CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 076775/S-018

Name: Nicotine Polacrilex Gum USP, 2 mg

Sponsor: L. Perrigo Company

Approval Date: August 30, 2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076775/S-018

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Tentative Approval Letter	
Labeling	**X**
Labeling Review(s)	**X**
Medical Review(s)	
Chemistry Review(s)	
Bioequivalence Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Other Review(s)	**X**
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076775/S-018

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Rockville MD 20855

ANDA 076775/S-018

L. Perrigo Company
Attention: Gregory Shawaryn
515 Eastern Avenue
Allegan, MI 49010

Dear Sir:

This is in reference to your supplemental new drug application dated March 18, 2011, submitted pursuant to 21 CFR 314.70 as a Supplement – Changes Being Effected, and accepted as a Prior Approval Supplement, regarding your abbreviated new drug application for Nicotine Polacrilex Gum USP, 2 mg (Regular).

Reference is also made to your amendment dated August 2, 2011.

This supplemental new drug application provides the addition of a 10 count package of Nicotine Polacrilex Gum USP, 2 mg.

We have completed the review of your application and it is approved.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

CONTENT OF LABELING

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

Labeling Technical Qs and As" at
http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the following address or by facsimile at 301-847-8444:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The materials submitted are being retained in our files.

Sincerely,

{See appended electronic signature page}

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

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/s/

LILLIE D GOLSON
08/30/2011
for Wm. Peter Rickman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076775/S-018

LABELING

FINAL PRINTED LABELING
Nicotine Polacrilex Gum, 2 mg
10-count carton

STANDARD FORMAT
TYPE SIZES:
TITLE: 10 pt Helvetica Neue 77 Bold Cond Oblique
TITLE (continued): 8 pt Helvetica Neue 77 Bold Cond Oblique
(continued) 8 pt Helvetica Neue 57 Cond
HEADINGS: 8 pt Helvetica Neue 77 Bold Cond Oblique
SUBHEADINGS: 6 pt Helvetica Neue 77 Bold Cond
TEXT: 6 pt Helvetica Neue 57 Cond
LEADING: 6.5 pt
BULLETS: 5 pt Square with 2 M'S spacing between statements
TELEPHONE #: 6 pt Helvetica Neue 77 Bold Cond
HEAVY LINES: 1.5 pt
HAIRLINES: 0.5 pt

7.29.11

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076775/S-018

LABELING REVIEWS

Labeling Review Branch
Division of Labeling and Program Support
Office of Generic Drugs

Labeling Supplement Review

Application Number: 076775/S-018

Name of Drug: Nicotine Polacrilex Gum USP, 2 mg (Regular)

Applicant: L. Perrigo Company

Material Reviewed: (specify labeling pieces)
Submission Date(s):
March 18, 2011 Submitted as a CBE; changed to a PAS (Container Label)

Background and Summary

1. This supplemental application provides for the addition of a smaller 10 count package of Nicotine Polacrilex Gum USP, 2 mg. Historically, the Agency had concerns that a smaller package would be promotional and may contribute to abuse and misuse as a result of a potentially lower price. A consult was requested by OGD to the Division of Nonprescription Clinical Evaluation (DNCE) on Perrigo's proposal. DNCE concludes that there is no clear evidence that either the nicotine gum or lozenge forms are drug products which are likely to be abused by any age group, including adolescents, and makes the following recommendations (the full consult review can be found in DARRTS):

   Recommendations
   a. DNCE agrees that the 10-piece package size for the 2 mg nicotine gum is acceptable under the conditions proposed by Perrigo.
   b. We also recommend Perrigo market the 4 mg gum in a 10-piece package.
   c. Consumers should be made aware this product is to "start or continue a quit attempt" and this may not be a full day's supply. DNCE suggests OGD consider a way to include this in the product labeling.

2. Model Labeling: Nicorette® Gum (Nicotine Polacrilex, USP), 2 mg, NDA 018612.S-056, approved May 17, 2011. This supplement provides for the change in format of the consumer information leaflet from a booklet to a leaflet based document.

3. Patent/Exclusivity: None

Review

The labeling supplement is not acceptable for approval. Based on the recommendations made by DNCE, the following comments will be communicated to the firm.

1. Consumers should be made aware this product is to “start or continue a quit attempt” and a 10 piece package may not be a full day’s supply for all quitters depending on their current stage in their quit attempt. Please state on your carton labeling that this package size my not be a full day’s supply.
2. We recommend that you market the 4 mg strength in a 10 piece package in order to avoid encouraging consumers to purchase the 2 mg gum in the smaller, less expensive package instead of the 4 mg gum which may be a more appropriate dose.

Recommendation

The submitted labeling is NOT acceptable for approval.

{see appended electronic signature}

Lisa Kwok
Labeling Reviewer

Supervisory Comment/Concurrence:

{see appended electronic signature}

Lillie Golson
Team Leader

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/s/

LISA H KWOK
07/14/2011

LILLIE D GOLSON
07/14/2011

Labeling Review Branch
Division of Labeling and Program Support
Office of Generic Drugs

Labeling Supplement Review #2

Application Number: 076775/S-018

Name of Drug: Nicotine Polacrilex Gum USP, 2 mg (Regular)

Applicant: L. Perrigo Company

Material Reviewed: (specify labeling pieces)

Submission Date(s):
August 2, 2011: Amendment to PAS CR letter (Carton Labeling)

Background and Summary

1. This supplemental application provides for the addition of a smaller 10 count package of Nicotine Polacrilex Gum USP, 2 mg. Historically, the Agency had concerns that a smaller package would be promotional and may contribute to abuse and misuse as a result of a potentially lower price. A consult was requested by OGD to the Division of Nonprescription Clinical Evaluation (DNCE) on Perrigo's proposal. DNCE concludes that there is no clear evidence that either the nicotine gum or lozenge forms are drug products which are likely to be abused by any age group, including adolescents, and makes the following recommendations (the full consult review can be found in DARRTS):

   Recommendations
   a. DNCE agrees that the 10-piece package size for the 2 mg nicotine gum is acceptable under the conditions proposed by Perrigo.
   b. We also recommend Perrigo market the 4 mg gum in a 10-piece package.
   c. Consumers should be made aware this product is to "start or continue a quit attempt" and this may not be a full day's supply. DNCE suggests OGD consider a way to include this in the product labeling.

   Therefore, the following comments were communicated to the firm in a CR letter on 7/14/2011.

   - Consumers should be made aware this product is to "start or continue a quit attempt" and a 10 piece package may not be a full day's supply for all quitters depending on their current stage in their quit attempt. Please state on your carton labeling that this package size my not be a full day's supply.
   - We recommend that you market the 4 mg strength in a 10 piece package in order to avoid encouraging consumers to purchase the 2 mg gum in the smaller, less expensive package instead of the 4 mg gum which may be a more appropriate dose.

2. Model Labeling: Nicorette® Gum (Nicotine Polacrilex, USP), 2 mg, NDA 018612.S-056, approved May 17, 2011. This supplement provides for the change in format of the consumer information leaflet from a booklet to a leaflet based document.

3. Patent/Exclusivity: None

Review

Perrigo provides the following response in their amendment dated 8/2/11:

1. **Consumers should be made aware this product is to "start or continue a quit attempt" and a 10 piece package may not be a full day's supply for all quitters depending on their current state in their quit attempt. Please state on your carton labeling that this package size may not be a full day's supply.**

   Perrigo has added the following footnote below the net contents line "*This package size may not be a full day's supply; it is intended to start or continue a quit attempt." The carton art previously submitted on March 18, 2011 has been updated to incorporate the recommended text, please refer to the updated carton labeling provided in Attachment 2. A side-by-side comparison of the previously submitted art and the current art is included in Attachment 3.

2. **We recommend that you market the 4 mg strength in a 10 piece package in order to avoid encouraging consumers to purchase the 2 mg gum in the smaller, less expensive package instead of the 4 mg gum which may be a more appropriate dose.**

   We acknowledge the recommendation and as a result (in addition to the submission made for the 2mg dated on March 18, 2011) a submission is being made today to ANDA 76-789, Nicotine Polacrilex Gum USP, 4 mg (Regular) to request approval to commercially market a 10 count package. The art included in that submission addresses the above-mentioned comment 1. A copy of the cover letter has been included for your reference in Attachment 4.

In addition Perrigo states that:

Upon approval of this supplemental application, Perrigo intends to (b) (4) (b) (4) (b) (4) This implementation will be reported in the annual reports for the following ANDAs:

ANDA 76-776: Nicotine Polacrilex Gum USP, 2 mg (Orange, Uncoated)
ANDA 76-777: Nicotine Polacrilex Gum USP, 2 mg (Mint, Coated)
ANDA 78-325: Nicotine Polacrilex Gum USP, 2 mg (Mint, Uncoated)
ANDA 78-547: Nicotine Polacrilex Gum USP, 2 mg (Regular, Coated)
ANDA 78-967: Nicotine Polacrilex Gum USP, 2 mg (Orange, Coated)
ANDA 91-349: Nicotine Polacrilex Gum USP, 2 mg (Cinnamon, Coated)

Rather than being submitted as annual reports, the Agency would like these changes to be submitted as CBE supplements to ensure that the verbiage has been added. Lillie Golson

contacted Gregory Shawryn of Perrigo Company on August 25, 2011 and requested these changes be submitted as CBE supplements.

Recommendation

The submitted labeling is acceptable for approval.

{see appended electronic signature}

Lisa Kwok
Labeling Reviewer

Supervisory Comment/Concurrence:

{see appended electronic signature}

Lillie Golson
Team Leader

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

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/s/

LISA H KWOK
08/29/2011

LILLIE D GOLSON
08/30/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076775/S-018

OTHER REVIEW

Date: May 27, 2011

From: Priscilla Callahan-Lyon, M.D.
Medical Officer
Division of Nonprescription Clinical Evaluation

Through: Daiva Shetty, M.D.
Clinical Team Leader
Division of Nonprescription Clinical Evaluation

Andrea Leonard-Segal, M.D., M.S.
Director
Division of Nonprescription Clinical Evaluation

To: Lisa Kwok, Pharm. D.
Labeling Reviewer
Office of Generic Drugs

Subject: Nicotine Polacrilex Gum, ANDA 076-775/S-018

Tracking Number: 2011.560.A.00003

Introduction

The Review Team in the Office of Generic Drugs (OGD) requested the opinion of the Division of Nonprescription Clinical Evaluation (DNCE) on a proposal by Perrigo for a smaller package size (10-pieces) of their nicotine polacrilex gum (ANDA 076-775), a generic version of Nicorette gum 2 mg (NDA 018-612).

Background

Nicotine polacrilex was approved for smoking cessation in 1984 as a 2 mg chewing gum product. It was made available over-the-counter in 1996. As one of the original conditions of approval, "trial size" or "sample" packs of the gum may not be offered. In 2005, FDA received a proposal from Perrigo for marketing a 20-count package of nicotine polacrilex gum. The rationale provided by Perrigo included the following points:

- Perrigo does not view or treat the 20-count package as a trial or sample package. It is labeled and marketed in a container similar to the 50-count package and has no indications that it is intended to be used as a trial or sample size.
- The 20-count package is consistent with approved dosing for the nicotine gum. In weeks 10 through 12 of treatment, the recommended dose is one piece of gum every 4 to 8 hours. Depending on the usage pattern, a 20-count package could provide enough gum for a week.
- Offering the 20-count package may make the product more affordable for consumer who cannot purchase a larger quantity due to the expense.
- The 20-count package would be useful for travelers who forget the nicotine gum and don't wish to buy a large supply for only a few days.
- One concern leading to the conditions for approval was the potential for abuse of the nicotine gum – particularly by adolescents. Perrigo noted that during approval of mint-flavored nicotine gum in 1998, FDA addressed this issue and concluded that concerns of abuse had not been borne out by experience.

After consultation, DNCE and OGD agreed to the 20-count package. In the reply to OGD, the DNCE director wrote "Given that 20 pieces is approximately a one day supply of the maximum amount of the drug that can be used in 24 hours (24 pieces), we do not feel that this constitutes a sample size. Therefore, as long as the drug facts labeling and the directions for a quit indication are unchanged, we are not opposed to a 20-count size. We strongly feel that a one day supply of the drug containing the maximum amount that can be used in 24 hours should be the minimum count size marketed."

Review

Perrigo has now submitted a 'Changes Being Effected Labeling Supplement' (ANDA 076-775/S-018) to the Office of Generic Drugs proposing a 10-count package of nicotine polacrilex 2 mg gum. To support this proposal, Perrigo offers the following rationale:

- The 20-count package has been approved and marketed for 6 years and there is no evidence the concerns FDA had are warranted. Specifically, there is no evidence of the smaller package size encouraging inappropriate use or increasing the safety risks of the product. Perrigo has not been informed of an occurrence or observed any correlation of package size or price on the abuse or underage use of nicotine polacrilex gum during the seven years the company has been marketing the product.

- The availability of a 10-count package would lead to a price comparable to a pack of cigarettes. This could provide a more affordable option for smokers who may want to quit.
- A smaller package size allows consumers who forgot their nicotine gum product the option of purchasing a small supply to help them through the day.
- For consumers with limited financial means, a smaller package size may allow them to continue treatment until the next pay period; a larger, more expensive package size may not be a viable option.
- All safety information and warnings will be included on the labeling for any package size.
- A smaller package size may be more convenient for consumers who are traveling.
- Towards the end of the treatment period, fewer pieces of gum are needed and a smaller package size provides more flexibility for the consumer.

Perrigo plans to continue with their previously approved 'Marketing and Surveillance Plan.' The marketing restrictions are to prevent inappropriate sale of the nicotine gum product to minors and to safeguard against potential abuse or misuse of the gum. The mechanisms for the marketing restrictions include:

- Distribution of Perrigo nicotine polacrilex gum is limited to intermediate distributors and retailers who comply with the conditions for approval:
    - 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 age cannot be verified
- Most retail outlets of Perrigo nicotine gum use UPC bar code scanners that prompt the cashier to require identification (similar to purchasing tobacco products).
- Trial or sample packages of Perrigo nicotine gum are not marketed.
- Each piece of gum is secured in a child-resistant blister.
- Each retail carton is secured with adhesive.
- Package design does not appeal to teenagers or children; the design is approved by Perrigo's Regulatory Affairs department.

In addition, Perrigo provides training to the distributors and retailers to emphasize the sales restrictions. Retailers are encouraged to participate in an anti-theft program including use of a theft surveillance tag and shelving the product in an appropriate area of the store.

The surveillance plan is to ensure compliance with the approved labeling and to identify use of Perrigo nicotine gum by consumers less than 18 years of age. The mechanisms for the surveillance plan include:

- (b) (4)
- 

Discussion

Perrigo has proposed marketing a 10-piece package of nicotine polacrilex 2 mg gum. They have proposed a rationale for this which has three principle components:

1. The 10-piece packages would be more economical.

This is not a valid rationale. As marketers of the products, Perrigo establishes the product price. If Perrigo is concerned that the packages of gum be priced similarly to a pack of cigarettes, they can control this.

2. The 10-piece packages would provide additional consumer convenience.

The convenience of a smaller package size bears consideration. Individuals may taper the dose of the gum at different rates and having access to packages of varying sizes provides more flexibility. Near the end of a treatment course for smoking cessation, a consumer may only need 3 to 6 pieces of gum per day (one piece every 4 to 8 hours). Perrigo also mentions the advantages for consumers who may be traveling or who may forget their nicotine gum supply. Having the smaller package size could be more convenient for these individuals.

The 10-piece package would also provide the 'minimum suggested dose' for the initial phase of quitting. The current approved labeling states: "to improve your chances of quitting, use at least 9 pieces (of gum) per day for the first 6 weeks." The 10-piece package could be a one-day supply for some consumers but it is important to note that ten pieces may not be a full day's supply for heavier smokers, especially early in their quit attempt.

3. There is no significant risk of misuse or abuse due to smaller package sizes – particularly in the adolescent population.

The potential risk for misuse or abuse of the gum has been a significant concern in the past; the adolescent population has been of particular concern. As noted by Perrigo, during the 1998 approval for mint flavored nicotine polacrilex gum, the FDA noted that over the years since nicotine polacrilex gum was originally approve the early concerns about abuse had been allayed by the paucity of reports. Since 1998, the marketers of nicotine polacrilex products – generic and brand-name – have continued to conduct post-marketing surveillance for product abuse.

In 2008, FDA requested that GlaxoSmithKline (GSK) evaluate the potential for misuse or abuse of nicotine polacrilex gum or lozenge in all populations as part of the safety information submitted for NDA 22-360. GSK submitted post-marketing safety data from their worldwide database, the World Health Organization (WHO) International Drug Monitoring program, the FDA Adverse Event Reporting System database, Drug Abuse and Overdose from the Drug Abuse Warning Network (DAWN), and Toxic Exposure Surveillance System data from the American Association of Poison Control Centers. The DAWN search found no mention of nicotine among the drug products included in the reports. There were no aggregate emergency department reports found in the published literature. Data submitted included the following:

GlaxoSmithKline (GSK) database

Table 1 summarizes the GSK USA and Worldwide Database of all reports through a data lock point of 31 August, 2008. There were thousands of reported events but few (< 5%) were serious and even fewer were medically verified.

Table 1: Summary of Use, Extended Length of Use, and Serious Events for Gum and Lozenge in All Populations from GSK Database

	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge
Events Reported	19,202	11,181
Serious Events Reported	837 (4.4%)	375 (3.3%)
Medically Verified and Serious	173 (0.9%)	10 (<0.1%)
Total Episodes of Use	19335	11243
Duration of Use Known	7628 (39.4%)	5391 (47.9%)
Use ≤ 6 months	6361 (83.4%)	4895 (90.8%)
Use 6 months – 1 year	217 (2.8%)	114 (2.1%)
Use 1year – 2 years	221 (2.9%)	168 (3.1%)
Use > 2 years	829 (10.9%)	214 (4.0%)

Source: NDA 22-360 Clinical Review; Page 28; Table 12

GSK also performed a search specifically looking for evidence of misuse or abuse by children under age 18. These results are presented in Table 2. It should be noted that detailed information is not available for these case reports and the data may be incomplete. The most significant pattern is that most cases of exposure to nicotine polacrilex by children under age 12 were due to accidental exposure.

Table 2: Summary of Case Reports in Children < 18 from GSK Worldwide Database

	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge
Age < 12	Total:13 - Of these 13 4 coded as Intentional Drug Misuse 4 coded as Accidental Overdose 2 listed as Serious 1 Acc OD in 20mo old – resolved 1 in-utero exposure – baby born at 25 wks – mom smoked and used gum – baby had multiple birth defects[a]	Total: 12 – Of these 12 8 coded as Accidental Exposure 2 coded as Drug Administration Error 1 listed as Serious 16mo chewed ½ lozenge, treated with charcoal; recovered
Age 12-17	Total: 37 – Of these 37 the most common AEs were nausea, vomiting, and abdominal pain 1 listed as Serious (16yo took 20 pieces of 4mg in 17 hrs-passed out & hit head) 2 coded as Intentional Misuse 1 coded as Intentional Misuse/OD (the serious case above) 1 coded as Administration Error/OD 1 coded as Nicotine Dependence	Total: 9 – Of these the most common AEs were nausea, vomiting, abdominal pain, and throat irritation 1 coded as Intentional Misuse 1 coded as Accidental Exposure 1 coded as Intentional Misuse & Nicotine Dependence

[a] It is unclear that the defects are related to exposure to the gum

Source: NDA 22-360 Clinical Review; Page 34; Table 21

World Health Organization (WHO)

The WHO database was searched for *drug dependence and/or drug abuse* in the data set with Nicorette® and Commit® through September, 2008. Age was specified in 55% of the consumers of the gum and 80.7% of the consumers using the lozenge. For cases listed as 'drug abuse' or 'drug dependence,' none of the consumers were < 18 years of age. The results are summarized in Table 3. Though the number of events is small, serious events are more commonly reported with the lozenge. (The opposite was true in the AERS data base.) The "abuse, misuse, overdose" pattern noted with the gum is most likely related to consumers who use the gum for a longer period than indicated on the labeling. This pattern of "abuse" was noted in all databases.

Table 3: Summary of Abuse, Misuse, Overdose, and Serious Events for Gum and Lozenge in All Populations from WHO Database

	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge
Total Events Reported	982	637
Total Serious Events	29 (2.9%)	83 (13.0%)
Total Abuse, Misuse, Overdose	415 (42.3%)	76 (11.9%)

Source: NDA 22-360 Clinical Review; Page 28; Table 14

FDA Adverse Event Reporting System (AERS)

The AERS database was searched from time of initial marketing up to Quarter 1 of 2008 for *drug abuse, intentional misuse, overdose, and dependence* terms for Nicorette® and Commit®. Table 4 shows that about 10% of the total events reported were serious events but details were lacking.

Table 4: Summary of Abuse, Misuse, Overdose, and Serious Events for Gum and Lozenge in All Populations from AERS Database

	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge
Total Events Reported	9409	3274
Total Serious Events	1183 (12.6%)	279 (8.5%)
Total Abuse, Misuse, Overdose or Dependence	3376 (35.9%)	732 (22.4%)

Source: NDA 22-360 Clinical Review; Page 28; Table 13

A search was done specifically looking for evidence of misuse or abuse by children under age 18. These results are presented in Table 5. The number of reported cases is very small and more commonly reported with the gum. This could be related to a longer marketing history.

Table 5: Summary of Case Reports in Children under age 18 from AERS Database

	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge
Age < 18	Total: 45 8-Abuse/Dependence/Overdose	Total: 8 2-Abuse/Dependence/Overdose

Source: NDA 22-360 Clinical Review; Page 35; Table 23

American Association of Poison Control Centers (AAPCC)

Data was collected on the number of exposure cases to nicotine pharmaceuticals from 1997 to 2006. Distinguishing between the formulations (patch/gum/lozenge) is not possible. Table 6 shows there is no increase in the number of exposures over 10 year period. The major reason for exposure was unintentional.

Table 6: Case of Exposure to Nicotine pharmaceuticals; 1997 – 2006; AAPCC database

Year	Number of Exposures	Age in Years			Reason			
		<6	6- 19	>19	Unintentional	Intentional	Other	Adverse Reaction
1997	856	189	73	545	460	99	1	294
1998	725	189	81	415	423	73	1	225
1999	750	221	80	409	481	77	2	189
2000	743	257	77	402	483	72	3	183
2001	676	258	75	339	472	66	0	135
2002	808	320	79	404	557	72	1	176
2003	725	260	75	382	482	81	2	155
2004	867	358	84	420	618	79	2	160
2005	1024	437	91	493	727	109	3	178
2006	924	446	80	344	698	55	0	169
Total	**8098**	**2935**	**795**	**4176**	**5401**	**783**	**15**	**1864**

Source: NDA 22-360 Clinical Review; Page 29; Table 15

In addition, the concern of misuse or abuse of NRT products was discussed during the public workshop on 'Risks and Benefits of Long-Term Use of Nicotine Replacement Therapy Products' held in October, 2010. The experts at the workshop all agreed that the risk of abuse of these products is very low.

After consideration of the Perrigo rationale and the GSK postmarketing safety data, there is no clear evidence that either the nicotine polacrilex gum or lozenge forms are drug products which are likely to be abused by any age group, including adolescents. The addition of more appealing flavors and smaller packages over the last several years has not changed this pattern.

FDA has also been concerned about the use of nicotine replacement products for temporary abstinence. This concern was not addressed by Perrigo. In fact, they go to great lengths to state that the smaller package size products will be labeled and marketed in exactly the same way as larger package sizes. The approved indication for this product is smoking cessation. The package sizes have been selected to encourage consumers to purchase enough of the drug product to either complete or make significant progress toward quitting smoking. The 10-piece package size, which focuses on convenience and economy, will clearly not be enough for a consumer to complete a cessation protocol and may not even be enough for an entire day for some consumers.

Some consumers may use the smaller size package to obtain a supply of nicotine polacrilex for the purpose of abating acute withdrawal symptoms and providing relief in situations of enforced temporary abstinence. This probably also occurs with the currently available package sizes. The 'off-label' use of the product is a known risk of any over-the-counter medication. DNCE does

believe, however, that marketing a package of less than 9 pieces of gum (the 'minimum suggested initial daily dose') would be tantamount to sanctioning 'off-label use' and DNCE could not support that.

There is some concern that Perrigo only proposes the 2 mg gum to be marketed in the 10-piece package. This could "lure" consumers to the smaller size gum due to the smaller, less expensive package size when the 4 mg gum may be a more appropriate dose. Perrigo should consider marketing both doses in the smaller package size to avoid this confusion.

Conclusions

1. As long as the labeling and marketing plans for the 10-piece package of gum are unchanged from the 20-piece and larger packages, we have no reason to believe that this smaller package size will have a significant effect on the usage pattern of nicotine polacrilex gum. By contrast, we would consider a package size of less than nine pieces of gum to be inappropriate. The currently approved package labeling recommends at least '9 pieces per day for the first 6 weeks.' Providing fewer than nine pieces would be less than a full day's supply for anyone in the early stages of their quit attempt; it could inadvertently sanction use of the product for temporary abstinence, which is not an approved indication.
2. Consumers should be made aware that the 10-piece package may not be a full day's supply for all quitters depending on their current stage in their quit attempt.
3. Perrigo should consider offering both the 4 mg and 2 mg gum in the 10-piece package size in order to avoid encouraging consumers to purchase the 2 mg gum in the smaller, less expensive package instead of the 4 mg gum which may be a more appropriate dose.

Recommendations

1. DNCE agrees that the 10-piece package size for the 2 mg nicotine gum is acceptable under the conditions proposed by Perrigo.
2. We also recommend Perrigo market the 4 mg gum in a 10-piece package.
3. Consumers should be made aware this product is to "start or continue a quit attempt" and this may not be a full day's supply. DNCE suggests OGD consider a way to include this in the product labeling.

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

/s/

PRISCILLA R CALLAHAN-LYON
05/27/2011

DAIVA SHETTY
05/27/2011

ANDREA LEONARD SEGAL
05/27/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076775/S-018

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

March 18, 2011

Special Supplement-
Changes Being Effected
Labeling Supplement

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

Via ESG (Gateway)

RE: ANDA 76-775
Nicotine Polacrilex Gum USP, 2 mg (Regular)

Dear Dr. Webber:

Reference is made to the telephone conversation held on January 5, 2011, between Lilli Golson of OGD and Barinder Sandhu of Perrigo, on the possibility of commercially marketing a packaging size of less than 20 pieces of gum. As a follow-up to that discussion, Perrigo is proposing the addition of a 10-count package (configured with already approved packaging components). Included in Attachment 1 is an example of Final Printed Labeling for the proposed 10-count. This representative label is identical to our currently approved labels with the exception of the net contents of 10.

Historically, Perrigo has engaged in similar discussions with FDA seeking approval for a smaller packaging configuration. A letter dated June 21, 2005 was written to Mr. W. Peter Rickman, whereby Perrigo helped to mitigate FDA's concerns of commercially marketing a 20-count package by presenting several arguments and evidence in support of the 20-count (Attachment 2). FDA's primary concern was that the use of a 20-count package would be promotional, and may contribute to abuse and misuse as a result of a potentially lower price. These concerns were addressed by Perrigo and thus, the 20-count package continues to be commercially available.

Since approval and now being on the US market for 6 years with the 20-count package, there is no direct evidence that would support and/or help to warrant the concerns previously held by FDA regarding the lower packaging counts. Thus, marketing a lower packaging size will not introduce and/or encourage an inappropriate use and/or increase safety risks that are already inherent with the product, as outlined in the label. In fact, over the 7 years of domestic store brand distribution of Nicotine Polacrilex Gum products, Perrigo has not been informed of an actual occurrence and/or observed any direct correlation of package size /or price on abuse /or underage use of Nicotine Polacrilex Gum.

In the absence of actual evidence based arguments and/or direct correlation of package size /or price on abuse /or underage use of Nicotine Polacrilex Gum, Perrigo believes there are several benefits that a 10-count packaging option can provide smokers who are trying to quit smoking.

We are requesting approval of the addition of the 10-count package based on the following benefits and also when considering that there is no direct evidence that a smaller packaging configuration will result in inappropriate use and/or safety issues:

- The availability of the 10 count package would lead to a comparable price point relative to a pack of cigarettes. This will reduce the one-time purchase price of Nicotine Polacrilex Gums so they are comparable in cost to one pack of cigarettes. A more affordable option for smokers that may want to reduce or quit smoking by providing a pack size available that is not potentially beyond their need or financial means.
- A consumer who uses Nicotine Polacrilex Gum products to quit smoking but who has forgotten to take their Nicotine Polacrilex Gum products with them on any given day is faced with the dilemma – to avoid a relapse by purchasing a small pack unit to help them through the day, or relapse.
- No consumer should be forced to decline to purchase the product (and resume smoking) simply because of the unnecessary cost and inconvenience associated with the larger packaging units. Thus, a smaller package size could help consumers with limited financial means to continue treatment until the next pay period; whereas, a larger package size may not be a viable option.
- The addition of the 10-count package would not change or impact the strong labeling warnings that are already stated on the label. Irrespective of the count size all safety information is included on the label to ensure that the consumer is informed on how to use the product safely and effectively.
- A smaller pack size helps consumer's traveling and who only need enough gum pieces to last several days while on their trip.
- Towards the end of the treatment period a consumer may only require a fewer number of gum pieces prior to the completion of the recommended course of treatment.

Additionally, the 10 count package will be subject of the approved Marketing and Surveillance Plan (Attachment 3). In particular:

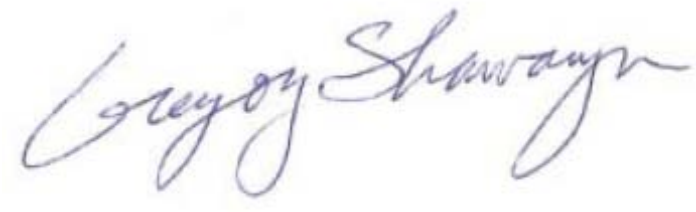
- The product will not be for sale to those under 18 years of age.
- Proof of age will be required.
- The product will not be for sale in vending machines or from any source where proof of age cannot be verified.
- The package design will not appeal to teenagers or children.
- All other provisions in the Plan will continue in place.

Upon receiving notice of acceptability of this supplemental application, Perrigo intends to [redacted] (b) (4) This implementation will be reported in the respective annual reports.

If you have any questions or need any additional information, please feel free to contact me in the manner most convenient to you:

Telephone: 269-673-9181
Fax: 269-673-7655
E-mail: gregory.shawaryn@perrigo.com

Respectfully submitted,



Gregory Shawaryn
Regulatory Affairs Project Manager

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2011-0513	
TO *(Division/Office)* DNCE - HFD-560 Thru: Darrell Jenkins; Mary Vienna, ONP HFD-560			FROM: Lisa Kwok	
DATE: 4/13/2011	IND NO.	ANDA NO. 076775/S-018	TYPE OF DOCUMENT Supplement Original	DATE OF DOCUMENT 3/18/2011,
NAME OF DRUG Nicotine Polacrilex Gum USP		PRIORITY CONSIDERATION 60 days	CLASSIFICATION OF DRUG Smoking Cessation	DESIRED COMPLETION DATE 6/12/2011

NAME OF FIRM Perrigo

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
X 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
This consult is in reference to Perrigo's Nicotine Polacrilex Gum, a generic version of Nicorette Gum, NDA 018612. Perrigo submitted a supplement on 3/18/11 (see attached) proposing the addition of a 10-count package. Is the smaller package size acceptable?

Background history: In 2005, generic firms proposed a package of 20 gums. The Agency's concern for a smaller package was that it would be promotional, and may contribute to abuse and misues as a result of a potentially lower price. A consult was requested by OGD to DNCE in 2005 for Watson's ANDAs. DNCE accepted the new package size of 20. (Please see attached for the consult response.)

SIGNATURE OF REQUESTER Lisa Kwok	METHOD OF DE LIVERY *(Check one)* DARRTS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

Please file 76-568

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 21, 2005

TO: Michelle Dillahunt, Pham D.
Labeling Reviewer
Office of Generic Drugs, HFD-617

FROM: Laura Shay, RN, MS
Regulatory Project Manger
Division of Nonprescription Clinical Evaluation: HFD-560
Office of Nonprescription Products

THROUGH: Curtis Rosebraugh, MD, MPH CJR
Division Director
Division of Nonprescription Clinical Evaluation: HFD-560
Office of Nonprescription Products

SUBJECT: 20 count package size for nicotine polacrilex gum
ANDA(S) 76-569/S-003; 74-507/S-035; 74-707/S-030; 76-568/S-003

The following is a response to your June 8, 2005 Request for Consultation regarding a labeling supplement you received from Watson Laboratories proposing to market a new 20 count package size for their approved nicotine polacrilex gum:

Approval letters submitted to the reference listed drugs for nicotine polacrilex gum state that a company can not distribute their product in a sample size. No reference is made to a minimal non-sample package size. Given that 20 pieces is approximately a one day supply of the maximum amount of the drug that can be used in 24 hours (24 pieces), we do not feel that this constitutes a sample size. Therefore, as long as the drug facts labeling and the directions for a quit indication are unchanged, we are not opposed to a 20 count size. We strongly feel that a one day supply of the drug containing the maximum amount that can be used in 24 hours should be the minimum count size marketed.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 076775/S-018

L. Perrigo Company
Attention: Barinder Sandhu
515 Eastern Avenue
Alleganm MI 49010

Dear Sir:

This refers to your supplemental new drug application dated March 18, 2011, submitted under section 505 (j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Nicotine Polarcrilex Gum USP, 2 mg.

You requested review as a "Supplement - Changes Being Effected in Zero days."

The supplemental application provides for the addition of a 10-count package size.

Reference is also made to the April 12, 2011 telephone conversation between Lillie Golson of this Administration and Barinder Sandhu of L. Perrigo Company in which you were informed that the proposed change should not be initiated. The change that you described is not, in our opinion, the kind permitted by regulation to be put into effect in advance of approval of the supplement. Rather, the change is major change that requires approval of the supplement before a product with the change can be distributed.

This letter is to notify you that an approved supplement is required for the proposed change and that the supplement is under review. Please do not implement the proposed change until you receive notification that the supplemental application is approved. Distribution of the drug is also subject to requirements for validation of the change.

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

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/s/

LILLIE D GOLSON
04/19/2011
for Wm. Peter Rickman

CBE Routing Form

This form is to accompany all CBE Supplements. Upon completion, File in DFS.

I. To be completed:

LETTER DATE: 3/18/2011
APPLICATION: 76-775 SUPPLEMENT(S): 018

Submitted as: ☒ **CBE-Zero** ☐ **CBE-30** ☐ **Labeling CBE**

II. To be completed by the Chemistry/Micro Division Staff:

This qualifies as:

Chemistry and/or Micro PM	Chemistry and/or Micro TL	Chem. Div./ Deputy Div. Dir. *
SELECT CBE TYPE	SELECT CBE TYPE	SELECT CBE TYPE
Endorsement:	Endorsement:	Endorsement:
see below sec. 4 & 5	see below sec. 4 & 5	

* Div/ Deputy Director Signature needed only when:
1.) CBE is elevated to a PAS or 2.) PM/TL recommend different actions

III. Labeling CBE:

Granted: ☐ Denied: ☒

Team Leader Endorsement: ldg Decision Date: 4/12/2011

IV. Basis for Decision/Comments:

V. We are denying the CBE request and changing it to a PAS because new drugs had denied the smaller package size of 10s in the past (2005) and OGD does not have the authority to overrule that decision. I told Mr. Shawaryn that we would send Perrigo's arguments as a consult to the division once again to see if the thinking had changed concerning this.

VI. Approval By Inspection:

Upon review at the Team level it was determined that the supportive data provided for the proposed change is sufficient for the approval of the supplement and needs no further input from the primary reviewer.

Changes deemed via TL: Acceptable By-Inspection: ☐ **YES**
Comments/Endorsement:

VII. Project Manager Chemistry Team: SELECT TEAM #

Prepare letter and notify applicant by telephone when CBE is denied because it is a Prior Approval Supplement. DATE:_____

Notify applicant by telephone that inappropriate CBE category used. DATE: _____

Request that applicant withdraw supplement, and submit the changes with the next Annual Report. DATE: _____

VIII. Document Room: Record appropriate CBE code and file in archival submission.
Granted (GR); Doesn't qualify, inappropriate CBE category (DC); Doesn't qualify, it's AR (DA); Doesn't qualify, it's a PAS (DN)

FINAL DECISION: SELECT FINAL DECISION DATE: _____

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

/s/

LISA H KWOK
04/13/2011

LILLIE D GOLSON
04/19/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Rockville MD 20855

ANDA 076775/S-018 **COMPLETE RESPONSE**

L. Perrigo Company
Attention: Gregory Shawaryn
515 Eastern Avenue
Allegan, MI 49010

Dear Sir:

This is in reference to your supplemental new drug application dated March 18, 2011, submitted pursuant to 21 CFR 314.70 as Supplement – Changes Being Effected, and accepted as Prior Approval Supplement, regarding your abbreviated new drug application for Nicotine Polacrilex Gum USP, 2 mg (Regular).

This supplemental new drug application provides the addition of a 10 count package of Nicotine Polacrilex Gum USP, 2 mg.

We have completed the review of your application and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address this issue.

CARTON (10s)

1. Consumers should be made aware this product is to "start or continue a quit attempt" and a 10 piece package may not be a full day's supply for all quitters depending on their current stage in their quit attempt. Please state on your carton labeling that this package size my not be a full day's supply.

2. We recommend that you market the 4 mg strength in a 10 piece package in order to avoid encouraging consumers to purchase the 2 mg gum in the smaller, less expensive package instead of the 4 mg gum which may be a more appropriate dose.

Please submit your response as an amendment to this supplemental application and state on the top right of the cover letter "Amendment to Complete Response Action S-018". To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

In addition to final printed labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved.

If you have any questions, please contact Lisa Kwok, labeling reviewer, at (240) 276-8980 or by e-mail at lisa.kwok@fda.hhs.gov.

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/

LILLIE D GOLSON
07/14/2011
for Wm. Peter Rickman

August 2, 2011

Amendment to Complete Response Action S-018

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

Via ESG (Gateway)

RE: ANDA 76-775
Nicotine Polacrilex Gum USP, 2 mg (Regular)

Dear Dr. Webber:

Reference is made to the Labeling Supplement submitted to the above ANDA on March 18, 2011 and to the Complete Response letter issued by the Agency dated July 14, 2011. In this letter, provided as Attachment 1, the Agency made 2 comments/requests relative to the supplement. The comments are repeated below in bold with the Perrigo response following.

1. **Consumers should be made aware this product is to "start or continue a quit attempt" and a 10 piece package may not be a full day's supply for all quitters depending on their current state in their quit attempt. Please state on your carton labeling that this package size may not be a full day's supply.**

Perrigo has added the following footnote below the net contents line "*This package size may not be a full day's supply; it is intended to start or continue a quit attempt." The carton art previously submitted on March 18, 2011 has been updated to incorporate the recommended text, please refer to the updated carton labeling provided in Attachment 2. A side-by-side comparison of the previously submitted art and the current art is included in Attachment 3.

2. **We recommend that you market the 4 mg strength in a 10 piece package in order to avoid encouraging consumers to purchase the 2 mg gum in the smaller, less expensive package instead of the 4 mg gum which may be a more appropriate dose.**

We acknowledge the recommendation and as a result (in addition to the submission made for the 2mg dated on March 18, 2011) a submission is being made today to ANDA 76-789, Nicotine Polacrilex Gum USP, 4 mg (Regular) to request approval to commercially market a 10 count package. The art included in that submission addresses the above-mentioned comment 1. A copy of the cover letter has been included for your reference in Attachment 4.

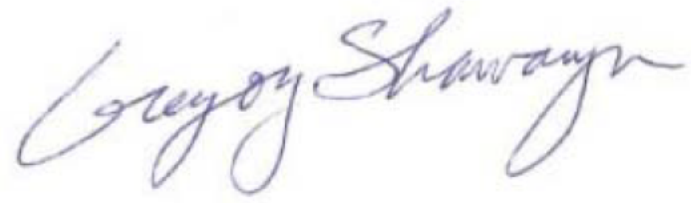
Upon approval of this supplemental application, Perrigo intends to [redacted] (b) (4) This implementation will be reported in the annual reports for the following ANDAs:

ANDA 76-776: Nicotine Polacrilex Gum USP, 2 mg (Orange, Uncoated)
ANDA 76-777: Nicotine Polacrilex Gum USP, 2 mg (Mint, Coated)
ANDA 78-325: Nicotine Polacrilex Gum USP, 2 mg (Mint, Uncoated)
ANDA 78-547: Nicotine Polacrilex Gum USP, 2 mg (Regular, Coated)
ANDA 78-967: Nicotine Polacrilex Gum USP, 2 mg (Orange, Coated)
ANDA 91-349: Nicotine Polacrilex Gum USP, 2 mg (Cinnamon, Coated)

If you have any questions or need any additional information, please feel free to contact me in the manner most convenient to you:

Telephone:	269-673-9181
Fax:	269-673-7655
E-mail:	gregory.shawaryn@perrigo.com

Respectfully submitted,



Gregory Shawaryn
Regulatory Affairs Project Manager