	79.5	73.4

F2 metric, biostudy strengths compared to other strength(s) Phosphate Buffer (0.0125M) + 0.1% SLS			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**
4 mg	2 mg	76.9	61.5

Dissolution Comment:
The firm previously acknowledged accepting the DBE-recommended dissolution method [Phosphate Buffer (0.05M) pH 7.4; NLT (b) (4) in 30 minutes] for its Nicotine Polacrilex Gum Original Flavor and Mint Flavor with spec of NLT (b) (4) in 30 minutes. For its Nicotine Polacrilex Gum (Coated Fruit), 4 mg and 2 mg, the tested units cannot meet the dissolution specification of NLT (b) (4) %(Q) in 30 minutes. In this application, the firm conducted dissolution

testing using Phosphate Buffer (0.0125M) pH 7.4 + 0.1% SLS as the dissolution medium. The proposed dissolution method for the Nicotine Polacrilex Gum (Coated Fruit) is acceptable to DBE with an alternative dissolution specification of NLT (b) (4) (Q) in 30 minutes. The firm should acknowledge its acceptance of the DBE-recommended specification.

3.9 Waiver Request(s)

Strengths for which waivers are requested	2 mg (ANDA 79-044)
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes (using the modified dissolution medium (Phosphate Buffer (0.0125M) pH 7.4+ 0.1% SLS)
Waivers granted?	Yes
If not then why?	N/A

3.10 Deficiency Comments

The firm dissolution testing using a modified DBE-recommended method is acceptable. Based on the data submitted, the firm is requested to acknowledge an alternative dissolution specification:

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

3.11 Recommendations

1. The bioequivalence study conducted under fasting conditions by Watson Laboratories, Inc. on its Nicotine polacrilex 4 mg gum (Fruit Flavor), lot no. RD1407 comparing it to Nicorette® 4 mg gum (Fruit Chill™ flavor), lot HA935A manufactured by GlaxoSmithKline is acceptable.

2. The chew-out (drug-release) study conducted as a component of the bioequivalence study on its Nicotine polacrilex 4 mg gum (Fruit Flavor), lot no. RD1407 comparing it to Nicorette® 4 mg gum (Fruit Chill™ flavor), lot HA935A manufactured by GlaxoSmithKline is acceptable.

3. The multi-dose chew-out (drug release) study conducted by Watson Laboratories, Inc. on its Nicotine polacrilex 4 mg gum (Fruit Flavor), lot no. RD1407 comparing it to Nicorette® 4 mg gum (Fruit Chill™ flavor), lot HA935A manufactured by GlaxoSmithKline is acceptable.

4. The multi-dose chew-out (drug release) study conducted by Watson Laboratories, Inc. on its Nicotine polacrilex 2 mg gum (Fruit Flavor), lot no. RD1408 comparing it to Nicorette® 4 mg gum (Fruit Chill™ flavor), lot HA925A manufactured by GlaxoSmithKline is acceptable.

5. The in vitro dissolution testing conducted by the firm is acceptable, however, the firm's proposed specification of NLT [(b) (4)] (Q) in 30 minutes is not acceptable. Based on the data submitted, the DBE recommends an alternative specification of NLT [(b) (4)] (Q) in 30 minutes for the test product. The firm is requested to acknowledge the DBE-recommended specification.

The dissolution should be conducted using the following dissolution method and specification:

Device:	[(b) (4)]
Jaw Distance:	1.2 mm
Jaw Angle:	20°
Medium:	Phosphate Buffer, 0.0125M, pH 7.4 + 0.1% SLS
Volume:	20 mL
Temperature:	37 ± 0.5°C
Stroke Frequency:	50 cycles per minute
Rec Sampling Times:	5, 8, 12, 16, 22, 30, and 45 minutes
DBE-recommended Specification:	**NLT [(b) (4)] (Q) dissolved in 30 minutes**

The firm is requested to acknowledge the DBE-recommended specification above.

6. The Division of Chemistry should be informed about the [(b) (4)] overages in the 2 mg and 4 mg test products, respectively.

From the bioequivalence point of view, the firm has met the requirements of in vivo testing. However, the application is incomplete pending firm's acknowledgment of its acceptance of the DBE-recommended specification given above.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
The Division of Chemistry	The Division of Chemistry should be informed about the [(b) (4)] overage in the 2 mg and 4 mg strengths of the test products, respectively.

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	R06-1613
Study Title	A Pharmacokinetic Study of Watson 4 mg Nicotine Polacrilex Coated Gum, Fruit Flavor, and GlaxoSmithKline (Nicorette® Fruit Chill™) 4 mg Nicotine Polacrilex Gum in Healthy Adult Smokers
Clinical Site (Name & Address)	PRACS Institute, Ltd. 4801 Amber Valley Parkway Fargo, ND 58104 (701) 239-4750
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	**Period I**: January 30, 2007; **Period II**: February 6, 2007
Analytical Site (Name & Address)	(b) (4)
Analysis Dates (Plasma)	February 15 – 28, 2007
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	29 Days (Plasma)

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Nicotine Polacrilex Coated Gum, Fruit Flavor, 4 mg	Nicorette® Fruit Chill™, 4 mg (Nicotine Polacrilex Coated Gum)
Manufacturer	Watson Laboratories, Inc.	Pfizer Health AB for GlaxoSmithKline Consumer Healthcare, L.P.
Batch/Lot No.	RD1407	HA935A
Manufacture Date	Nov 2006	N/A
Expiration Date	N/A	12/2007
Strength	4 mg	4 mg
Dosage Form	Gum	Gum
Bio-Batch Size	(b) (4)	N/A

Production Batch Size	(b) (4)	N/A
Potency (Assay)	97.0%	104.3%
Content Uniformity (mean, %CV)	97.4%, %CV 1.8	N/A
Dose Administered	4 mg	4 mg
Route of Administration	Oral transmucosal with a 30 minutes chewing interval	Oral transmucosal with a 30 minutes chewing interval

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

Number of Subjects	50 dosed (48 completed)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 Days
Randomization Scheme	**AB**:1,3,5,7,10,11,,15,17,18,21,24,27,29,**30**,31,35,38,39,40,41,42,45,47, 48,49 **BA**:2,4,6,8,9,12,13,14,16,19,20,22,23,25,26,28,32,33,**34**,36,37,43,44,46,50
Blood Sampling Times	-0.25, -0.167 and -0.083 hours pre-dose; during dose administration at 0.083, 0.167, 0.333, and 0.5 hours; and after dose administration at 0.667, 0.833, 1,1.25, 1.5, 2,4,6,8, 10, 12, and 16 hours
Blood Volume Collected/Sample	6 mL
Blood Sample Processing/Storage	-20 ^{0}C $\pm$ 10^{0}C
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	At least 10.5 hrs. No smoking for 36 hrs prior the study and until the last blood sampling. Checked by monitoring expired CO performed at random times (CO < 10 ppm).
Length of Confinement	60 hours (36 hours prior to the first scheduled chewing session and 24 hours post-dosing)
Safety Monitoring	Vital signs, clinical lab evaluation, physical exams, and 12-lead ECG

Comments on Study Design: The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Pharmacokinetic Study, Study #: R06-1613			
		Treatment Groups	
		Test Product N=46	Reference Product N=46
Age (years)	Mean ± SD	27.22 ± 7.50	27.22 ± 7.50
	Range	18 - 45	18 - 45
Age Groups	< 18	-	-
	18 – 40	42 (91.30%)	42 (91.30%)
	41 – 64	4 (8.70%)	4 (8.70%)
	65 – 75	-	-
	> 75	-	-
Sex	Male	32 (69.57%)	32 (69.57%)
	Female	14 (30.43%)	14 (30.43%)
Race	Asian	-	-
	Black	-	-
	Caucasian	41(89%)	41(89%)
	Hispanic	-	-
	Other	5(11%)	5(11%)
BMI	Mean + SD	25.60 ± 3.12	25.60 ± 3.12
	Range	19.7 - 31.6	19.7 - 31.6

Table 8. Dropout Information, Fasting Bioequivalence Study

Pharmacokinetic Study, Study #: R06-1613			
Subject No.	**Reason**	**Period**	**Replaced?**
30	Elected to withdraw prior to Period II dose administration due to scheduling conflict.	1	No
34	Subject was dropped prior to Period II dosing due to positive drug screen	1	No

Reviewer's Note: Subjects 23 and 50 excluded from statistical analyses due to predose levels > 5% Cmax. Therefore only 46 subjects were analyzed.

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups Pharmacokinetic Study #: R06-1613	
	Test N=49	Reference N=49
	n (%)	n (%)
Gastrointestinal disorders		
Eructation	5 (10.20%)	5 (10.20%)
Hiccups	8 (16.33%)	4 (8.16%)
Nausea	-	1 (2.04%)
Stomatitis	1 (2.04%)	3 (6.12%)
Throat irritation	9 (18.37%)	8 (16.33%)
General disorders and administration site conditions		
Hyperhidrosis	-	1 (2.04%)
Pallor	-	1 (2.04%)
Infections and infestations		
Pharyngitis	1 (2.04%)	-
Nervous system disorders		
Dizziness	2 (4.08%)	2 (4.08%)
Headache	2 (4.08%)	-
Respiratory, thoracic and mediastinal disorders		
Cough	18 (36.73%)	9 (18.37%)
Total Subjects Reporting at Least One Adverse Event	30 (61.22%)	21 (42.86%)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Pharmacokinetic Study, Study #: R06-1613		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Concomitant medication	47	N/A
Lifestyle guideline violation	N/A	36
Subject evaluation (CO measurement)	N/A	33
Subject not queried for adverse event	N/A	22
Repeat chemistry safety lab after exit not completed for subject 22	N/A	N/A
Repeat urine drug screen not collected	01	13

Comments on Dropouts/Adverse Events/Protocol Deviations: The protocol deviations and adverse events reported for the subjects included in the analysis were judged to have no significant impact on determination of bioequivalence.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Pharmacokinetic Study #: R06-1613 Nicotine in Plasma								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.500	0.900	1.50	4.50	12.5	35.0	80.0	100
Inter day Precision (%CV)	3.53	4.73	4.76	2.75	3.33	1.93	2.49	1.71
Inter day Accuracy (%Actual)	99.5	101	101	99.6	101	99.1	99.6	101
Linearity	(Range of R^2 values) 0.9996 - 1.000							
Linearity Range (ng/mL)	0.500 – 100							
Sensitivity/LOQ (ng/mL)	0.500							

Pharmacokinetic Study #: R06-1613 Nicotine in Plasma					
Parameter	**Quality Control Samples**				
Concentration (ng/mL)	1.00	2.50	7.50	20.0	75.0
Inter day Precision (%CV)	4.29	3.41	3.95	2.88	4.29
Inter day Accuracy (%Actual)	101	98.9	99.5	99.6	97.9

Comments on Study Assay Validation: Acceptable.

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

Comments on Chromatograms: Acceptable.

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

Pharmacokinetic Study #: R06-1613 Nicotine in Plasma		
SOP No.	**Effective Date of SOP**	**SOP Title**
LP-BA-002	15-Jan-2006	Guidelines for Excluding Data from Bioanalytical Assays
LP-BA-012	01-Sept-2006	Conduct of an Analytical Study

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	N/A (no PK repeats)
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	N/A
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays: Acceptable

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Fasting Bioequivalence Study, Study No.R06-1613 N=46						
		Test		Reference		Ratio
Parameter	Unit	Mean	CV%	Mean	CV%	(T/R)
AUCT	ng hr/mL	28.74	27.47	32.85	24.05	0.87
AUCI	ng hr/mL	30.82	26.53	34.94	22.94	0.88
CMAX	ng/mL	8.63	27.91	10.03	21.68	0.86
TMAX	hr	0.97	28.97	0.92	24.62	1.06
KE	hr-1	0.33	19.42	0.33	15.07	1.00
THALF	hr	2.15	19.60	2.12	15.45	1.01

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

Drug name - Nicotine Dose 4 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. No.R06-1613				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	27.66	31.81	0.87	83.37 – 90.69
AUC∞ (hr *ng/ml)	29.75	33.95	0.88	84.27 – 91.12
Cmax (ng/ml)	8.29	9.78	0.85	80.95 – 88.79

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Drug name - Nicotine Dose 4 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. No.R06-1613 N=46					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	27.66	31.81	0.87	83.37	90.69
AUC∞ (hr *ng/ml)	29.75	33.95	0.88	84.27	91.12
Cmax (ng/ml)	8.29	9.78	0.85	80.95	88.79

Table 17. Additional Study Information, Fasting Study No. R06-1613

Root mean square error, AUC0-t	0.1200	
Root mean square error, AUC∞	0.1116	
Root mean square error, Cmax	0.1318	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	All	All
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	None	None
first measurable drug concentration as Cmax	None	None
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	46	0.93	0.88	0.96
Reference	46	0.94	0.86	0.97

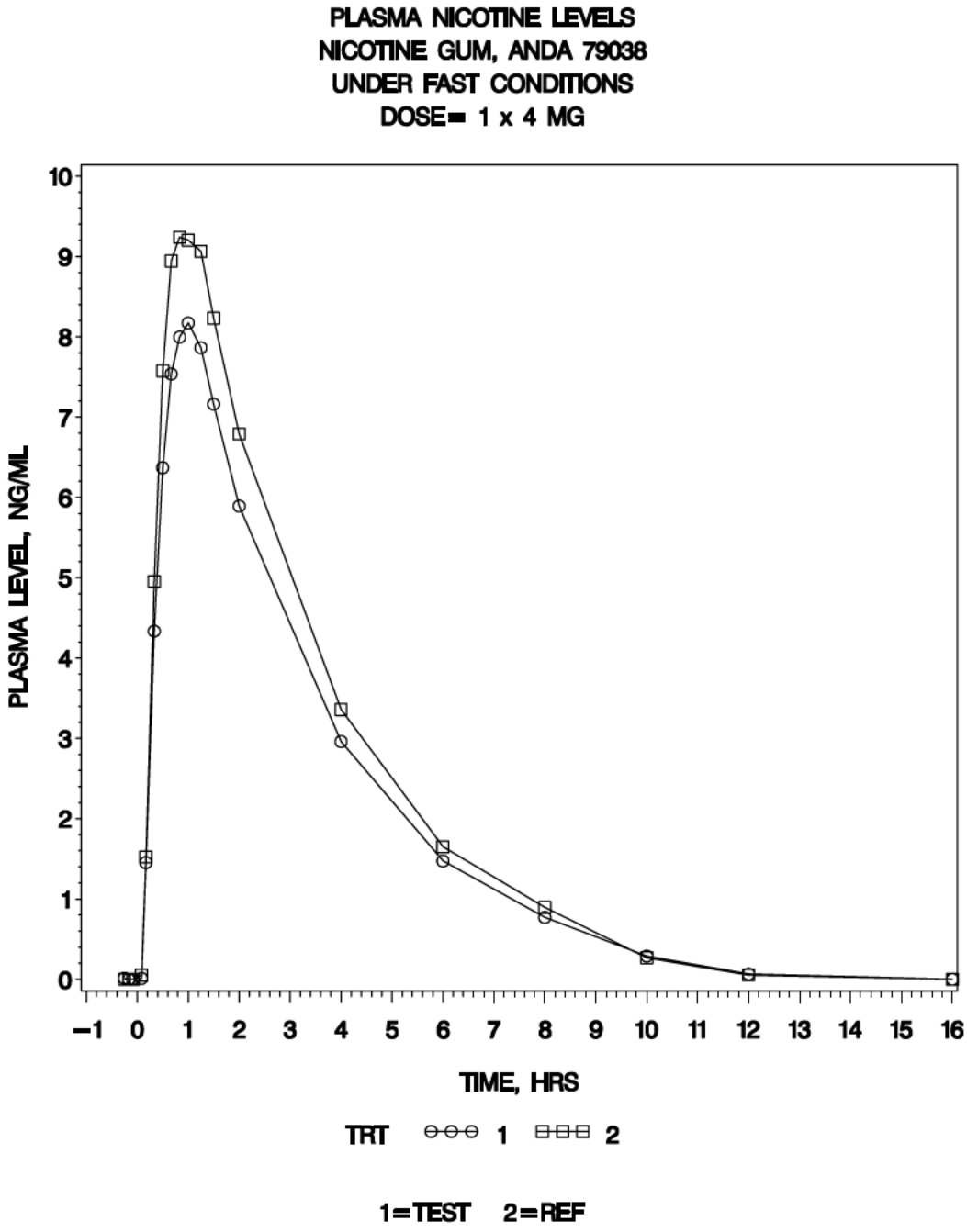
Comments on Pharmacokinetic and Statistical Analysis: The 90% confidence intervals for AUCt, AUCi, and Cmax were within the acceptable range limits of 80-125%. The reviewer's statistical recalculations of the PK parameters are in agreement with the firm's results.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: Acceptable

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

Nicotine in Plasma					
Time (hr)	Test (n=46)		Reference (n=46)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
-0.25	0.01	678.23	0.00	.	.
-0.167	0.00	.	0.00	.	.
-0.083	0.00	.	0.00	.	.
0.083	0.01	678.23	0.05	388.44	0.23
0.167	1.45	45.72	1.52	55.43	0.95
0.333	4.34	34.66	4.96	35.00	0.88
0.5	6.37	31.66	7.58	23.27	0.84
0.667	7.54	26.43	8.95	24.81	0.84
0.833	8.00	27.85	9.24	23.42	0.87
1	8.17	30.79	9.21	23.11	0.89
1.25	7.86	29.55	9.06	24.45	0.87
1.5	7.16	26.23	8.23	24.09	0.87
2	5.89	25.29	6.79	22.95	0.87
4	2.96	28.58	3.36	26.00	0.88
6	1.47	33.71	1.65	30.38	0.89
8	0.77	61.54	0.90	38.37	0.86
10	0.29	129.68	0.27	134.73	1.08
12	0.06	295.86	0.05	332.33	1.20
16	0.00	.	0.00	.	.

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



4.1.2 Single-dose Chew-out Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	R06-1613
Study Title	A Pharmacokinetic Study of Watson 4 mg Nicotine Polacrilex Coated Gum, Fruit Flavor, and GlaxoSmithKline (Nicorette® Fruit Chill™) 4 mg Nicotine Polacrilex Gum in Healthy Adult Smokers
Clinical Site (Name & Address)	PRACS Institute, Ltd.; Fargo, North Dakota
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	Period I: January 30, 2007; Period II: February 6, 2007
Analytical Site (Name & Address)	PRACS Institute, Ltd.; Fargo, North Dakota
Analysis Dates (Chewed Gum)	February 12 - 13, 2007
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	15 days (Chewed Gum)

Table 20. Product Information

Product	**Test**	**Reference**
Treatment ID	A	B
Product Name	Nicotine Polacrilex Coated Gum, Fruit Flavor, 4 mg	Nicorette® Fruit Chill™, 4 mg (Nicotine Polacrilex Coated Gum)
Manufacturer	Watson Laboratories, Inc.	Pfizer Health AB for GlaxoSmithKline Consumer Healthcare, L.P.
Batch/Lot No.	RD1407	HA935A
Manufacture Date	Nov 2006	N/A
Expiration Date	N/A	12/2007
Strength	4 mg	4 mg
Dosage Form	Gum	Gum
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	97.0%	104.3%
Content Uniformity (mean, %CV)	97.4%, %CV 1.8	N/A
Dose Administered	4 mg	4 mg
Route of Administration	Oral transmucosal	Oral transmucosal

Table 21. Study Design, Single-Dose Chew-Out Study

No. of Subjects	50 dosed (48 completed)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 Days
Randomization Scheme	Same as in PK Study
Blood Sampling Times	Not Applicable
Blood Volume Collected/Sample	Not Applicable
Blood Sample Processing/Storage	Not Applicable
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting Before Meal	At least 10 hrs. No smoking for 36 hrs prior the study and until the last blood sampling. Checked by monitoring expired CO performed at random times (CO < 10 ppm).
Length of Confinement	60 hours (36 hours prior to the first scheduled chewing session and 24 hours post-dosing)
Safety Monitoring	Sitting blood pressure and heart rate were measured before the chewing session (dosing) during each study period.
Chewing Session	The gum was chewed three times every 4 seconds for each one of the six durations on one side of the mouth and then move the gum to the other side of the mouth to repeat the chewing. Each treatment period included a total of 6 chewing sessions of different durations (30, 22, 16, 12, 8, and 5 minutes). The first chewing session was 30 minutes and subsequent sessions were of decreasing duration. Each chewing session was separated by at least 1.25 hours.

Comments on Study Design: The study design is acceptable.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Single-Dose Chew out Study

Pharmacokinetic Study, Study #: R06-1613			
		Treatment Groups	
		Test Product N=46	Reference Product N=46
Age (years)	Mean ± SD	27.22 ± 7.50	27.22 ± 7.50
	Range	18 - 45	18 - 45
Age Groups	< 18	-	-
	18 – 40	42 (91.30%)	42 (91.30%)
	41 – 64	4 (8.70%)	4 (8.70%)
	65 – 75	-	-
	> 75	-	-
Sex	Male	32 (69.57%)	32 (69.57%)
	Female	14 (30.43%)	14 (30.43%)
Race	Asian	-	-
	Black	-	-
	Caucasian	41(89%)	41(89%)
	Hispanic	-	-
	Other	5(11%)	5(11%)
BMI	Mean + SD	25.60 ± 3.12	25.60 ± 3.12
	Range	19.7 - 31.6	19.7 - 31.6

Table 23. Dropout Information, Single-Dose Chew-Out Study

Pharmacokinetic Study, Study #: R06-1613			
Subject No.	Reason	Period	Replaced?
30	Elected to withdraw prior to Period II dose administration due to scheduling conflict.	1	No
34	Subject was dropped prior to Period II dosing due to positive drug screen	1	No

Table 24. Study Adverse Events, Single-Dose Chew-Out Study

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups Pharmacokinetic Study #: R06-1613	
	Test N=49	Reference N=49
	n (%)	n (%)
Gastrointestinal disorders		
Eructation	5 (10.20%)	5 (10.20%)
Hiccups	8 (16.33%)	4 (8.16%)
Nausea	-	1 (2.04%)
Stomatitis	1 (2.04%)	3 (6.12%)
Throat irritation	9 (18.37%)	8 (16.33%)
General disorders and administration site conditions		
Hyperhidrosis	-	1 (2.04%)
Pallor	-	1 (2.04%)
Infections and infestations		
Pharyngitis	1 (2.04%)	-
Nervous system disorders		
Dizziness	2 (4.08%)	2 (4.08%)
Headache	2 (4.08%)	-
Respiratory, thoracic and mediastinal disorders		
Cough	18 (36.73%)	9 (18.37%)
Total Subjects Reporting at Least One Adverse Event	30 (61.22%)	21 (42.86%)

Table 25. Protocol Deviations, Single-Dose Chew-Out Study

Pharmacokinetic Study, Study #: R06-1613		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Concomitant medication	47	N/A
Lifestyle guideline violation	N/A	36
Subject evaluation (CO measurement)	N/A	33
Subject not queried for adverse event	N/A	22
Repeat chemistry safety lab after exit not completed for subject 22	N/A	N/A
Repeat urine drug screen not collected	01	13

Comments on Adverse Events/Protocol Deviations: The protocol deviations and adverse events reported for the subjects included in the analysis were judged to have no significant impact on determination of bioequivalence.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Single-Dose Chew-Out Study

Pharmacokinetic Study #: R06-1613 Nicotine in Chewed Gum								
Parameter	**Standard Curve Samples**							
Concentration (µg/unit)	100	200	500	1000	2250	3150	3870	4500
Interday Precision (%CV) *	-	-	-	-	-	-	-	-
Interday %Bias (%Actual)	6.00	0.50	-3.20	-4.20	1.33	0.95	-0.52	0.67
Linearity	0.9995							
Linearity Range (µg/unit)	100 – 4500							
Sensitivity/LOQ (µg/unit)	100							

Pharmacokinetic Study #: R06-1613 Nicotine in Chewed Gum			
Parameter	**Quality Control Samples**		
Concentration (µg/unit)	300	2000	3500
Interday Precision (%CV)	1.45	0.51	0.74
Interday %Bias (%Actual)	2.33	4.50	4.00

* No %CV is calculated because there were only two singlet curves run for this study.

Comments on Study Assay Validation: Acceptable.

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

Comments on Chromatograms: Acceptable.

Table 27. SOP's Dealing with Bioanalytical Repeats of Single-Dose Chew-Out Study Samples

PK Study #: R06-1613 (30 minute Chewing Piece Only) and Salivary Dissolution Study #: R06-1612 Nicotine in Chewed Gum		
SOP No.	**Effective Date of SOP**	**SOP Title**
405_07 Version 01	08/15/2005	Sample Repeats, Re-Injections and Re-Integrations

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	N/A (no PK repeats)
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	N/A
If no, reason for disagreement	N/A

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean for Percent Nicotine Released from Nicotine Gum 4 mg

Residual Nicotine in Cud – Component of Fasting PK Study, Study No. R06-1613									
Parameter (in 30 minutes)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
Percent Released (%)	78.65	8.80	57.75	92.27	84.36	11.45	56.80	101.1	0.93

Table 30. Geometric Means and 90% Confidence Intervals for Percent Nicotine Released from Nicotine Gum – Reviewer Calculated

Drug name: Nicotine Dose: 4 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Residual Nicotine in Cud – Component of Fasting PK Study, Study No. R06-1613						
Parameter	Test		Reference		Point Estimate	90% C.I.
	Mean	SE	Mean	SE		
Ln Percent Nicotine Release	78.65	0.47	84.36	0.47	0.94	92.21-94.86

Table 31. Additional Study Information

Root mean square error, Ln Percent	0.04111

Comments on Pharmacokinetic and Statistical Analysis: The reviewer ran the ANOVA for the residual nicotine in cuds and calculated the 90% CI for nicotine concentrations. The test/reference mean ratio of nicotine in the gums after a 30 minutes chewing interval is within 80-125% range..

Summary/Conclusions, Single-Dose Chew-out Study: Acceptable.

4.1.3 Multi-dose Chew-out Study

4.1.3.1 Study Design

Table 32. Study Information

Study Number	R06-1612
Study Title	Comparative, Randomized, 4 Period, 2 Sequence, Crossover **Salivary Dissolution Study** of Watson Nicotine Polacrilex Coated Gum, Fruit Flavor (2 mg and 4 mg) and GlaxoSmithKline (Nicorette® Fruit Chill™) Nicotine Polacrilex Gum (2 mg and 4 mg) in Healthy Adult Smokers
Clinical Site (Name & Address)	PRACS Institute, Ltd.; Fargo, North Dakota
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	Period I: January 15, 2007; Period II: January 16, 2007 Period III: February 1, 2007; Period IV: February 2, 2007
Analytical Site (Name & Address)	PRACS Institute, Ltd.; Fargo, North Dakota
Analysis Dates (Plasma)	January 18 – February 8, 2007
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	24 days

Table 33. Product Information – Salivary Dissolution Study

Salivary Dissolution Study, Study #: R06-1612				
Product	**Test 1 (A)**	**Reference 1 (B)**	**Test 2 (C)**	**Reference 2 (D)**
Treatment ID	A	B	C	D
Product Name	Nicotine Polacrilex Coated Gum, Fruit Flavor, 4 mg	Nicorette® Fruit Chill™, 4 mg (Nicotine Polacrilex Coated Gum)	Nicotine Polacrilex Coated Gum, Fruit Flavor, 2 mg	Nicorette® Fruit Chill™, 2 mg (Nicotine Polacrilex Coated Gum)
Manufacturer	Watson Laboratories, Inc.	Pfizer Health AB (For GlaxoSmithKline Consumer Healthcare, L.P.)	Watson Laboratories, Inc.	Pfizer Health AB (For GlaxoSmithKline Consumer Healthcare, L.P.)
Batch/Lot No.	RD1407	HA935A	RD1408	HA925A
Manufacture Date	Nov. 2006	N/A	Jan. 2007	N/A
Expiration Date	N/A	12/2007	N/A	12/2007
Strength	4 mg	4 mg	2 mg	2 mg
Dosage Form	Gum	Gum	Gum	Gum
Bio-batch Size	(b) (4)	N/A	(b) (4)	N/A
Production Batch Size		N/A		N/A
Potency	97.0%	104.3%	100.4%	102.1%
Content Uniformity	97.4%	N/A	99.5%	N/A

(mean, %CV)	%CV 1.8		%CV 1.5	
Dose Administered	4 mg	4 mg	2 mg	2 mg
Route of Administration	Oral transmucosal	Oral transmucosal	Oral transmucosal	Oral transmucosal

Table 34. Study Design, Multiple-Dose Chew-Out Study

No. of Subjects	20
No. of Sequences	2
No. of Periods	4
No. of Treatments	4
No. of Groups	1
Washout Period	First dose of each study period will be separated by 24 hrs.
Randomization Scheme	ABCD:4,5,7,8,9,10,15,16,19,20 BADC:1,2,3,6,**11**,12,13,14,17,18
Blood Sampling Times	N/A (the concentration of nicotine remaining in the gum after chewing was analyzed)
Blood Volume Collected/Sample	Nicotine in gum collected for analysis
Blood Sample Processing/Storage	Nicotine in gum collected for analysis
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting Before Meal	N/A
Length of Confinement	12 hours prior to first scheduled chewing session through completion of the last chewing session on Day #4.
Safety Monitoring	Vital signs obtained prior to first chewing session daily.
Chewing Session	The gum was chewed three times every 4 seconds for each one of the six durations on one side of the mouth and then move the gum to the other side of the mouth to repeat the chewing. Each treatment period included a total of 6 chewing sessions of different durations (30, 22, 16, 12, 8, and 5 minutes). The first chewing session was 30 minutes and subsequent sessions were of decreasing duration. Each chewing session was separated by at least 1.25 hours.

Comments on Study Design: The study design is acceptable.

4.1.3.2 Clinical Results

Table 35. Demographics Profile of Subjects Completing the Multi-Dose Chew-Out Study

Salivary Dissolution Study, Study #: R06-1612					
		Treatment Groups			
		Test 1 (A) Product N=20[1]	Reference 1 (B) Product N=20[1]	Test 2 (C) Product N=19[1]	Reference 2 (D) Product N=19[1]
Age (years)	Mean ± SD	26.95 ± 6.98	26.95 ± 6.98	26.26 ± 6.44	26.26 ± 6.44
	Range	18 - 44	18 - 44	18 - 44	18 - 44
Age Groups	< 18	-	-	-	-
	18 – 39	18 (90.00%)	18 (90.00%)	18 (94.74%)	18 (94.74%)
	40 – 64	2 (10.00%)	2 (10.00%)	1 (5.26%)	1 (5.26%)
	65 – 75	-	-	-	-
	> 75	-	-	-	-
Sex	Male	15 (75.00%)	15 (75.00%)	14 (73.68%)	14 (73.68%)
	Female	5 (25.00%)	5 (25.00%)	5 (26.32%)	5 (26.32%)
Race	Asian	-	-	-	-
	Black	1 (5.00%)	1 (5.00%)	-	-
	Caucasian	19 (95.00%)	19 (95.00%)	19 (100.00%)	19 (100.00%)
	Hispanic	-	-	-	-
	Other	-	-	-	-
BMI	Mean ± SD	25.37 ± 3.18	25.37 ± 3.18	25.35 ± 3.27	25.35 ± 3.27
	Range	20.7 - 32	20.7 - 32	20.7 - 32	20.7 - 32
Other Factors					

Table 36. Dropout Information, Multiple-Dose Chew-Out Study

Salivary Dissolution Study, Study #: R06-1612			
Subject No.	**Reason**	**Period**	**Replaced?**
11	Subject withdrew consent prior to Period III check-in and was subsequently lost to follow-up.	II	No

Table 37. Study Adverse Events, Multiple-Dose Chew-Out Study

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups			
	Salivary Dissolution Study, Study #: R06-1612			
	Test 1 (A) N=20[2]	Reference 1 (B) N=20[2]	Test 2 (C) N=19[2]	Reference 2 (D) N=19[2]
	n (%)[3]	n (%)[3]	n (%)[3]	n (%)[3]
Gastrointestinal disorders				
Eructation	4 (20.00%)	3 (15.00%)	3 (15.79%)	1 (5.26%)
Gingival disorder	-	-	1 (5.26%)	-
Stomatitis	11 (55.00%)	12 (60.00%)	12 (63.16%)	7 (36.84%)
Throat irritation	3 (15.00%)	6 (30.00%)	8 (42.11%)	9 (47.37%)
Tongue discoloration	1 (5.00%)	2 (10.00%)	4 (21.05%)	-
Musculoskeletal and connective tissue disorders				
Flank pain	1 (5.00%)	-	-	-
Respiratory, thoracic and mediastinal disorders				
Cough	5 (25.00%)	9 (45.00%)	9 (47.37%)	6 (31.58%)
Hiccup	4 (20.00%)	2 (10.00%)	2 (10.53%)	4 (21.05%)
Pharyngeal erythema	10 (50.00%)	6 (30.00%)	3 (15.79%)	5 (26.32%)
Pharyngolaryngeal pain	-	1 (5.00%)	-	-
Sneezing	-	-	1 (5.26%)	-
Skin and subcutaneous disorders				
Skin atrophy	-	1 (5.00%)	-	1 (5.26%)
Total Subjects Reporting at Least One Adverse Event	19 (95.00%)	19 (95.00%)	17 (89.47%)	16 (84.21%)

Test 1 (A): Nicotine Polacrilex Coated Gum, Fruit Flavor, 4 mg, [Lot No. RD1407
Reference 1 (B): Nicorette® Fruit Chill™, 4 mg, (Nicotine Polacrilex Coated Gum), Lot No. HA935A
Test 2 (C): Nicotine Polacrilex Coated Gum, Fruit Flavor, 2 mg, Lot No. RD1408
Reference 2 (D): Nicorette® Fruit Chill™, 2 mg (Nicotine Polacrilex Coated Gum), [Lot No. HA925A

Table 38. Protocol Deviations, Multi-Dose Chew-Out Study

Salivary Dissolution Study, Study #: R06-1612		
Type	**Subject #s (Test)**	**Subject #s (Reference)**
Subject reported prescription medication use during the study.	N/A	10

Comments on Adverse Events/Protocol Deviations: The protocol deviations and adverse events reported for the subjects included in the analysis were judged to have no significant impact on determination of bioequivalence.

4.1.3.3 Bioanalytical Results

Table 39. Assay Validation – Within the Multi-Dose Chew-Out Study

Summary of Standard Curve and QC Data for Chewed Gum Sample Analyses (in the Salivary Dissolution Study)

Salivary Dissolution Study #: R06-1612 Nicotine in Chewed Gum								
Parameter	**Standard Curve Samples**							
Concentration (µg/unit)	100	200	500	1000	2250	3150	3870	4500
Interday Precision (%CV)	3.82	0.46	2.49	2.38	1.35	0.95	0.39	0.37
Interday %Bias (%Actual)	3.00	0.00	-1.20	-2.90	0.89	-0.63	-0.26	0.89
Linearity	0.9994 – 1.0000							
Linearity Range (µg/unit)	100 – 4500							
Sensitivity/LOQ (µg/unit)	100							

Salivary Dissolution Study #: R06-1612 Nicotine in Chewed Gum			
Parameter	**Quality Control Samples**		
Concentration (µg/unit)	300	2000	3500
Interday Precision (%CV)	1.73	2.49	1.10
Interday %Bias (%Actual)	0.00	1.00	2.57

Comments on Study Assay Validation: Acceptable.

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

Comments on Chromatograms: Acceptable.

Table 40. SOP's Dealing with Bioanalytical Repeats of Multi-Dose Chew-Out Study Samples

PK Study #: R06-1613 (30 minute Chewing Piece Only) and Salivary Dissolution Study #: R06-1612 Nicotine in Chewed Gum		
SOP No.	**Effective Date of SOP**	**SOP Title**
405_07 Version 01	08/15/2005	Sample Repeats, Re-Injections and Re-Integrations

Table 41. Additional Comments on Repeat Assays

Were all SOPs followed?	N/A (no repeat assays)
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	N/A
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays: incomplete due to deficiencies cited above.

4.1.3.4 Pharmacokinetic Results

Table 42. Arithmetic Means

Percentage of Dose Released After Chewing a Gum for Indicated Duration

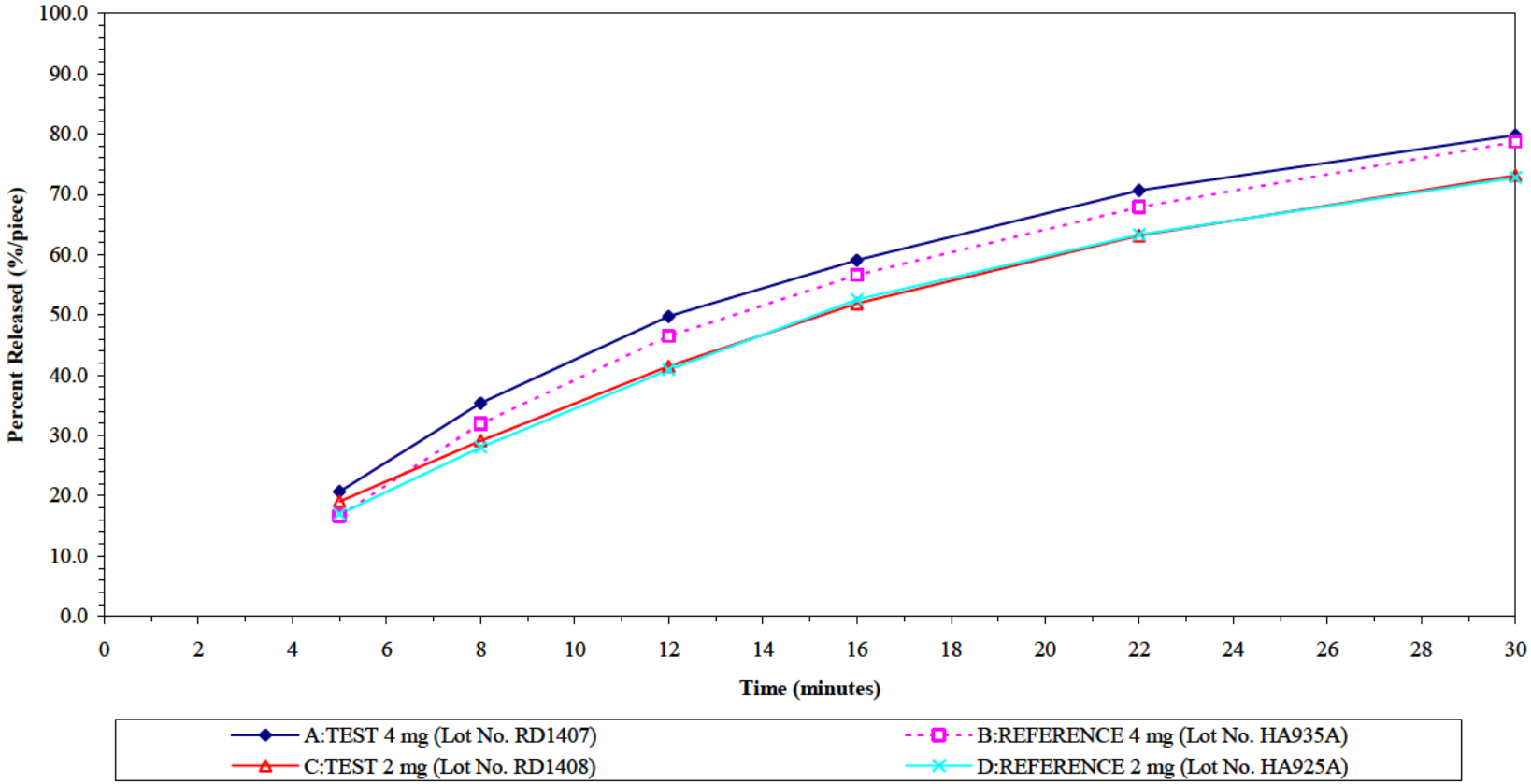
Chewing Duration (minutes)	Test – 4 mg Lot # RD1407 Percent (%) Released			Nicorette® - 4 mg Lot #HA935A Percent (%) Released			
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**	**T/R**
5	20.71	30.73	(b) (4)	16.69	36.77	(b) (4)	1.24
8	35.39	18.35		31.93	25.15		1.11
12	49.77	14.40		46.49	16.76		1.07
16	59.07	11.04		56.65	15.14		1.04
22	70.64	9.61		67.91	11.50		1.04
30	79.82	6.92		78.69	8.85		**1.01**

Chewing Duration (minutes)	Test – 2 mg Lot # RD1408 Percent (%) Released	Nicorette® - 2 mg Lot #HA925A Percent (%) Released

	Mean	%CV	Range	Mean	%CV	Range	T/R
5	19.09	17.49	(b) (4)	17.01	28.98	(b) (4)	1.12
8	29.15	13.97		28.06	20.85		1.04
12	41.47	12.19		40.90	13.70		1.01
16	51.91	13.79		52.58	14.93		0.99
22	63.18	10.54		63.33	14.41		0.99
30	73.15	8.66		72.83	11.78		**1.00**

Mean Chewed Cud Data (0-30 minutes) – Percent Nicotine Released from Cud (Based on Initial Amount)

4 mg Products: N=20 and 2 mg Products: N=19



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

The Test/Reference ratios for the percent nicotine released during the 30 minute chewing duration for 2 mg and 4 mg were 1.00 and 1.01, respectively. These are within the acceptable limits of 0.80-1.25 ratio. The study is incomplete due to deficiencies cited above.

4.2 Formulation Data

Ingredient / Grade	Amount (mg) / Tablet		Amount (%) / Tablet	
	2 mg Strength	4 mg Strength	2 mg Strength	4 mg Strength

(b) (4)

[redacted]

Is there an overage of the active pharmaceutical ingredient (API)?	YES
If the answer is yes, has the appropriate chemistry division been notified?	YES
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	NO
Comments on the drug product formulation:	Pharm/Tox consult submitted for Xylitol, Acesulfame Potassium, DC Yellow #10 Lake, Sucralose and Titanium

	Dioxide (see Reg. Support Comments below). The formulation is acceptable based on full Pharm-Tox consult report (see full report below).

Reviewer's Note: The RLD and the approved ANDA 74-707 Nicotine Polacrilex 4 mg formulation includes a (b) (4) overage. ANDAs 76-779 and 78326 have (b) (4) overage.

OGD REGULATORY SUPPORT (David Skanchy) – PHARM-TOX CONSULT TO ONP-DNCE HFD-560 (1/18/08; Consult No. 2008-0193)

This consult supercedes and replaces any previous excipient tox consult for ANDAs 78-697, 78-699, 79-216, 79-219, 79-044 and 79-038. The three similar formulations in these nicotine gum ANDA's were consolidated (with review division concurrence) into a single consult due to the significant overlap in information. To summarize, the original consult was for the mint flavor formulation and the consult included xylitol, acesulfame potassium, hydroxypropyl cellulose, and titanium dioxide (ANDAs 78-697 and 78-699). The fruit flavor adds the excipient Sucralose (79-044 and 79-038) to the consult. The cinnamon flavor adds hypromellose and FD&C Red #40 to the consult (79-216 and 79-219). This consult covers all seven excipients listed above across the three formulations. Except for new information on the added excipients, which are in the EDR for each ANDA listed above, all of the information on the common excipients in the consult is duplicated in each. All the relevant information on the fruit and cinnamon formulations is in edr, including the components and compositions statements. The complete tox information for all seven excipients listed above is in the files for ANDAs 79-216 and 79-219 since this formulation contains all of the excipients.

Pharm Tox Report (N 078699 N 000 20-Dec-2006)

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation (DNCE)
Tel 301-796-2080
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From: Wafa Harrouk, Ph.D., Pharmacologist/Toxicologist, DNCE
Via: Paul Brown, Ph.D., Associate Director, Pharmacology/Toxicology, OND
Andrea Leonard-Segal, M.D., Division Director, DNCE
To: David Skanchy, Ph.D.
Chemist
Division Chemistry II
Office of Generic Products

HFD-560 Consult #: 7093; Generics consult #: 2008-0193

Subject: The Office of Generics is consulting the toxicologist at the Office of Non Prescription Products, DNCE regarding the use of higher than previously approved doses for several excipients in nicotine polacrilex gum coated (2 & 4 mg). These are: Acesulfame potassium, (b) (4) hydroxypropylcellulsoe, titanium oxide, xylitol, sucralose, hypermellose, and FD&C red #40, all of which are covered under the following ANDAs: 78-697, 78-699, 79-216, 79-219, 79-044, 79-038, 78-697 and 78-699

Material Reviewed: Toxicology reviews for excipients used in food and cosmetic products
Date: February 11, 2008

Background: The office of Generics refused to file ANDA 78-699 because the concentration of the inactive ingredients Xylitol, Acesulfame Potassium, (b) (4) Flavor (b) (4) in the proposed product exceeded the previously approved maximum concentration of these inactive ingredients in a buccally administered drug product. The Office of Generics requested additional justification to demonstrate the safe use of the higher concentration of these excipients from examples of approved drug products administered by the same route of administration, which contain these inactive ingredients in the same concentration range. In response, the sponsor has submitted literature reviews which included scientific position papers and monographs published by the World Health Organization, FDA/CFSAN, the European Food Safety Authority (EFSA) and the Cosmetic Ingredient Review (CIR). A table summarizing the previously approved and the proposed new doses is included at the end of this review.

CONSULT REPLY

Acesulfame Potassium NF: The proposed dose for the use of acesulfame potassium in the nicotine gum for the ANDAs in question is (b) (4) /day if a maximum number of 24 pieces of gum were to be consumed per day (b) (4) /kg/day for a 60 kg person). This represents an increase of (b) (4) mg from the already approved dose of 48 mg/day obtained by consuming 24 pieces of gum/day. A review by the World Health Organization (WHO; food additive series 28[1], 1991) has reviewed all the available toxicity studies conducted for acesulfame potassium and concluded that the rat is an appropriate species model for humans. Based on the 2-year rat carcinogenicity bioassay, a no adverse effect level (NOAEL) value of 1500 mg/kg/day and an acceptable daily intake (ADI) value of 0-15 mg/kg/body weight in humans were established. The 2-year oral carcinogenicity studies (2 studies in two different strains of rats) as well as other toxicity studies were conducted mostly via oral gavage and thus did not address the buccal toxicity concern. Although no buccal study was conducted or referenced, the sponsor provided data on the pharmacokinetic profile for acesulfame potassium in multiple species. There does not appear to be a potential for metabolism or accumulation of acesulfame potassium in tissues (plasma half life= 1.5 hrs) and urinary excretion is rapid and complete (90% of the dose was excreted within the first 24 hrs). The only additional information that could be discerned from a buccal study would be that of a local toxicity concern for the higher concentration of acesulfame potassium.

Recommendation: The increase in the maximum total concentration of acesulfame potassium in the proposed new formulation does not seem to have a potential cause for concern based on the amount of data available on the safety profile for this ingredient. The new proposed dose should be safe for human consumption based on the large safety margins established for using this product as a food additive ingredient. No new no clinical studies are recommended but the office can ask for additional human safety data if there is any concern over the safety of buccal administration for the new formulation. No new pharmacology/ toxicology studies are recommended for this ingredient.

(b) (4): The proposed dose for the use of (b) (4) in the nicotine gum for the ANDAs in question in this consult is (b) (4) mg/day if a maximum number of 24 pieces of gum were to be consumed (b) (4) mg/kg/day for a 60 kg person). This represents an increase of (b) (4) mg from the already approved dosage of (b) (4) mg/day obtained by consuming 24 pieces of gum/day. A review by the Joint Food & Agriculture Organization (FAO)/WHO Expert Committee on Food Additives (referred to as JEFCA) based on the National Toxicology Program's (NTP) mouse 2-year carcinogenicity bioassay established a NOAEL value of (b) (4) mg/kg/day and an acceptable daily intake (ADI) value for (b) (4) of (b) (4) /kg/body weight in humans ((b) (4) mg/kg/day for a 60 kg person). (b) (4) is listed as generally recognized as safe (GRAS) as a flavoring in foods and has been approved at levels of (b) (4) mg/lozenge in anti-tussive lozenges. No buccal study was conducted or referenced.

Recommendation: The new proposed dose should be safe for human consumption based on the large safety margins established for using (b) (4) as a GRAS food additive ingredient. No new no clinical studies are recommended but the office can ask for additional human safety

[1] www.inchem.org/documents/jefca/iecmono (b) (4) tm

data if there is any concern over the safety of buccal administration for the new formulation. No new pharmacology/toxicology studies are recommended for this ingredient.

Titanium dioxide (TiO_2)**:** TiO_2 is widely used as a coloring agent in foods in addition to its use in cosmetics at concentrations up to 1% by weight with no restrictions on the levels of use. The proposed dose for the use of TiO_2 in the nicotine gum for the ANDA in question in this consult is (b) (4) mg/piece. Assuming daily consumption of 24 pieces of gum, a maximum total dose of (b) (4) mg/day (equivalent to (b) (4) mg/kg/day for a 60 kg person) is projected. Previously approved oral doses (1387 mg/capsule) far exceed the proposed buccal doses. There are no FDA approved buccal TiO_2 doses and no buccal study was conducted or referenced. Dietary exposure to TiO_2 studied in a chronic toxicity study (103 weeks) at doses up to 5% (50,000 ppm) did not show any toxicological or carcinogenic effects. Oral exposure to TiO_2 did not show any accumulation in the tissues and was negative in *in vitro* genotoxicity assays.
Recommendation: The new proposed dose should be safe for human consumption based on the large safety margins established for using TiO_2 as a GRAS food additive ingredient and as an approved ingredient in oral capsules where higher doses were already approved. As a safeguard the Office can ask for additional human safety data if there is any concern over the safety of buccal administration. No new pharmacology/toxicology studies are recommended for this ingredient.

Xylitol: The proposed maximum dose is (b) (4) g/day if 24 pieces of gum were to be consumed. This represents an increase from the already approved dosage of ~ 5 g/day which is obtained by consuming 24 pieces of gum/day. The Scientific Committee for Food (SCF) of the European Union (EU) found that consuming Xylitol at a dose up to 20 g/person/day was acceptable and did not have undesirable laxative effects. Xylitol is listed as an inactive ingredient of approved drug products and has long been used in food as a low caloric sugar substitute. Human data for daily consumption of xylitol at up to 67 mg/day by adults for 2 years and up to 80 g/day for children aged 7-16 years of age (duration not indicated) did not increase the incidence of adverse effects. Children consuming 65 g/day had an increased incidence of flatulence and transient diarrhea.
Recommendation: The new proposed dose should be safe for human consumption based on the long history of using xylitol in chewing gums via the buccal route of exposure as well as in other artificially sweetened products. No new pharmacology/toxicology studies are recommended for this ingredient.

Sucralose: The proposed dose of (b) (4) mg/piece does not exceed the previously approved dose of 5.75 mg/piece. The only issue raised for sucralose is the lack of buccal studies. There are no FDA approved buccal sucralose products and no buccal study was conducted or referenced.
Recommendation: The new proposed dose should be safe for human consumption based on the large safety margins established for using sucralose as a food additive and an inactive ingredient in drug products. As a safeguard the Office can ask for additional human safety data if there is any concern over the safety of buccal administration. No new pharmacology/ toxicology studies are recommended for this ingredient.

Hydroxypropyl Cellulose (HPC): The proposed dose for the use of HPC in the nicotine gum for the ANDAs in question in this consult is (b) (4) mg/day if a maximum number of 24 pieces of gum were to be consumed (b) (4) mg/kg/day for a 60 kg person). The previously approved sublingual/buccal dose by FDA is 1 mg/ tablet. However, HPC is also listed in the inactive ingredient list with an approved maximum dose 240 mg/tablet for oral consumption. HPC

seems to be inert and is not absorbed from the digestive system. A review by JEFCA[2] concluded that HPC and other modified celluloses are safe for use in foods without the need to set an ADI limit. No buccal study was conducted or referenced.
Recommendation: The new proposed dose should be safe for human consumption based on the large safety margins established for using HPC as a GRAS food additive ingredient and as an approved ingredient in oral tablets. As a safeguard the Office can ask for additional human safety data if there is any concern over the safety of buccal administration. No new pharmacology/toxicology studies are recommended for this ingredient.

Hypromellose: Hypromellose, formerly known as hydroxypropylmethylcellulose (HPMC), is a widely used cellulose ether used in the fabrication of hydrophilic matrices. Hypromellose provides the release of a drug in a controlled manner, effectively increasing the duration of release of a drug to prolong its therapeutic effect. HPMC and other cellulose derivatives pass without metabolic changes through the GI tract following oral administration. The proposed dose for the use of hypromellose in the nicotine gum for the ANDA in question i (b) (4) mg/tablet. Assuming a maximum number of 24 pieces of gum were to be consumed, this would equate to a total dose of (b) (4) mg/day (equivalent to (b) (4) mg/kg/day for a 60 kg person). The proposed new dose represents an increase from the already approved 2.25 mg/tablet. JECFA concluded that modified celluloses, as a group (including HPMC), are of very low toxicity. However, the evaluation notes the observation of adverse gastrointestinal effects (e.g., laxative effect) in clinical studies at high doses and recommends an upper safe level of 30 g/person/day of dietary fiber in general. A GRAS notification letter was submitted to CFSAN in 2007 (Notice # GRN 000213) to allow the use of HPMC in foods at levels up to 20 g/person/day[3] but CFSAN hasn't made a decision on this petition as of 2/7/2008. There are no FDA approved buccal hypromellose doses and no buccal study was conducted or referenced.
Recommendation: The new proposed dose should be safe for human consumption based on the large safety margins established for using hypromellose as a GRAS food additive ingredient and as an approved ingredient in oral drug tablets. As a safeguard the Office can ask for additional human safety data if there is any concern over the safety of buccal administration.

FD&C red # 40: FD&C red dye #40 is a food dye additive which is also referred to as Allura red AC dye and has been approved for use without limits in foods and drugs. Red #40 is approved in oral drug products at doses up to 73.2 mg/capsule, 21.25 mg/oral tablet but the only listed approved buccal dose is 0.006 mg. The sponsor argues against the potential for

[2] www.inchem.org/documents/jecfa/jecmono/v05je54 htm
[3] CFSAN Office of Food Additive Safety, March 27, 2007

buccal irritation based on the experience of the dye in other oral drugs where neither systemic nor local toxicity/irritation was noted.
Recommendation: The new proposed dose should be safe for human consumption based on the large safety margins established for using FD&C red #40 as a GRAS food additive ingredient and as an approved ingredient in oral drug tablets. As a safeguard the Office can ask for additional human safety data if there is any concern over the safety of buccal administration.

Overall Conclusion/Recommendation: The sponsor should provide a stronger rationale that would obviate the need to conduct additional human studies to eliminate the concern over the

buccal safety and irritation resulting from the use of the new nicotine gum formulation.
No clinical studies cannot provide these data. There are no new no clinical studies needed. If further guidance is required on clinical buccal studies, we recommend that you consult with the appropriate CDER dental reviewers.

Ingredient	**Approved dose**	**Route of admin.**	**Total approved max exposure (if known)**	**Proposed dose***	**Total max exposure for proposed dose (max 24 pieces/day)**
1. Acesulfame K NF	2.00 mg/piece	*Buccal/chewing gum*	48.00 mg/day	(b) (4) mg/piece	(b) (4) mg/day
	3.00 mg/tablet	Buccal***/ Sublingual-tablet	N/A		
	117 mg/dose**	Oral/powder for solution	N/A		
2. (b) (4)	(b) (4) mg/piece	*Buccal/chewing gum*	(b) (4) mg/day	(b) (4) mg/piece	(b) (4) mg/day
Total (b) (4)	(b) (4) mg/piece		(b) (4) mg/day		(b) (4) mg/day
	(b) (4) mg/tablet**	Oral/tablet	N/A		
3. hydroxypropylcellulose	1.00 mg/tablet	*Buccal/sublingual tablet*	N/A	(b) (4) mg/piece	(b) (4) mg/day
	240.00 mg/tablet**	Oral/tablet	N/A		
4. Titanium dioxide USP****	1387.00 mg/capsule**	Oral/capsule	N/A	(b) (4) mg/piece	(b) (4) mg/day
5. Xylitol NF	203.60 mg/piece	*Buccal/chewing gum*	4886.4 mg/day	(b) (4) mg/piece	(b) (4) mg/day
6. Sucralose	5.75 mg/piece**	Oral/tablet	N/A	(b) (4) mg/piece	(b) (4) mg/day
7. Hypromellose	2.25 mg/tablet	*Buccal/tablet*	N/A	(b) (4) mg/piece	(b) (4) mg/day
	480 mg/tablet**	Oral tablet	N/A		
8. FD&C red, # 40	0.006 mg/tablet	*Buccal/sublingual tablet*	N/A	(b) (4) g/piece	(b) (4) mg/day
	73.20 mg/capsule**	Oral tablet	N/A		

*, the proposed route of administration is via the buccal route. The highest doses were adopted from the various proposed formulations to assume the worst case scenario fro each ingredient
**highest oral level per dose listed in inactive ingredient database
***Buccal and sublingual route treated as the same

INGREDIENT	LARGEST AMOUNT PROPOSED (mg/gum)	IIG BUCCAL ROUTE, DOSAGE FORM
(b) (4) **Gum Base**	(b) (4)	729.60
Xylitol, (b) (4)		**203.6**
Sodium Carbonate, NF		30.00
Sodium Bicarbonate, USP		10.00
Magnesium Oxide, USP (b) (4)		7.20
(b) (4)		(b) (4)
(b) (4)		(b) (4)
(b) (4)		(b) (4)
(b) (4)		(b) (4)
Acesulfame Potassium[2] NF		2.0
Sucralose, NF		Not listed
(b) (4) **Flavor** (b) (4)		N/A
(b) (4) **Flavor**		N/A
Acacia, NF		9.1
Titanium Dioxide[3], USP		Not listed

4.3 Dissolution Data

Dissolution Review Path	

Table 43. Dissolution Data

Watson's proposed in vitro testing method found acceptable by DBE (6/4/07) (74-507, SCF-038; 74-707, SCF-033 & 76568, SCF-006)	
Device:	(b) (4)
Jaw Distance:	1.2 mm
Jaw Angle:	20°
Medium:	Phosphate Buffer (0.05M), pH 7.4 **OR** Phosphate Buffer (0.0125 M), pH 7.4 + **0.1% SLS**
Volume:	20 mL
Temperature:	37 ± 0.5°C
Stroke Frequency:	50 cycles per minute
Recommended Sampling Times:	5, 8, 12, 16, 22, 30, and 45 minutes
DBE-recommended Specification:	NLT (b) (4) (Q) dissolved in 30 min

Medium: Phosphate Buffer, pH 7.4

Sampling Time (minutes)	Test – 4 mg, Lot # RD1407 Percent Released			RLD (Nicorette®) - 4 mg, Lot #HA935A Percent Released		
	Mean	Range	%CV	Mean	Range	%CV
5	17.2	(b) (4)	8.5	37.6	(b) (4)	4.8
8	28.6		12.9	62.6		3.0
12	38.9		14.1	80.0		1.4
16	45.7		14.3	89.6		1.5
22	52..3		12.7	96.3		1.3
30	58.0		11.9	100.9		0.9
45	65.0		12.1	103.6		1.4
Sampling Time (minutes)	**Test – 2 mg, Lot # RD1408 Percent Released**			**RLD (Nicorette®) - 2 mg, Lot #HA925A Percent Released**		
	Mean	**Range**	**%CV**	**Mean**	**Range**	**%CV**
5	20.0	(b) (4)	12.3	34.6	(b) (4)	10.4
8	30.9		17.1	59.0		9.3
12	39.8		18.8	76.2		6.3
16	45.0		17.9	87.1		5.0
22	50.5		17.2	96.1		3.7
30	55.2		16.5	101.4		3.5
45	61.2		15.6	104.5		3.0

Medium: Phosphate Buffer, pH 7.4 + 0.1% SLS

Sampling Time (minutes)	Test – 4 mg, Lot # RD1407 Percent Released	RLD (Nicorette®) - 4 mg, Lot #HA935A Percent Released

	Mean	Range	%CV	Mean	Range	%CV
5	33.6	(b) (4)	5.5	41.1	(b) (4)	6.6
8	60.0		4.6	64.6		4.2
12	79.4		3.0	80.4		3.3
16	86.1		2.0	89.5		2.4
22	88.7		1.8	95.9		2.0
30	89.8		1.7	99.1		1.6
45	91.2		2.0	101.6		1.7
Sampling Time (minutes)	**Test – 2 mg, Lot # RD1408 Percent Released**			**RLD (Nicorette®) - 2 mg, Lot #HA925A Percent Released**		
	Mean	**Range**	**%CV**	**Mean**	**Range**	**%CV**
5	38.1	(b) (4)	7.5	34.8	(b) (4)	5.8
8	62.5		6.4	56.6		4.7
12	80.4		3.2	74.6		4.2
16	87.7		2.1	84.8		4.1
22	91.3		1.5	92.9		3.4
30	93.1		1.6	97.2		3.1
45	94.3		1.9	99.8		2.2

F2				
	4 mg	2 mg	2 mg vs 4 mg	
	Test vs. RLD	**Test vs. RLD**	**Test**	**RLD**
Phosphate (0.05M)	20.6	20.9	79.5	73.4
Phosphate (0.0125M) + 0.1% SLS	65.8	66.0	76.9	61.5

Mastication (Drug Release):
A method for the extraction of nicotine from Nicotine Polacrilex coated cinnamon flavored gum was developed using the (b) (4) mastication device.

Device Description
The device consists of (b) (4) mastication modules. Each module consists of a thermo-jacketed (b) (4) test cell whose temperature is maintained (b) (4). Each of the (b) (4) cells contains two vertically oriented pistons holding upper and lower mastication surfaces (jaws). The cells are filled with media and the chewing gum is loaded onto the lower mastication surface. The mastication process is controlled by up and down strokes of the lower surface in combination with a twisting movement of the upper surface, which provides mastication of the chewing gum and at the same time agitation of the media. (b) (4) are used to support the test gum and are placed above and below the gum to help with centering and to prevent fragmentation of the gum. The medium is sampled at certain time points and analyzed for drug content to create a drug release profile. The procedure allows retrieval of the residual gum cud, if necessary, for further analysis (determination of residual nicotine).

Mastication Parameters and Rationale

Dissolution Parameters		***Rationale***
Apparatus	Chewing machine	Suitable for release chewing gum dosage form

Medium	USP Phosphate Buffer, pH 7.4	The release was compared to the chew out study and this media was selected in which the release is very similar and the results indicate that no significant difference was observed as evidenced by f2 metric (more than 50). Phosphate Buffer, pH 7.4 was chosen as QC medium since it gives an acceptable release rate and variability
Volume	20 mL	Commonly used volume of mastication medium
Jaw Distance	1.2 mm	The suitable jaw distance for this product
Rotational Jaw angle	20^{o}C	The suitable rotational jaw angle for this product
Chewing Frequency	50 chews/minute	The suitable chews/min for this product
Temperature	37 ^{o}C	Typical mastication testing temperature

The analytical method used for the analysis of nicotine was validated and found acceptable by the DBE (N 076568 SCF 006 AB 07-Feb-2007).

Figure 2. Dissolution Profiles

N/A

4.4 Detailed Regulatory History (If Applicable)

N/A

4.5 Consult Reviews

N/A

Following this page, 51 pages withheld in full - (b)(4)

i	j	Means	LSMean(i)-LSMean(j)
			(b) (4)

4.7 Additional Attachments

N/A

BIOEQUIVALENCE DEFICIENCIES

ANDA: 79-038 and 79-044

APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Nicotine Polacrilex Coated Gum (Fruit Flavor), 4 mg and 2 mg

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

Your dissolution testing method is acceptable. However, your proposed dissolution specification of NLT (b) (4)% (Q) in 30 minutes is not acceptable. Based on the dissolution data you submitted, the Division of Bioequivalence is recommending an alternative specification of NLT (b) (4)% (Q) dissolved in 30 minutes for your Nicotine Polacrilex Coated Gum (Fruit Flavor) drug product. Please acknowledge your acceptance of the following dissolution method and specification.

Device:	(b) (4)
Jaw Distance:	1.2 mm
Jaw Angle:	20°
Medium:	Phosphate Buffer, 0.0125M, pH 7.4 + 0.1% SLS
Volume:	20 mL
Temperature:	37 ± 0.5°C
Stroke Frequency:	50 cycles per minute
Rec Sampling Times:	5, 8, 12, 16, 22, 30, and 45 minutes
DBE-recommended Specification:	**NLT (b) (4) (Q) dissolved in 30 minutes**

Sincerely yours,

{See appended electronic signature page}

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

4.8 Outcome Page

ANDAs: 79038 and 79044

COMPLETED ASSIGNMENT FOR 79038 ID: 5196

Reviewer: Nwakama, Patrick **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5196	6/1/2007	Bioequivalence Study	Fasting Study	1	1
5196	6/1/2007	Bioequivalence Study	Multi Dose Study	1	1
5196	6/1/2007	Other	Dissolution Waiver	1	1
				Bean Total:	3

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

/s/

Patrick E. Nwakama
4/10/2008 10:01:26 AM
BIOPHARMACEUTICS

Chandra S. Chaurasia
4/10/2008 12:32:14 PM
BIOPHARMACEUTICS

Moheb H. Makary
4/10/2008 03:00:44 PM
BIOPHARMACEUTICS
For Dr. Dale P. Conner, Director, Division of Bioequivalence

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	79-038
Drug Product Name	Nicotine Polacrilex Gum
Strength	4 mg (Coated Fruit)
Applicant Name	Watson Pharmaceuticals
Submission Date	May 02, 2008
Reviewer	Aaron Sigler, Pharm.D.

EXECUTIVE SUMMARY

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

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

The application is complete.

COMMENTS:

None

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

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

Enter Review Productivity and Generate Report

http://cdsogd1/bioprod

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

/s/

Aaron Sigler
5/7/2008 02:36:29 PM
BIOPHARMACEUTICS

Barbara Davit
5/7/2008 05:09:31 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-038

OTHER REVIEWS

MEDICAL CONSULTATION

To:	**David Skanchy, Ph.D., Team Leader** **Division of Chemistry II, Office of Generic Drugs**
Re:	**Nicotine Polacrilex Gum** **Coated Mint, Cinnamon and Fruit, 2 and 4 mg** **ANDAs 78-697, 78-699, 79-044, 79-038, 79-216, 79-219**
Sponsor:	**Watson Labs**
RLD:	**Nicorette** **GlaxoSmithKline** **N18612**
Date of Review:	**May 5, 2009**
Consultant:	**Nancy Chang, M.D.** **Medical Officer, Office of Generic Drugs**
Through:	**Dena Hixon, M.D.** **Associate Director for Medical Affairs** **Office of Generic Drugs**

Background

ANDAs 78-697, 78-699, 79-044, 79-038, 79-216, and 79-219 for Nicotine Polacrilex Gum contain eight excipients that exceed previously approved levels listed in the IIG for buccal administration. A pharm/tox consult concluded that all of the ingredients were reasonably safe for systemic exposure at the levels proposed; however, OGD was asked to consider the need for additional human safety data to address the potential for local buccal toxicity.

There are 3 basic formulations proposed: mint, fruit and cinnamon gums. The formulations differ in their composition with respect to the excipients of interest.

A previous clinical review (December 2008) of the available safety data for these formulations, including a literature and regulatory review of the ingredients and products of concern, made the following conclusions:

- If the gum coatings can be demonstrated to dissolve quickly in the mouth, then no additional studies should be required to assess local toxicity potential of the coating ingredients, particularly given the extensive experience with the use of these ingredients in foods.

- The mint gum (b) (4) has already been approved and would therefore be considered safe from a local toxicity standpoint. However, the fruit and cinnamon gums contain excipients (b) (4) that have not been previously approved for mucosal application or that exceed levels previously approved for oral mucosal application.

- Review of the eight excipients in question concluded that except for sucralose and FD&C Red #40, the excipient levels found in the fruit and cinnamon (b) (4) were acceptable because they were similar to or lower than levels found in other products intended for oral mucosal administration.

The sponsor was sent the following deficiency on 12/19/08:

> According to 21CFR 314.94(a)(9)(ii), you must identify and characterize the inactive ingredients in the proposed drug products and provide information demonstrating that such inactive ingredients do not affect the safety of the proposed drug product. The following inactive ingredients are present in at least one of the proposed products in amounts or concentrations exceeding those present in any approved drug product for oral transmucosal administration. The levels of these inactive ingredients have been determined to be acceptable from the standpoint of systemic exposure by the oral route of administration. However, you have not provided evidence that the proposed levels of these inactive ingredients will not increase the potential for local toxicity (e.g. oral mucosal irritation) compared to that of the RLD.
>
> Acesufame K
> (b) (4)
> Hydroxypropylcellulose
> Titanium dioxide
> Xylitol
> Sucralose
> Hypromellose
> FD&C Red #40
>
> You must provide evidence that the Watson product will not cause any more local toxicity at the site of administration than that caused by the RLD. Such evidence may be provided from a comparative human local toxicity study comparing the irritation potential of Watson's product to that of the RLD. If you decide to conduct such a study, you should submit a protocol to OGD for review and concurrence prior to initiating the study.
>
> Alternatively, you may provide substantial information that would obviate the need to conduct such a study. Such information would include comparative data on local exposure to each of these ingredients (i.e. surface area, duration, frequency and chronicity, amounts, concentrations of exposure) from other products available in the marketplace that deliver sustained oral mucosal

exposures to these excipients and have an established record of safety. The necessary information needed would include a comparison between the marketed products and the proposed product regarding the amounts and concentrations of the relevant ingredients in each product, the exposed surface area of the product unit, the frequency and duration of oral exposure to each unit, and the usual frequency and chronicity of dosing/ ingestion. The information you submit must demonstrate that oral mucosal exposure to these excipients from other marketed products is similar to or greater than that from your proposed products in all of the characteristics listed above. In addition, you must submit data to show that such exposure has been found not to cause any significant oral irritation.

While adverse events data and oral examination data from the BE and salivary dissolution studies submitted to your ANDAs are considered supportive, such data are not sufficient to establish that your products have no more irritation potential compared to the RLD. These studies are not considered definitive because:

a. The nicotine gum products were not administered strictly according to labeling in these studies. In particular, it appears that subjects were not instructed to park the gum periodically against the oral mucosal surface.
b. These studies were not specifically designed to assess comparative local toxicity with specific prospective endpoints, and the oral examination data were qualitative and non-standardized.
c. The products were not used according to the maximum allowed use in labeling, which would provide a maximum irritation potential.

Guidelines for acceptable use in foods are generally considered only supportive to the extent that such guidelines are generally based on systemic toxicity data from orally administered products, and not on potential for local toxicity that may result from prolonged contact in the mouth.

If satisfactory evidence can be provided to show that there would not be appreciable mucosal exposure from the ingredients in the coating (e.g. if the coating ingredients very rapidly dissolve and disappear from the mouth with chewing), then the gum (b) (4) would be considered the primary source for local irritation potential. In this case, the concentrations and amounts of the inactive ingredients contained in the (b) (4) of the formulations will be the primary focus of concern.

Sponsor Responses to Deficiency

Watson submitted a telephone amendment on 1/16/09 containing a stripping study of their coated fruit and cinnamon formulations to demonstrate the rapidity with which the coating ingredients dissolve in saliva fluid with a chewing/mastication simulation, along with additional information to support the safety of the excipients in their proposed products.

In addition, another amendment was submitted on 3/19/09 to provide Watson's analysis of the amounts of FD&C Red No. 40 contained in some marketed products.

Stripping Study

Watson used a mastication device consisting of temperature-maintained (b) (4) test cells, each containing two vertical pistons holding upper and lower mastication surfaces. The cells were filled with 20 mL simulated saliva fluid and the gum was supported on the lower mastication surface using (b) (4). The mastication process was simulated by up and down strokes of the lower surface (50 chews/min.), along with a twisting movement of the upper surface. The gums tested were "conditioned" in the fluid-filled vessels for 30 seconds prior to chewing. Removal of the coating was assessed after chewing periods of 30 seconds, 1 minute, and 2 minutes by visual inspection of the media and the gum.

Watson reports that after 30 seconds of chewing in this model, the coating is dissolved, as demonstrated by cloudiness of the media and no coating left on the (b) (4) The cloudiness of the media was stated not to be increased after 1 minute of chewing. As no quantitative data were presented, presumably the cloudiness and (b) (4) inspection assessments were qualitative.

Based on the results of the stripping study, Watson concludes that there is no appreciable mucosal exposure from the coating ingredients, and that the gum (b) (4) should be considered the primary source for local irritation potential.

Evaluation of (b) (4) Ingredients

Hydroxypropylcellulose, **Titanium Dioxide** and **Hypromellose** are (b) (4) (b) (4), so no further discussion of their local irritation potential was provided.

(b) (4)

Consistent with the previous clinical review, Watson reports that the amounts of (b) (4) (b) (4) in their proposed gum (b) (4) do not exceed the amount in a previously approved buccal gum.

Watson provided a consultant toxicology review to address local toxicity concerns for FD&C Red No 40, xylitol, acesulfame potassium, and sucralose. The review notes that all four of these ingredients are associated with a very low degree of acute toxicity and that none is strongly acidic or alkaline in solution.

Acesulfame K

Acesulfame K is present in the (b) (4) of the fruit and cinnamon formulations, at (b) (4) mg and (b) (4) mg/piece, respectively.

Watson reports that the amounts of Acesulfame K in their proposed (b) (4) formulations (b) (4) the amount present in another buccal chewing gum, but are less than those approved for a sublingual tablet and an oral troche. In the previous clinical review, it was confirmed that the acesulfame K in the approved comparator product was contained (b) (4) within the gum (b) (4) that the proposed amounts in the Watson product

exceed these levels by approximately (b) (4)%, and that the approved sublingual product exceeds the Watson product in both total amount and % w/w of acesulfame K. In addition, acesulfame K is highly water soluble, which would minimize its potential for prolonged contact with the oral mucosa.

Watson states that their search of TOXLINE and MEDLINE revealed no indication that acesulfame K in candy or other products causes any local adverse effects in the mouth.

Xylitol

Xylitol is present in all three flavors, in similar amounts ranging from (b) (4) mg/tablet in the (b) (4) Consistent with the previous clinical review, Watson reports that the highest level of xylitol in their (b) (4) formulations (found in the cinnamon gum) (b) (4) (b) (4) exceeds (by (b) (4)%) the amount already approved in another buccal chewing gum. In the previous clinical review, it was confirmed that the xylitol in the approved comparator product was contained (b) (4) within the gum (b) (4) In addition, Watson states that their review of published safety data give no indication of any irritating or other local effect, and that the high water solubility of xylitol would minimize its potential for prolonged contact with the oral mucosa.

Watson cites a long-term clinical study of children who were provided gum containing xylitol at up to 9g/day for 40 months with no reported adverse effects. This is almost (b) (4) the amount of xylitol that would be provided in the maximum dose of their nicotine gum.

Sucralose

Sucralose is present in the fruit and cinnamon gum (b) (4) at a level of (b) (4)mg/piece. Watson describes the widespread use of sucralose in products such as hard candies and cough drops and cites a 2008 WHO approval of sucralose use at levels up to 5000 mg/kg in chewing gum (compared to (b) (4) mg/kg in Watson's proposed nicotine gum). Watson analyzed sucralose levels in wild cherry flavor Chloraseptic Lozenges and sugar free Life Savers and found levels of (b) (4) mg/piece and (b) (4) mg/piece, respectively. Watson cites FDA's Tentative Final Monograph for Oral Healthcare Drug Products (53FR2346) as allowing products such as Chloraseptic Lozenges to be dosed at 2 lozenges every 4 hours, not to exceed 24 lozenges in 24 hours. Watson states that these lozenges are similar in surface area to their nicotine gums, and that these lozenges dissolve in the oral cavity after approximately 15 minutes.

Nicorette is to be given according to the following schedule, with a maximum recommended dose of 24 pieces per day:

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

The gum is to be chewed slowly until it tingles, and then parked between cheek and gum until the tingle is gone. The chewing/parking cycle is repeated until most of the tingle is gone (about 30 minutes).

Watson conducted an analysis of the amounts of sucralose present in Nicorette Fruit Chill and Cinnamon Surge products and found that these formulations contained (b) (4) mg/piece and (b) (4) mg/piece, respectively.

The following components/composition table for the RLD Freshfruit gum (provided by Dr. Skanchy, OGD, DCII) is generally consistent with Watson's analysis. However, the sucralose in this formulation is not contained in the gum (b) (4).

Table 3.2.P.1-1 Formulation of the Nicorette® 2 mg Freshfruit coated chewing gum

Component	Reference to Quality Standards	Function	2 mg chewing gum (b) (4)

Watson's search of the TOXLINE and MEDLINE databases revealed no indication that sucralose in candy or other products causes any local adverse effects in the mouth. In addition, the high water solubility of sucralose is thought to minimize the potential for prolonged contact with the oral mucosa.

FD&C Red #40 Lake

As described by Watson, the Lake is [redacted] It is present in Watson's cinnamon gum [redacted] at up to [redacted] mg/piece. Watson reports that FD&C Red #40 is the highest-volume FDA-certified food color, with FDA approval for use in drugs with no limitation on the level of usage other than "in amounts consistent with good manufacturing practice" (21 CFR 74.1340). This citation includes drugs intended for use in the area of the eye.

Watson conducted TOXLINE and MEDLINE searches without finding any indication of local oral toxicity for FD&C Red #40. Watson also cites single application studies in rabbits (WHO 1980) in which FD&C Red #40 was applied to abraded skin at doses up to 10 g/kg and repeated daily for 3 weeks without evidence of irritation.

Watson states that FD&C Red #40 Lake is used at the same percent level or higher in lipstick formulations with no signs of adverse events (reference cited but not provided for review).

In their amendment of 3/19/09, Watson provides the results of their analysis of the amounts of FD&C Red #40 present in various commercial products.

Table 1: Amount of FD&C Red # 40 in Sucrets Lozenges, Target® sugar free cough drop and Sugar Free Life Savers® (from Watson's analysis)

Product	Amount of FD&C Red No. 40 (mg)
Sucrets Lozenges – Vapor cherry flavor	[redacted] mg/piece
Target® Sugar Free Cough Drop	[redacted] mg/piece
Sugar Free Life Savers –Red	[redacted] mg/piece

As described above, FDA's tentative final monograph for oral healthcare drug products allows dosing of lozenges at 2 every 4 hours, not to exceed 24 lozenges in 24 hours.

Summary/Conclusions

1. Watson was asked to provide evidence of safety with respect to the local toxicity potential of eight excipients that were present in amounts higher than those present in approved drug products for oral mucosal administration. A previous clinical review had concluded that if Watson could demonstrate that there would not be substantial mucosal exposure from the ingredients in the coatings (i.e. if the coating ingredients dissolve rapidly in the mouth), then the ingredients in the gum [redacted] would be considered the primary source for local irritation potential. A detailed scientific and regulatory review of each excipient further concluded that if the gum coatings could be discounted with respect to local irritation potential, then the excipients of primary concern are sucralose and FD&C Red #40.

2. Stripping study

Watson conducted their stripping study for the purpose of demonstrating that the gum coating ingredients are rapidly dissolved with chewing.

There were several weakness of this study:

The 30 second "conditioning" period prior to chewing is not representative of clinical conditions, and the reported stripping of the coating after 30 seconds of simulated chewing was in fact after 30 seconds immersed in media and then 30 seconds of chewing in media.

No information is provided to validate the model used, and variables such as the composition and volume of media, the mastication surfaces, and the mastication mechanisms and forces may not be representative of the clinical setting.

Only qualitative assessments of the removal of the coating were provided.

Nevertheless, this study does provide some reasonable evidence that the coating is likely to be substantially dissolved fairly quickly with chewing, and that therefore, the gum coating ingredients are unlikely to be a source of local mucosal toxicity. Watson's conclusion is further substantiated by the firm's validation methodologies which include a procedure for removing the entire coating with mild agitation for 2 minutes in approximately 6 mL of water per piece (per DCII, Dr. Skanchy).

3. Consistent with the previous clinical review, Watson has provided reasonable evidence that the levels of acesulfame K, (b) (4), hydroxypropylcellulose, titanium dioxide, xylitol and hypromellose are likely to be safe with respect to local toxicity potential.

4. Although specific oral irritation data were not presented, Watson has provided reasonable evidence that the proposed levels of sucralose and FD&C #40 have not been associated with oral mucosal toxicity and are unlikely to do so. They have provided evidence of the high prevalence of use of these excipients in food and medicinal products, along with measured levels found in specific marketed comparator products that are likely to provide similar or higher levels of exposure relative to Watson's proposed nicotine gum product.

Recommendations

There is adequate evidence to support the safety of the excipients in Watson's proposed nicotine gum products, and therefore, these products may be approved from a clinical safety standpoint.

As recommended in the previous clinical review:

1. When possible, systematic assessments for local toxicity during the course of BE studies and other human studies should be considered for all drugs that are administered by the buccal/transmucosal route. It should be noted that while such data might provide supportive evidence of safety, studies that are not specifically

designed for the purpose of comparing local toxicity with the RLD are not sufficient, in and of themselves, to establish safety with respect to local toxicity. In this case, local toxicity was evaluated in the human ANDA trials and these data were generally reassuring, although the evaluations were non-standardized and the products were not administered strictly according to labeling.

2. If possible, only the excipients and amounts contained in the (b) (4) should be listed in the IIG for the buccal route of administration if the mint and/or other formulations of nicotine gum are approved. Otherwise, these products may be inappropriately cited to support the safety of future products intended for buccal administration. The ingredients in the coating should be considered as orally administered.

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

/s/

Nancy Chang
5/5/2009 12:49:44 PM
MEDICAL OFFICER

Dena Hixon
5/5/2009 12:54:23 PM
MEDICAL OFFICER
I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-038

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

ORIGINAL

June 1, 2007

79038

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

RECEIVED
JUN 4 2007
OGD

RE: Original ANDA – CTD Format
Nicotine Polacrilex Gum, 4 mg (Coated Fruit)

Dear Mr. Buehler:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act, enclosed is an original Abbreviated New Drug Application for Nicotine Polacrilex Gum, 4 mg (Coated Fruit) being submitted in CTD format. This application consists of the following volumes:

Module 1	Administrative Information and Prescribing Information: Debarment, patent and exclusivity certifications, labeling, signed financial disclosure statement, and environmental impact statement.
Module 2	Common Technical Document Summaries.
Module 3 (Volumes 1 – 4)	Executed Batch Records, Manufacturing and packaging records, certificates of analysis, components and composition, and raw material control data, Container/closure, finished product controls, methods validation, stability data.
Module 4	N/A for ANDA submissions
Module 5	Bioequivalence/Bioavailability study report and Chew-out study data report

A full table of contents precedes each appropriately paginated volume.

Pursuant to 21 CFR §314.97, we certify that a true copy of the chemistry, manufacturing and controls data was submitted to Mr. Otto Vitillo, Director, Domestic Investigational Branch, Food and Drug Administration (NYK-DO), 158-15 Liberty Avenue, Jamaica, New York, 11433. Subsequent amendments or supplements containing chemistry, manufacturing and controls data will also be submitted to the District Field Office.

We have also included in this submission an extra copy of our cover letter. Please acknowledge by date stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If there are any comments or questions about this application, please contact me at (631) 693-8038.

Sincerely,
Watson Laboratories, Inc.

Meredith Seay for

Beverly Bailey
Manager, Regulatory Affairs

Watson

August 27, 2007

N/mC

Mr. Wm. Peter Rickman
Director, Division of Labeling and Program Support
Office of Generic Drugs (HFD-610)
Center for Drug Evaluation and Research
7500 Standish Place
Food and Drug Administration
Rockville, Maryland 20855

New Correspondence

RE: Nicotine Polacrilex Gum USP, 4 mg (coated fruit); ANDA 79-038

Dear Mr. Rickman:

Watson Laboratories, Inc. herewith submits new correspondence to the above referenced Abbreviated New Drug Application dated June 1, 2007. This submission is in response to a telephone contact with Saundra Middleton, Project Manager, OGD on August 20, 2007. During this contact, Watson informed the Agency that we would be submitting additional published articles to support the safety of the proposed levels of acesulfame potassium, sucralose, titanium dioxide, and D&C yellow no. 10 used in our formulation for Nicotine Polacrilex Gum USP, 4 mg (coated fruit). The studies provided with this submission were referenced in the report prepared by our expert toxicologist that was included in our original ANDA, but the full study reports were not included at that time. The attached reports include studies performed in both rodent species and non-rodent species.

The following published articles that support the safety of the oral administration for the referenced inactive ingredients are included:

- **Acesulfame potassium**: (in addition to the study included with our original ANDA)
  - Scientific Committee for Food (SCF). 1985. Reports of the scientific committee for food. Sixteenth series. Commission of the European communities. ***(Attachment 1)***

- **Sucralose:** (in addition to the two studies included with our original ANDA)
  - Food and Drug Administration (FDA). Food Additives Permitted for Direct Addition to Food for Human Consumption; Sucralose, Final Rule *Fed. Reg.*, 64:43908-09. ***(Attachment 2)***
  - World Health Organization (WHO) 1991b. Trichlorogalactosucrose. Toxicological evaluation of certain food additives. WHO Food Additive Series: 28. Prepared by the thirty-seventh meeting of the joint FAO/WHO Expert Committee on Food Additives (JECFA) ***(Attachment 3)***
  - World Health Organization (WHO) 1989. Trichlorogalactosucrose. Toxicological evaluation of certain food additives and contaminants. WHO Food Additive Series: 24. ***(Attachment 4)***

- **Titanium dioxide:** (in addition to the study submitted with our original ANDA)
  - Bernard, B K, Osheroff, M R, Hofmann, A, Mennear, J H. Toxicology and Carcinogenesis Studies of Dietary Titanium Dioxide-Coated MICA in Male and Female Fischer 344 Rats. Journal of Toxicology and Environmental Health, 29:417-429, 1990. (Attachment X) ***(Attachment 5))***
  - JECFA (1969); Thirtieth Report of the Joint FAO/WHO Expert Committee on Food Additives FAO Nutrition Meetings Report Series WHO Technical Report Series, FAS 70.36/NMRS 46A-JECFA 13/55 to titanium dioxide (INS 171) (Attachment X) ***(Attachment 6)***
  - World Health Organization (WHO). 1969. FAO nutrition meetings report series: 46A. Thirteenth report of the Joint FAO/WHO Expert Committee on food additives. ***(Attachment 7)***
- **D&C Yellow #10:** (in addition to the study submitted with our original ANDA)
  - World Health Organization (WHO) 1969. Toxicological evaluation of Some Food Colours, Emulsifiers, Stabilizers, Anti-Caking Agents and Certain Other Substances. FAO Nutrition Meetings Reports Series No. 46A WHO/FOOD ADD/70.36 ***(Attachment 8)***

As requested, a compact disc containing the studies included with this submission, as well as the studies previously submitted with our ANDA on June 1, 2007, is also provided in ***Attachment 9.***

Watson trusts that this submission satisfactorily addresses any safety concerns regarding the inactive ingredient levels in our formulation.

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (845) 278-3736, or by fax at (845) 278-3741.

Sincerely,

Meredith Selby
Associate Director, Regulatory Affairs
Watson Laboratories, Inc.

Watson

September 19, 2007

Mr. Wm. Peter Rickman
Director, Division of Labeling and Program Support
Office of Generic Drugs (HFD-610)
Center for Drug Evaluation and Research
7500 Standish Place
Food and Drug Administration
Rockville, Maryland 20855

NEW CORRESP
N/MC
New Correspondence

RE: Nicotine Polacrilex Gum USP, 4 mg (Coated Fruit); ANDA 79-038

Dear Mr. Rickman:

Watson Laboratories, Inc. hereby submits new correspondence to the referenced Abbreviated New Drug Application dated June 1, 2007. This submission is in response to the September 12, 2007 email from Peter Chen, Project Manager, Regulatory Support Branch, OGD. During this contact, the following items were requested to be submitted as "New Correspondence" within 5 business days:

1. Please provide a samples statement of availability and identify the lot numbers for the drug substance and drug product lots used to support the ANDA.

Revised ANDA pages are included in Attachment 1 which include statements of availability and lot numbers for both the drug substance and drug product.

2. Please provide the qualitative and quantitative composition for the components used in the inactives (b) (4) Flavor (b) (4) and (b) (4) Flavor.

As this information is considered proprietary, the flavor manufacturers submitted this information in controlled correspondences which were included in the original ANDA in Module 3.2.P.1 on pages 204 and 206. The controlled correspondence number assigned by FDA for the (b) (4) flavor is 07-0700. For the (b) (4) Flavor, the manufacturer is resubmitting this information as "Confidential Correspondence" directly to the ANDA.

3. The electronic attachment submitted along with your new correspondence dated August 27, 2007 is not organized in exactly the same order as the hardcopy. Please organize your electronic file to contain the same information and in the same order as your hardcopy submission for both the August 27, 2007 correspondence and June 1, 2007 original submission section 3.2.P.1, and resubmit.

The compact disc containing the literature references included in Module 3.2.P.1 was not an electronic attachment to the ANDA, the information was provided electronically as a courtesy based on contacts with Saundra Middleton, OGD, in regard to a previously submitted ANDA. We are, however, providing a new electronic copy in Attachment 2 with the literature in the order they appeared in the paper copies. The electronic copy also contains a "Table of Contents" file with links to the various literature references contained on the disc.

4. Please also provide contact names and phone numbers for all contract facilities.

Included in Attachment 3 is a list of all the contract facilities included in the ANDA with contact names and phone numbers indicated.

5. Please state the components to be tested at those facilities.

Included in Attachment 4 is a list of the ingredient tests that were performed at the contract laboratories, however, Watson Laboratories, Inc., reserves the right to use the listed contract laboratories for any general testing of the active and/or inactive ingredients.

6. Please provide cGMP certifications for (b) (4) and (b) (4).

cGMP Certification letters for (b) (4) and (b) (4) are included in Attachment 5.

7. Please provide analytical procedures for the inactive (b) (4)

Page 2 of the Specification and Procedure for (b) (4) was inadvertently omitted in the original ANDA. For completeness, WLI is resubmitting the (b) (4) Specification and Procedure, which includes the analytical procedure, in Attachment 6.

Watson trusts that the responses provided satisfactorily address the concerns raised in the September 12, 2007 email from Peter Chen. It is our understanding that upon receipt and review of this correspondence, the original ANDA filing date of June 1, 2007 will be applied to this ANDA.

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (845) 278-3736, or by fax at (845) 278-3741.

Sincerely,

Meredith Selby

Meredith Selby
Associate Director, Regulatory Affairs
Watson Laboratories, Inc.

cc: fax copy to Peter Chen, Project Manager, Regulatory Support Branch

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 79-038 **FIRM NAME**: WATSON LABORATORIES, INC.

PIV: NO **Electronic or Paper Submission:** PAPER (CTD FORMAT)

RELATED APPLICATION(S): SEE 79-044 FOR NICOTINE POLACRILEX GUM, 2 MG (COATED FRUIT) FROM WATSON LABORATORIES, INC. PN 6/6/07 (RLD NICORETTE)

First Generic Product Received? NO

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	☐
☐ **BST**	☒ **BDI**	

DRUG NAME: NICOTINE POLACRILEX
DOSAGE FORM: GUM, 4 MG (COATED FRUIT)

Random Queue: 10
Chem Team Leader: Naiqi Ya PM: Tom Hinchliffe Labeling Reviewer: Michelle Dillahunt

Letter Date: JUNE 1, 2007 **Received Date**: JUNE 4, 2007

Comments: EC - 1 YES **On Cards:** YES
Therapeutic Code: 2030700 NICOTINE STUDY

Archival copy: PAPER (CTD FORMAT) **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Peter Chen **Date 9/26/2007**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: _____	**Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

September 19, 2007 New Correspondence (9/21/07 NC is a refax of 9/19/07 NC)

The following comment will be added to the ACK letter:
Please provide cGMP certification for [redacted]

June 1, 2007 Original

9/12/2007 Tcon Meredith Selby (845-278-3736)

Please provide a response to the following items as a NC to the ANDA within 5 business days.

1. Please provide a samples statement of availability and identify the lot numbers for the drug substance and drug product lots used to support the ANDA.
(OK per 9/19/2007 NC)
2. Please provide the qualitative and quantitative composition for the components used in the inactives [redacted] Flavor [redacted] and [redacted] Flavor [redacted].
(OK per 9/19/07 NC)
9/19/2007 NC sponsor referenced control 07-0700 for [redacted] Flavor [redacted].
However, this control is superceded by new information currently located.
[redacted]
Also see control 05-0687 which contains the C&C for [redacted]. Note the [redacted]% w/w given by the sponsor is inaccurate.
[redacted]
9/19/2007 NC sponsor stated supplier for [redacted] will submit a confidential correspondence to the ANDA for the C&C for [redacted]. [redacted] submitted this information on 9/19/2007 and a copy is attached below.
(Inactives justified)
3. The electronic attachment submitted along with your new correspondence dated August 27, 2007 is not organized in exactly the same order as the hardcopy. Please organize your electronic file to contain the same information and in the same order as your hardcopy submission for both the August 27, 2007 correspondence and June 1, 2007 original submission section 3.2.P.1, and resubmit.
(OK per 9/19/2007 NC)
4. Please provide contact names and phone numbers for all contract facilities.
(OK per 9/19/2007 NC)
5. Please state the components to be tested at those facilities.
(9/19/2007 NC states "Watson... reserves the right to use the listed contract laboratories for any general testing of active and/or inactive ingredients." All the facilities listed are added to EES.)
6. Please provide cGMP certifications for [redacted] c., and [redacted]
(9/19/2007 NC still missing certification for [redacted]
Comment 1: Please provide cGMP certification for [redacted]
7. Please provide analytical procedures for the inactive [redacted].
(OK per 9/19/2007 NC)

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2** **Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) OTC YES	☒
1.2	**Cover Letter** Dated: JUNE 1, 2007	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) none	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) YES 3454	☒
1.3.5	**1.3.5.1** **Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2** **Patent Certification** 1. Patent number(s) 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☒ PIII ☐ PIV ☐ No Relevant Patents ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient submitted DMF (b) (4) b. Type III DMF authorization letter(s) for container closure submitted DMF (b) (4) 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) n/a	☒

1.12.11	**Basis for Submission** NDA# : 20-066 Ref Listed Drug: NICORETTE Firm: GLAXOSMITHKLINE ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same as RLD 2. Active ingredients Same as RLD 3. Inactive ingredients 4. Route of administration Same as RLD 5. Dosage Form Same as RLD 6. Strength Same as RLD	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) submitted **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained submitted **1.14.1.3** 1 package insert (content of labeling) submitted electronically submitted ***Was a proprietary name request submitted? (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained submitted **1.14.3.3** 1 RLD label and 1 RLD container label submitted	☒

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: __X_PDF (archive) _X_ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) __X_ YES _____ NO** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** **2.3.S.1** **General Information** **2.3.S.2** **Manufacture** **2.3.S.3** **Characterization** **2.3.S.4** **Control of Drug Substance** **2.3.S.5** **Reference Standards or Materials** **2.3.S.6** **Container Closure System** **2.3.S.7** **Stability** **2.3.P** **Drug Product** **2.3.P.1** **Description and Composition of the Drug Product** **2.3.P.2** **Pharmaceutical Development** **2.3.P.2.1** **Components of the Drug Product** **2.3.P.2.1.1** **Drug Substance** **2.3.P.2.1.2** **Excipients** **2.3.P.2.2** **Drug Product** **2.3.P.2.3** **Manufacturing Process Development** **2.3.P.2.4** **Container Closure System** **2.3.P.3** **Manufacture** **2.3.P.4** **Control of Excipients** **2.3.P.5** **Control of Drug Product** **2.3.P.6** **Reference Standards or Materials** **2.3.P.7** **Container Closure System** **2.3.P.8** **Stability**	☒

2.7	**Clinical Summary (Bioequivalence)** **E-Submission: __X_PDF (archive) _X_ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview** **2.7.1.2** **Summary of Results of Individual Studies** **2.7.1.3** **Comparison and Analyses of Results Across Studies** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies Table 2. Statistical Summary of the Comparative BA Data Table 4. Summary of In Vitro Dissolution Studies **2.7.1.4** **Appendix**	☒

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature submitted** **3.2.S.1.2** **Structure submitted** **3.2.S.1.3** **General Properties submitted**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers submitted 2. Manufacturing Responsibilities submitted 3. Type II DMF number for API DMF (b) (4) 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization submitted**	☒

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1** **Specification** Testing specifications and data from drug substance manufacturer(s) submitted **3.2.S.4.2** **Analytical Procedures** submitted **3.2.S.4.3** **Validation of Analytical Procedures** **1.** Spectra and chromatograms for reference standards and test samples submitted 2. Samples-Statement of Availability and Identification of: a. Drug Substance missing (OK per 9/19/2007 NC) b. Same lot number(s) yes **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) submitted 2. Applicant certificate of analysis submitted Lot 1099 **3.2.S.4.5** **Justification of Specification submitted**	☒
3.2.S.5	**Reference Standards or Materials submitted**	☒
3.2.S.6	**Container Closure Systems submitted**	☒
3.2.S.7	**Stability Reference to DMF**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition submitted 2) Inactive ingredients are appropriate per IIG See control 07-0700 and 05-0687 for inactive [redacted] (b) (4) Missing Q1/Q2 for inactives [redacted] (b) (4) Flavor [redacted] (b) (4) and [redacted] (b) (4) [redacted] (b) (4) Flavor (OK per 9/19/2007 NC) Sponsor has submitted pharm/tox data for these inactives in 6/1/2007 original section 3.2.P.1 and 8/27/2007 NC; however, the electronic attachment containing the studies is not organized in the same fashion as the hardcopy to the ANDA. (OK per 9/19/2007 NC) Pharm/Tox consult submitted for Xylitol, Acesulfame Potassium, DC Yellow #10 Lake, Sucralose and Titanium Dioxide.	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report submitted	☒

3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) 2. CGMP Certification: YES 3. Function or Responsibility 4. CFN or FEI numbers Please also provide contact names and phone numbers for all contract facilities. (OK per 9/19/2007 NC) Please state the components to be tested at those facilities. (OK per 9/19/2007 NC) Please provide cGMP certifications for [redacted] (b) (4)., and [redacted] (b) (4) (9/19/2007 NC still missing certification for [redacted] (b) (4) Certification requested on the ACK letter: *Please provide cGMP certification for* [redacted] (b) (4) **3.2.P.3.2** **Batch Formula** Batch Formulation submitted **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process submitted 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified MBR TY [redacted] (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization NA 4. Reprocessing Statement submitted **3.2.P.3.4** **Controls of Critical Steps and Intermediates submitted** **3.2.P.3.5** **Process Validation and/or Evaluation** 1. Microbiological sterilization validation NA 2. Filter validation (if aseptic fill) NA	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified submitted **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) submitted 2. Suppliers' COA (specifications and test results) submitted **3.2.P.4.2** **Analytical Procedures** Please provide analytical procedures for the inactive [redacted] (b) (4) (OK per 9/19/2007 NC) **3.2.P.4.3** **Validation of Analytical Procedures** **3.2.P.4.4** **Justification of Specifications** Applicant COA submitted	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** submitted **3.2.P.5.2** **Analytical Procedures** submitted **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Missing (OK per 9/19/2007 NC) 2. Same lot numbers yes **3.2.P.5.4** **Batch Analysis** Certificate of Analysis for Finished Dosage Form submitted Lot #RD1407 **3.2.P.5.5** **Characterization of Impurities submitted** **3.2.P.5.6** **Justification of Specifications submitted**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) submitted 2. Components Specification and Test Data submitted 3. Packaging Configuration and Sizes unit dose blisters 4. Container/Closure Testing submitted 5. Source of supply and suppliers address submitted	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted 2. Expiration Dating Period 24 months **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments submitted **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data submitted 2. Batch numbers on stability records the same as the test batch **yes**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S** **Executed Batch Records for drug substance (if available)** **3.2.R.2.S** **Comparability Protocols** **3.2.R.3.S** **Methods Validation Package** NO Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☐

MODULE 3
3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation submitted Theoretical Yield (b) (4) pieces (b) (4) from MBR; however, reconciliation indicates TY of (b) (4) pieces CMC review issue Actual Yield (b) (4) Packaged Yield (b) (4) **3.2.R.1.P.2** **Information on Components** **3.2.R.2.P** **Comparability Protocols** **3.2.R.3.P** **Methods Validation Package** submitted Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5
CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** Test Lot RD1407 RLD Lot HA935A **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

	5.3.1.2 **Comparative BA/BE Study Reports** 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 6. Demographic Profile of Subjects Completing the Comparative BA Study Table 7. Incidence of Adverse Events in Individual Studies Table 8. Reanalysis of Study Samples **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 4. Summary of In Vitro Dissolution Studies Table 5. Formulation Data **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 3. Bioanalytical Method Validation **5.3.7** **Case Report Forms and Individual Patient Listing**	☐
5.4	**Literature References**	
	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) fasting 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) yes	☒

Nicotine Polacrilex Coated Gum, Fruit Flavor
Dose (1 x 4 mg)
Geometric Means[1], Ratio of Means, and 90% Confidence Intervals
Ln-Transformed Data
Fasted Bioequivalence Study, Study #: R06-1613
N=46[2]

Parameter	Test	Reference	% Ratio	90% C.I.
AUC_{0-t}	27.66	31.81	86.96	(83.37, 90.69)
$AUC_{0-\infty}$	29.75	33.95	87.63	(84.27, 91.12)
C_{max}	8.29	9.78	84.78	(80.95, 88.79)

[1]Geometric means are based on least squares means of ln-transformed values
[2]Subjects used in final statistical report

2. EDR Email: Data Files Submitted: YES SENT TO EDR
3. In-Vitro Dissolution: YES Salivation dissolution(chew-out) study

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/10/2006 C. Bina

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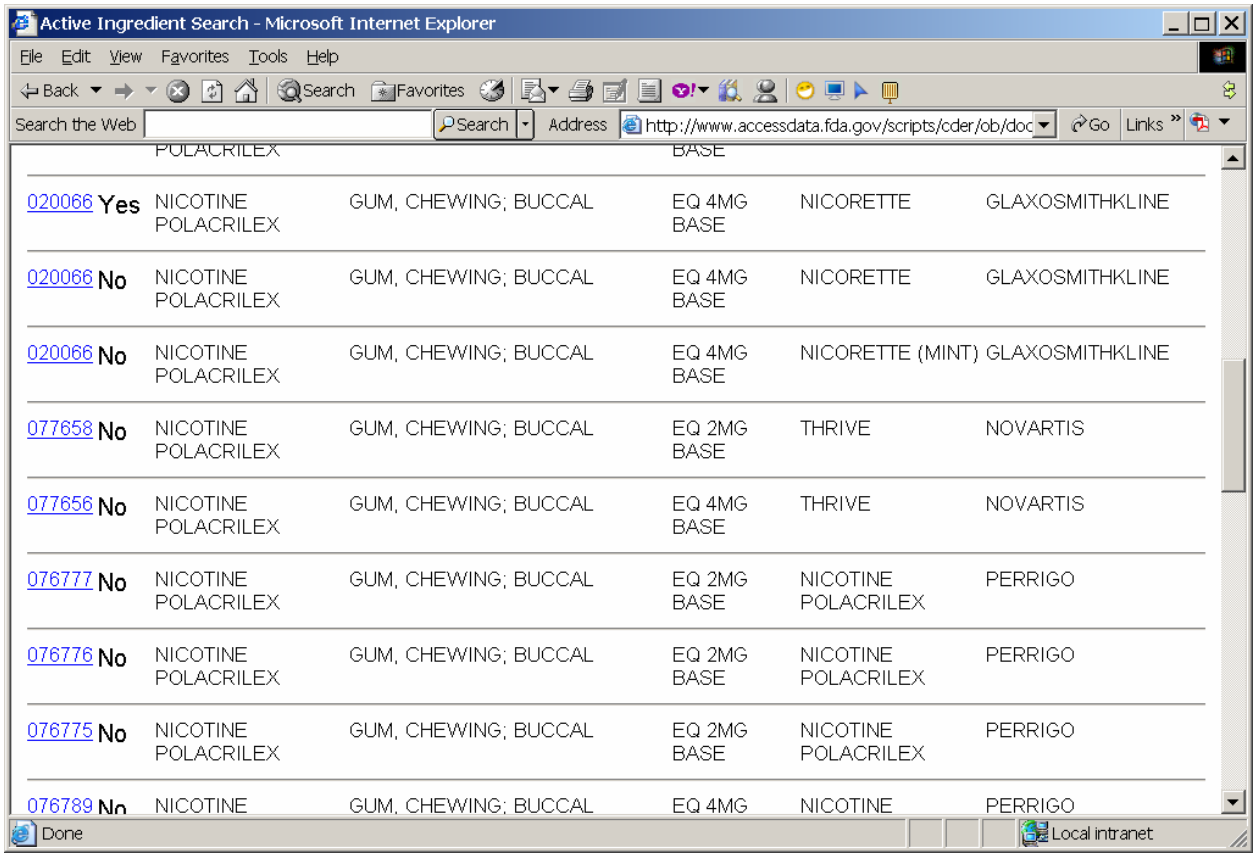

		POLACRILEX		BASE		
020066	Yes	NICOTINE POLACRILEX	GUM, CHEWING; BUCCAL	EQ 4MG BASE	NICORETTE	GLAXOSMITHKLINE
020066	No	NICOTINE POLACRILEX	GUM, CHEWING; BUCCAL	EQ 4MG BASE	NICORETTE	GLAXOSMITHKLINE
020066	No	NICOTINE POLACRILEX	GUM, CHEWING; BUCCAL	EQ 4MG BASE	NICORETTE (MINT)	GLAXOSMITHKLINE
077658	No	NICOTINE POLACRILEX	GUM, CHEWING; BUCCAL	EQ 2MG BASE	THRIVE	NOVARTIS
077656	No	NICOTINE POLACRILEX	GUM, CHEWING; BUCCAL	EQ 4MG BASE	THRIVE	NOVARTIS
076777	No	NICOTINE POLACRILEX	GUM, CHEWING; BUCCAL	EQ 2MG BASE	NICOTINE POLACRILEX	PERRIGO
076776	No	NICOTINE POLACRILEX	GUM, CHEWING; BUCCAL	EQ 2MG BASE	NICOTINE POLACRILEX	PERRIGO
076775	No	NICOTINE POLACRILEX	GUM, CHEWING; BUCCAL	EQ 2MG BASE	NICOTINE POLACRILEX	PERRIGO
076789	No	NICOTINE	GUM, CHEWING; BUCCAL	EQ 4MG	NICOTINE	PERRIGO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2007-0155	
TO *(Division/Office)* DNRD - HFD-560 Thru: David Hilfiker, ONP HFD-560			FROM: Peter Chen OGD/DLPS/RSB	
DATE: 9/26/2007	IND NO.	ANDA NO. 079038	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 9/19/2007,
NAME OF DRUG NICOTINE POLACRILEX		PRIORITY CONSIDERATION 60 days	CLASSIFICATION OF DRUG NICOTINE/TOBACCO DEPENDENCY	DESIRED COMPLETION DATE 11/25/2007

NAME OF FIRM WATSON LABS

REASON FOR REQUEST

I. GENERAL

Γ NEW PROTOCOL
Γ PROGRESS REPORT
Γ NEW CORRESPONDENCE
Γ DRUG ADVERTISING
Γ ADVERSE REACTION REPORT
Γ MANUFACTURING CHANGE/ADDITION
Γ MEETING PLANNED BY _____
Γ PRE NDA MEETING
Γ END OF PHASE II MEETING
Γ RESUBMISSION
Γ SAFETY/EFFICACY
Γ PAPER NDA
Γ CONTROL SUPPLEMENT
Γ RESPONSE TO DEFICPENCY LETTER
Γ FINAL PRINTED LABELING
Γ LABELING REVISION
Γ ORIGINAL NEW CORRESPONDENCE
Γ FORMULATIVE REVIEW
X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

DISSOLUTION
PROTOCOL-- BIOPHARMACEUTICS
IN--VIVO WAIVER REQUEST
DEFICIENCY LETTER RESPONSE
BIOAVAILABILITY STUDIES
PHASE IV STUDIES

IV.DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
SUMMARY OF ADVERSE EXPERIENCE
POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL PRECLINICAL

COMMENTS
OGD is requesting a pharm/tox consult. Please review the information provided and provide your analysis and conclusion for whether the levels proposed for the 5 inactives are justified in a buccal/chewing gum dosage form.

Xylitol (b) (4) mg/gum
Acesulfame potassium (b) (4) mg/gum
Sucralose (b) (4) /gum
Dye DC Yellow #10 (b) (4) mg/gum
Titanium dioxide (b) (4) mg/gum
Related ANDAs: 79-044,78-699,78-697
Please cc Benjamin Danso, HFD-617 (benjamin.danso@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

SIGNATURE OF REQUESTER Peter Chen	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Martin Shimer

9/28/2007 01:13:38 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 79-038

Watson Laboratories, Inc.
Attention: Meredith Selby
33 Ralph Avenue, P.O. Box 30
Copiague, NY 11726-0030

Dear Madam:

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 September 12, 2007 and your correspondence dated September 19 and September 21, 2007.

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

DATE OF APPLICATION: June 1, 2007

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 4, 2007

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

In the interim, please provide a statement of cGMP certification for (b) (4) This was not provided in the September 19, 2007 new correspondence.

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
301-827-5771

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

Martin Shimer
9/28/2007 01:13:09 PM
Signing for Wm Peter Rickman

Watson

November 16, 2007

Mr. Gary Buehler, Director
Office of Generic Drugs (HFD-610)
Center of Drug Evaluation and Research, FDA
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855

ORIG AMENDMENT
N-AM

Minor Amendment

RE: Nicotine Polacrilex Gum USP, 4 mg (Coated Fruit); ANDA 79-038

Dear Mr. Buehler:

Reference is made to the ANDA "Acceptable For Filing" letter dated September 28, 2007 which requested a statement of cGMP certification for [redacted] (b) (4) for the referenced ANDA. The FDA acceptance letter is included as **Attachment 1**.

The cGMP statement for [redacted] (b) (4) was included in Attachment 5 of Watson Laboratories, Inc.'s (WLI) "New Correspondence" dated September 19, 2007, however, in accordance with your request, WLI is resubmitting the cGMP statement for [redacted] (b) (4) to the referenced ANDA. (**Attachment 2**).

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (631)693-8038 or by fax at (631)693-8896.

Sincerely,
Watson Laboratories, Inc.

Meredith Sully for

AibinYou, RAC
Manager, Regulatory Affairs

RECEIVED
NOV 19 2007
OGD

Watson

December 17, 2007

Dale P. Connor, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
CDER Food and Drug Administration
Document Control Room, Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N-000-AB

BIOEQUIVALENCY AMENDMENT

RE: Nicotine Polacrilex Gum USP, 4 mg (Coated Fruit); ANDA 79-038
Nicotine Polacrilex Gum USP, 2 mg (Coated Fruit); ANDA 79-044

Dear Dr. Conner:

Reference is made to the Bioequivalence deficiency letter dated March 15, 2007 for **ANDA 74-707/S- 033, Nicotine Polacrilex Gum USP, 4 mg (Original), ANDA 74-507/S-038, Nicotine Polacrilex Gum USP, 2 mg (Original),** and **ANDA** (b) (4) (b) (4). In that correspondence the Agency requested mastication data for the Watson Nicotine Polacrilex Gum USP (Original) using three different media (phosphate buffer pH 7.4, phosphate buffer pH 7.4 + 0.1% SLS, and Water) and two different instrument conditions (Jaw Distance 1.2 mm and 5.0 mm) from those previously submitted by Watson. In response, Watson provided the requested information on May 11, 2007, which resulted in a telephone contact by Mr. Aaron Sigler (Project Manager) on June 4, 2007, indicating the Agency's recommendation for the use of phosphate buffer pH 7.4 as the medium and 1.2 mm as the jaw distance for mastication testing for all future Nicotine gum products.

The Mastication test results accompanying Watson's **Nicotine Polacrilex Gum USP, 4 & 2 mg (Coated Fruit) ANDA #s: 79-038 and 79-044** original submissions were based on the use of different instrument parameters and media conditions from those recommended by the Agency (June 4, 2007 telephone contact). Therefore, Watson is proactively providing mastication results for the coated fruit gum products using phosphate buffer pH 7.4 and phosphate buffer pH 7.4 + 0.1% SLS, two media initially recommended by the Agency.

RECEIVED
DEC 18 2007
OGD

The additional mastication testing in the two media was conducted on Watson's Nicotine Polacrilex Gum USP, (Coated Fruit) and Nicorette® Fruit Chill™, 2 mg and 4 mg as described below:

Device:	(b) (4)
Jaw Distance:	1.2 mm
Jaw Angle:	20°
Media:	USP phosphate buffer (0.05M) pH 7.4 or phosphate buffer (0.0125M) pH 7.4 + 0.1% SLS
Volume:	20 mL
Temperature:	37 ± 0.5°C
Stroke Frequency:	50 cycles per minute
Sampling Times:	5, 8, 12, 16, 22, 30 and 45 minutes, or at least until 85% of the API is released
Q Value:	Not less than (b) (4)% at 30 minutes (FDA recommended Q value for all gum products, as per telephone correspondence dated June 4, 2007)

The concentration of phosphate buffer was decreased to 0.0125M in the presence of SLS to avoid precipitation of SLS.

The following Coated Fruit Gum products listed in Table 1 were tested:

Table 1. Lot #s, Manufacturing Dates/Expiration Dates of Watson's Nicotine Polacrilex Gum USP, (Coated Fruit) and Nicorette® Fruit Chill™(RLD), 2 mg and 4 mg

Strength (mg)	Watson (Test)		Nicorette® Fruit Chill™ (Reference)	
	Lot #	Manuf. Date	Lot #	Exp. Date
2	RD1408	01/07	HA925A	12/07
4	RD1407	11/06	HA935A	12/07

The individual (n = 12 units) and summary (Mean, Range, Standard Deviation, %CV) mastication data are provided in the attachments listed below:

- Watson Nicotine Polacrilex Gum, USP (Coated Fruit), 4 mg, phosphate buffer, pH 7.4 (**Attachment 1**).
- Watson Nicotine Polacrilex Gum, USP (Coated Fruit), 2 mg, phosphate buffer, pH 7.4 (**Attachment 2**).
- GSK Nicorette® Fruit Chill™, 4 mg, phosphate buffer, pH 7.4 (**Attachment 3**).
- GSK Nicorette® Fruit Chill™, 2 mg, phosphate buffer, pH 7.4 (**Attachment 4**).

- Watson Nicotine Polacrilex Gum (Coated Fruit), 4 mg, phosphate buffer pH 7.4 + SLS, (**Attachment 5**).
- Watson Nicotine Polacrilex Gum (Coated Fruit), 2 mg, phosphate buffer pH 7.4 + SLS (**Attachment 6**).
- GSK Nicorette® Fruit Chill™, 4 mg, phosphate buffer pH 7.4 + SLS (**Attachment 7**).
- GSK Nicorette® Fruit Chill™, 2 mg, phosphate buffer pH 7.4 + SLS (**Attachment 8**).

The data are also included in SAS electronic format on CD (**enclosed**).

The Similarity Factor (f_2) values for comparison of mastication profiles for test and reference formulations are provided in **Attachment 9** and summarized in Table 2 below.

Table 2. Similarity Factor (f_2) Values of Watson's Nicotine Polacrilex Gum USP, (Coated Fruit) (WPI), and Nicorette® Fruit Chill™ (RLD), 2 mg and 4 mg

Medium	4 mg	2 mg	2 mg vs 4 mg	
	WPI vs RLD	WPI vs RLD	WPI	RLD
Phosphate	20.6	20.9	79.5	73.4
Phosphate + SLS	65.8	66.0	76.9	61.5

For the phosphate medium, some f_2 values are less than 50 and all Watson products do not meet a Q value of (b) (4)% dissolved at 30 minutes. However, for the phosphate + SLS medium, all f_2 values are greater than 50 and all Watson products meet a Q value of (b) (4)% dissolved at 30 minutes. These data suggest that phosphate + SLS is a suitable medium for quality-control testing specifically of Watson's Coated Fruit gum products.

Watson is seeking the Agency's concurrence regarding the appropriateness of the phosphate + SLS media for the future use of quality-control mastication testing for Watson's Coated Fruit gum products.

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (631) 693-8038, or by fax at (631) 693-8896.

Sincerely,
Watson Laboratories, Inc.

Meredith Selby for

Aibin You
Manager, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION** **Consult No: 2008-0193**	
TO *(Division/Office)* ONP-DNCE, Thru: Leah Christl			**FROM:** David Skanchy	
DATE: 1/18/2008	**IND NO.**	**ANDA NO.** 78-699	**TYPE OF DOCUMENT** Original	**DATE OF DOCUMENT** 4/23/2007,
NAME OF DRUG Nicotine Polacrilex Gums Coated		**PRIORITY CONSIDERATION** 30 days	**CLASSIFICATION OF DRUG** Nicotine dependency	**DESIRED COMPLETION DATE** 2/17/2008

NAME OF FIRM Watson

REASON FOR REQUEST

I. GENERAL

- ✆ NEW PROTOCOL
- ✆ PROGRESS REPORT
- ✆ NEW CORRESPONDENCE
- ✆ DRUG ADVERTISING
- ✆ ADVERSE REACTION REPORT
- ✆ MANUFACTURING CHANGE/ADDITION
- ✆ MEETING PLANNED BY _____
- ✆ PRE NDA MEETING
- ✆ END OF PHASE II MEETING
- ✆ RESUBMISSION
- ✆ SAFETY/EFFICACY
- ✆ PAPER NDA
- ✆ CONTROL SUPPLEMENT
- ✆ RESPONSE TO DEFICPENCY LETTER
- ✆ FINAL PRINTED LABELING
- ✆ LABELING REVISION
- ✆ ORIGINAL NEW CORRESPONDENCE
- ✆ FORMULATIVE REVIEW
- X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
✆ TYPE A OR B NDA REVIEW ✆ END QF PHASE II MEETING ✆ CONTROLLED STUDI ES ✆ PROTOCOL REVIEW ✆ OTHER	✆ CHEMISTRY ✆ PHARMACOLOGY ✆ BIOPHARMACEUTICS ✆ OTHER

III.BIOPHARMACEUTICS

- DISSOLUTION
- PROTOCOL-- BIOPHARMACEUTICS
- IN--VIVO WAIVER REQUEST
- DEFICIENCY LETTER RESPONSE
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

IV.DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
- COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- _SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL PRECLINICAL

COMMENTS

This consult supercedes and replaces any previous excipient tox consult for ANDAs 78-697, 78-699, 79-216, 79-219, 79-044 and 79-038. The three similar formulations in these nicotine gum ANDA's were consolidated (with review division concurrence)into a single consult due to the significant overlap in information. To summarize, the original consult was for the mint flavor formulation and the consult included xylitol, acesulfame potassium, hydroxypropyl cellulose, and titanium dioxide (ANDAs 78-697 and 78-699). The fruit flavor adds the excipient Sucralose (79-044 and 79-038) to the consult. The cinnamon flavor adds hypromellose and FD&C Red #40 to the consult (79-216 and 79-219). This consult covers all seven excipients listed above across the three formulations. Except for new information on the added excipients, which are in the EDR for each ANDA listed above, all of the information on the common excipients in the consult are duplicated in each. All the relevant information on the fruit and cinnamon formulations is in edr, including the components and compositions statements (see electronic QOS). The complete tox information for all seven excipients listed above is in the files for ANDAs 79-216 and 79-219 since this formulation contains all of the excipients. Please cc Benjamin Danso, HFD-617 (benjamin.danso@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

SIGNATURE OF REQUESTER Dave Skanchy	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA

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

/s/

Benjamin Danso
1/18/2008 07:35:52 AM

Watson

April 9, 2008

Mr. Gary Buehler, Director
Office of Generic Drugs, HFD-615
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

RE: Nicotine Polacrilex Gum USP, 4 mg (Coated Fruit); ANDA 79-038

Dear Dr. Buehler:

Reference is made to the Telephone Deficiency letter, dated March 31, 2008, faxed by Mr. Tom Hinchliffe, Office of Generic Drugs, providing comments on above listed Abbreviated New Drug Application (ANDA) submitted on June 1, 2007 (**Attachment 1**). Watson Laboratories, Inc. hereby submits our responses to the deficiency letter in this Telephone Amendment.

The following is an item-by-item response to the chemistry deficiencies:

1. (b) (4) **We note that similar information was provided in supplements to your already approved gum products (ANDA's 74-507 and 74-707).**

(b) (4)

Following this page, 1 page withheld in full - (b)(4)

Pursuant to 21 CFR §314.97, we certify that a true field copy of this correspondence has been sent by overnight courier to Mr. Otto Vitillo, Director, Domestic Investigational Branch, Food and Drug Administration (NYK-DO), 158-15 Liberty Avenue, Jamaica, New York, 11433.

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (631)693-8038 or by fax at (631)693-8896.

Sincerely,
Watson Laboratories, Inc.

Aibin You
Manager, Regulatory Affairs

CC: fax copy to Mr. Tom Hinchliffe, Office of Generic Drugs, 240-276-8582

BIOEQUIVALENCY AMENDMENT

ANDA 79-038 and 79-044

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Watson Laboratories, Inc TEL: 631-693-8038

ATTN: Beverly Bailey FAX: 631-693-8896

FROM: Christina Thompson PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on June 1, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nicotine Polacrilex gum (coated fruit) 2 mg and 4 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **1** 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:

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 79-038 and 79-044

APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Nicotine Polacrilex Coated Gum (Fruit Flavor), 4 mg and 2 mg

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

Your dissolution testing method is acceptable. However, your proposed dissolution specification of NLT (b)(4)%(Q) in 30 minutes is not acceptable. Based on the dissolution data you submitted, the Division of Bioequivalence is recommending an alternative specification of NLT (b)(4)%(Q) dissolved in 30 minutes for your Nicotine Polacrilex Coated Gum (Fruit Flavor) drug product. Please acknowledge your acceptance of the following dissolution method and specification.

Device:	(b)(4)
Jaw Distance:	1.2 mm
Jaw Angle:	20°
Medium:	Phosphate Buffer, 0.0125M, pH 7.4 + 0.1% SLS
Volume:	20 mL
Temperature:	37 ± 0.5°C
Stroke Frequency:	50 cycles per minute
Rec Sampling Times:	5, 8, 12, 16, 22, 30, and 45 minutes
DBE-recommended Specification:	**NLT (b)(4)%(Q) dissolved in 30 minutes**

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

Barbara Davit
4/22/2008 02:04:17 PM
Signing for Dale P Conner

Watson

May 2, 2008

Dale P. Connor, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
CDER Food and Drug Administration
Document Control Room, Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

BIOEQUIVALENCY AMENDMENT

RE: Nicotine Polacrilex Gum USP, 4 mg (Coated Fruit); ANDA 79-038

Dear Dr. Conner:

Reference is made to the Bioequivalence Deficiency letter, dated April 22, 2008 (**ATTACHMENT 1**), faxed by Ms. Christina Thompson, Division of Bioequivalence, Office of Generic Drugs, providing comments on above referenced Abbreviated New Drug Application (ANDA) submitted on June 1, 2007. Watson Laboratories, Inc. hereby submits our responses to the deficiency letter in this Bioequivalency Amendment.

Comment:

- **Your dissolution testing method is acceptable. However, your proposed dissolution specification of NLT (b) (4)% (Q) in 30 minutes is not acceptable. Based on the dissolution data you submitted, the Division of Bioequivalence is recommending an alternative specification of NLT (b) (4)% (Q) dissolved in 30 minutes for your Nicotine Polacrilex Coated Gum (Fruit Flavor) drug product. Please acknowledge your acceptance of the following dissolution method and specification.**

Device:	(b) (4)
Jaw Distance:	**1.2 mm**
Jaw Angle:	**20°**
Medium:	**Phosphate Buffer, 0.0125M, pH 7.4 + 0.1% SLS**
Volume:	**20 mL**
Temperature:	**37 ± 0.5°C**
Stroke Frequency	**50 cycles per minute**
Rec Sampling Times:	**5, 8, 12, 16, 22, 30, and 45 minutes**
DBE- recommended Specification:	**NLT (b) (4)%(Q) dissolved in 30 minutes**

Response: WLI hereby acknowledges the acceptance of above listed dissolution (mastication) method and specification recommended by the Agency. We will update the relevant CMC information, such as Finished Product and Stability Specifications and Procedures, and Method Validation Report, in our next CMC amendment.

WLI trusts that the response provided satisfactorily addresses the concerns raised in the April 22, 2008 Bioequivalence Deficiency letter faxed by Ms. Christina Thompson.

As per the Agency's request, WLI is submitting this correspondence electronically in Adobe Acrobat portable document format (pdf) on the enclosed compact disc. The cover letter and 356h form are also being submitted in hard copy.

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (631) 693-8038 or by fax at (631) 693-8896.

Sincerely,
Watson Laboratories, Inc.

Meredith Scm fw/

Aibin You
Manager, Regulatory Affairs

Watson

May 9, 2008

Mr. Gary Buehler, Director
Office of Generic Drugs, HFD-615
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

MINOR AMENDMENT

RE: Nicotine Polacrilex Gum USP, 4 mg (Coated Fruit); ANDA 79-038

Dear Dr. Buehler:

Watson Laboratories, Inc. hereby submits a Minor Amendment to the above referenced Abbreviated New Drug Application (ANDA) submitted on June 1, 2007.

Included in this amendment are:

- Updated Finished Product Specifications and Procedures, Stability Specifications and Procedures, and Method Validation Report
- Updated Description and Composition of the drug product
- Updated Manufacturing Batch Records and Master Quality Records

1. The Finished Product Specifications and Procedures, Stability Specifications and Procedures, and Method Validation Report are being updated based on the Agency's (Division of Bioequivalence, Office of Generic Drugs) recommendation regarding the mastication (dissolution) method and specification for the above referenced ANDA in the Bioequivalence Deficiency letter, dated April 22, 2008 (**ATTACHMENT 1**) and is described as follows:

Device:	(b) (4)
Jaw Distance:	**1.2 mm**
Jaw Angle:	**20°**
Medium:	**Phosphate Buffer, 0.0125M, pH 7.4 + 0.1% SLS**
Volume:	**20 mL**
Temperature:	**37 ± 0.5°C**
Stroke Frequency	**50 cycles per minute**
Rec Sampling Times:	**5, 8, 12, 16, 22, 30, and 45 minutes**
DBE- recommended Specification:	**NLT (b) (4) % (Q) dissolved in 30 minutes**

The revised Finished Product Specifications and Procedures, Stability Specifications and Procedures, and Method Validation Report are provided in **ATTACHMENT 2, 3 and 4**, respectively.

Please note: The imprinting information is also being removed from the product description in anticipation that the imprinting waiver will be granted by the Agency.

2. Watson is updating the Description and Composition of the drug product information under Modules 2.3.P.1 and 3.2.P to remove imprinting information in anticipation that the imprinting waiver will be granted by the Agency. The updated pages of Module 2.3.P.1, 3.2.P.1, 3.2.P.2 and 3.2.P.3 are included in **ATTACHMENT 5**.

3. Watson is also updating the following Manufacturing Batch Records and Master Quality Records in this submission:

- (b) (4)
-
-
-
-

(b) (4)

Following this page, 1 page withheld in full - (b)(4)

(b) (4)

As per the Agency's request, WLI is submitting this correspondence electronically in Adobe Acrobat portable document format (pdf) on the enclosed compact disc. The cover letter and 356h form are also being submitted in hard copy.

Pursuant to 21 CFR §314.97, we certify that a true field copy of this correspondence has been sent by overnight courier to Mr. Otto Vitillo, Director, Domestic Investigational Branch, Food and Drug Administration (NYK-DO), 158-15 Liberty Avenue, Jamaica, New York, 11433.

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (631) 693-8038 or by fax at (631) 693-8896.

Sincerely,
Watson Laboratories, Inc.

Aibin You
Manager, Regulatory Affairs

Watson

June 25, 2008

Mr. Wm. Peter Rickman
Director, Division of Labeling and Program Support
Office of Generic Drugs, HFD-610
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20855

LABELING AMENDMENT

RE: Nicotine Polacrilex Gum USP, 4 mg (Coated Fruit); ANDA 79-038

Dear Mr. Rickman:

Watson Laboratories, Inc. hereby submits a Labeling Amendment to the above referenced Abbreviated New Drug Application (ANDA) submitted on June 1, 2007. The Labeling Amendment is being submitted based on the Agency's comments, dated April 11, 2008 and May 28, 2008 for Watson's other coated gum products - **Nicotine Polacrilex Gum USP, 2 mg and 4 mg (Coated Mint), ANDAs 78-699 and 78-697.**

Included in this Labeling Amendment are:

1. A detailed marketing and surveillance plan **(ATTACHMENT 1)** designed to ensure that retailers and distributors of our products will only sell them to persons 18 years of age or older.

2. **CARTON** (b) (4)

   We have
   - Deleted "(b) (4)" from the carton labeling.
   - Revised the established name "Nicotine Polacrilex Gum USP, 4 mg (Nicotine)" to be the most prominent on the carton labeling.
   - Revised the amount of Calcium to be 115 mg.
   - Updated the NDC number.

   The revised carton labeling is provided electronically (pdf) in the enclosed compact disc.

3. **Amounts of Calcium and Sodium on the Carton Labeling**

   We have recalculated the amounts of Calcium and Sodium, and the amount of Calcium has been corrected to be 115 mg and reflected in the revised carton labeling. The amount of Sodium (8 mg) remains the same.

4. CARTON – 40s, 100s (b) (4)

Although we have included all the package sizes of (b) (4) 40, (b) (4) 100, (b) (4) in the application, at this time Watson only intends to market package sizes of 40, 100, and (b) (4) Therefore, in this submission, we are only providing carton labeling for package sizes of 40, 100 and (b) (4) Carton labeling for other package sizes will be provided if and when marketing is intended.

The carton labeling for package sizes 40, 100 and (b) (4) are included electronically (pdf) in the enclosed compact disc.

5. AUDIO CD

Two copies of the audio CDs are provided in **ATTACHMENT 2**.

6. CD SCRIPT

The CD script (English and Spanish versions) is provided in **ATTACHMENT 3**. The Spanish version is accompanied by a copy of certification of translation from TRANSPERFECT Translations - the translator, certifying the translation from English to Spanish for Watson's CD script is true and accurate.

7. USER'S GUIDE

The User's Guide has been revised to delete ' (b) (4), and the (b) (4) from page 3 and is included in the enclosed compact disc.

In this submission, we are providing a copy of certification of translation (**ATTACHMENT 4**) from TRANSPERFECT Translations - the translator, certifying the translation from English to Spanish for Watson's user's Guide are true and accurate.

According to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA, we are providing the final printed carton labeling and user's guide electronically (pdf) in the enclosed compact disc.

To facilitate Agency's review of the submission, and in accordance with 21CFR 314.94 (a)(8)(IV), a side-by-side comparison of our proposed labeling for the carton and user's guide, versus the reference listed drug's labeling, with all differences annotated and explained is being provided in **ATTACHMENT 5**.

As per the Agency's request, WLI is submitting this correspondence electronically in Adobe Acrobat portable document format (pdf) on the enclosed compact disc. The cover letter and 356h form are also being submitted in hard copy.

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (631) 693-8038 or by fax at (631) 693-8896.

Sincerely,
Watson Laboratories, Inc.

Aibin You
Manager, Regulatory Affairs

Watson

July 3, 2008

Mr. Wm. Peter Rickman
Director, Division of Labeling and Program Support
Office of Generic Drugs, HFD-610
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20855

LABELING AMENDMENT

RE: Nicotine Polacrilex Gum USP, 4 mg (Coated Fruit); ANDA 79-038

Dear Mr. Rickman:

Reference is made to above referenced Abbreviated New Drug Application (ANDA) submitted on June 1, 2007 and the Labeling Amendment Submitted on June 25, 2008.

Reference is also made to the July 2, 2008 Telephone Contact from Ms. Michelle Dillahunt, Division of Labeling and Program Support, Office of Generic Drugs, providing comments on above listed Abbreviated New Drug Application (ANDA).

Watson Laboratories, Inc. (WLI) hereby submits our responses to the comments in this Labeling Amendment.

Comment:

- **The Compact Disc (CD) included in the Labeling Amendment dated June 25, 2008 did not contain any carton labeling.**

Response:

The carton labeling of package sizes of 40, 100, (b) (4), and the side-by-side comparison of our proposed carton labeling (b) (4) count) versus the reference listed drug's labeling were inadvertently missing from the compact disc (CD) included in the Labeling Amendment dated June 25, 2008.

Watson hereby resubmits the CD in this Labeling Amendment. The CD contains the following labeling information:

- Carton labeling of package sizes of 40, 100, (b) (4)
- User's Guide
- A side-by-side comparison of our proposed labeling for the carton and user's guide, versus the reference listed drug's labeling

Watson trusts that the response provided satisfactorily addresses the concerns raised in the July 2, 2008 Telephone Contact from Ms. Michelle Dillahunt.

As per the Agency's request, WLI is submitting this correspondence electronically in Adobe Acrobat portable document format (pdf) on the enclosed compact disc. The cover letter and 356h form are also being submitted in hard copy.

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (631) 693-8038 or by fax at (631) 693-8896.

Sincerely,
Watson Laboratories, Inc.

Meredith Kelly for

Aibin You
Manager, Regulatory Affairs

Watson

August 11, 2008

Mr. Gary Buehler, Director
Office of Generic Drugs, HFD-615
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

RE: Nicotine Polacrilex Gum USP, 4 mg (Coated Fruit); ANDA 79-038

Dear Dr. Buehler:

Watson Laboratory Inc. (WLI) hereby submits a Telephone Amendment to the above referenced Abbreviated New Drug Application (ANDA) dated June 1, 2007. The amendment is being submitted in response to the July 24, 2008 Telephone Contact from Dr. Dave Skanchy, Office of Generic Drugs, recommending a Telephone Amendment be submitted based on the Agency's comments outlined in the Telephone Deficiency Letter, dated June 18, 2008 (**ATTACHMENT 1**) for Watson's other coated gum products - **Nicotine Polacrilex Gum USP, 2 mg and 4 mg (Coated Mint), ANDAs 78-699 and 78-697.**

In addition, this amendment is being submitted to provide the following:

1. Withdrawal of [redacted] (b) (4) as a Contract facility. Watson hereby withdraws [redacted] (b) (4) as a contract testing facility from the application, without prejudice to refiling.

2. Updated Master Quality Record (MQR 306). The Updated Master Quality Record is provided in **ATTACHMENT 2** with detailed changes summarized on the cover page.

The following is an item-by-item response to the chemistry (residual solvent) deficiencies:

Comments:

Please note that the new USP<467> chapter on residual solvents is effective on July 01, 2008. You therefore must meet the new requirements prior to approval of this ANDA. In order to comply with the new USP <467> requirements please provide the information listed below in your response. Reference is also made to the Office of Generic Drug's communication entitled "Residual Solvents Acceptability Letter" posted on the OGD website. The Letter is available at the following link:
(http://www.fda.gov.cder/ogd/#new).

Following this page, 5 pages withheld in full - (b)(4)

the residual solvents and/or levels present. Watson will notify the Agency under the appropriate reporting category.

Watson Laboratories, Inc. trusts that the responses provided satisfactorily address the concerns raised in the FDA Telephone Deficiency letter dated June 18, 2008 and the July 24, 2008 Telephone Contact from Dr. Dave Skanchy.

As per the Agency's request, WLI is submitting this correspondence electronically in Adobe Acrobat portable document format (pdf) on the enclosed compact disc. The cover letter and 356h form are also being submitted in hard copy.

Pursuant to 21 CFR §314.97, we certify that a true field copy of this correspondence has been sent by overnight courier to Mr. Otto Vitillo, Director, Domestic Investigational Branch, Food and Drug Administration (NYK-DO), 158-15 Liberty Avenue, Jamaica, New York, 11433.

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (631) 693-8038 or by fax at (631) 693-8896.

Sincerely,
Watson Laboratories, Inc.

Meredith Sun for

Aibin You
Manager, Regulatory Affairs

CC: E-mail copy to Dr. David Skanchy, Office of Generic Drugs at David.Skanchy@FDA.HHS.gov

Watson

August 14, 2008

Mr. Gary Buehler, Director
Office of Generic Drugs, HFD-615
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

RE: Nicotine Polacrilex Gum USP, 4 mg (Coated Fruit); ANDA 79-038

Dear Dr. Buehler:

Watson Laboratories, Inc. (WLI) hereby submits a Telephone Amendment to the above referenced Abbreviated New Drug Application (ANDA) dated June 1, 2007. This submission is in response to the July 30, 2008 Telephone Contact from Dr. Dave Skanchy, Office of Generic Drugs. During the Telephone Contact, the following item was requested to be submitted as a Telephone Amendment.

Comment:

- **Please provide calculation of the calcium amount for your Nicotine Polacrilex Gum, USP, Coated Fruit and Coated Cinnamon applications**

Response: For our Nicotine gum products, calcium only comes from the excipient – [(b) (4)] The amount of calcium in our gum product is calculated based on the maximum level of [(b) (4)] stated in the Vendor's Certificate of Composition.

The [(b) (4)] used in our exhibit batch was manufactured by [(b) (4)], therefore, for the currently submitted carton labeling, the amount of calcium was calculated based on the maximum level of [(b) (4)] stated in the [(b) (4)] Certificate of Composition **(ATTACHMENT 1),** and the detailed calculation of calcium amount in each formulation is included in **ATTACHMENT 2.**

Please note, after initial manufacture of our exhibit batch, the manufacturer of [(b) (4)] has gone out of business and the formulation has been transferred to a new manufacturer – [(b) (4)] For our commercial manufacturing, [(b) (4)] will come from [(b) (4)] at the address below:

[(b) (4)]

Even though the two materials are considered equivalent, [(b) (4)] specification of [(b) (4)] as stated in their Certificate of Composition (**ATTACHMENT 3**). The new calcium amount for our commercial product is calculated as shown in **ATTACHMENT 4**.

Watson proposes to maintain the calcium amount presented in the currently submitted labeling (115 mg) since the two materials are considered equivalent and interchangeable, and as illustrated by the attached calculations, the calcium amount included in the currently submitted labeling, which was calculated based on [(b) (4)] material, represents a [(b) (4)] material), and should not pose any safety concerns to the consumers.

Watson commits to reevaluate the calcium amount when we change the supplier of [(b) (4)] or if the supplier changes their manufacturing process in a way that could affect the level of calcium present in their product. Watson will notify the Agency under the appropriate reporting category.

Watson Laboratories, Inc. trusts that the responses provided satisfactorily address the concerns raised in the July 30, 2008 Telephone Contact from Dr. Dave Skanchy.

As per the Agency's request, WLI is submitting this correspondence electronically in Adobe Acrobat portable document format (pdf) on the enclosed compact disc. The cover letter and 356h form are also being submitted in hard copy.

Pursuant to 21 CFR §314.97, we certify that a true field copy of this correspondence has been sent by overnight courier to Mr. Otto Vitillo, Director, Domestic Investigational Branch, Food and Drug Administration (NYK-DO), 158-15 Liberty Avenue, Jamaica, New York, 11433.

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (631) 693-8038 or by fax at (631) 693-8896.

Sincerely,
Watson Laboratories, Inc.

Meredith Selby for/

Aibin You
Manager, Regulatory Affairs

CC: E-mail copy to Dr. David Skanchy, Office of Generic Drugs at David.Skanchy@FDA.HHS.gov

Watson

September 19, 2008

Mr. Gary Buehler, Director
Office of Generic Drugs, HFD-615
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

RE: Nicotine Polacrilex Gum USP, 4 mg (Coated Fruit); ANDA 79-038

Dear Dr. Buehler:

Watson Laboratories, Inc. (WLI) hereby submits a Telephone Amendment to the above referenced Abbreviated New Drug Application (ANDA) dated June 1, 2007. This submission is in response to the August 27, 2008 Telephone Contact from Dr. Dave Skanchy, Office of Generic Drugs. During the Telephone Contact, the following item was requested to be submitted as a Telephone Amendment.

Comment:

- **Please provide oral examination data from your Bioequivalence studies (PK and chew out) for the coated nicotine gum applications**

Response: The oral examination data from our Bioequivalence studies (PK Bioequivalence study R06-1613 and chew out study R06-1612) along with the Oral Assessment Narrative are included in **ATTACHMENT 1**. The raw data is also included in SAS transport format in the enclosed CD.

Watson Laboratories, Inc. trusts that the response provided satisfactorily addresses the concerns raised in the August 27, 2008 Telephone Contact from Dr. Dave Skanchy.

As per the Agency's request, WLI is submitting this correspondence electronically in Adobe Acrobat portable document format (pdf) on the enclosed compact disc. The cover letter and 356h form are also being submitted in hard copy.

Pursuant to 21 CFR §314.97, we certify that a true field copy of this correspondence has been sent by overnight courier to Mr. Otto Vitillo, Director, Domestic Investigational Branch, Food and Drug Administration (NYK-DO), 158-15 Liberty Avenue, Jamaica, New York, 11433.

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (631) 693-8038 or by fax at (631) 693-8896.

Sincerely,
Watson Laboratories, Inc.

Meredith Selby for

Aibin You
Manager, Regulatory Affairs

CC: E-mail copy to Dr. David Skanchy, Office of Generic Drugs at David.Skanchy@FDA.HHS.gov

Watson

January 16, 2009

Mr. Gary Buehler, Director
Office of Generic Drugs, HFD-615
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

RE: Nicotine Polacrilex Gum USP, 4 mg (Coated Fruit); ANDA 79-038

Dear Dr. Buehler:

Watson Laboratories, Inc. (WLI) hereby submits a Telephone Amendment to the above referenced Abbreviated New Drug Application (ANDA) dated June 1, 2007. This submission is in response to the December 19, 2008 Telephone Deficiency (**ATTACHMENT 1**) faxed by Dr. Tom Hinchliffe, Project Manager, Office of Generic Drugs, concerning the local toxicity potential of the formulation.

Comment:

According to 21 CFR314.94 (a)(9)(ii), you must identify and characterize the inactive ingredients in the proposed drug products and provide information demonstrating that such inactive ingredients do not affect the safety of the proposed drug product. The following inactive ingredients are present in at least one of the proposed products in amounts or concentrations exceeding those present in any approved drug products for oral transmucosal administration. The levels of these inactive ingredients have been determined to be acceptable from the standpoint of systemic exposure by the oral route of administration. However, you have not provided evidence that the proposed levels of these inactive ingredients will not increase the potential for local toxicity (e.g. oral mucosal irritation) compared to that of the RLD.

Acesufame K
(b) (4)

Hydroxypropylcellulose
Titanium Dioxide
Xylitol
Sucralose
Hypromellose
FD&C Red #40

You must provide evidence that the Watson product will not cause any more local toxicity at the site of administration than that caused by the RLD. Such evidence may be provided from a comparative human local toxicity study comparing the irritation potential of Watson's product to

that of the RLD. If you decide to conduct such a study, you should submit a protocol to OGD for review and concurrence prior to initiating the study.

Alternatively, you may provide substantial information that would obviate the need to conduct such a study. Such information would include comparative data on local exposure to each of these ingredients (i.e. surface area, duration, frequency and chronicity, amounts, concentrations of exposure) from other products available in the marketplace that deliver sustained oral mucosal exposures to these excipients and have an established record of safety. The necessary information needed would include a comparison between the marketed products and the proposed product regarding the amounts and concentrations of the relevant ingredients in each product, the exposed surface area of the product unit, the frequency and duration of oral exposure to each unit, and the usual frequency and chronicity of dosing/ingesting. The information you submit must demonstrate that oral mucosal exposure to these excipients from other marketed products is similar to or greater than that from your proposed products in all of the characteristics listed above. In addition, you must submit data to show that such exposure has been found not to cause any significant oral irritation.

While adverse events data and oral examination data from the BE and salivary dissolution studies submitted to your ANDAs are considered supportive, such data are not sufficient to establish that your products have no more irritation potential compared to the RLD. These studies are not considered definitive because:

- **A. The nicotine gum products were not administrated strictly according to labeling in these studies. In particular, it appears that subjects were not instructed to park the gum periodically against the oral mucosal surface.**
- **B. These studies were not specifically designed to assess comparative local toxicity with specific prospective endpoints, and the oral examination data were qualitative and non-standardized.**
- **C. The products were not used according to the maximum allowed use in labeling, which would provide a maximum irritation potential.**

Guideline for acceptable use in foods are generally considered only supportive to the extent that such guidelines are generally based on systemic toxicity data from orally administered products, and not on potential for local toxicity that may result from prolonged contact in the mouth.

If satisfactory evidence can be provided to show that there would not be appreciable mucosal exposure from the ingredients in the coating (e.g. if the coating ingredients very rapidly dissolve and disappear from the mouth with chewing), then the gum (b) (4) would be considered be the primary source for local irritation potential. In this case, the concentrations and amounts of the inactive ingredients contained in the (b) (4) of the formulations will be the primary focus of concern.

Response: In order to demonstrate that the coating materials rapidly dissolve in the saliva fluid and disappear from the mouth with chewing, Watson has conducted a stripping study comparing our coated fruit and cinnamon formulations against the FDA approved coated mint products (ANDA 78-699 and 78-697). The study showed that the coating ingredients in our coated fruit and cinnamon formulations performed similarly as the FDA approved coated mint products, very rapidly dissolved in

the saliva fluid within 30 seconds of chewing/mastication (Please see the detailed study report included in **ATTACHMENT 2**).

Based on this evidence, it can be concluded that there will be no appreciable mucosal exposure from the coating ingredients, and the gum (b) (4) are the primary source for local irritation potential.

Therefore, the concentrations and amounts of the inactive ingredients (excipients) in the (b) (4) of the formulations are the primary focus in the following discussion. Since (b) (4) The (b) (4) five excipients present in the gum (b) (4) are: Acesufame K, (b) (4) Xylitol, Sucralose and FD&C Red # 40. The safe use of these excipients is addressed below:

Please refer to **Table 1** for the amount of excipients in the gum (b) (4) comparing to IIG limits

Table 1: Amount of excipients (mg) in the gum (b) (4) comparing to IIG limits

Excipient	Coated Fruit		Coated Cinnamon		IIG Limit
	2 mg	4 mg	2 mg	4 mg	Buccal
Acesufame K	(b) (4)				2.00 (3.00 mg for sublingual tablet, 6.00 mg for oral troche)
(b) (4)					(b) (4)
Xylitol					203.60
Sucralose					Not listed
FD&C Red # 40					0.006

Acesufame K

As demonstrated in **Table 1**, Watson's proposed amount of Acesufame K (gum (b) (4) is (b) (4) the IIG limit of 2.00 mg for the buccal chewing gum, and is well below the 3.00 mg limit for the sublingual tablet and well below the 6.00 mg limit for an oral troche. Sublingual and oral troche administration has a pattern of local exposure similar to buccal administration; therefore, the local safety of Acesufame K at the level proposed by Watson is well supported by the IIG limit of sublingual tablet and oral troche and should not pose any local safety concern to the consumer. Further, the safe use of Acesufame K is supported and substantiated by the attached scientific opinion letter (**ATTACHMENT 3**).

(b) (4)

As demonstrated in **Table 1,** (b) (4) present in Watson's coated fruit formulations. The amount in the gum (b) (4) mg for both the 2 and 4 strengths, which is the same as the amount listed in the IIG database for the buccal chewing gum product and therefore the safe use of (b) (4) at the level proposed by Watson is well supported and should not pose any local safety concern to the consumer.

Xylitol

Coated Fruit Formulations

As demonstrated in **Table 1**, the amount of Xylitol in Watson's coated fruit formulations (gum [(b) (4)] is well below the amount listed in the IIG database (203.60 mg) for the buccal chewing gum product and therefore the safe use of Xylitol at the level proposed by Watson is well supported and substantiated and should not pose any local safety concern to the consumer.

Coated Cinnamon Formulations

As demonstrated in **Table 1,** the amount of Xylitol in Watson's coated cinnamon formulations (gum [(b) (4)] is only [(b) (4)] over the amount listed in the IIG database for the buccal chewing gum product ([(b) (4)] mg versus 203.60 mg, a difference of only [(b) (4)]%). There is no reason to believe the small difference in the amount will cause any local safety concern, given the extensive history of xylitol used in products that include prolonged buccal contact (candy, gum, toothpaste, etc., see http://www.nextag.com/serv/main/buyer/OutPDir.jsp?nxtg=4d1c0a24052e-12F7087F90C1AFF1&search=xylitol+candy&perpagePersistent=60&node=2700000). The safe use of Xylitol in Watson's coated cinnamon formulations is further supported and substantiated by the attached scientific opinion letter (**ATTACHMENT 3).**

Sucralose

Sucralose is approved by FDA as "a sweetener in foods generally, in accordance with current good manufacturing practice in an amount not to exceed that reasonably required to accomplish the intended effect" (21 CFR §172.831). These include products like hard candies and cough drops that are commonly in prolonged contact with buccal or other oral mucosa during consumption. The World Health Organization (WHO 2008) has approved sucralose in a wide variety of food products, including at up to 5,000 mg/kg in chewing gum (compared to [(b) (4)] mg/kg in Watson's nicotine polacrilex gum product).

For example, both the wild cherry flavor Chloraseptic Lozenges and sugar free Life Savers® contain sucralose (please refer to labeling included in **ATTACHMENT 4**) . Watson has conducted an analysis and revealed that the amounts of sucralose in the wild cherry flavor Chloraseptic Lozenges and sugar free Life Savers® are at a level higher than that proposed by Watson in our coated fruit and coated cinnamon formulations (**Table 2**).

As described in FDA's Tentative Final Monograph (TFM) for **Oral Healthcare Drug Products: Anesthetic, Astringent, Antimicrobial, Debriding, Demulcent, Expectorant, Decongestant** (53FR2346), products such as Chloraseptic Lozenges may be dosed at 2 lozenges every 4 hours, not to exceed 24 lozenges in 24 hours. The lozenge is similar in surface area to the nicotine polacrilex gum as is the dosage regimen. A lozenge is meant to be in the oral cavity for the amount of time it takes for the lozenge to slowly dissolve and release its active ingredients, approximately 15 minutes per lozenge, resulting in an exposure scenario comparable to that for Watson's nicotine polacrilex gum. Therefore, the

safe use of sucralose in Watson's formulations at the proposed level is well supported and substantiated and should not pose any safety concern to the consumer.

Table 2: Amount of Sucralose in Chloraseptic Lozenges and Sugar Free Life Savers® (from Watson's analysis)

Product	Amount of Sucralose (mg)
Chloraseptic Lozenges	(b) (4) mg/piece
Sugar Free Life Savers	mg/piece

Further, while sucralose is not currently listed in FDA's IIG database for buccal chewing gum product, it is used in the Reference Listed Drug – Nicorette® Fruit Chill and Cinnamon Surge (please refer to **ATTACHMENT 5** for Nicorette's labeling for confirmation).

Watson also conducted an analysis and revealed that the amounts of sucralose in Nicorette's products are at a level higher than the level proposed by Watson in our coated fruit and coated cinnamon formulations (**Table 3**), therefore, the safe use of sucralose in Watson's formulations at the proposed level is well supported and substantiated and will not cause any more local toxicity at the site of administration than the RLD.

Table 3: Amount of Sucralose in Nicorette's Fruit Chill and Cinnamon Surge (from Watson's analysis)

Product		Amount of Sucralose (mg)
Nicorette® Fruit Chill	4 mg (lot# KF848A, Exp.: 04/10)	(b) (4) mg/piece
Nicorette ® Cinnamon Surge	4 mg (lot # IE839A, Exp.: 04/09)	mg/piece

The safe use of Sucralose in Watson's formulations is further supported by the attached scientific opinion letter (**ATTACHMENT 3).**

FD&C Red # 40

FD&C Red No. 40 is approved by FDA for use in foods and drugs under 21 CFR 74.340 (foods) and 74.1340 (drugs) with no limitation on the level of usage other than "in amounts consistent with good manufacturing practice." FD&C Red No. 40 is the highest-volume FDA-certified food color, with more than 6 million pounds of FD&C Red No. 40 and more than 1.8 million pounds of FD&C Red No. 40 Aluminum Lake certified in fiscal year 2008 (http://www.cfsan.fda.gov/~dms/col-08-4.html).

FD&C Red No. 40 is extensively used in a wide variety of foods, (http://www.red40.com/pages/foods/candy.html; http://www.candyfavorites.com/shop/candy-ingredients-wrapped.php; http://www.red40.com/pages/foods/bakery.html; http://www.red40.com/pages/foods/cereals.html; http://www.red40.com/pages/foods/dairy.html; http://www.red40.com/pages/foods/sauces.html; http://www.red40.com/pages/foods/snacks.html and beverages (http://www.red40.com/pages/foods/drinks.html). These include products like hard candies, lollipops and gums that are commonly in prolonged contact with buccal or other oral mucosa during consumption.

As described previously, Lozenge has an exposure scenario comparable to that for Watson's nicotine polacrilex gum. Like Watson's nicotine polacrilex gum, Chloraseptic Lozenges, wild cherry flavor also contain FD&C Red #40 and sucralose (see copy of labeling in **ATTACHMENT 5**), resulting in a similar pattern and level of exposure to these ingredients.

Given the broad, virtually unrestricted approval under 21 CFR 74.340 and 74.1340, and its widespread use, it is difficult to understand the basis for FDA's concerns regarding Watson's proposed usage. The safe use of FD&C red #40 in Watson's coated cinnamon formulations is further supported and substantiated by the attached scientific opinion letter (**ATTACHMENT 3).**

Watson Laboratories, Inc. trusts that the response provided satisfactorily addresses the concerns raised in the December 19, 2008 Telephone Deficiency faxed by Dr. Tom Hinchliffe.

As per the Agency's request, WLI is submitting this correspondence electronically in Adobe Acrobat portable document format (pdf) on the enclosed compact disc. The cover letter and 356h form are also being submitted in hard copy.

Pursuant to 21 CFR §314.97, we certify that a true field copy of this correspondence has been sent by overnight courier to Mr. Otto Vitillo, Director, Domestic Investigational Branch, Food and Drug Administration (NYK-DO), 158-15 Liberty Avenue, Jamaica, New York, 11433.

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (631) 693-8038 or by fax at (631) 693-8896.

Sincerely,
Watson Laboratories, Inc.

Meredith Silk for

Aibin You
Manager, Regulatory Affairs

CC: E-mail copy to Dr. David Skanchy, Office of Generic Drugs at David.Skanchy@FDA.HHS.gov

Watson

May 22, 2009

Mr. Wm. Peter Rickman
Director, Division of Labeling and Program Support
Office of Generic Drugs, HFD-610
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20855

LABELING AMENDMENT

RE: Nicotine Polacrilex Gum USP, 2 mg (Coated Cinnamon); ANDA 79-216
Nicotine Polacrilex Gum USP, 4 mg (Coated Cinnamon); ANDA 79-219
Nicotine Polacrilex Gum USP, 2 mg (Coated Fruit); ANDA 79-044
Nicotine Polacrilex Gum USP, 4 mg (Coated Fruit); ANDA 79-038

Dear Mr. Rickman:

Reference is made to the May 18, 2009 telephone contact from Ms. Michelle Dillahunt, Division of Labeling and Program Support, Office of Generic Drugs to Ms. Joyce DelGaudio of Watson. Ms. Dillahunt called to inform us that the Reference Listed Drug (RLD), Nicorette, had gained approval for a new dosing regimen. Ms. Dillahunt stated that in order for Watson to gain approval for the above referenced pending Abbreviated New Drug Applications (ANDAs), we should revise our labeling in accordance with the RLD.

Watson Laboratories, Inc. (WLI) hereby is submitting revised labeling to comply with the Agency's request.

WLI is submitting electronically in Adobe Acrobat portable document format (pdf) on the enclosed compact disk, the following:

- Final Printed Carton Labels for the 40 and 100 count sizes.
- User's Guide with certified Spanish translation.
- Side-by-side comparison of Watson's revised carton label versus the RLD, Nicorette carton label. Note: The Nicorette Fruit Chill carton label was used in the side-by-side comparison of the cinnamon products. The Cinnamon RLD label provided by Ms. Dillahunt was not legible.
- Side-by-side comparison of Watson's revised user's guide versus the RLD, Nicorette user's guide.

As per the Agency's request, WLI is submitting this supplement electronically in Adobe Acrobat portable document format (PDF) on the enclosed compact disc. The cover letter and 356h form are being submitted in hard copy.

Watson trusts that this submission satisfactorily addresses the Agency's request, and priority review will be given to gain approval of the pending applications.

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (631) 693-8038 or by fax at (631) 693-8896.

Sincerely,
Watson Laboratories, Inc.

Meredith Seeley for

Beverly Bailey
Manager, Regulatory Affairs

Watson

July 1, 2009

Mr. Gary Buehler, Director
Office of Generic Drugs, HFD-615
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

RE: Nicotine Polacrilex Gum USP, 2 mg (Coated Fruit); ANDA 79-038
Nicotine Polacrilex Gum USP, 4 mg (Coated Fruit); ANDA 79-044
Nicotine Polacrilex Gum USP, 2 mg (Coated Cinnamon); ANDA 79-216
Nicotine Polacrilex Gum USP, 4 mg (Coated Cinnamon); ANDA 79-219

Dear Dr. Buehler:

Reference is made to the Chemistry Comments, faxed on June 25, 2009, by David Skanchy, Chemistry Reviewer of the Office of Generic Drugs providing comments on the above listed Abbreviated New Drug Application(s) (ANDA) (**Attachment 1**). Watson Laboratories, Inc. hereby submits our responses to the chemistry comments in this Telephone Amendment.

Comment 1

(b) (4)

Response: (b) (4) The results for the aforementioned tests were within specification limits. The test results were incorporated in the updated Certificate of Analysis provided in **Attachment 2**.

Note: We have provided test result on the (b) (4) sample testing is the same as originally submitted to the ANDA with minor editorial changes.

Comment 2

We note that you have added the requested compliance statement for USP<467> Residual Solvents to your drug product release specifications. In an effort to harmonize these statements we now have more specific guidance on the format of the statement. Please submit a revised drug product specification with a USP<467> statement meeting the following criteria:

a. **The statement should appear as a line item test, similar in format to all of the other required tests listed on the specification (footnoted statements are no longer acceptable).**
b. **The statement should indicate compliance according to (b) (4), consistent with data and calculations you provided.**

Response: Per the Agency's request, the compliance statement for USP<467> Residual Solvents was revised and incorporated in the revised Finished Product Specifications and Procedure, **Attachment 3**.

Comment 3

Please update the (b) (4) specification and test protocol in the following manner.

a. (b) (4)

b.

Response: The USP test methods and specifications were always considered as the industry standard for (b) (4) used in our approved and marketed nicotine polacrilex gum drug products, including nicotine polacrilex gum coated mint ANDAs 78-699 and 78-697, which were approved on December 29, 2008.

(b) (4)

(b) (4)

used in the manufacture of the drug products.

Watson Inc. trusts that the responses provided satisfactorily address the concerns raised in the Chemistry Comments letter.

Pursuant to 21 CFR §314.97, we certify that a true field copy of this correspondence has been sent by overnight courier to Mr. Otto Vitillo, Director, Domestic Investigational Branch, Food and Drug Administration (NYK-DO), 158-15 Liberty Avenue, Jamaica, New York, 11433.

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (631)693-8038 or by fax at (631)693-8896.

Sincerely,
Watson Laboratories, Inc.

Beverly Bailey
Manager, Regulatory Affairs

CC: Dr. David Skanchy, Chemistry Reviewer

Watson

July 2, 2009

Mr. Gary Buehler, Director
Office of Generic Drugs, HFD-615
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

COMMITMENTS TO JULY 1, 2009 TELEPHONE AMENDMENT

RE: Nicotine Polacrilex Gum USP, 2 mg (Coated Fruit); ANDA 79-044
Nicotine Polacrilex Gum USP, 4 mg (Coated Fruit); ANDA 79-038
Nicotine Polacrilex Gum USP, 2 mg (Coated Cinnamon); ANDA 79-216
Nicotine Polacrilex Gum USP, 4 mg (Coated Cinnamon); ANDA 79-219

Dear Dr. Buehler:

This is in reference to the July 2, 2009 telephone contact from Dr. David Skanchy, Chemistry Reviewer of the Office of Generic Drugs to Watson Laboratories, Inc. (WLI) requesting modified commitment to comments 2 and 3 of the July 1, 2009 Telephone Amendment for the above referenced pending Abbreviated New Drug Applications (ANDA). Watson hereby provides the following modified commitments as requested by the Agency.

Commitment to Comment 2

WLI, Copiague commit to (b) (4) are included in this submission for your review in **Attachment 1**.

Commitment to Comment 3

WLI, Copiague commit to submit (b) (4) used in the manufacturing of the drug products.

Watson Inc. trusts that the responses provided satisfactorily address the Agency's request.

Pursuant to 21 CFR §314.97, we certify that a true field copy of this correspondence has been sent by overnight courier to Mr. Otto Vitillo, Director, Domestic Investigational Branch, Food and Drug Administration (NYK-DO), 158-15 Liberty Avenue, Jamaica, New York, 11433.

We have also included in this submission an additional copy of our cover letter. Please acknowledge by date-stamping this letter upon receipt and forwarding this copy to us in the self-stamped envelope provided for your convenience.

If you have any comments or questions concerning this submission, please contact me by phone at (631)693-8038 or by fax at (631)693-8896.

Sincerely,
Watson Laboratories, Inc.

K. K. Jos for

Beverly Bailey
Manager, Regulatory Affairs

CC: Dr. David Skanchy, Chemistry Reviewer

OGD APPROVAL ROUTING SUMMARY

ANDA # 79-038 Applicant Watson Laboratories, Inc.
Drug Nicotine Polacrilex Coated Gum USP, 4 mg (Fruit) Strength(s) _____

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

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer** Chief, Reg. Support Branch	Date 19 May 2009 Initials MHS	Date 7/8/09 Initials rlw

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = Nicorette NDA# 20-066
Date Checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐
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 ☐ Date settled:
Is applicant eligible for 180 day Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.
Comments: ANDA submitted on 6/4/2007, BOS=Nicorette Fruit Chill NDA 20-066, PI and PII cert provided. ANDA ack for filing on 6/4/2007(LO dated 9/28/2007). There are no remaining patents or exclusivities which protect the RLD. This ANDA is eligible for immediate Full Approval.

2. Project Manager, Thomas Hinchliffe Team 10 Review Support Branch	Date 5/15/09 Initials toh	Date 5/15/09 Initials toh

Original Rec'd date June 4, 2007
Date Acceptable for Filing June 4, 2007
Patent Certification (type) II
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes ☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments: DATE OF APPLICATION: June 1, 2007

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 12/15/2008
Date of Office Bio Review 5/7/2008
Date of Labeling Approv. Sum 8/15/2008
Labeling Acceptable Email Rec'd Yes ☒ No ☐
Labeling Acceptable Email filed Yes ☒ No ☐
Date of Sterility Assur. App. na
Methods Val. Samples Pending Yes ☐ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

3. Labeling Endorsement

Reviewer:	Labeling Team Leader:
Date 6/16/09	Date 6/16/09
Name/Initials MD	Name/Initials LG

Comments:
Labeling rev Acceptable June 16, 2009.

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 7/8/09
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments: N/A. There are no patents listed in the current "Orange Book" for this drug product.

5. Div. Dir./Deputy Dir. Date 7/6/09
Chemistry Div. II Initials FF

Comments: Commitment to update [redacted] (b) (4), together with updating the approved ANDAs. CMC ok.

6. Frank Holcombe **First Generics Only** Date 7/8/09
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
N/A. Multiple ANDAs have been approved for this drug product. This represents a product line extension.

7. Vacant Date _____
Deputy Dir., DLPS Initials _____
RLD = Nicorette Gum 4 mg (base) (Coated, Fruit Chill)
GlaxoSmithKline NDA 20-066

8. Peter Rickman Date 7/8/09
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Bioequivalence studies: (1) Fasting on the 4 mg strength, (2) single-dose chew out on the 4 mg strength, and (3) multi-dose chew out on both the 2 mg and 4 mg tablet strengths found acceptable. In-vitro dissolution studies also found acceptable. Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 4/10/98 and 5/7/08. Note: These studies were reviewed concurrently with Watson's ANDA 79-044 for Nicotine Polacrilex Gum USP, 2 mg.

Final-printed labeling (FPL) found acceptable for approval 6/22/09.

CMC found acceptable for approval (Chemistry Review #1).

OR

8. Robert L. West Date 7/8/09
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 12/15/08 (Verified 7/8/09). No "OAI" Alerts noted.

There are no patents or exclusivity listed in the current "Orange Book" for this drug product.

This ANDA is recommended for approval.

9. Gary Buehler Date 7/8/09
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Thomas Hinchliffe Team 10 Date 7/8/09
Review Support Branch Initials se
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
11amTime notified of approval by phone 11:25amTime approval letter faxed

FDA Notification:
7/8/09Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
7/8/09Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 020066 Product 002 in the OB_OTC list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through May, 2009
Patent and Generic Drug Product Data Last Updated: July 07, 2009

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/s/

Simon Eng

7/8/2009 02:46:57 PM