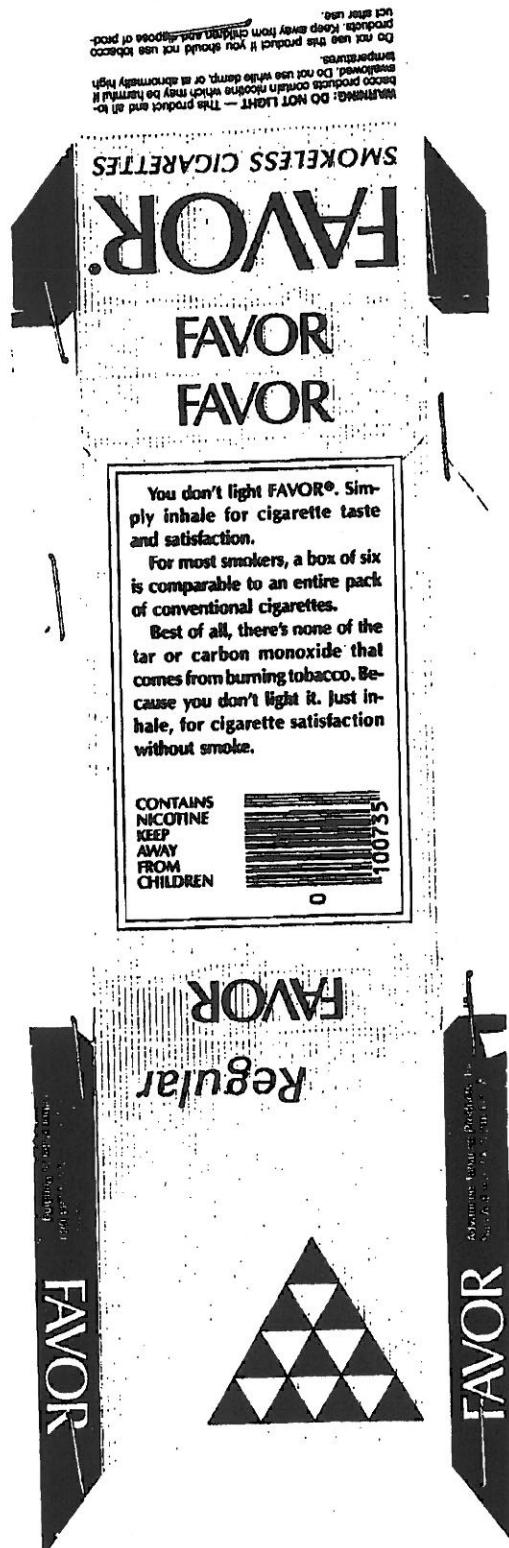


**Smoking Everywhere, Inc.**  
**Nicotine Background Materials**  
**Index to Administrative Record**

<b>Document Date</b>	<b>Description</b>	<b>Bates Number</b>
9/11/1985	Packaging and promotional literature for Favor Smokeless Cigarettes	000001-000009
2/9/1987	Letter from Daniel L. Michels, Director, Office of Compliance, Center for Drugs and Biologics, to Philip Ray, Director, Advanced Tobacco Products Inc. re: Favor Smokeless Cigarettes Regular, Menthol, and Lights; Favor Smoke-Free Cigarettes Regular, Menthol, and Lights	000010-000011
4/9/2002	Warning Letter to Larry and Pat Frieders, The Compounding Pharmacy and Techni-Med Inc.	000012-000014
4/9/2002	Warning Letter from David Horowitz, Esq, Acting Director, Office of Compliance, CDER, to Hank Abbott and Rosalee Virusso, Bird's Hill Pharmacy	000015-000017
7/1/2002	Letter from Dennis Baker, Associate Commissioner for Regulatory Affairs, FDA, to William Schultz, Carlos Angulo, Meredith Cabe, Matthew Myers, and William Corr re: Docket No. 01P-0573	000018-000022
12/13/2007	Memorandum from Stephen J. Heishman, Ph.D., Chief, Nicotine Psychology Unit, NIDA Intramural Research Program, NIH, to Michael Levy, Division of New Drug and Labeling Compliance, CDER, FDA re: Report on Nicotine Pharmacology, Nicotine Dependence, and Reasons for Smoking	000023-000047
3/11/2008	Memorandum from Celia Winchell, M.D., Medical Team Leader, Addiction Drug Products, DAARP, to Michael Levy, Division of New Drug and Labeling Compliance re: Nicogel	000048-000052
4/30/2008	Memorandum from Keith K. Burkhart, M.D., Senior Advisor for Medical Toxicology to the Director of OND/CDER, to Michael Levy, Division of New Drug and Labeling Compliance re: Nicogel	000053-000057

Document Date	Description	Bates Number
8/4/2008	Letter from Otto D. Vitillo, District Director, New York District Office, to Frederick H. Branding, Reed Smith Sachnowoff & Weaver re: Entry No. 112-7769262-2/Nicogel Hand Gel	000058-000080

# INDIVIDUAL PACK LABEL



E.I.R. EXHIBIT # 3  
ADVANCED TOBACCO PRODUCTS  
DATED 9/11/85  
INVESTIGATOR RIA RIA  
PAGE 1 OF 1

NIC 000001

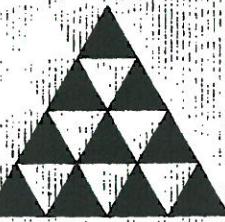
# FAVOR

SMOKELESS CIGARETTES

INDIVIDUAL BOX LABEL

CRUSH PROOF BOX CONTAINS TEN PACKS OF SIX

Menthol



SMOKELESS CIGARETTES

# FAVOR®

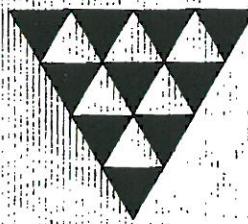
Menthol

SMOKELESS CIGARETTES

# FAVOR®

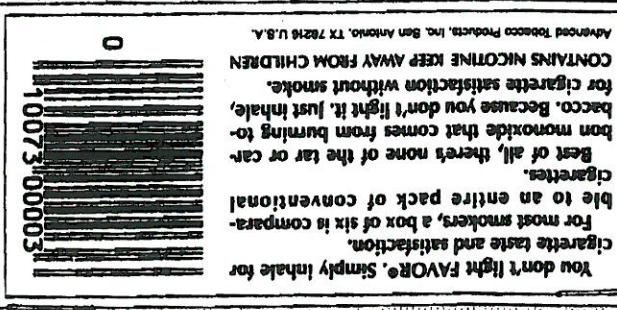
# FAVOR®

SMOKELESS CIGARETTES



Menthol

CRUSH PROOF BOX CONTAINS TEN PACKS OF SIX



# FAVOR

SMOKELESS CIGARETTES

E.I.R. INVESTIGATOR  
ADVANCED TOBACCO INVESTIGATORS  
DATED 5/1/88  
INVESTIGATOR #113  
PAGE - 68 - MADE IN U.S.A.

NIC 000002

S.I.R. EXHIBIT #  
ADVANCED TOBACCO PRODUCTS INC.  
DATED 9/11/89  
INVESTIGATOR RIA REA  
PAGE 1 OF 1

## PROMOTIONAL LITERATURE

### FAVOR® SMOKELESS CIGARETTES

#### **What are they?**

FAVOR looks and feels like a cigarette. But instead of tobacco leaf, FAVOR contains only nicotine and tobacco flavours.

#### **How do I use them?**

You use FAVOR as you would a regular cigarette, except you don't light it. You still inhale —just as you would with a burning cigarette—for full tobacco pleasure and satisfaction. But since you don't light FAVOR, you don't get any of the tar and carbon monoxide that comes from burning tobacco.

#### **How long do they last?**

For most smokers, a pack of six usually lasts as long as a conventional pack of cigarettes. Because you don't light FAVOR, you can put it back in box or pocket until the next time you're ready to enjoy it. You'll know FAVOR is depleted when you no longer get the "smoking" sensation of pleasure and satisfaction.

#### **Where can I use them?**

You can enjoy FAVOR anywhere. Especially in places where smoking is not permitted or just doesn't fit in.

FAVOR is available in regular, menthol, and light.

**FAVOR. Cigarette satisfaction. No smoke!**

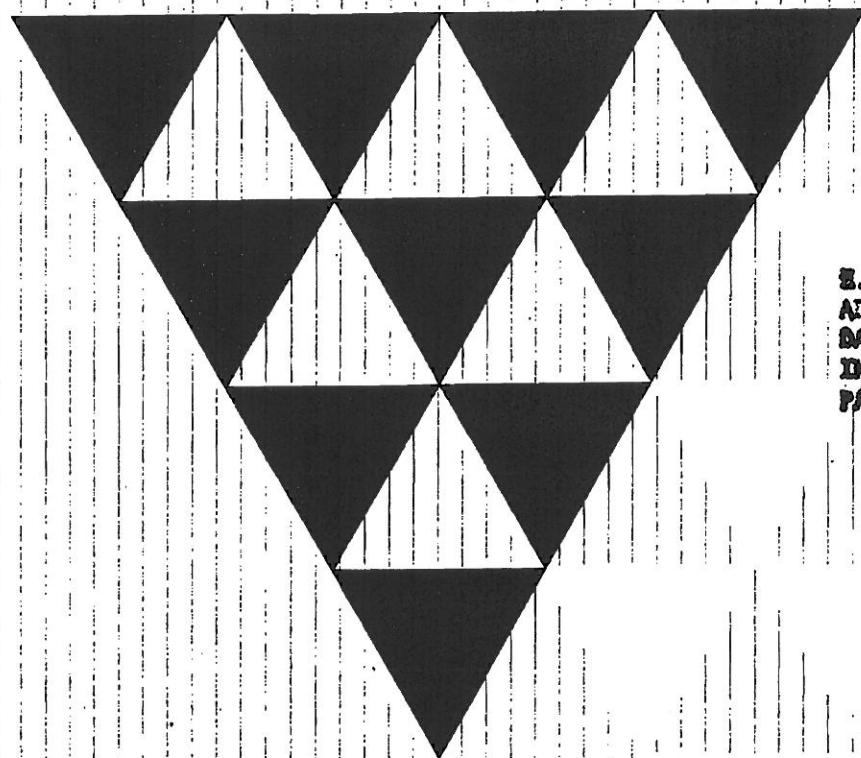
Advanced Tobacco Products Inc., San Antonio, TX 78216

©1985

NIC 000003

PROMOTIONAL

PAMPHLET



E.I.R. EXHIBIT 3  
ADVANCED TOBACCO PRODUCTS INC.  
DATED 9/11/85  
INVESTIGATOR RIA REA  
PAGE 09

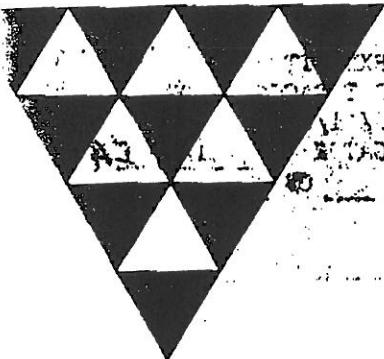
*Introducing*

**FAVOR®**

The Revolutionary New  
**SMOKELESS CIGARETTE**

NIC 000004

# The FAVOR® Story

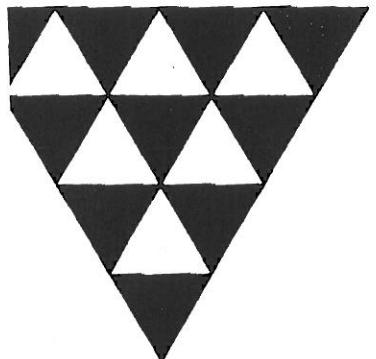


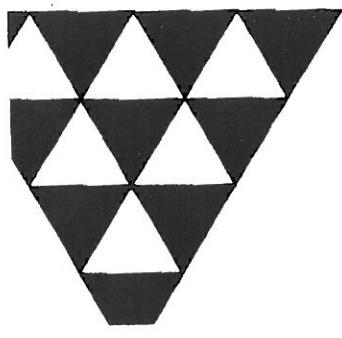
FAVOR® smokeless cigarettes...the revolutionary new cigarette that gives your customers tobacco flavour and satisfaction with one major difference. No smoke. FAVOR® looks and feels just like a cigarette, and it gives the tobacco pleasure and satisfaction of a cigarette. But you don't light FAVOR® — so there's no smoke, tar or carbon monoxide as with burning tobacco.

Instead of tobacco leaf, FAVOR® contains tobacco flavour and a small amount of nicotine. When you inhale, these ingredients are released, providing tobacco taste and satisfaction. For most smokers, a pack of six FAVOR® cigarettes will last as long as a conventional pack of cigarettes. And because FAVOR® doesn't burn, it can be placed back in the box and enjoyed again later. A FAVOR® cigarette is depleted when you no longer get the "smoking" sensation of pleasure and satisfaction.

FAVOR®... regular, menthol and lights are offered in packages of six and in ten-pack cartons. In short, tobacco flavour and nicotine satisfaction anytime, anywhere. In the presence of anyone.

## Research Proven

- 
- The smokeless cigarette has the same calming effect as regular cigarettes.
  - 68% of the respondents said they would be very interested in a tobacco product that contained no harmful tars or gases.
  - 96% said that they would like to try the product.
  - 72% said they were very likely to purchase such a cigarette product on a trial basis.
  - 70% said they could think of occasions where they would use a product like a smokeless cigarette.
  - After trying the product, 74% said they were likely to use the product.
  - 85% of the 18-35 year olds said they were very likely to purchase smokeless cigarettes.
  - 97% of the 18-35 year old females said they were very likely to purchase as did 78% of the males 18-35.
  - 86% of NON-MENTHOL SMOKERS were very likely to somewhat likely to purchase as were 82% of menthol smokers.
  - The lower the tar group, the more likely they were to purchase.



**DO YOURSELF A FAVOR® ...**  
take part in one of the many ...

NIC 000005

I.R. EXHIBIT # 3  
ADVANCED TOBACCO PRODUCTS INC.  
MED 9/11/85  
INVESTIGATOR RIA REA  
ME OF

# "The job was for nonsmokers only. I went for the interview anyway."



"The ad in the paper said they were looking for an executive secretary.

You wouldn't believe the money. One problem though: the ad said 'nonsmokers only.'

I decided to go anyway. I wanted this job.

So I'm sitting in the interview. Things are going well.

Then it happens.

'Do you smoke?' he asks.

If you're a smoker, you can imagine how I felt.

I thought about it, then reached in my purse. Out comes Favor.

'Yes,' I said. 'I smoke. But at work I use these. Favor Smokeless Cigarettes. You don't light them, you just inhale. There's no smoke, no ashes.'

He said, 'Well, I see you type 90 words per minute, take shorthand at 120 words per minute, and have some pretty impressive references.'

I said, 'That's right. But what about the smoking?'

He smiled and said, 'What about it?' Introducing new Favor, the world's first smokeless cigarette.

Enjoy tobacco taste and satisfaction with none of the tar or carbon monoxide found in cigarette smoke.

Look for  
Favor in Regular,  
Menthol, and  
Lights, wherever  
cigarettes  
are sold.

Tobacco flavor  
and satisfaction.  
No smoke.



NIC 000006

© 1984 Advanced Tobacco Products, Inc.

# "It ticks me off when people tell me when and where to smoke."



"I smoke. Smoked for 30 years.

And yes, it ticks me off that people are always telling me when and where to smoke.

I remember when it was nobody else's business.

Not so anymore.

One day I decided I'd had enough of it. Enough of 'Sit here' and 'Sit there.' 'Smoke here.' 'Smoke there.'

I gave Favor a try. It was quite a surprise.

Favor is a new smokeless cigarette. You don't light it, you just inhale.

It looks like a regular smoke. Draws like a regular smoke. Tastes

like a regular smoke.

But there's no smoke to it. So there's none of the tar or carbon monoxide found in cigarette smoke.

Just real tobacco satisfaction and taste.

On the subject of satisfaction, there's another reason I like Favor so much.

Because nothing feels better than pulling one out in the middle of a nonsmoking area.

And knowing there's not a single thing they can say about it."

Introducing new Favor, the world's first smokeless cigarette.

Enjoy tobacco taste and satisfaction with none of the tar or carbon monoxide found in cigarette smoke.

Look for  
Favor in Regular,  
Menthol, and  
Lights, wherever  
cigarettes  
are sold.

Tobacco flavor  
and satisfaction.  
No smoke.



NIC 000007

©1984 Advanced Tobacco Products, Inc.

# "I never felt comfortable smoking in my parents' house."



"I smoke. My folks don't. No matter how old I get, I'll never feel good about lighting one up in their house.

If you smoke, you know what I mean. Maybe it's the same when you visit your folks, or go see friends who don't smoke.

Anyway, I'd be out on the back porch as much as I'd be in the house. What a pain.

The other day I heard about Favor, this new smokeless cigarette.

I thought 'Yeah, sure.'

My wife suggested I pick up some.

I did. Unbelievable. You don't light them, you just inhale.

No matches. No ashtrays. No smoke.

Just real tobacco satisfaction and flavor, with none of the tar or carbon monoxide found in cigarette smoke.

Even if you don't intend to give up your regular brand of cigarettes, pick up Favor anyway.

Use it in those situations where you'd just as soon not light a cigarette.

Or when there's no back porch handy."

Introducing new Favor, the world's first smokeless cigarette.

Enjoy tobacco taste and satisfaction with none of the tar or carbon monoxide found in cigarette smoke.

Look for Favor in Regular, Menthol, and Lights, wherever cigarettes are sold.

Tobacco flavor and satisfaction. No smoke.



NIC 000008

© 1984 American Tobacco Products Inc.

# Now you can enjoy cigarettes without smoke.

What appears to be a typical cigarette is, in fact, a cigarette so revolutionary that it promises to change the way Americans think about smoking. It is Favor. The world's first smokeless cigarette.

Favor is the first cigarette to deliver tobacco flavor and satisfaction without anytime, anywhere, around anyone.

To enjoy Favor, simply inhale. Inside, pure tobacco extract and flavoring furnish tobacco taste and satisfaction.

You don't light it.

In every respect, except one, Favor is a true cigarette. It's made with cigarette paper. It's tipped with a cigarette filter.

Its weight, feel, and length are identical to any filter king. There is, however, one startling difference: you do not set fire to the end of this cigarette.

There is nothing to light, nothing to burn, nothing to create smoke.

Nothing to be concerned about, even in the presence of the most militant nonsmoker.

You simply inhale. And enjoy.

Your question, of course, is,

"What does Favor taste like?"

The answer is, "A cigarette."

To understand the true taste, pursue-

chase a pack and try this simple test. Take your first few puffs with your eyes closed. Shut out the visual difference that comes from not seeing smoke.

Inhale deeply, then exhale as if you were blowing out cigarette smoke.

Decide for yourself if the satisfaction of using Favor is not equivalent to that obtained from smoking your usual brand.

Minus the smoke, of course.

As you inhale you'll notice the tobacco taste. Then you'll experience the same drawing sensation characteristic of all cigarettes. Next comes the smooth feeling of satisfaction that makes a cigarette so enjoyable in the first place.

The enjoyment is further enhanced by the knowledge that Favor contains none of the tar or carbon monoxide found in cigarette smoke.

Aside from this, you can well imagine the other benefits of doing with-

out smoke.

Gone are the holes burnt in clothing and car seats.

Gone are the withering glares of nonsmokers.

Gone is the need for matches, lighters, and ashtrays.

Gone is the inevitable feeling that strikes long before intermission arrives.

At last comes the opportunity to do something that's becoming more and more difficult every day.

That is, to simply enjoy a peaceful cigarette, whenever, wherever, and in whatever company you choose.

For smokers everywhere, the break-through comes not a moment too soon.

Try Favor. Look for it in Regular, Menthol, and Lights whenever cigarettes are sold.



Tobacco flavor and satisfaction. No smoke.

©1984 Advanced Tobacco Products, Inc.

NIC 000009



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

February 9, 1987

Food and Drug Administration  
Bethesda, MD 20205REGULATORY LETTER

## CERTIFIED

J. Philip Ray, Director  
Advanced Tobacco Products Inc.  
121 Interpark Boulevard  
Suite 108  
San Antonio, Texas 78216

Re: Favor Smokeless Cigarettes Regular  
Favor Smokeless Cigarettes Menthol  
Favor Smokeless Cigarettes Lights  
Favor Smoke-Free Cigarettes Regular  
Favor Smoke-Free Cigarettes Menthol  
Favor Smoke-Free Cigarettes Lights

Ref. No. 87-HFN-312-06

Dear Mr. Ray:

This letter is in reference to your marketed products listed above, Favor Smokeless Cigarettes Regular, Menthol, and Lights; Favor Smoke-Free Cigarettes Regular, Menthol and Lights (Favor). Each Favor consists of a plug impregnated with a nicotine solution inserted within a small tube corresponding in appearance to a conventional cigarette which you have described as a novel nicotine delivery system and a method of administering nicotine by inhalation of nicotine vapor.

We have reviewed labeling and promotional literature of Advanced Tobacco Products, Inc., and other written materials issued by or on behalf of your firm, such as a registration statement filed in January, 1984, with the Securities and Exchange Commission (SEC) (Form S-1, File No. 2-88812), Amendment No. 1 to Form S-1 (filed with the SEC April 17, 1984), Company Responses to SEC Comments (filed with the SEC April 17, 1984), and your form 10-K annual report for the fiscal year ended June 30, 1984 (filed with the SEC October 30, 1984).

The materials referred to above contain statements which represent and suggest that Favor is a novel nicotine delivery system; that each pack of six will have a nicotine delivery capacity intended to satisfy the average smoker of conventional cigarettes for an entire day; that Favor delivers an amount of nicotine per inhalation within a range of amounts delivered per inhalation from many conventional combustible cigarettes; that the quantity of nicotine required to produce the effect on the nervous system which most cigarette smokers are accustomed is small relative to the amounts of other alkaloids regularly consumed by typical users; and that it is an alternative for conventional cigarette smokers who desire nicotine pleasure. A paper submitted to the SEC by or on behalf of your firm, to support your firm's conclusion that Favor and conventional

NIC 000010

Page 2, J. Philip Ray, Director

cigarettes have the same or equivalent nicotine delivery (Jacobson, Jacobson, and Ray, Nicotine Vapor Inhalation: Alternative Method of Nicotine Delivery), purports to describe a practical and apparently satisfying method of administering nicotine by inhalation of nicotine vapor through a non-combustible cigarette designed by one of the authors (J.P. Ray); states that it is likely that nicotine has addicting qualities and is the primary ingredient which motivates smoking; and states that the authors have demonstrated that meaningful levels of serum nicotine and urine cotinine are achieved by inhalation.

Your materials submitted to the SEC include references to reports in the medical literature concerning the effects of nicotine. The medical literature clearly recognizes that nicotine is well absorbed from the lungs; that it has potent pharmacologic effects, including effects on the nervous system; and that nicotine is a drug of dependence.

In view of the above, it is our position that Favor is a nicotine delivery system intended to satisfy a nicotine dependence and to affect the structure and one or more functions of the body. Because of its intended uses, Favor is a drug as defined within section 201(g) of the Federal Food, Drug, and Cosmetic Act (Act). In addition, we regard Favor to be a new drug within the meaning of section 201(p) of the Act because Favor's composition is such that it is not generally recognized, among qualified experts, as safe and effective for use under the conditions prescribed, recommended, or suggested in its labeling.

Since Favor is a new drug within the meaning of the Act and no approval of an application filed pursuant to section 505(b) of the Act is effective for it, Favor may not be introduced or delivered for introduction into interstate commerce under section 505(a) of the Act. Thus, continued marketing of Favor would be in violation of the Act and the marketing of Favor products such as the ones listed above should be discontinued.

We request that you reply within ten (10) days of the receipt of this letter stating the action you will take to discontinue Favor's marketing. If corrective action is not promptly undertaken, the Food and Drug Administration is prepared to initiate legal action to enforce the law. The Federal Food, Drug, and Cosmetic Act provides for seizure of illegal products and/or injunction against the manufacturer and/or distributor of illegal products, 21 U.S.C. 332 and 334.

Sincerely yours,



Daniel L. Michels  
Director  
Office of Compliance  
Center for Drugs and Biologics



Food and Drug Administration  
Rockville MD 20857

**WARNING LETTER**

April 9, 2002

Larry and Pat Frieders  
Pharmacist  
The Compounding Pharmacy  
575 W. Illinois Ave.  
Aurora, IL 60506

Larry and Pat Frieders  
Pharmacist  
Techni-Med, Inc.  
575 W. Illinois Ave.  
Aurora, IL 60506

Dear Mr. and Ms. Frieders:

This letter concerns Nicotine Lollipops and Nicotine Lip Balm which are currently marketed by your firm as shown on your Internet site [www.thecompounder.com](http://www.thecompounder.com). According to information on this site, Nicotine Lollipops consist of Nicotine Salicylate combined with a natural sweetener, and flavorings in a sugar-free base, and is available in a 2 mg. dosage. According to information on this site, Nicotine Lip Balm consists of nicotine salicylate in a flavored, sweetened (no sugar added) vehicle. Based on the descriptions of these products on your Internet site, the Nicotine Lollipops and Nicotine Lip Balm are intended as an aid for smoking cessation or to reduce nicotine addiction.

The intended uses noted above are conveyed through claims for Nicotine Lollipops on your Internet site. These include statements such as "...What is the Nicotine Lollipop? It is Nicotine Salicylate ...For most people who smoke a pack of cigarettes per day the 2mg strength is perfect...How do I use the Nicotine Lollipop? Place the lollipop in your mouth when you feel the urge to smoke...Leave it there until the urge passes and then replace the lollipop into the bag...Re-use the same lollipop next time the urge strikes...One lollipop usually last 4 to 5 cigarette breaks. How can nicotine replacement help me quit smoking? They help smokers quit by suppressing the symptoms of nicotine withdrawal.... The Nicotine lollipop can greatly assist those people who really want to quit smoking... The lollipop allows the individual to control the amount of nicotine taken based on the body's need at the time. A significant element of cigarette smoking is psychological and Nicotine lollipops deal with both the hand-to-mouth fixation and the physical dependence on nicotine..."

NIC 000012

The intended uses noted above for Nicotine Lip Balm are conveyed through claims on your Internet site. These include statements such as "...Nicotine Lip Balm...looks like chapstick...Licking your lips can help you Lick The Habit...Applying the balm to your lips leaves a thin film that contains 0.2 to 0.4mg of nicotine (each tube provides 75 to 150 doses of nicotine). It is absorbed into your body through your lips and when you lick them. This product is for use by people who smoke regularly...help relieve the craving for nicotine...designed to help a person quit...discreetly apply the lip balm to your lips and the nicotine craving will subside..."

Based on the intended uses established by your Internet site, your Nicotine Lollipops, 2 mg. and Nicotine Lip Balm, 0.2 mg., and 0.4 mg., are "drugs" as defined by section 201(g) of the Federal Food, Drug, and Cosmetic Act (the Act). The Nicotine Lollipops, 2 mg., and Nicotine Lip Balm, 0.2 mg., and 0.4 mg., do not qualify for the exemptions from sections 505 and 502(f)(1) provided under section 503A of the Act since, according to your Internet site, you do not appear to require prescriptions to be presented to compound the products. Among other requirements, to qualify for the statutory exemption provided by Section 503A, drugs must be compounded based on the receipt of valid prescription orders from licensed practitioners. You must also use only those bulk drug substances that conform to Section 503A(b)(1)(A). Nicotine salicylate, which is reportedly used in all of your Nicotine Lollipops and Nicotine Lip Balm products, is not a component of an FDA approved drug, is not listed in a United States Pharmacopoeia (USP) or National Formulary (NF) monograph, and was not nominated for inclusion in a list of bulk drug substances for compounding. Although nicotine and nicotine polacrilex are components of FDA approved drugs and are listed in the USP/NF, nicotine salicylate is not. Therefore, nicotine salicylate is not permitted for use in compounding.

Your Nicotine Lollipops, 2 mg., and Nicotine Lip Balm, 0.2 mg., and 0.4 mg., are also subject to Title 21 of the Code of Federal Regulations (CFR) section 310.544. Under that regulation, they are "new drugs" as defined by section 201(p) of the Act. Under Section 505(a) of the Act, a "new drug" may not be introduced or delivered for introduction into interstate commerce unless an FDA-approved new drug application (NDA) is in effect for such drug. We note that your Nicotine Lollipops, 2 mg., and Nicotine Lip Balm, 0.2 mg., and 0.4 mg., drug products are not the subject of FDA-approved NDAs and, therefore, they may not be marketed in the United States. The continued distribution of these products without approved NDAs violates Section 505 of the Act.

Nicotine Lollipops, 2 mg., and Nicotine Lip Balm, 0.2 mg., and 0.4 mg., are misbranded within the meaning of section 502(o) of the Act in that they are manufactured in an establishment not duly registered under section 510 of the Act and they have not been listed as required by section 510(j) of the Act. In addition, Nicotine Lollipops, 2 mg., and Nicotine Lip Balm, 0.2 mg., and 0.4 mg., may be misbranded under section 502(f)(1) of the Act on the grounds that their labeling fails to bear adequate directions for the uses for which they are being offered and they would not be exempt from this requirement under 21 CFR section 201.115 since they are unapproved new drugs. These

Page 3 - Larry and Pat Frieders

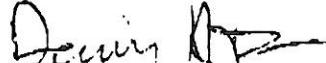
products may also be misbranded under Section 502(f)(2) of the Act on the grounds that their labeling fails to bear such adequate warnings against use by children where their use may be dangerous to health.

This letter is not intended to be an all-inclusive review of your Internet sites and the products your firm may market. The violations of the Act described above are not intended to be an all-inclusive list of the deficiencies of you and your firm. It is your responsibility to ensure that all drug products manufactured and distributed by your firm are in compliance with Federal laws and regulations. Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Possible actions include seizure and/or injunction.

We request that you reply in writing within fifteen (15) days of your receipt of this letter stating the action your firm will take to discontinue marketing of these drug products. Your response should be directed to Melvin F. Szymanski, Compliance Officer, at the U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Compliance, Metropark North I, Room 200, 7520 Standish Place, Rockville, MD 20855.

Sincerely yours,

  
David J. Horowitz, Esq.  
Acting Director,  
Office of Compliance  
Center for Drug Evaluation and Research

cc:



NIC 000014



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857WARNING LETTER

April 9, 2002

Hank Abbott  
Pharmacist  
Bird's Hill Pharmacy  
401 Great Plain Ave.  
P.O. Box 558  
Needham, MA 02492

Rosalee Virusso  
Pharmacist  
Bird's Hill Pharmacy  
401 Great Plain Avenue  
P.O. Box 558  
Needham, MA 02492

Dear Mr. Abbott and Ms. Virusso:

This letter concerns Nicotine Lollipops, which are currently marketed by your firm as shown on your Internet site [www.birdshill.com](http://www.birdshill.com). According to information on this site, your product consists of Nicotine Salicylate combined with a natural sweetener, and flavorings in a sugar-free base, and is available in 2 mg., or 4 mg. dosages. Based on this product's description on your Internet site, the Nicotine Lollipops are intended as an aid for smoking cessation or to reduce nicotine addiction.

The intended uses noted above are conveyed through claims on your Internet site. These include statements such as "...we recommend those who smoke in excess 1 ½ packs per day start with the 4 mg lollipop for approximately 2 to 3 weeks then move down to the 2 mg lollipops for another 2 to 3 weeks. For those that smoke less than 1 ½ packs per day, the recommended dose is 2 mg for approximately 4 to 5 weeks. Use: Place the lollipop in the mouth when you feel the urge to smoke. Leave it there until the urge is over. Once the urge passes, replace the lollipop in the bag provided and reuse the next time the urge strikes. One lollipop is usually last 4 to 5 cigarette breaks." "...The lollipops, ... are intended to help smokers quit their tobacco habit by suppressing symptoms of nicotine withdrawal. All of the replacement methods allow the individual to start with larger doses of nicotine and wean themselves over a period of time."

"...Nicotine lollipops used by themselves...greatly assist those individuals who really want to quit smoking." "...Nicotine Lollipops allows the individual to control the amount of nicotine taken in based on the body's needs."

NIC 000015

Based on the intended uses established by your Internet site, your Nicotine Lollipops, 2 mg. and 4 mg., are "drugs" as defined by Section 201(g) of the Federal Food, Drug, and Cosmetic Act (the Act). The Nicotine Lollipops do not qualify for the exemptions from sections 505 and 502(f)(1) provided under section 503A of the Act since you offer to sell the products without a prescription. Among other requirements, to qualify for the statutory exemptions provided by Section 503A, drugs must be compounded based on the receipt of valid prescription orders from licensed practitioners. You must also use only those bulk substances that conform to Section 503A(b)(1)(A). Nicotine salicylate is not a component of an FDA approved drug, is not listed in a United States Pharmacopoeia (USP) or National Formulary (NF) monograph, and was not nominated for inclusion in a list of bulk drug substances for compounding. Although nicotine and nicotine polacrilex are components of FDA approved drugs and are listed in the USP/NF, nicotine salicylate is not. Therefore, nicotine salicylate is not permitted for use in compounding.

Your Nicotine Lollipops, 2 mg., and 4 mg., are also subject to Title 21 of the Code of Federal Regulations (CFR) section 310.544. Under that regulation, they are "new drugs" as defined by section 201(p) of the Act. Under section 505(a) of the Act, a "new drug" may not be introduced or delivered for introduction into interstate commerce unless an FDA- approved new drug application (NDA) is in effect for such drug. We note that your Nicotine Lollipops drug products are not the subject of FDA-approved NDAs and, therefore, they may not be marketed in the United States. The continued distribution of these products without approved NDAs violates Section 505 of the Act.

In addition, your Nicotine Lollipops, 2 mg. and 4 mg., are misbranded within the meaning of section 502(o) of the Act in that they are manufactured in an establishment not duly registered under section 510 of the Act and they have not been listed as required by section 510(j) of the Act. They may also be misbranded under section 502(f)(1) of the Act on the grounds that their labeling fails to bear adequate directions for the uses for which they are being offered and they would not be exempt from this requirement under 21 CFR section 201.115 since they are unapproved new drugs. These products may also be misbranded under Section 502(f)(2) of the Act on the grounds that their labeling fails to bear such adequate warnings against use by children where their use may be dangerous to health.

This letter is not intended to be an all-inclusive review of your Internet site and the products marketed by your firm and is not intended to be an all-inclusive list of deficiencies of you and your firm. It is your responsibility to ensure that all drug

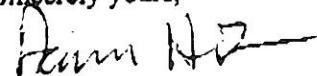
Page 3 - Hank Abbott and Rosalee Virusso

products manufactured and distributed by your firm are in compliance with Federal laws and regulations. Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Possible actions include seizure and/or injunction.

We request that you reply in writing within fifteen (15) days of your receipt of this letter stating the action your firm will take to discontinue marketing of these drug products. Your response should be directed to Melvin F. Szymanski, Compliance Officer, at the U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Compliance, Metropark North I, Room 200, 7520 Standish Place, Rockville, MD 20855.

Sincerely yours,



David J. Horowitz, Esq.  
Acting Director  
Office of Compliance  
Center for Drug Evaluation and Research

NIC 000017



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

0839 '02 JIL 17 P240

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

July 1, 2002

By Telefax and First Class Mail

William B. Schultz  
Carlos T. Angulo  
Meredith E. Cabe  
Zuckerman Spaeder LLP  
1201 Connecticut Avenue, NW  
Washington, DC 20036

Matthew Myers  
William Corr  
National Center for Tobacco-Free Kids, Inc.  
1400 Eye Street, NW, Suite 1200  
Washington, DC 20005

Re: Docket No. 01P-0573

Dear Messrs. Schultz, Angulo, Myers, and Corr and Ms. Cabe:

This responds to your citizen petition,<sup>1</sup> dated December 18, 2001, in which you request that the Food and Drug Administration (FDA):

- Classify and regulate Nicotine Water as a "drug" under the Federal Food, Drug, and Cosmetic Act; or, in the alternative,
- Classify and regulate Nicotine Water as a "food" containing an unapproved food additive under the Act.

<sup>1</sup> The petition was submitted by the National Center for Tobacco-Free Kids, the American Cancer Society, the American College of Preventative Medicine, the American Heart Association, the American Legacy Foundation, the American Lung Association, the American Medical Association, the American Public Health Association, the American Society of Addiction Medicine, the American Society of Clinical Oncologists, the American Thoracic Society, the Latino Council on Alcohol and Tobacco, the National Association of Local Boards of Health, the National Education Association, the Oncology Nursing Society, Oral Health America, National Spit Tobacco Education Program, and the Partnership for Prevention.

01P-0573

PAV/

NIC 000018

Petition at 2.

As discussed and for the reasons set out below, we grant your petition.

Your petition asserts that S & F Garret sells Nicotine Water over the Internet at [www.nicotinewater.com](http://www.nicotinewater.com), and that the product contains water and pharmaceutical grade nicotine. Currently, this site offers to sell a product called NICO Water through a company called QuickTests ("QT5"). It is unclear whether NICO Water and Nicotine Water are in fact the same product. It appears from the website, for example, that NICO Water contains a slightly different active ingredient, nicotine polacrilex. However, both the website and separate promotional material issued by S & F Garret and the Nicotine Beverage Corporation, which operate [nicotinewater.com](http://nicotinewater.com), indicate that the two products are covered by the same patent (U.S. Patent 6,268,386) (see "New Patented Nicotine Beverages for Smoking Cessation, Energy & Weight Loss," at [www.prweb.com/releases/2001/8/prweb27201.php](http://www.prweb.com/releases/2001/8/prweb27201.php) (copy attached)), suggesting that the products are identical or that QT5 is a licensee or successor of S & F Garret and/or the Nicotine Beverage Corporation.<sup>2</sup> In any event, the issues presented by these products are identical for purposes of the following analysis. Thus, we refer to the two products collectively as 'Nicotine Water.'

*Nicotine Water Is Not a Dietary Supplement*

You assert in your petition that, notwithstanding the claims made by its manufacturer, Nicotine Water cannot be marketed as a dietary supplement because its active ingredient was first marketed as an approved new drug (Petition at 13-15).

We agree. Section 201(ff)(3)(B)(i) of the Federal Food, Drug, and Cosmetic Act ("the Act") expressly states that the term "dietary supplement" does not include "an article that is approved as a new drug under section 505, certified as an antibiotic under section 507, or licensed as a biologic under section 351 of the Public Health Service Act" which was not marketed as a dietary supplement or as a food before such approval, certification, or licensing. Here, the principal active ingredient in Nicotine Water is nicotine or nicotine polacrilex. Both are active ingredients in FDA-approved drugs (including Nicoderm CQ, Prostep, Habitrol, and Nicorette). We are unaware of any evidence that either was marketed as a food or dietary supplement before the drugs that contained those active ingredients were first approved. Consequently, Nicotine Water that contains nicotine or nicotine polacrilex as an active ingredient is excluded from the definition of "dietary supplement" under section 201(ff)(3)(B)(i) of the Act. See *Pharmanex v. Shalala*, 221 F.3d 1151 (10th Cir. 2000).

*Nicotine Water Is Marketed As a Drug Under the Act*

<sup>2</sup> FDA obtained information about NICO Water and QT5 by accessing the Internet address cited in Tab A of your petition. The Internet site now offers NICO Water sold by QT5, but still references U.S. Patent 6,268,386, which is the same patent cited by S & F Garret and the Nicotine Beverage Corporation for Nicotine Water.

Your petition also maintains that Nicotine Water is a drug under the Act because it is intended to treat or mitigate nicotine addiction (Petition at 5-11) and to affect the structure or function of the body (*id.* at 17, n. 30). In support of this argument, Tab A to your petition contains information and product claims that you downloaded from [www.nicotinewater.com](http://www.nicotinewater.com). FDA agrees that, as marketed by S&F Garret, the Nicotine Beverage Corporation, and/or QT5, Nicotine Water is a "drug" under the FFDCA.

The manufacturer website materials that you attached to your petition as Tab A include smoking cessation and related claims for Nicotine Water. Specifically, the manufacturer claims that Nicotine Water:

- Is designed for "[p]eople who may or may not wish to quit smoking but cannot smoke at their place of work." (Petition at Tab A; see also "New Patented Nicotine Beverages for Smoking Cessation, Energy & Weight Loss");
- Is designed for "[p]eople who wish to quit smoking" (*id.*);
- "Contains the nicotine equivalent of 2 cigarettes" per bottle (Petition at Tab A); and
- Should not be consumed in quantities greater than "2 bottles per hour. A light smoker may find that it does not even require a full bottle per hour to quench their [sic] need whereas a heavy smoker may require a full 2 bottles per hour." (*Id.*)

S & F Garret and the Nicotine Beverage Corporation also issued marketing materials that describe Nicotine Water as a smoking cessation product:

- "*More effective than the Patch or Gum using Less Nicotine*" (see "New Patented Nicotine Beverages for Smoking Cessation, Energy & Weight Loss" (emphasis added));
- "[a] Method of delivering Nicotine *to reduce use of tobacco products.*" (See *id.* (emphasis added)); and
- "Preferred Nine to one in double blind tests over the Patch & Gum" (*id.*).

Moreover, the patent cited by S & F Garret and the Nicotine Beverage Corporation (in its marketing materials and on its website) and QT5 (on its website) describes Nicotine Water as:

- "A method of delivering nicotine or an alkaloid to an individual *to reduce said individual's use of tobacco products* comprising providing [sic] a beverage with a nicotine or alkaloid having similar physiological activity, the nicotine content being between 0.0001% and 0.1%." (emphasis added)

Section 201(g)(1) of the Act, defines "drug," in part, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and as "articles (other than food) intended to affect the structure or any function of the body." This definition of drug thus turns in large measure on the question of intended use. 21 CFR 201.128 interprets "intended use" as the objective intent of persons legally responsible for the labeling of drugs. It further states that:

The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised...

That the manufacturer may have designated its product as something other than a drug or may have made subjective claims of intent is not determinative. See *National Nutritional Foods Ass'n v. Mathews*, 557 F.2d 325, 334 (2d Cir. 1977) ('FDA is not bound by the manufacturer's subjective claims of intent but can find actual therapeutic intent on the basis of objective evidence'); *United States v. Undetermined Quantities of an Article of Drug, Labeled as "Exachol,"* 716 F. Supp. 787, 791 (S.D.N.Y. 1989) (product may be found to be a drug even if its labeling states that it is not a drug); *United States v. An Article . . . Consisting of 216 Individually Cartoned Bottles . . . Labeled in Part: "Sudden Change,"* 409 F.2d 734, 739 (2d Cir. 1969) (fact that an article is a cosmetic does not preclude its being a drug for purposes of the Act); see also *Bradley v. United States*, 264 F. 79 (5<sup>th</sup> Cir. 1920) (firm shipping mineral water and representing that the water possessed curative or alleviative properties cannot claim that the product was water and not a drug). Therefore, the manufacturer's claims that Nicotine Water is a dietary supplement are not dispositive.

We agree that, as marketed, Nicotine Water is a "drug" as defined by section 201(g)(1)(B) and (C) of the Act. Nicotine addiction has been determined to be a disease (see, e.g., Department of Health and Human Services, *The Health Consequences of Smoking: Nicotine Addiction, a Report of the Surgeon General*, pages 169-216 (1988)). S & F Garret and the Nicotine Beverage Corporation have promoted and described Nicotine Water as useful in the treatment or mitigation of that disease. Collectively, the claims identified above show that S & F Garret, the Nicotine Beverage Corporation, and QT5 are selling Nicotine Water to help people stop smoking. Accordingly, as marketed, Nicotine Water is a drug within the meaning of sections 201(g)(1)(B) and (C) of the Act.<sup>3</sup>

<sup>3</sup> The definition of drug in section 201(g)(1)(C) of the Act expressly excludes food. However, neither Nicotine Water itself nor the nicotine and nicotine polacrilex ingredients are food within the meaning of 201(g)(1)(C) of the Act because they are not being consumed for their taste, aroma, or nutritive value. See *Nutrilab, Inc. v. Schweiker*, 713 F.2d 335 (7th Cir. 1983). Indeed, U.S. Patent 6,268,386, which S & F Garret cites throughout its promotional material and QT5 cites on [www.nicotinewater.com](http://www.nicotinewater.com), states that the nicotine/water ratio in Nicotine Water is based, in part, on "a fluid amount sufficient to mask as much as the nicotine taste as reasonable"

Based on the smoking cessation and related claims identified in Tab A to your petition, Nicotine Water is also a "new drug" within the meaning of section 201(p) of the Act because no one has submitted to FDA any information to show that it is generally recognized among qualified experts as safe and effective for its suggested uses. Under sections 505(a) and 301(d) of the Act, a new drug may not be introduced or delivered for introduction into interstate commerce unless an FDA-approved New Drug Application (NDA) is in effect for that drug.<sup>4</sup>

*Conclusion*

For the reasons stated above, we agree that:

- Nicotine Water is not a dietary supplement;
- As marketed, Nicotine Water is a drug; and
- As marketed, Nicotine Water is a new drug and an unapproved new drug.

Sincerely,



Dennis E. Baker  
Associate Commissioner for Regulatory Affairs

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(emphasis added). Unlike a food, Nicotine Water is also sold with suggested dosing information that varies depending on whether a person is a light or heavy smoker. In addition, foods do not typically compare themselves to FDA-approved drugs in terms of product efficacy. As noted, some marketing material for Nicotine Water suggests that the product is more effective for smoking cessation than nicotine patches or gum. Finally, S & F Garret states in its promotional material that Nicotine Water "should not be part of a regular dietary program"—in other words, Nicotine Water is not to be used as a food.

<sup>4</sup> Since the agency agrees that, as marketed, Nicotine Water is a drug and an unapproved new drug, we need not consider at this time whether the product would be adulterated if regulated as a food.

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

National Institutes of Health

**Memorandum****Date:** 13 December 2007

**To:** Michael Levy  
Division of New Drug and Labeling Compliance, CDER, FDA

**From:** Stephen J. Heishman, Ph.D.  
Chief, Nicotine Psychopharmacology Unit, NIDA Intramural Research Program, NIH

**Re:** Report on Nicotine Pharmacology, Nicotine Dependence, and Reasons for Smoking

**Executive Summary**

Nicotine is the drug in tobacco products that causes addiction. When cigarettes are smoked, nicotine is absorbed via the lungs and distributed rapidly to all body tissues, including the brain. Nicotine produces its many effects by binding to certain types of receptors that are located on nerve cells throughout the body and brain. The binding of nicotine to its receptor is like a key fitting into a lock. The binding process causes structural changes to the receptor that cause a cascade of biochemical actions that ultimately results in nicotine's effects in the body and brain. In the body, nicotine increases heart rate and blood pressure through direct stimulation of the nervous system and indirectly by causing the release of adrenaline. In the brain, nicotine causes the release of various neurotransmitters, the chemicals that nerve cells use to communicate with each other. Release of these neurotransmitters is responsible for nicotine's rewarding effects and its effects on mood, cognition, and behavior.

Most adult smokers begin smoking and become addicted to nicotine as teenagers. As nicotine use continues, smokers become tolerant to and physically dependent on nicotine. Structural changes to nicotine's receptors in the brain underlie the development of tolerance and

physical dependence. Tolerance is defined as decreased responsiveness to nicotine as a result of prior exposure to nicotine. Tolerance typically leads to increased smoking. Physical dependence has developed when withdrawal symptoms are experienced if someone stops smoking. The unpleasant nicotine withdrawal syndrome often causes people trying to quit smoking to relapse after a few days. There are a number of medications that alleviate withdrawal symptoms and increase the chance of someone quitting successfully.

People smoke for a variety of reasons. When adolescents first begin to smoke, they are influenced primarily by external factors such as peer pressure, family smoking practices, social settings, and cigarette cost. As addiction develops, internal factors also begin to sustain smoking, because the smoker's body has adapted to nicotine and to stop would mean the onset of nicotine withdrawal and craving. Also, the long-term smoker has experienced numerous environmental cues that, through learning processes, automatically trigger smoking. Besides avoiding withdrawal and craving, reasons for smoking include alleviation of stress and negative mood, enhancement of thinking, concerns over weight gain, stimulation, and relief of boredom, all of which are rewarding to the smoker. Another important motivation to smoke is the satisfaction derived from a cigarette. Cigarette satisfaction is best thought of as a combination of the rewarding effects of nicotine (as listed above) and the non-nicotine sensory aspects of smoking. Sensory effects include how the smoke tastes in the mouth, how it feels in the back of the throat, how it feels when inhaled, and how it smells. These sensory effects are created by the chemical interactions of nicotine and non-nicotine components of tobacco as a cigarette is burned. One example is the addition of menthol to cigarettes, which acts to numb the airways making it easier to inhale smoke deeply. Thus, in general, the addicted smoker seeks positive effects of nicotine and the pleasure from puffing on a cigarette, and at the same time, they seek to avoid negative states, such as nicotine withdrawal.

## **I. Definitions and Terminology**

The term *drug dependence* is often used synonymously with the terms *drug addiction* or *drug abuse* (Heishman & Henningfield, 1992). In this report, *nicotine dependence* is defined as a disorder comprising two components: addiction and withdrawal. *Nicotine addiction* refers to the repetitive, compulsive use of tobacco despite harm to the user, the development of tolerance to nicotine's aversive effects, difficulty quitting smoking, and relapse to smoking during quit attempts. *Nicotine withdrawal* is evidence of adaptations to the nervous system that occur with chronic nicotine exposure, termed physical dependence. These physiological adaptations require nicotine to maintain normal body functions. When tobacco use is discontinued, withdrawal signs and symptoms emerge that are opposite to the effects of nicotine and can result in relapse to smoking during a quit attempt.

## **II. Effects of Smoking/Nicotine on the Structure and Function of the Body**

### *Overview of Pharmacology*

Nicotine was isolated from the tobacco plant, *Nicotiana tabacum*, in 1828. Nicotine delivered through tobacco smoke is readily absorbed from the small airways of the lungs and is distributed rapidly to the body via arterial circulation, reaching the brain within 20 seconds (Benowitz, 1996). Half of a dose of nicotine is eliminated from the body in 2-3 hours and is metabolized mainly in the liver.

The complex pharmacological effects of nicotine are expressed through its interaction with specific receptors, termed nicotinic acetylcholine receptors (nAChRs), which are located on nerve cells throughout the body and brain. The binding of nicotine to its receptor is like a key fitting a lock. When nicotine binds, the receptor changes shape and opens, resulting in a cascade of biochemical actions that ultimately produce nicotine's effects. In the body, one effect of

nicotine is to increase heart rate and blood pressure. This occurs through stimulation of the sympathetic nervous system and release of adrenaline from the adrenal gland (mimicking the flight or fight response that occurs when we face danger). Nicotine also stimulates numerous sensory receptors, including pressure receptors in the skin and internal organs, thermal receptors in the skin and tongue, and pain receptors (Taylor, 2001). In the brain, nicotine stimulates the vomiting reflex located in the brainstem and increases breathing rate. Larger doses may cause convulsions and death due to respiratory failure. The fatal dose of nicotine in adults is 60 mg (Taylor, 2001). Cigarettes made in the United States typically contain 6-9 mg of nicotine, most of which is destroyed as the cigarette burns. The average amount of nicotine reaching the bloodstream and brain from smoking one cigarette is 1-3 mg (Benowitz et al., 1991). Nicotine binding to different nAChRs in the brain stimulates the release of various neurotransmitters, which are the chemicals that nerve cells use to communicate with each other. The neurotransmitters released by nicotine stimulation are involved in cognition, mood state regulation, and various behaviors, including those relevant to nicotine dependence. These nicotine-induced changes in the brain will be discussed in greater detail below.

#### *Moving from Initial Tobacco Use to Nicotine Addiction*

The initiation of tobacco use and the development of nicotine dependence typically occur during adolescence (U.S. Department of Health and Human Services [USDHHS], 1994). Initial use of tobacco is primarily influenced by psychosocial and economic factors, such as self-esteem, curiosity, peer influence, cigarette availability and cost, parental style, and marketing of tobacco products (Chassin et al., 2005; USDHHS, 1994). For some individuals, occasional smoking gradually escalates to daily smoking. Approximately one third of those who try cigarettes become nicotine dependent (Anthony et al., 1994), and the typical interval from first cigarette to

daily smoking is 1-2 years (Kandel et al., 2007; Robinson et al., 2004). Although psychosocial and economic factors continue to influence smoking behavior once a person is addicted, the pharmacological effects of nicotine and avoidance of withdrawal are critical in the maintenance of nicotine dependence.

The most important effect of nicotine with respect to the development of addiction is that nicotine functions as a positive reinforcer (USDHHS, 1988). A positive reinforcer is anything that strengthens behaviors leading to its occurrence. Thus, nicotine reinforces the behavior (smoking) that leads to its delivery. Through normal learning processes, primary reinforcers, such as nicotine, become conditioned to environmental stimuli. These environmental stimuli then become secondary reinforcers, serving as signals for smoking. For example, if drinking coffee and smoking occur together frequently, then over time, a cup of coffee will become a signal to smoke. Conditioning occurs most rapidly when two stimuli are paired repeatedly. Each day, a smoker experiences hundreds of pairings of nicotine puffs with environmental events, such that the behaviors of seeking, lighting, and smoking cigarettes become automatic.

Two other processes that develop as a person graduates from occasional to daily smoking are tolerance and physical dependence. Tolerance is defined as decreased responsiveness to an effect of a drug resulting from prior exposure to the drug. When tolerance attenuates the desired effects of a drug, the typical result is an escalation in drug dose or frequency of use to attain the original effect of the drug. Daily smokers lose some degree of tolerance overnight, such that the first cigarettes of the day are reported as the strongest or the best cigarettes (Jarvik et al., 1993). As smoking continues during the day, tolerance increases, and effects diminish. Physical dependence refers to an altered physiological state resulting from prior drug exposure and requiring continued drug use for normal functioning. Physical dependence is revealed by a withdrawal syndrome, consisting of observable signs and subjective symptoms, that occurs when

drug taking stops. Specific nicotine withdrawal symptoms vary across individuals, but are generally unpleasant and frequently intolerable, and most smokers attempting to quit smoking relapse before the syndrome begins to subside (Hughes, 2007a, 2007b). The neurobiological substrates of tolerance, physical dependence, and nicotine reinforcement are discussed in the next two sections.

#### *Functional States of nAChRs*

nAChRs comprise a family of receptors that are widely distributed in the brain and body. The majority of nAChRs in the brain are located on nerve cells and modulate the cell's release of neurotransmitter. Neurotransmitters are the chemicals that nerve cells use to communicate with each other, and such communication is the basis of all thoughts and behaviors. In the brain of nonsmokers, the naturally-occurring neurotransmitter acetylcholine (ACh) binds to nAChRs to influence the release of nearly all known neurotransmitters, which underlie a variety of functions including cognition, mood, movement, and pain sensation (Di Matteo et al., 2007). When nicotine enters the brain, it also binds with nAChRs to mimic the effect of ACh. The various effects of nicotine are determined by the different locations and functions of nerve cells that have nAChRs.

As mentioned above, when ACh or nicotine binds with nAChRs, the receptor undergoes a structural change from a resting state to an active state, which stimulates the nerve cell. When nAChRs are activated, they usually then become desensitized or unresponsive to ACh or nicotine for variable lengths of time. A rapid pulse of nicotine (e.g., from a cigarette puff) causes activation of many nAChRs, whereas slightly longer nicotine exposure produces desensitization. In addition to these immediate effects of nicotine on receptor structure and function, chronic exposure to nicotine results in an increased number of nAChRs, a process termed receptor up-

regulation (Gaimarri et al., 2007). Chronic nicotine exposure also causes long-lasting desensitization of nAChRs. This complex, seemingly paradoxical array of nicotine-induced changes in nAChRs (greater numbers, but reduced sensitivity) may underlie the development of tolerance and physical dependence (Dani & Heinemann, 1996; Wonnacott et al., 2005).

For example, short-term receptor desensitization (inactivation) may be responsible for acute tolerance, where repeated doses of nicotine over 1-2 hours results in diminished responding across the nicotine exposures (Perkins et al., 1994, 1995). Chronic tolerance is observed when smokers show a blunted response to nicotine compared with nonsmokers and may be the result of long-lasting inactivation of nAChRs. After overnight tobacco abstinence, nicotine blood levels decline and smokers begin to experience the discomfort of nicotine withdrawal (USDHHS, 1988). During abstinence, inactivated nAChRs begin to recover to the active state. As the excessive number of nAChRs (due to up-regulation) become responsive, there may be increased activity in nerve pathways that underlie the anxiety, restlessness, and craving associated with nicotine withdrawal (Dani & Heinemann, 1996). Another possible mechanism underlying withdrawal involves the fact that nAChRs are located on nerve cells in various brain areas that use the neurotransmitter dopamine (DA). When nicotine binds to nAChRs, DA is released. In the absence of nicotine stimulation, there is a decrease in DA release, which might underlie the negative emotional state characteristic of nicotine withdrawal (Kenny & Markou, 2001).

### *Brain Reward Pathways*

As previously stated, nicotine binds with nAChRs in the brain, stimulating the release of multiple neurotransmitters (Di Matteo et al., 2007). This neurotransmitter release in various brain pathways is thought to underlie the many psychological and behavioral effects of nicotine. One such brain circuit, the mesolimbic pathway, comprises nerve cell bodies in the brainstem

that send projections upward to the cerebral cortex and to many other brain regions, including the limbic system, which is involved in processing of emotions and memory. The mesolimbic pathway has been recognized for decades as being central to mediating the effects of natural rewards (e.g., food, sex) and the rewarding effects of addictive drugs (Wise & Bozarth, 1987; Wonnacott et al., 2005). Numerous studies have shown that DA release in the mesolimbic pathway is the brain's representation of a rewarding stimulus, signaling to the person that something is desirable and should be approached. Activity in the mesolimbic pathway is now considered to be a common mechanism for the rewarding effects of abused drugs (Pich et al., 1997; Wonnacott et al., 2005). nAChRs are located on DA-containing nerve cells in the mesolimbic pathway. Nicotine, like other addictive drugs, stimulates the release of DA in this pathway. Many animal studies have documented the critical role of the mesolimbic DA system in the rewarding effects of nicotine (Balfour, 2004; Corrigall et al., 1994; Di Chiara, 2002).

### **III. Nicotine Withdrawal**

#### *Course and Symptomatology*

Observation of a withdrawal syndrome that emerges when drug taking ceases is evidence of the cellular adaptations that occur with chronic drug use, resulting in a state of physical dependence. A person who is physically dependent on a drug requires continued use of the drug to function normally. If drug intake stops, a withdrawal syndrome begins within 24 hours that is typically opposite in nature to the effect of the drug (O'Brien, 2001). Animal studies indicate that daily nicotine exposure for 1-4 weeks is necessary for physical dependence to develop (Kota et al., 2007; Semenova et al., 2007). Although there is variability in time course across smokers (Piasecki et al., 1998, 2003), most withdrawal symptoms appear within 1-2 days after tobacco abstinence, peak in intensity within 7 days, and resolve within 2-4 weeks (Hughes, 2007a).

Epidemiological data suggest that about 50% of smokers attempting to quit smoking experience significant withdrawal, which can impair daily functioning and lead to smoking relapse (Hughes, 2007b).

The nicotine withdrawal syndrome has been characterized (Hughes et al., 1990; Hughes, 2007a), and diagnostic criteria have been established by the American Psychiatric Association in the *Diagnostic and Statistical Manual of Mental Disorders*, 4<sup>th</sup> edition (DSM-IV; American Psychiatric Association, 2000) and by the World Health Organization in the *International Classification of Diseases*, 10<sup>th</sup> revision (ICD-10, World Health Organization, 1993). Both DSM-IV and ICD-10 list the following six withdrawal signs and symptoms: anxiety, difficulty concentrating, negative mood, increased appetite, insomnia, and irritability. Additionally, DSM-IV lists restlessness and decreased heart rate, and ICD-10 lists craving for tobacco, increased cough, malaise or weakness, and mouth ulceration.

#### *Alleviation of Withdrawal*

The initial medications approved by the FDA to help people stop smoking deliver nicotine with the intent to replace, at least partially, the nicotine obtained from cigarettes and to provide nicotine-induced effects. Nicotine replacement therapy (NRT) medication is intended to reduce the severity of nicotine withdrawal symptoms, thereby increasing the probability of a successful quit attempt. Studies have shown that NRT products can substantially alleviate most withdrawal symptoms, but do not entirely eliminate tobacco craving (Henningfield et al., 2005). Current NRT medications include the transdermal patch, which provides long-term, passive administration of nicotine, and several products that provide acute dosing: gum, nasal spray, inhaler, and lozenge. All forms of NRT are safe and effective and are considered to be first-line medications in the treatment of nicotine dependence (Fiore et al., 2000). Combined use of patch

and acute dosage forms during heightened craving episodes is also effective. For example, the nicotine patch reduces ongoing craving, but does not reduce craving elicited by a smoking-related cue in the laboratory (Tiffany et al., 2000). In contrast, nicotine gum does alleviate cue-elicited craving (Shiffman et al., 2003). In the real-world, the cues that trigger cigarette craving are the numerous stimuli that have been conditioned to years of smoking, such as a cup of coffee, an alcoholic drink, talking on the telephone, getting into the car, finishing a meal, a stressful situation, or seeing a friend.

There are currently two non-nicotine medications approved for treating nicotine dependence. Bupropion (Zyban) was originally approved as an anti-depressant (Wellbutrin). Although depression is more prevalent among smokers than nonsmokers and depressed mood is a symptom of nicotine withdrawal, bupropion's efficacy in smoking cessation is probably not due to its anti-depressant effects (Hays & Ebbert, 2007). Bupropion reduces withdrawal symptoms and has been shown in many studies to be effective in treating nicotine dependence. The other FDA-approved non-nicotine medication is varenicline (Chantix). Varenicline binds to one type of nAChR, which is known to be involved in the rewarding, nicotine-induced release of DA in the mesolimbic pathway (Oncken et al., 2007). When varenicline binds to the nAChR, it causes the release of about half the DA released by nicotine. This lower level of DA is thought to attenuate craving and other withdrawal symptoms. As varenicline occupies the nAChR site, it also blocks nicotine from binding. This action prevents nicotine from producing a rewarding effect (large DA release) if a relapse to smoking occurs. In clinical trials, varenicline has been shown to increase success in achieving long-term tobacco abstinence (Jorenby et al., 2006; Oncken et al., 2006; Tonstad et al., 2006).

Not all withdrawal relief involves nicotine replacement or drugs that mimic or block nicotine's actions at nAChRs in the brain. Smoking nicotine-free cigarettes can produce short-

term reductions in tobacco craving and other withdrawal symptoms (Brauer et al., 2001; Butschky et al., 1995; Pickworth et al., 1999) and can reduce the size of puffs taken from nicotine-containing cigarettes (Rose et al., 2003). These studies emphasize the importance of non-nicotine (i.e., sensory and motor) factors in the maintenance of smoking (Rose, 2006), which will be discussed further in the next section.

#### **IV. Reasons for Smoking**

People smoke for a variety of reasons. A chronic smoker is tolerant to and physically dependent on nicotine and to stop smoking would mean the onset of nicotine withdrawal and craving. Other reasons include enhancement of thinking, alleviation of stress and negative mood, concerns over weight gain, stimulation, relief of boredom, and cigarette satisfaction, which encompasses the aforementioned rewarding effects of nicotine coupled with the non-nicotine sensory effects of smoking. Additionally, the chronic smoker experiences numerous environmental cues that trigger smoking, contributing to the automatic nature of smoking. In broad terms, smokers seek positive effects of nicotine and the pleasure from puffing on a cigarette, and at the same time, they seek to avoid negative states, such as stress and nicotine withdrawal.

The reasons for initial smoking are different from those when a person is dependent. When adolescents first begin to smoke, they are influenced primarily by external factors, such as peer pressure, family smoking practices, social settings, and cigarette cost. In contrast, the habitual smoking of an addict is influenced by physiological adaptations to nicotine and conditioned cues that trigger continued smoking (Baker et al., 2004a; Piasecki et al., 2007). The focus of this section will be on the reasons for smoking in nicotine-dependent individuals. At the most basic level of analysis, people smoke to experience the beneficial, pleasurable effects of

cigarettes (positive reinforcement) and to avoid aversive states, such as withdrawal or stress (negative reinforcement). Whether positive or negative reinforcement processes are more important in influencing drug dependence has been debated (Baker et al., 2004b); however, it is clear that both processes are critical in the development of nicotine dependence.

Piper et al. (2004) proposed a conceptualization of nicotine dependence based on smoking motivations. I have grouped them in three categories: positive reinforcement, negative reinforcement, and addiction-related processes. Data from the experimental literature is included to illustrate certain concepts.

### *Positive Reinforcement Processes*

*Positive reinforcement.* One reason people smoke is because of the reinforcing and rewarding effects of nicotine produced in the brain. As noted earlier, nicotine functions as a positive reinforcer by strengthening the behaviors leading to its delivery. Numerous studies have documented that animals (Corrigall, 1999) and humans (Harvey et al., 2004) will emit thousands of responses (e.g., lever presses) to receive intravenous injections of nicotine. A related concept to reinforcement is reward, which is defined as the subjective, hedonic value given to a drug (Everitt & Robbins, 2005). Rewarding effects of nicotine are typically measured by self-report questionnaires assessing *liking, good effects, high, head rush, stimulated, and relaxed*. Nicotine reliably increases subjective ratings of such positive, rewarding states (Garrett & Griffiths, 2001; Kalman & Smith, 2005; Perkins et al., 2003).

*Associative learning.* As noted previously, when a primary reinforcer, such as nicotine, is repeatedly paired with an environmental stimulus over time, that stimulus gains reinforcing effects through associate learning processes and is referred to as a conditioned or secondary reinforcer. Because each puff from a cigarette delivers a discrete dose of nicotine to the brain,

there are hundreds of opportunities each day for environmental stimuli to become associated with smoking. Eventually, these conditioned reinforcers come to control habitual smoking or can trigger relapse during a quit attempt (Baker et al., 2004a). Examples include all the preferred locations and times a person smokes (e.g., in the car, on the phone, after a meal, coffee break), during a stressful experience, and the sight or smell of a cigarette.

*Smoking satisfaction.* Smoking satisfaction refers to a combination of the rewarding effects of nicotine, described above, and the non-nicotine sensory aspects of smoking. The taste and sensory effects are created by the chemical interactions of nicotine and non-nicotine components of tobacco as a cigarette is burned. Smokers' enjoyment of the taste and sensory effects of cigarettes is another example of associative learning, as initially unpleasant stimuli (such as irritation of the throat) become repeatedly paired with delivery of nicotine. The role of sensory effects of smoking probably helps explain why NRT does not entirely alleviate craving for cigarettes and why such craving can sometimes be partially alleviated by throat irritants (Behm et al., 1993).

Sensory research is a priority of cigarette manufacturers because sensory factors play an important role in determining puffing behavior (e.g., depth of inhalation). The tobacco industry has tailored the sensory properties of cigarettes to the preferences of specific gender, age, and ethnic populations (Carpenter et al., 2007). Non-industry research has also examined the sensory and movement cues associated with smoking (Rose, 2006). The movement components (handling, puffing, inhaling) alone do not elicit much smoking satisfaction, whereas the sensory components (taste, smell, airway sensations) appear to play an important role in cigarette satisfaction (Rose, 2006). However, nicotine also plays a critical role in smoking satisfaction because nicotine-free cigarettes are consistently rated as less satisfying than nicotine-containing cigarettes (Rose, 2006). To measure the nicotine and non-nicotine effects of cigarettes, Rose and

colleagues developed the Cigarette Evaluation Questionnaire (CEQ) that has been recently validated (Cappelleri et al., 2007). The CEQ comprises five aspects (smoking satisfaction, psychological reward, aversion, enjoyment of respiratory tract sensations, and craving reduction) and has been used to determine the effect of medications to reduce smoking reward. For example, Rose et al. (1998) found that when smokers were administered mecamylamine, a nAChR blocking drug, and then allowed to smoke, they reported lower smoking reward as measured by the CEQ, including decreased smoking satisfaction, enjoyment of respiratory tract sensations, and craving. This finding suggests that mecamylamine and similar nAChR blocking drugs might be effective aids in quitting smoking.

#### *Negative Reinforcement Processes*

*Negative reinforcement.* This process strengthens a response that results in the removal of an aversive state. An important example of negative reinforcement in addiction is using a drug to relieve withdrawal discomfort, which increases the likelihood that the drug will be used again when withdrawal is experienced. Avoidance of negative mood states is thought to influence much of smoking behavior in nicotine-dependent smokers (Baker et al., 2004b). The reduction of stress, a common aversive state, is frequently reported as a reason for smoking; however, studies are equivocal in support of smoking's ability to decrease stress (Baker et al., 2004a) and some studies suggest that smoking actually increases stress (Parrott, 1998). An alternative view is that smokers are genetically and environmentally predisposed to experience increased stress and negative mood and thus smoke to self-medicate unhealthy emotional states (Gilbert, 1995).

*Craving.* One of the most common symptoms reported by people trying to quit smoking is an intense urge or craving for cigarettes. Studies have shown that the greater the intensity or

frequency of a person's craving when trying to quit smoking, the greater the likelihood that they will relapse (e.g., Killen et al., 2006). The reduction of craving by smoking follows the process of negative reinforcement described above. Smokers know that a cigarette can readily alleviate the unpleasant state of craving. Various forms of nicotine, especially those that are quickly absorbed such as gum and nasal spray, can also decrease the urge to smoke, thereby helping people quit smoking (Henningfield et al., 2005). Craving is typically thought of as one component of nicotine withdrawal, but it can also occur in the absence of tobacco deprivation. Laboratory studies have demonstrated that smoking-related cues or audiotaped imagery scripts that describe smoking situations can evoke self-reported craving in smokers who are not tobacco deprived (Carter & Tiffany, 1999; Lee et al., 2007). Nicotine can reduce such cue-elicited craving as well as withdrawal-induced craving (Shiffman et al., 2003).

*Performance enhancement.* Smokers report that smoking helps them concentrate and improves thinking; however, there is only limited experimental evidence that smoking or nicotine truly enhances cognitive performance (Bell et al., 1999; Heishman, 1998; Myers et al., 2007). The best evidence of nicotine enhancing cognition is in the areas of attention and memory; however, other cognitive processes, such as learning, reasoning, or decision-making, have not been investigated. The most common finding from laboratory studies is that tobacco abstinence impairs cognition and that smoking merely reverses these deficits (Heishman et al., 1994). This may give smokers the perception that smoking enhances cognition above their normal baseline.

#### *Addiction-Related Processes*

*Tolerance.* Tolerance is a physiological process in which chronic nicotine exposure produces a state of decreased responsiveness to nicotine, perhaps due to inactivation of nAChRs. Thus, the same dose of nicotine produces less of the desired effect, which motivates the smoker to increase their intake of nicotine. This could be accomplished by smoking more cigarettes or taking larger puffs from each cigarette or both. Tolerance to several of nicotine's effects has been demonstrated within a single experimental session (Perkins et al., 1994, 1995) and across 8 days of repeated dosing (Heishman & Henningfield, 2000).

*Automaticity.* Like any behavior that is repeated many times each day, smoking can become habitual in the sense that it is controlled by automatic cognitive processes, which are fast, reflexive, and operate without conscious awareness (Tiffany, 1990). For example, without thinking about it, a smoker may light a cigarette at the beginning of every telephone conversation. When such automatic processes are blocked (e.g., by an empty cigarette pack), the urge for a cigarette reaches conscious awareness, and craving is experienced. Smokers who exhibit a high degree of automatic smoking (e.g., don't remember lighting the cigarette in their hand) typically have a harder time quitting (Piper et al., 2004).

*Weight control.* Nicotine functions as an appetite suppressant. Many smokers are motivated to continue smoking to control their weight or because of concern over weight gain if they stop smoking. Smokers weigh on average 7-9 lb. less than nonsmokers, and the weight gain seen after quitting smoking also averages 7-9 lb. (Klesges et al., 1989). When individuals relapse after quitting, their weight decreases to levels seen before quitting (Perkins, 1993). Thus, it is clear that smoking helps control body weight. Evidence indicates that concerns over weight gain, rather than weight gain itself, contribute to continued smoking and appear to deter quit attempts, especially among women (French & Jeffery, 1995; Perkins et al., 1997).

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FDA CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF ANALGESIA, ANESTHESIA, AND RHEUMATOLOGY PRODUCTS  
HFD-170: 10903 New Hampshire Avenue, Silver Spring, MD 20993

To: Michael Levy, Division of New Drug and Labeling Compliance  
Through: Bob A. Rappaport, M.D., Director, Division of Analgesia, Anesthesia and  
Rheumatology Products  
Through: Rigoberto Roca, M.D., Deputy Division Director, Division of Analgesia,  
Anesthesia and Rheumatology Products  
From: Celia Winchell, M.D., Medical Team Leader, Addiction Drug Products, DAARP  
Re: Nicogel  
Date: 3/11/08

The Division of New Drugs and Labeling Compliance has requested consultation in connection with a product known as Nicogel, a hand gel product derived from tobacco matter. FDA has detained a shipment of Nicogel, and is seeking medical information from DAARP regarding the pharmacological effects of nicotine and the symptoms of nicotine withdrawal.

Examples of claims made for Nicogel include the following:

- "Cigarette Satisfaction in a Hand Gel"
- "Smoking Satisfaction in a Hand Gel"
- "Cigarette Alternative"
- "When should I apply Nicogel? Whenever you feel the need to smoke or use tobacco products."
- "Why Nicogel instead of smoking? Nicogel is a revolutionary cigarette alternative which fully satisfies your urge to smoke as easily as rubbing a little gel on your hands. In less than a minute, Nicogel absorbs in to your skin and you'll begin to feel like you've just smoked."

We are asked to address the following issues:

- (1) How do cigarette smoking and nicotine affect the structure and/or function of the body? Please limit your consult to the physical effects of smoking and nicotine related to the claims made for Nicogel. Your consult need not address the many adverse health consequences (e.g., cancer, cardiovascular disease, etc.) associated with smoking.
- (2) What are the physical effects on the body associated with nicotine withdrawal, and how do cigarette smoking and nicotine mitigate those effects?

Dr. Keith Burkhart will be preparing an answer to the first question. This document responds to the second question, regarding the physical effects of nicotine withdrawal and the effects of cigarette smoking and nicotine on those effects.

### *Tobacco Dependence*

Tobacco dependence (attributable primarily to the main psychoactive component in tobacco, nicotine) is considered by FDA to be a disease, and is included in the World Health Organization's International Classification of Disease (ICD-10)<sup>i</sup>. In this context, "dependence" and "addiction" may be understood to be synonymous, and information about tobacco dependence/addiction may be understood to apply equally to nicotine dependence/addiction. The US Department of Health and Human Services has noted that "Tobacco dependence is now increasingly recognized as a chronic disease, one that typically requires ongoing assessment and repeated intervention."<sup>ii</sup> Nicotine dependence is listed as a diagnosis in the Diagnostic and Statistical Manual of the American Psychiatry Association (DSM-IV-TR)<sup>iii</sup>, and the condition is generally characterized by the same symptoms as other substance dependence diagnoses, namely, "a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues use of the substance despite significant substance-related problems. There is a pattern of repeated self-administration that can result in tolerance, withdrawal, and compulsive drug-taking behavior."

Diagnostic criteria for Substance Dependence, generically, are listed in the DSM-IV-TR as follows:

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

- (1) tolerance, as defined by either of the following:
  - (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
  - (b) markedly diminished effect with continued use of the same amount of the substance
- (2) withdrawal, as manifested by either of the following:
  - (a) the characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for Withdrawal from the specific substances)
  - (b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
- (3) the substance is often taken in larger amounts or over a longer period than was intended
- (4) there is a persistent desire or unsuccessful efforts to cut down or control substance use
- (5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects
- (6) important social, occupational, or recreational activities are given up or reduced because of substance use
- (7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced

depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

However, it is noted that:

Some of the generic Dependence criteria do not appear to apply to nicotine, whereas others require further explanation. Tolerance to nicotine is manifested by a more intense effect of nicotine the first time it is used during the day and the absence of nausea and dizziness with repeated intake, despite regular use of substantial amounts of nicotine. *Cessation of nicotine use produces a well-defined withdrawal syndrome that is described below.* [emphasis added] Many individuals who use nicotine take nicotine to relieve or to avoid withdrawal symptoms when they wake up in the morning or after being in a situation where use is restricted (e.g., at work or on an airplane). Individuals who smoke and other individuals who use nicotine are likely to find that they use up their supply of cigarettes or other nicotine-containing products faster than originally intended. Although more than 80% of individuals who smoke express a desire to stop smoking and 35% try to stop each year, less than 5% are successful in unaided attempts to quit. Spending a great deal of time in using the substance is best exemplified by chain-smoking. Because nicotine sources are readily and legally available, spending a great deal of time attempting to procure nicotine would be rare. Giving up important social, occupational, or recreational activities can occur when an individual forgoes an activity because it occurs in smoking-restricted areas. Continued use despite knowledge of medical problems related to smoking is a particularly important health problem (e.g., an individual who continues to smoke despite having a tobacco-induced general medical condition such as bronchitis or chronic obstructive lung disease).<sup>iv</sup>

Products intended to treat tobacco dependence are generally regulated as drugs or combination products by the Center for Drug Evaluation and Research. Many of these products use an agonist treatment strategy, that is, they provide nicotine to ease withdrawal symptoms that tobacco-dependent individuals experience when they attempt to stop using tobacco. The nicotine is provided through pharmaceutical sources that provide nicotine without other associated tobacco-related toxins. (Examples include nicotine chewing pieces ("gum," such as Nicorette); transdermal systems ("patches," such as Nicoderm), nasal spray, and lozenges.) In addition, the delivery systems do not provide the rapid spikes of nicotine to the brain that smokers receive from cigarettes; this is intended to make the nicotine in these products less reinforcing and easier for patients to discontinue.

#### *Nicotine Withdrawal*

According to the DSM-IV-TR,

The essential feature of Nicotine Withdrawal is the presence of a characteristic withdrawal syndrome that develops after the abrupt cessation of, or reduction in, the use of nicotine-containing products following a prolonged period (at least several weeks) of daily use (Criteria A and B). The withdrawal syndrome includes four or more of the following: dysphoric or depressed mood; insomnia; irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness or impatience; decreased heart rate; and increased appetite or weight gain. The withdrawal symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (Criterion C). The symptoms must not be due to a general medical condition and are not better accounted for by another mental disorder (Criterion D).

These criteria are confirmed by experimental work in which chronic smokers were observed during abstinence in controlled settings or in outpatient settings during

treatment with placebo.<sup>v</sup> Similar findings are also noted after discontinuation of nicotine replacement therapies.<sup>vi</sup>

It is generally accepted that withdrawal symptoms associated with discontinuation of a given dependence-producing drug can be mitigated or treated by administration of the drug or a related drug.

The Agency has previously recognized that the administration of nicotine can mitigate or treat withdrawal symptoms during abstinence from tobacco. For example, Nicorette Gum was first approved in 1984 (NDA 18-612, Nicorette 2 mg) with an indication statement reading:

Nicorette is indicated as a temporary aid to the cigarette smoker seeking to give up his or her smoking habit while participating in a behavioral modification program under medical or dental supervision.

Subsequently an NDA was submitted for Nicorette DS (NDA 20-066, Nicorette 4 mg). Upon the approval, in 1992, of NDA 20-066, both products shared a common package insert. The indication for the package insert for Nicorette Gum then read:

Nicorette treatment is indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. Nicorette treatment should be used as a part of a comprehensive behavioral smoking cessation program.

Several relevant studies of nicotine's ability to relieve withdrawal symptoms in abstinent smokers have been published. However, there are no well-established paradigms for demonstrating the acute withdrawal-relief effects of nicotine, and a variety of approaches have been taken to research this question. A review of the short-term effects of nicotine gum on tobacco withdrawal symptoms was included in a 1984 monograph published by the National Institute on Drug Abuse<sup>vii</sup>, and more recently, a 2001 review of studies of the effect of nicotine replacement on the acute symptoms of nicotine withdrawal identified 13 studies evaluating the effect of transmucosal nicotine (delivered in various dosage forms) on symptoms of nicotine withdrawal<sup>viii</sup>. Studies used various patient-reported measures of withdrawal symptoms. In general, no study showed an effect of nicotine replacement on all aspects of nicotine withdrawal, but most studies showed effects of nicotine on one or more individual symptoms of withdrawal. Taken collectively, the studies demonstrate that nicotine reduces group mean scores of overall withdrawal discomfort, and has particular effects on symptoms such as irritability, anxiety, tension, frustration, impatience.

<sup>i</sup> ICD-10 International Statistical Classification of Diseases, 10<sup>th</sup> Revision, Second Edition, World Health Organization 2007.

<sup>ii</sup> Fiore MC, Bailey WC, Cohen SJ, et al. Treating Tobacco Use and Dependence: Clinical Practice Guideline. Rockville MD: U.S. Department of Health and Human Services, Public Health Service, June 2000.

<sup>iii</sup> Diagnostic and Statistical Manual—Text Revision (DSM-IV-TR, 2000, American Psychiatric Association), page 192

<sup>iv</sup> Diagnostic and Statistical Manual—Text Revision (DSM-IV-TR, 2000, American Psychiatric Association), page 264

<sup>v</sup> Hatsukami, Hughes, and Pickens, Characterization of Tobacco Withdrawal: Physiological and Subjective Effects, NIDA Research Monograph 53, 1984

<sup>vi</sup> Ibid

<sup>vii</sup> Pharmacological Adjuncts in Smoking Cessation, NIDA Research Monograph 53, 1984, Chapters 5 – 9.

<sup>viii</sup> West and Schiffman, Effect of oral nicotine dosing forms on cigarette withdrawal symptoms and craving: a systematic review, Psychopharmacology (2001) 155:115-122.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF ANALGESIA, ANESTHESIA, AND RHEUMATOLOGY PRODUCTS  
HFD-170: 10903 New Hampshire Avenue, Silver Spring, MD 20993

To: Michael Levy, Division of New Drug and Labeling Compliance  
Through: Bob A. Rappaport, M.D., Director, Division of Analgesia, Anesthesia and Rheumatology Products (DAARP)  
From: Keith K. Burkhart, M.D., Senior Advisor for Medical Toxicology to the Director of OND/CDER *KKB*  
Re: Nicogel  
Date: 4/30/2008

The Division of New Drugs and Labeling Compliance has requested a consultation in connection with a product known as Nicogel, a hand gel product derived from tobacco matter. FDA detained a shipment of Nicogel, and DNDLC has requested a consult from DAARP.

Examples of claims made for Nicogel include the following:

- "Cigarette Satisfaction in a Hand Gel"
- "Smoking Satisfaction in a Hand Gel"
- "Cigarette Alternative"
- "When should I apply Nicogel? Whenever you feel the need to smoke or use tobacco products."
- "Why Nicogel instead of smoking? Nicogel is a revolutionary cigarette alternative which fully satisfies your urge to smoke as easily as rubbing a little gel on your hands. In less than a minute, Nicogel absorbs in to your skin and you'll begin to feel like you've just smoked."

We are asked to address the following issues:

- (1) How do cigarette smoking and nicotine affect the structure and/or function of the body? Please limit your consult to the physical effects of smoking and nicotine related to the claims made for Nicogel. Your consult need not address the many adverse health consequences (e.g., cancer, cardiovascular disease, etc.) associated with smoking.
- (2) What are the physical effects on the body associated with nicotine withdrawal, and how do cigarette smoking and nicotine mitigate those effects?

Question 1 is answered in this reply, while Celia Winchell, M.D., Medical Team Leader, Addiction Drug Products, DAARP answers Question 2 in a separate consultation. Additionally, a consult was requested regarding the use of Nicogel, which I will discuss below.

**Answer to Consult Question 1 above.**

Nicotine is well absorbed by multiple routes including the respiratory tract, skin, oral tissue, and intestinal tract. The dermal absorption of nicotine is illustrated by green tobacco sickness, which is characterized by nausea, vomiting and dizziness, and results from dermal contact of tobacco harvesters with moist tobacco plants.<sup>1</sup>

Cigarette smoking delivers nicotine in the particulate matter inhaled by the smoker. Tobacco that is used to manufacture cigarettes contains 0.5-8.0% nicotine by weight.<sup>2</sup> Hundreds of substances are inhaled during cigarette smoking, but the absorption of nicotine is generally considered a key physiologic result from the act of cigarette smoking.<sup>3</sup> The intake of nicotine from cigarette smoking is highly variable but is reported to average 1 mg per cigarette (range 0.37-3.47 mg).<sup>4</sup> A cigarette smoker will adjust his/her use to maintain an average nicotine concentration approximately 30 ng/mL.<sup>5</sup>

After absorption, nicotine undergoes rapid distribution. Inhaled nicotine reaches the brain in just seconds.<sup>5</sup> Other routes of absorption do not achieve brain concentrations as quickly. Therefore dermal absorption of nicotine is not expected to produce the almost instantaneous effects of rapid brain delivery of nicotine.

Nicotine affects the structure and function of the body by acting on the autonomic nervous system. Nicotine binds to a subset of acetylcholine receptors that are referred to as nicotine receptors. These receptors are found throughout the body including the nervous system (central, ganglia, and neuromuscular junction), adrenal gland, and the chemoreceptors of the carotid and aortic bodies. Nicotine acts to elevate other neurotransmitters such as serotonin and B-endorphin that impact mood. Within the brain, the limbic system, midbrain, and brainstem have a high density of nicotine receptors. The dose of nicotine typically delivered by cigarette use will activate the reticular activating system (RAS) in the brainstem to increase the level of alertness. Cigarette smoking or the administration of nicotine also produces electroencephalographic changes consistent with arousal.<sup>3</sup> Memory and attention are facilitated, while aggression, depression, stress and irritability are decreased. Many smokers believe that smoking helps them to concentrate and elevates their mood.

At high doses, nicotine exposure can be fatal. A potentially lethal dose is approximately 1 mg/kg.<sup>2</sup> Excessive stimulation of nicotine receptors produces muscle twitching, seizures, rapid heart rate and elevated blood pressure. Depressed stimulation may follow resulting in slow heart rates, low blood pressure, and muscle paralysis. Death may result from respiratory and/or heart failure.<sup>6</sup>

Nicotine clearly alters the structure and function of the body. The dose, as noted above, determines the degree of alteration. While a low dose would have a minor effect, higher doses can result in life threatening toxicity.<sup>2</sup>

**Answers to Questions in the consult request dated October 10, 2007.**

1. It is our understanding that tobacco users consume tobacco products at a rate that is based on the user's addiction to nicotine. If larger dosages of Nicogel may be needed to satisfy (mitigate/treat) the symptoms of nicotine addiction, would these larger dosages also expose the user to higher dosages of Nicogel's other tobacco-derived chemical compounds? If so, would this increase the potential health risks of this product to consumers?

**Answer:** Nicogel is a hand gel made from liquefied tobacco. It contains diethylene glycol monoethyl ether (DGME). If other tobacco ingredients are not extracted by the manufacturer and they remain in the final product, DGME may act as a solvent and enhance their absorption based upon their physicochemical properties. DGME appears to act by increasing solubility to enhance penetration into the human skin, specifically the stratum corneum layer.<sup>7</sup> If some of the remaining ingredients in Nicogel would be toxic or carcinogenic, then potential health risks may be present.

2. As noted above, Nicogel contains DGME. From our review of literature available on the Internet, it appears that this ingredient is used to enhance the skin's permeability (see attached Google references). Do you agree that this ingredient in Nicogel can have this effect? Would this ingredient enhance the skin's permeability and facilitate absorption of nicotine and the other water-soluble chemical constituents of tobacco contained in Nicogel?

**Answer:** DGME is a solvent that may enhance the skin absorption of nicotine. A review of the literature notes a number of drugs where DGME appears to contribute to enhanced dermal absorption.<sup>8-14</sup> It is therefore likely that DGME may enhance the absorption of nicotine and other substances contained in the final product (See Question 3).

It is also noted that there are two FDA approved drug products that contain DGME: an estradiol formulation, Elestrin, (NDA 21813) contains [redacted] DGME, and a dapsone containing product, Aczone, (NDA 21794) contains [redacted] DGME. DGME is also used in cosmetics. For Elestrin, using the maximum recommended dose of 1.7 g/day would lead to an exposure of [redacted] DGME/day. For Aczone, the dose is one pea-sized amount twice per day. In the clinical trials, mean daily exposure was 1.3g +/- 1.1g. This would represent [redacted] DGME.

3. If Nicogel's present formulation changes, either qualitatively or quantitatively, especially given the raw agricultural source for these ingredients, and if future batches of Nicogel were to contain higher levels of the water-soluble chemical constituents of tobacco (including nicotine), would Nicogel pose even greater health risks for consumers particularly when a skin permeation enhancer, like DGME, is included in the formulation?

**Answer:** The final concentration of nicotine in Nicogel will most likely determine the health risk. Based on the current information, the amount of nicotine from internal testing of the detained product is 0.003% nicotine and an average of 42% DGME. With a 0.8 ml

application (i.e., the labeled content of a single foil pouch), the maximum potential delivered dose of nicotine from that application would be 0.024 mg or 24 micrograms [0.003% (or 3 mg/100 mL) X 0.8 mL]. Toxicity in children is not expected with exposures less than 0.1 mg/kg. However, because a 50 mL container may contain up to 1.5 mgs of nicotine, this amount may represent a potential health risk to children, if a 10 kg child were to absorb the nicotine in 30 mLs or more of the product.

For DGME, based on the sample of the detained product, the exposure per dose would be 336 mg/dose (42 g/100mL X 0.8 mL). Therefore, the use of 3 doses per day would exceed the daily exposure to DGME in Elestrin and is 2-3 times the average daily exposure to DGME for Aczone. Based on my review of the published literature, the safety of the amount of DGME that would be applied in 3 or more daily doses of Nicogel has not been evaluated.

It is difficult to comment upon any additional risk that DGME may pose regarding the absorption of nicotine, because clinical trial data are not available. As noted above, however, nicotine is very well absorbed through the skin, especially when it is moist. The medical literature contains many reports of green tobacco illness.<sup>15</sup> Workers coming into contact with wet tobacco leaves will absorb nicotine and may develop toxicity.<sup>16</sup> Nicogel is water based, and this also may contribute to its absorption. There are no data establishing whether DGME increases either the rate or percentage of absorption of nicotine; however, its use in other drug products and many other formulations suggest that enhanced nicotine skin penetration is likely.

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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

US Food & Drug Administration  
New York District  
158-15 Liberty Ave.  
Jamaica, NY 11433

August 4, 2008

**VIA FEDERAL EXPRESS**

Frederick H. Branding  
Reed Smith Sachnow & Weaver  
10 South Wacker Drive  
Chicago, IL 60606-7507

Re: Entry No. 112-7769262-2/Nicogel Hand Gel

Dear Mr. Branding:

On or about August 14, 2007, Apollo Health and Beauty Care c/o Blue Whale Worldwide, 321 Courtland Avenue, Woodbridge, Ontario, Canada, shipped 100 packets of a product described as "Nicogel Tobacco Hand Gel" to Blue Whale Worldwide ("Blue Whale"), 630 Norlyn Court, King of Prussia, Pennsylvania. The shipment was presented at Newark Airport, Elizabeth, New Jersey (Port of Entry 4671), and assigned Entry Number 112-7769262-2.

We have determined that the product in Entry No. 112-7769262-2, Nicogel, appears to be a new drug that lacks an approved new drug application as required by the Federal Food, Drug, and Cosmetic Act ("FD&C Act"). See 21 U.S.C. § 355(a). Nicogel appears to be a "drug" within the meaning of 21 U.S.C. § 321(g)(1)(C) because it appears to be intended to affect the structure or function of the body and 21 U.S.C. § 321(g)(1)(B) because it appears to be intended for use in the mitigation, treatment, or prevention of disease. Nicogel is a "new drug" as defined by 21 U.S.C. § 321(p) because it is not generally recognized as safe and effective for use under the conditions prescribed, recommended, or suggested in its labeling. Nicogel appears to violate 21 U.S.C. § 355(a) because there is no approved new drug application or abbreviated new drug application on file with the United States Food and Drug Administration ("FDA") for Nicogel. We have also concluded that neither the Supreme Court's decision in *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000), nor Nicogel's classification under the Harmonized Tariff Schedule of the United States precludes FDA's exercise of jurisdiction over Nicogel. Accordingly, FDA intends to refuse admission to Entry No. 112-7769262-2, pursuant to 21 U.S.C. § 381(a)(3).

I. Background

A. Statutory Framework

Under the FD&C Act, the Secretary of Health and Human Services may request "samples of food, drugs, devices, and cosmetics which are being imported or offered for import into the United States . . ." 21 U.S.C. § 381(a). The FD&C Act further provides that "[i]f it appears from the examination of such samples or otherwise that . . . (3) such article is adulterated, misbranded, or in violation of section 355 of this title, . . . then such article shall be refused admission, except as provided in" 21 U.S.C. § 381(b). 21 U.S.C. § 381(a)(3) (emphasis added).

The FD&C Act thus does not require FDA to find that an article that is offered for importation is *actually* adulterated, misbranded, or in violation of 21 U.S.C. § 355 in order to refuse admission to that article; rather, the agency has "broad authority to prohibit import" of any article that "*appears*" to violate the FD&C Act. *Continental Seafoods, Inc. v. Schweiker*, 674 F.2d 38, 43 (D.C. Cir. 1982) (emphasis added); *see Goodwin v. United States*, 371 F. Supp. 433, 436 (S.D. Cal. 1972); *see also United States v. Food*, 2998 Cases, 64 F.3d 984, 992 (5th Cir. 1995) (FDA "can pursue the administrative procedures of § 381 and simply require reexportation of the goods," even where "the government lacks the ability to prove a violation of the [FD&C Act] by a preponderance of the evidence."); *Sugarman v. Forbragd*, 267 F. Supp. 817, 824 (N.D. Cal. 1967), *aff'd*, 405 F.2d 1189 (9th Cir. 1968), *cert. denied*, 395 U.S. 960 (1969); *K&K Merch. Group, Inc. v. Shalala*, No. 95Civ10082, 1996 U.S. Dist. LEXIS 4880, \*22-23 (S.D.N.Y. 1996) (noting "the wide discretionary power FDA enjoys to determine the factors regarding its decision to grant or refuse admission of imported goods"). If an article is refused admission, it must be exported within ninety days or it will be destroyed.

B. The Proceedings

As noted above, Entry No. 112-7769262-2 was shipped to Blue Whale and was presented at the FedEx facility at Newark Airport on or about August 14, 2007. Refs. 1&2. On September 5, 2007, Blue Whale submitted to the agency additional packaging and marketing materials for Nicogel. Ref. 3. After performing a preliminary review of these materials, on September 18, 2007, FDA issued a "Notice of FDA Action – Detention" for the entry, explaining that the shipment was detained because the product appeared to be a new drug that lacks an approved new drug application as required by 21 U.S.C. § 355. Refs. 4&5. The Notice, which was sent to Blue Whale as the listed consignee of the entry, specified that testimony regarding the admissibility of the entry must be submitted to FDA by October 9, 2007. Ref. 5 at 2. On September 21, 2007, you submitted, on behalf of Nicogel USA, LLC ("Nicogel USA") a letter arguing that the detained article is "a customarily marketed tobacco product" that "does not fall under the jurisdiction of [FDA]," and requested a hearing pursuant to 21 U.S.C. § 381(a) and 21 C.F.R. § 1.94(a). Ref. 6 at 1. On October 30, 2007, a hearing was held at the New York

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District Office. At the hearing, you and other Nicogel USA representatives<sup>1</sup> presented information and arguments in support of the position that Nicogel is a tobacco product that is outside FDA's jurisdiction. *See generally* Ref. 7 (import hearing transcript); Ref. 8 (company handout at hearing).

On January 31, 2008, you notified FDA that there had been a change of management at Nicogel USA and that Bill Whalen is no longer with the company. You asked FDA to refrain from taking any further action on the import entry until the new management had an opportunity to evaluate issues related to the import proceeding. This oral request was confirmed in an email dated February 19, 2008. *See* Ref. 9. On March 11, 2008, FDA notified you that the agency would not agree to an open-ended stay, but would agree not to issue a final decision in this import proceeding before April 4, 2008. Ref. 10.

On April 4, 2008, you submitted a "Supplement to Detention Hearing Record," including attachments A-E, as "further support why the detained product is a tobacco product and, therefore, not an unapproved new drug, as cited in FDA's Notice." Ref. 11 at 1. In that submission, you stated that Nicogel USA had changed its name to Innovative Tobacco Technologies, LLC and had decided to change the product name to either "BaccoGel" or "TobaccoGel." *Id.* at 2. On April 18, 2008, Nicogel USA submitted another attachment to the April 4 Supplement. Ref. 12.

As part of our review of Entry No. 112-7769262-2, we consulted Stephen J. Heishman, Ph.D., Chief of the Nicotine Psychopharmacology Unit, Clinical Pharmacology and Therapeutics Branch, National Institute on Drug Abuse Intramural Research Program, National Institutes of Health ("NIH"), concerning nicotine pharmacology, nicotine dependence, and the reasons people smoke tobacco. *See* Ref. 13. We also consulted the Division of Analgesia, Anesthesia and Rheumatology products, Office of New Drugs, Center for Drug Evaluation and Research ("CDER"), FDA, concerning, among other things, the pharmacological effects of nicotine and diethylene glycol monoethyl ether, and the symptoms of nicotine withdrawal. Refs. 14&15. In addition, the Division of Pharmaceutical Analysis ("DPA") in CDER analyzed samples of the detained product. Ref. 16.<sup>2</sup>

The decision to refuse admission to Entry No. 112-7769262-2 is based on a review of the entire record in this matter, including: the labeling, packaging, and promotional materials for Nicogel; your letters dated September 21, 2007, April 4, 2008, and April 18, 2008; information

<sup>1</sup> Among the attendees was William ("Bill") Whalen, who was, at that time, both President of Blue Whale and employed by Nicogel USA. Ref. 7 at 2, 3. You introduced Mr. Whalen as "CEO of Blue Whale Nicogel." *Id.* at 5.

<sup>2</sup> DPA performed quantitative analyses of nicotine, nicotine analogues or nicotine derivatives, and determined that the sample contained 0.003% nicotine. Ref. 16 at 1. DPA's microscopic examination of the product for the presence of tobacco stem or leaf fragments indicated the presence of plant material based on the identification of starch, but was not conclusive regarding whether the plant material was from tobacco. *Id.* at 3. Finally, DPA performed a quantitative analysis of diethylene glycol monoethyl ether ("DGME") and found the product to contain 42% DGME. DGME enhances the skin's permeability to facilitate transdermal absorption, *see* Ref. 14 at 3, and Bill Whalen stated at the hearing that DGME is added to the product to facilitate the body's absorption of Nicogel. Ref. 7 at 16.

and arguments that Bill Whalen and Nicogel USA presented at the October 30, 2007 hearing; and the materials referenced in this decision. Under the FD&C Act and FDA's regulations, only the owner and consignee have the right to submit testimony regarding a detained product. *See* 21 U.S.C. § 381; 21 C.F.R. § 1.94. Although we have requested documentation showing that Nicogel USA is the owner or consignee of the detained Nicogel, to date you have not submitted it.<sup>3</sup> We have nevertheless considered your various submissions on behalf of Nicogel USA in reaching our decision.

**C. The Detained Product**

Nicogel USA describes Nicogel as a hand gel made from liquefied tobacco that is marketed as a temporary or permanent replacement for smoking cigarettes. *See, e.g., Ref. 3 at 3; Ref. 7 at 7, 9-10; Ref. 6 at 2.* Nicogel contains several water-soluble chemical components, including nicotine, obtained through a water extraction process of tobacco. Ref. 6 at 2; *see also* Ref. 12 at 2, 4-6 (Supplement Attachment F); Ref. 7 at 13-14. The solution produced is further processed into a gel form for topical application to human skin. Ref. 7 at 15-16, 27-28. Nicogel USA has explained that the product contains unspecified particles derived from tobacco. *Id.* at 26-28; Ref. 8 at 5-6. Nicogel, however, is not designed to contain tobacco stem or leaf material. *See Ref. 6 at 2 ("the fiber of the tobacco plant [is] removed."); Ref. 7 at 7, 14 ("Nicogel is liquefied tobacco in a water-soluble gel with the plant fiber and the stem removed.").*

Entry No. 112-7769262-2 consists of individual packets labeled as containing 0.8 ml of Nicogel hand gel. Ref. 1 at 2, 5-8. According to information that Nicogel USA submitted to FDA, and as advertised on its Internet website ([www.nicogelusa.com](http://www.nicogelusa.com)), Nicogel USA has offered these individual packets in a 10-count box or "cig" pack, a 120-count "counter box," a 5-count "clip strip" box, and a sample consisting of 8 individual packets. *See Ref. 20 at 8; Ref. 21 at 9-10; Ref. 8 at 9; Ref. 3 at 1, 6-16.* In addition, the company markets a 50 ml pump bottle. Ref. 3 at 3; Ref. 18 at 9; Ref. 20 at 8. Nicogel USA has repeatedly emphasized that Nicogel is an "innovative" and "revolutionary" product and, as formulated and labeled, nothing like it has ever been commercially marketed in the United States. *See, e.g., Ref. 7 at 7; Ref. 8 at 3; Ref. 3 at 13.* It is "marketed to the adult tobacco consumer" for use "when one cannot smoke." Ref. 6 at 2.

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<sup>3</sup> On January 17, 2008, we notified you that only the owner or consignee of a detained entry is entitled to contest its detention and requested clarification regarding the relationship between Blue Whale and Nicogel USA. Ref. 17. The agency sought this clarification because Blue Whale is listed as the consignee on the import entry documents. Ref. 1 at 1. We have reiterated our request on several occasions. *See* Refs. 18&19.

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The label on the 0.8 ml individual packet of Nicogel includes the following statements:<sup>4</sup>

- **NICOGEL**

*Cigarette Satisfaction<sup>5</sup>*

*In a Hand Gel*

Rubs in Clear

- "0.8 ML/ONE APPLICATION LASTS FOR HOURS"
- "INGREDIENTS: water, extract of tobacco (40% v/v), diethylene glycol monoethyl ether . . ."

In addition, the outer containers for the 10-count box, 120-count box, and pump bottle include these statements:<sup>6</sup>

- "CIGARETTE ALTERNATIVE  
*Cigarette Satisfaction in a Hand Gel*"
- "Nicogel is a revolutionary cigarette alternative which fully satisfies your urge to smoke as easily as rubbing a little gel on your hands. In less than a minute, Nicogel absorbs into your skin and you'll begin to feel like you've just smoked."
- "Nicogel conveniently satisfies your urge to smoke while not affecting those around you."
- "Nicogel is a water-soluble gel with extract of tobacco."

The outer container for the pump bottle also includes this statement:

- "As more public places become smoke-free, Nicogel conveniently satisfies your cigarette cravings while not affecting those around you."

A document entitled "Frequently Asked Questions" that is inserted in the package for the 50 ml pump bottle includes these statements<sup>7</sup>:

<sup>4</sup> Ref. 1 at 7-8.

<sup>5</sup> Some of the 0.8 ml packets state "*Smoking Satisfaction in a Hand Gel*" instead of "*Cigarette Satisfaction in a Hand Gel*." See, e.g., Ref. 3 at 8.

<sup>6</sup> Ref. 3.

<sup>7</sup> Ref. 3 at 3-5.

- “**WHAT IS NICOGEL™?** . . . Nicogel was designed to be used as a cigarette replacement, during times when a smoker finds themselves [sic] in an environment in which they are not allowed to smoke, e.g., cinema, bar, restaurant, the work-place, in flight, etc.”
- “**HOW DO I APPLY NICOGEL™?** Nicogel couldn't be simpler to use: if you are a light smoker (<15 cigarettes per day) use 1 serving (sachet or press) and 2 servings if you are a heavy smoker (>15 cigarettes per day) . . . ”
- “**HOW DO I USE NICOGEL™ AS A CIGARETTE REPLACEMENT?** There are fewer and fewer place [sic] to smoke these days. More often than not smoking is not permitted in the work-place, cinemas, bars, restaurants, and in-flight. Nicogel™ offers a great alternative to bridge those gaps without resorting to medicines designed for quitting (such as the slow release of patches that can fall off or the terrible taste of gums). Many people use medicines for this purpose even though they are not licensed for this use. Use Nicogel™ whenever you feel the urge to smoke”
- “**CAN I USE NICOGEL™ TO REPLACE CIGARETTES COMPLETELY?** If you so wish.”<sup>8</sup>

Finally, the Nicogel USA Internet website ([nicogelusa.com](http://nicogelusa.com)) has included the following additional statements:<sup>9</sup>

- “Smoking Satisfaction in a Hand Gel.”
- “Nicogel® is a new cigarette alternative in the form of a hand gel.”
- “Cigarette satisfaction is as easy as rubbing a little Nicogel® on your hands.”
- “With Nicogel®, you are substituting one tobacco product for another and no longer need to go outside to smoke your favorite cigarette.”
- “Nicogel® is the perfect substitute for a cigarette when you are unable or it is inconvenient to smoke.”

<sup>8</sup> One of these Frequently Asked Questions states: “**DOES NICOGEL AFFECT MY LUNGS?** Nicogel will not affect your lungs in any way, allowing them recovery from the damage sustained whilst smoking.” Ref. 3 at 5. We are not aware of any studies having been conducted to substantiate this assertion.

<sup>9</sup> Ref. 20 ([www.nicogelusa.com](http://www.nicogelusa.com) as accessed on August 16, 2007); Ref. 35 ([www.nicogelusa.com](http://www.nicogelusa.com) as accessed June 9, 2008); *see also* Ref. 21. Consumers were able to purchase Nicogel through the [nicogelusa.com](http://www.nicogelusa.com) website. The [nicogelusa.com](http://www.nicogelusa.com) website included a hyperlink titled “Purchase.” *See, e.g.*, Refs. 21, 35. A consumer who clicked on the “Purchase” hyperlink was linked directly to another website that sold Nicogel products ([http://www.sunridgedistribution.com/index.cfm?fuseaction=category.display&category\\_id=8](http://www.sunridgedistribution.com/index.cfm?fuseaction=category.display&category_id=8)).

- “As more public places become smoke-free, Nicogel® is convenient to use . . . It's perfect for airplanes, theaters, offices, restaurants and virtually anywhere that prohibits smoking.”
- “Nicogel USA developed [its products] for the tobacco user who wants to join the growing number of fellow users who are finding out that you can ‘Beat the Ban’ with Nicogel®.”
- “Already a huge sensation in many parts of Europe, discover why so many people love using Nicogel® when they cannot light up.”
- “**Can I smoke and use Nicogel at the same time?**  
You probably won't want to, but as both are tobacco products, you can if you wish.”
- “**When should I apply Nicogel?**  
Whenever you feel the need to smoke or use tobacco products.”

As discussed more fully below, Nicogel's labeling and promotional materials collectively represent, directly and by implication, that consumers who use Nicogel will experience the same or similar physiological effects on the structure or function of the body as they would from the nicotine derived from traditional tobacco uses (*i.e.*, smoked or chewed tobacco). Moreover, claims for the product represent that Nicogel can prevent, mitigate or treat the withdrawal symptoms of nicotine addiction.

#### D. Cigarette Smoking and Nicotine

People smoke tobacco for a variety of reasons. For smokers who are addicted<sup>10</sup> to nicotine, a component of tobacco, a primary reason for smoking is to alleviate withdrawal symptoms and craving. Ref. 13 at 2, 7-8, 11, 14-15; *see also* Ref. 15 at 3. For these smokers, the body has adapted to nicotine, and abstinence produces withdrawal and craving. Ref. 13 at 2, 5, 7-9, 11. Indeed, regular smokers develop physical dependence,<sup>11</sup> which is caused by the cellular adaptation that results from chronic use and requires continued use for normal functioning. *Id.* at 1-3, 8-9. Moreover, a daily smoker will develop tolerance to nicotine – that is, decreased responsiveness to the drug – which typically results in using the drug more frequently or in higher doses. *Id.* at 2-3, 16.

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<sup>10</sup> Tobacco dependence and nicotine addiction are, in this context, synonymous. Ref. 15 at 2. (They may not be synonymous in all situations because it is possible to be dependent on nicotine from other sources, such as patches or gums. However, the promotional materials for Nicogel represent that it is intended to prevent, mitigate, and treat the withdrawal symptoms of nicotine addiction associated with cigarettes.)

<sup>11</sup> Physical dependence refers to an altered physiological state resulting from prior drug exposure and requiring continued drug use for normal functioning. Physical dependence is revealed by a withdrawal syndrome, consisting of observable signs and subjective symptoms, that occurs when drug taking stops. Ref. 13 at 5-6. As discussed below, the symptoms of nicotine withdrawal have been extensively characterized.

Besides avoiding withdrawal and craving, reasons for smoking include experiencing the pharmacologically rewarding effects of nicotine: stimulation, its effect on mood, alleviation of stress, enhancement of thinking, or to relieve boredom or stress. Ref. 13 at 2, 11-13, 15-16. Individuals may also smoke to control weight, because nicotine acts as an appetite suppressant. *Id.* at 16.

In addition, some smokers seek the non-nicotine sensory effects of smoking – how smoke tastes, how it smells, how it feels in the mouth and throat, and how it feels when inhaled. Ref. 13 at 2, 13. Some of these effects are produced by chemical interactions of the nicotine and other components of tobacco as a cigarette burns. In addition, nicotine acts as a positive reinforcer, strengthening and reinforcing behavior that leads to its continued use. *Id.* at 12. Through repeated or habitual use, long-term smokers “learn” to associate certain environmental cues with smoking. *Id.* at 2, 12-13. Thus, certain activities or exposure to certain stimuli automatically trigger smoking. *Id.* at 2, 5, 12-13, 16. For example, if drinking coffee and smoking occur together frequently, then over time, a cup of coffee will become a signal to smoke. *Id.* at 5; *see also id.* at 13, 16. Smokers’ enjoyment of the sensory aspects of smoking is also an example of associative learning, as stimuli that are initially unpleasant (e.g., irritation of the throat) become repeatedly paired with nicotine delivery. *Id.* at 13-14. Nevertheless, nicotine remains critical to the satisfaction that smokers derive from smoking, evidenced by the fact that smokers consistently rate nicotine-free cigarettes as less satisfying than cigarettes that do contain nicotine. *Id.* at 13.

Nicotine is well absorbed via many routes, including the respiratory tract, skin, buccal mucosa (the mucous membrane lining the mouth), and the intestinal tract. Ref. 14 at 2. After absorption, nicotine undergoes rapid distribution. *Id.* When a person smokes a cigarette, for example, nicotine is absorbed via the lungs and rapidly distributed throughout the body, including the brain. Ref. 13 at 1. Nicotine increases heart rate and blood pressure, by stimulating the sympathetic nervous system and release of adrenaline from the adrenal gland. Nicotine also increases the breathing rate, and at larger doses, can cause death due to respiratory failure. *Id.* at 4. Nicotine activates the reticular activating system in the brainstem to increase one’s level of alertness, and produces electroencephalographic changes consistent with arousal. Ref. 14 at 2. In addition, nicotine binds to nicotinic acetylcholine receptors (nAChRs) located on nerve cells throughout the brain and body, changing the structure of the receptors and activating them, thereby triggering a series of biochemical actions that produce a series of multiple, further effects on the body. Ref. 13 at 1, 3-4, 6; *see also* Ref. 14 at 2. When nicotine binds to the receptors, it stimulates the release of a variety of neurotransmitters that are involved in cognition, regulating mood states, movement, and pain sensation. Ref. 13 at 4, 6-7. Chronic exposure to nicotine increases the number of nAChRs, yet at the same time causes the receptors to become desensitized or unresponsive. *Id.* at 6-7. Nicotine’s effect on nAChRs also causes the release of dopamine in the mesolimbic pathway, which is the brain’s representation of a rewarding stimulus. These physiological effects of nicotine on nAChRs underlie the reinforcing effects of nicotine, which cause addiction. *Id.* at 1, 7-8, 12.

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Nicotine addiction, which is, in some contexts, synonymous with tobacco dependence or nicotine dependence, is a disease. Ref. 15 at 2; *see also* Ref. 13 at 3. In addition, both the American Psychiatric Association, in the *Diagnostic and Statistical Manual of Mental Disorders*, 4<sup>th</sup> edition ("DSM-IV"), and the World Health Organization, in the *International Classification of Diseases*, 10<sup>th</sup> revision ("ICD-10"), have identified diagnostic criteria for nicotine withdrawal. Ref. 13 at 9. The DSM-IV and ICD-10 criteria both include six withdrawal signs and symptoms: anxiety, difficulty concentrating, negative mood, increased appetite, insomnia, and irritability. *Id.* The DSM-IV identifies restlessness and decreased heart rate; the ICD-10 identifies craving for tobacco, increased cough, malaise or weakness, and mouth ulceration as diagnostic criteria for nicotine withdrawal. *Id.*; *see also* Ref. 15 at 3. Moreover, the DSM-IV explains that withdrawal itself may be manifested by an individual taking "the same (or a closely related) substance" in order to "relieve or avoid withdrawal symptoms," and that with respect to nicotine specifically, "[m]any individuals who use nicotine take nicotine to relieve or to avoid withdrawal symptoms when they wake up in the morning or after being in a situation where use is restricted (e.g., at work or on an airplane)." Ref. 15 at 2-3 (quoting DSM-IV).

It is generally accepted that withdrawal symptoms associated with discontinuation of a drug that produces dependence can be mitigated by administering that drug or a related drug. Ref. 15 at 4. A number of FDA-approved drug products intended to treat tobacco dependence provide nicotine to ease withdrawal symptoms associated with quitting smoking, and those products supply the nicotine without other tobacco-related toxins. *Id.* at 3; Ref. 13 at 9. Studies on the effects of nicotine on withdrawal have shown that the administration of nicotine will affect (reduce) one or more symptoms of withdrawal, such as irritability, anxiety, tension, frustration, or impatience. Ref. 15 at 4; *see also* Ref. 13 at 9-10.

## II. Nicogel Appears To Be an Unapproved New Drug

The FD&C Act prohibits the introduction, or delivery for introduction, into interstate commerce of any new drug without first receiving approval from FDA of a new drug application or abbreviated new drug application. 21 U.S.C. §§ 331(d), 355(a). The FD&C Act defines a "drug" to include, among other things, "articles (other than food) intended to affect the structure or any function of the body," 21 U.S.C. § 321(g)(1)(C), as well as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease." 21 U.S.C. § 321(g)(1)(B). Thus, whether an article, such as Nicogel, is a drug depends on its "intended use."

The "intended use" of a product refers, in turn, "to the objective intent of the persons legally responsible for the labeling of drugs." 21 C.F.R. § 201.128; *United States v. Lane Labs-USA, Inc.*, 324 F. Supp. 2d 547, 567 (D.N.J. 2004), *order modified by*, 328 F. Supp. 2d 520 (D.N.J. 2004), *aff'd*, 427 F.3d 219 (3d Cir. 2005). As explained in a longstanding FDA regulation, "The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. . . ." 21 C.F.R. § 201.128. Courts have widely supported FDA's consideration of the label and labeling of a product, advertising or promotional materials, and "any relevant source" in

determining a product's intended use. *See, e.g., United States v. Storage Spaces Designated Nos. "8" & "49,"* 777 F.2d 1363, 1366 (9th Cir. 1985); *Action on Smoking and Health v. Harris,* 655 F.2d 236, 239 (D.C. Cir. 1980); *Nat'l Nutritional Foods Assoc. v. Mathews,* 557 F.2d 325, 334 (2d Cir. 1977).

Because the standard is an objective one, in determining whether an article is a "drug" based on its intended use, the agency is not bound by the manufacturer's subjective claims of intent, but instead can establish intent on the basis of objective evidence. *See Lane Labs-USA,* 324 F. Supp. 2d at 567; *United States v. Undetermined Quantities of An Article of Drug . . . "EXACHOL,"* 716 F. Supp. 787, 791 (S.D.N.Y. 1989).

For the reasons discussed below, we conclude that Nicogel appears to be a drug because it appears to be intended both to affect the structure or function of the body, and to prevent, mitigate, or treat the withdrawal symptoms of nicotine addiction.

**A. Nicogel Appears to be a Drug Because It Is Intended To Affect the Structure or Function of the Body**

Our review of Nicogel's labeling and promotional materials compels the conclusion that Nicogel appears to be intended to affect the structure or function of the body, and therefore appears to be a drug within the meaning of 21 U.S.C. § 321(g)(1)(C). People smoke cigarettes in significant part to achieve the rewarding effects of nicotine, *see I.D. above*, and, as discussed in greater detail below, Nicogel USA has marketed Nicogel as a cigarette substitute capable of providing users "cigarette satisfaction" that lasts "for hours." Nicogel is a clear, odorless gel that is intended to be rubbed into the users' hands. As a result, the satisfaction that Nicogel purportedly provides "for hours" cannot objectively be understood to be based on any of the sensory aspects or physical movements associated with smoking. Rather, the claimed "cigarette satisfaction" can only be objectively understood to refer to the absorption of nicotine into the skin and bloodstream of the user and the resulting pharmacological effects of "satisfaction" one would experience from nicotine.

Nicogel's packaging states that the product will provide "cigarette satisfaction" such that in "less than a minute" after rubbing it on your skin, "you'll begin to feel like you've just smoked," and "one application lasts for hours." *See, e.g., Ref. 3 at 6; Ref. 1 at 7.* The packaging also states that the product is a "cigarette alternative" and that it provides "smoking satisfaction in a hand gel." Ref. 3. The statement of ingredients on the label claims that the product contains "extract of tobacco (40% v/v)." *See, e.g., Ref. 1 at 8; Ref. 3 at 8.* The nicogelusa.com website has expressly claimed that Nicogel is "the perfect substitute for a cigarette when you are unable or it is inconvenient to smoke." Ref. 20 at 1; Ref. 21 at 1; Ref. 35 at 1. It also explained that "Nicogel USA developed [its products] for the tobacco user who wants to join the growing number of fellow users who are finding out that you can 'Beat the Ban' with Nicogel®." Ref. 20 at 1-2; Ref. 21 at 1-2; Ref. 35 at 1. These (and other) product claims draw upon smokers' knowledge about the effects that tobacco and nicotine have on the structure and function of the body, particularly given that Nicogel USA has represented that Nicogel is marketed to "adult

tobacco consumer[s] for use when it is inconvenient to smoke, dip, or chew tobacco." Ref. 6 at 2.

As explained above, people smoke for a variety of reasons, including the desire to experience both the pharmacological effects of nicotine and the non-pharmacological or sensory aspects of smoking. The sensory aspects of smoking may include "how smoke tastes in the mouth, how it feels in the back of the throat, how it feels when inhaled, and how it smells." Ref. 13 at 2.

Nicogel, however, cannot satisfy any of the sensory needs or desires associated with smoking. The product is a clear,<sup>12</sup> odorless gel, which the product labeling instructs users to rub into their hands. *See, e.g.*, Ref. 1 at 7-8; Ref. 3 at 3, 4, 6; *see also* Ref. 20 at 1; Ref. 35 at 1. Hence, it would be readily apparent to consumers reviewing the Nicogel package and promotional materials that Nicogel does not - indeed, it cannot - provide the taste or aroma of a cigarette or smokeless tobacco product. It likewise cannot produce the sensations that smokers may experience upon placing a cigarette to their lips, or that they may feel in the mouth, throat, or lungs upon inhaling a cigarette. The physical action of rubbing one's hands together is also patently different than the repeated hand-to-mouth action or other movement (e.g., handling, puffing, inhaling) associated with drawing on a cigarette. Nicogel plainly is not made or marketed with the intent to offer product users any "satisfaction" in these areas. Likewise, Nicogel's representation that, in "less than a minute" after using the product, the user will "begin to feel like" she "just smoked" cannot be referring to any of the sensory aspects of smoking. The product's inability to furnish any of these sensory effects compels the conclusion that, when Nicogel USA claims that its product provides "cigarette satisfaction" and is a "cigarette alternative which fully satisfies your urge to smoke," the company is representing that Nicogel produces the pharmacological effects of "satisfaction" one would experience from nicotine alone. A product "will be deemed a drug for purposes of the [FD&C Act] where the labeling and promotional claims show intended uses that bring it within the drug definition." *United States v. An Article . . . Consisting of 216 Individually Cartoned Bottles, More or Less . . . Labeled in Part: "Sudden Change,"* 409 F.2d 734, 739 (2d Cir. 1969).

The product name is further evidence of Nicogel's intended use. The name blends "nico," which is a portion of the familiar word "nicotine," with "gel," in reference to the form of the product.<sup>13</sup> In the labeling, the product name appears often and in close proximity to numerous express references to cigarettes and tobacco, including "cigarette alternative," "cigarette satisfaction," "smoking satisfaction," "cigarette replacement," and "extract of tobacco." *See, e.g.*, Ref. 1 at 7-8; Ref. 3 at 3-16. Thus, use of the phrase "nico" in the product's name,<sup>14</sup> coupled with the product's claims, draws a clear connection between Nicogel and

<sup>12</sup> The product may appear to be tinted a light brown color when placed against a white background. Ref. 7 at 28.

<sup>13</sup> The visual image of the name uses black type for "nico" in contrast to white type against an oval-shaped blue background for "gel." *See, e.g.*, Ref. 8 at 9; Ref. 1 at 7. The presentation thus supplies visual cues that further distinguish the two portions of the name.

<sup>14</sup> We acknowledge that Nicogel USA has stated that the product name Nicogel is derived not from nicotine, but from the term *nicotiana tabacum*, which is the formal botanical name for the tobacco plant.

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nicotine so that consumers would reasonably infer that the product will deliver the effects of nicotine in tobacco. Cf. *United States v. Undetermined Quantities of Articles of Drug*, 145 F. Supp. 2d 692, 699-700 (D. Md. 2001) (articles marketed as street drug substitutes were "drugs" under the FD&C Act based in part on evidence that defendants used product names playing on street names for illegal street drugs).<sup>15</sup>

Finally, that Nicogel is intended to provide the pharmacological effects of nicotine is further evidenced by its dosing instructions, which are tied to how heavy a smoker the user is: "HOW DO I APPLY NICOGEL™? Nicogel couldn't be simpler to use: if you are a light smoker (<15 cigarettes per day) use 1 serving (sachet or press) and 2 servings if you are a heavy smoker (>15 cigarettes per day) . . ." Ref. 3 at 4. If the satisfaction supplied by using Nicogel were truly unrelated to the pharmacological effects of smoking and nicotine use, light and heavy smokers could presumably achieve "cigarette satisfaction" from the same dose.

Accordingly, given the evidence above, the agency concludes that Nicogel is intended to affect the structure or function of the body by delivering the same or similar

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Ref. 8 at 3; Ref. 7 at 7; Ref. 11 at 1. The company's assertion, however, speaks only to its subjective intent, and, as discussed above, we apply an objective standard in determining the intended use of a product. It is certainly reasonable for consumers to infer that the name "Nicogel," which is marketed to smokers, coupled with the claims made for the product, is a reference to the more familiar word nicotine, which is also derived from the botanical name for the tobacco plant. See Ref. 22; Ref. 23.

<sup>15</sup> In considering consumers' likely association of the product name with nicotine effects, we note that several other products associated with nicotine are also marketed with names that incorporate "nico" in the brand name. Indeed, many of the nicotine-replacement therapies that FDA has approved as drug products to aid smoking cessation, which have the express purpose of delivering nicotine to users, bear brand names (chosen by their manufacturers) that begin with "Nico-." See Nicorette gum (Ref. 24) (<http://www.nicorette.com/Nicorette.aspx>) (a gum that "provides a controlled amount of nicotine to your system" and "works as a temporary aid to help you quit smoking by reducing nicotine withdrawal symptoms until your body no longer needs nicotine."); NicoDerm and NicoDerm CQ (Ref. 25) (<http://www.nicodermcq.com/NicodermCQ.aspx>) ("a nicotine patch [that] . . . provide[s] a controlled release of nicotine for 24 hours at a slower, less intense pace than cigarettes" to "help you quit smoking by reducing nicotine withdrawal symptoms . . ."); and Nicotrol®NS and Nicotrol® Inhaler (Ref. 26) ([http://www.media.pfizer.com/files/products/ppi\\_nicotrol.pdf](http://www.media.pfizer.com/files/products/ppi_nicotrol.pdf)) (nicotine nasal spray and nicotine inhalation system "designed to help you quit smoking by reducing your urge to smoke"). The association of the phrase "nico" in the brand names for these products further supports the conclusion that consumers will interpret the name "Nicogel," presented in the context of the cigarette and smoking satisfaction references in the labeling for the product, as a claim that Nicogel users will experience the same or similar effects on the structure or function of the body as nicotine derived from smoking.

In your April 4, 2008 letter, you stated that Nicogel USA will be changing the name of the product to either "Tobaccogel" or "Baccogel." Ref. 11 at 2. This submission was untimely, as it was received almost six months after the October 9, 2007 deadline specified in FDA's Notice. Ref. 5 at 2. Moreover, the company's future plans regarding the name of its product are not relevant to our assessment of the product's status as a drug at the time it was presented for import. Finally, even if the products that are the subject of this proceeding were relabeled using either of the company's proposed names, the company has not indicated that it will make any other changes to its labeling and promotional materials to remove all of the drug claims. As discussed above, the labeling and promotional materials for Nicogel convey drug claims for the product. Therefore, merely changing the product's name would not alter our conclusion that the product is a drug based on its intended use.

pharmacological effects from nicotine that a smoker would derive from smoking a cigarette.

**B. Nicogel Appears to be a Drug Because it is Intended to Prevent, Treat, or Mitigate The Withdrawal Symptoms of Nicotine Addiction**

Nicotine addiction is a recognized disease. *See Ref. 15 at 2.* Nicotine withdrawal is itself an accepted medical condition. As noted above, the American Psychiatric Association in the *Diagnostic and Statistical Manual of Mental Disorders*, 4<sup>th</sup> edition (DSM-IV) and the World Health Organization in the *International Classification of Diseases*, 10<sup>th</sup> revision (ICD-10) both include diagnostic criteria for nicotine withdrawal, and there is compelling evidence that one reason people smoke is to alleviate the symptoms of withdrawal. *See Section I.D.* Here, the product labeling and promotional materials establish that Nicogel is intended for use in the prevention, mitigation, and treatment of the withdrawal symptoms of nicotine addiction. As a result, Nicogel appears to be a drug within the meaning of 21 U.S.C. § 321(g)(1)(B).

The promotional materials for Nicogel are aimed at nicotine-addicted tobacco users, *see, e.g.*, Ref. 6 at 2; Ref. 3 at 4, and promote the product as capable of satisfying their craving for tobacco or to alleviate other withdrawal symptoms. For instance, a question in the “Frequently Asked Questions” portion of the nicogelusa.com website has stated:

“When should I apply Nicogel?  
*Whenever you feel the need to smoke* or use tobacco products.” (emphasis added)<sup>16</sup>

The packaging for the product also claims:

“Nicogel is a revolutionary cigarette alternative which *fully satisfies your urge to smoke* as easily as rubbing a little gel on your hands. In less than a minute, Nicogel absorbs in to your skin and you’ll begin to *feel like you’ve just smoked.*” (packaging for 10-count box, 120-count box, and pump bottle) (emphasis added)

“Nicogel conveniently *satisfies your urge to smoke* while not affecting those around you.” (packaging for 10-count box, 120-count box) (emphasis added)

“As more public places become smoke-free, Nicogel conveniently *satisfies your cigarette cravings* while not affecting those around you.” (packaging for pump bottle) (emphasis added)<sup>17</sup>

As noted above, a “Frequently Asked Questions” package insert about the product also represents that Nicogel is a “cigarette replacement,” and compares Nicogel to FDA-approved nicotine replacement products that are approved for smoking cessation. *See Ref. 3 at 4* (“More often than not smoking is not permitted in the work-place, cinemas, bars, restaurants, and in-

<sup>16</sup> Ref. 20 at 5; Ref. 21 at 4; Ref. 35 at 6.

<sup>17</sup> Ref. 3 at 4, 6, 13.

flight. Nicogel™ offers a great alternative to *bridge those gaps without resorting to medicines designed for quitting (such as the slow release of patches that can fall off or the terrible taste of gums)*. Many people use medicines for this purpose even though they are not licensed for this use. *Use Nicogel™ whenever you feel the urge to smoke*" (emphasis added). Moreover, as noted previously, another question in the insert suggests that the appropriate serving size (i.e., dose) of Nicogel is based on whether the user is a light or heavy smoker. Ref. 3 at 4.

Nicogel USA's labeling and promotional materials have repeatedly touted Nicogel as a cigarette alternative when consumers are unable to smoke. Against this backdrop, the statement that "one application lasts for hours" (Ref. 1 at 7) is a particularly telling example of the product's intended use to prevent, treat, or mitigate nicotine withdrawal. As explained above, the product by its very nature is incapable of providing any non-pharmacological aspect of "satisfaction" that a cigarette might offer. Nicogel is a clear, odorless gel, to be applied to the skin; it is intended to be absorbed into the body transdermally (i.e., through the skin) without noticeable residue in seconds. The clear implication is that using Nicogel will stave off "for hours" a key symptom of nicotine withdrawal: the need/urge/craving to smoke a cigarette. Collectively, the statements and depictions in the labeling and promotional materials for the product represent that Nicogel will treat, mitigate, or prevent the withdrawal symptoms of nicotine addiction "for hours."

In sum, tobacco users smoke in large measure to sustain their addiction and to alleviate or prevent nicotine withdrawal symptoms. By touting Nicogel as "cigarette satisfaction in a hand gel," a "cigarette replacement," and a way to "fully satisf[y] your urge to smoke" that lasts "for hours," Nicogel USA has represented that using Nicogel will likewise prevent or alleviate nicotine withdrawal symptoms. Indeed, viewed as a whole, we believe that the statements and depictions used to promote Nicogel encourage consumers to use it for this purpose. We conclude that Nicogel is intended to prevent, mitigate, and treat the withdrawal symptoms of nicotine addiction. The product therefore appears to be a drug within the meaning of 21 U.S.C. § 321(g)(1)(B).

#### C. Nicogel Appears to be an Unapproved New Drug

Nicogel appears to be a "new drug" as defined by 21 U.S.C. § 321(p). If a product is a drug, then, as a matter of law, it is a "new drug" that must be approved by FDA before it can be lawfully distributed in interstate commerce, unless it is generally recognized among qualified experts as being safe and effective for the conditions prescribed, recommended, or suggested in its labeling. 21 U.S.C. §§ 321(p), 331(d), 355. "General recognition" of a drug as safe and effective must rest on a consensus among qualified experts based on adequate and well-controlled clinical trials that are published in the scientific and medical literature. See *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 629 (1973); *Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 652 (1973); *United States v. 225 Cartons, More or Less, of an Article of Drug*, 871 F.2d 409, 413 (3d Cir. 1989); *Tri-Bio Labs., Inc. v. United States*, 836 F.2d 135, 141-42 (3d Cir. 1987), cert. denied, 488 U.S. 818 (1988); *United States v. Undetermined Quantities . . . Equidantin*, 675 F.2d 994, 1000-01 (8th Cir. 1982); *Premo Pharm. Labs., Inc. v. United States*, 629 F.2d 795, 803-04 (2d Cir. 1980). As discussed above, the

labeling for Nicogel recommends and suggests that Nicogel will treat, mitigate, or prevent the withdrawal symptoms of nicotine addiction, and that it will affect the structure or function of the body by delivering the same or similar pharmacological effects from nicotine that a smoker would derive from smoking a cigarette.

The agency's search of the published scientific literature did not locate a single published study of Nicogel or nicotine hand gel for any indication. Ref. 27, 34. We are not aware of any information demonstrating that Nicogel or any hand gel containing nicotine is generally recognized as safe and effective for use under the conditions prescribed, recommended, or suggested in Nicogel's labeling. Accordingly, Nicogel is a "new drug." Because there is no approved new drug application or abbreviated new drug application in effect for the product, Nicogel appears to be an unapproved drug in violation of 21 U.S.C. § 355(a).<sup>18</sup>

### **III. Brown & Williamson Does Not Foreclose FDA's Jurisdiction Over Nicogel under the FD&C Act**

As its principal argument in response to the Notice of FDA Action - Detention, Nicogel USA argues that the Supreme Court's decision in *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000), precludes FDA's jurisdiction over "customarily marketed" tobacco products, including Nicogel.<sup>19</sup> See Ref. 6 at 1, 4-5. Nicogel USA's reliance on that decision is misplaced. In *Brown & Williamson*, the Supreme Court held that FDA exceeded its statutory authority when the agency attempted to regulate *cigarettes and smokeless tobacco products* under the FD&C Act, but expressly based its holding on Congress' enactment of an alternative regulatory scheme specifically for those particular products. The Court concluded that the existence of this alternative regulatory scheme was inconsistent with FDA's assertion that Congress intended the agency to regulate such products under the FD&C Act. *Brown & Williamson*, 529 U.S. at 142-43. But no such argument can be made for Nicogel. Congress has not established a regulatory scheme for a topically applied product such as Nicogel that in any way conflicts with FDA's jurisdiction over that product. In fact, the statute on which Nicogel USA chiefly relies, the Comprehensive Smokeless Tobacco Health Education Act, plainly does not apply to Nicogel, and Nicogel USA concedes as much. See 15 U.S.C. § 4408; Ref. 7 at 39. Accordingly, the Supreme Court's *Brown & Williamson* decision is inapposite.

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<sup>18</sup> As noted above, you have recently submitted the report of a manufacturing site audit of the Nicogel UK manufacturing facility "[t]o support further the product's tobacco origin and composition." Ref. 11 at 2; Ref. 12. You have also reported that Nicogel USA has retained a "physical-organic chemist," who is presently developing a "protocol for use in conducting an analysis of the finished tobacco gel product." Ref. 11 at 3. This information is untimely. See Ref. 5 at 2. Moreover, it is not relevant to the issue of Nicogel's status as a "drug" under the FD&C Act which, as discussed above, is determined based on the product's intended use.

<sup>19</sup> In your September 21, 2007 letter, you assert that a "customarily marketed tobacco product is a tobacco product for which the manufacturer makes no claims of therapeutic benefit." Ref. 6 at 4. As discussed below, even assuming for the sake of argument that you have correctly defined "customarily marketed" and that Nicogel were a customarily marketed tobacco product, *Brown & Williamson* does not preclude FDA's exercise of jurisdiction over the product.

A. Background

On August 28, 1996, FDA issued a final rule entitled "Regulations Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco to Protect Children and Adolescents." 61 Fed. Reg. 44396, 44418 (1996) ("Final Rule"). In its Final Rule, FDA extensively discussed the deleterious health effects of cigarette and smokeless tobacco use. Among other findings, the agency cited the fact that "more than 400,000 people die each year" from the health effects of cigarettes and smokeless tobacco products. *See* 529 U.S. at 134-35, citing 61 Fed. Reg. at 44398. FDA further determined that nicotine is a "drug" within the meaning of 21 U.S.C. § 321(g)(1)(C) and that cigarettes and smokeless tobacco products are "drug delivery devices." 61 Fed. Reg. at 44397, 44402. The Final Rule imposed numerous restrictions on the sale and marketing of cigarettes and smokeless tobacco products, with a goal of reducing demand for and access to such products by minors. *Id.* at 44397, 44399, 44402.

In its Final Rule, FDA determined that cigarettes and smokeless tobacco are intended to affect the structure and function of the body because nicotine "has significant pharmacological effects" on the body. 61 Fed. Reg. at 44629-31. Specifically, FDA found that nicotine "exerts psychoactive, or mood-altering, effects on the brain" that cause and sustain addiction, have both tranquilizing and stimulating effects, and control weight. *Id.* at 44631-32. Moreover, the agency concluded that the effects of nicotine on the body are widely known to consumers. *Id.* at 44630. Indeed, FDA reviewed numerous statements by the tobacco industry demonstrating that cigarettes were specifically designed to provide pharmacologically active doses of nicotine to the users, the products were intended to affect the structure and function of the body, and thus were subject to FDA regulation. *Id.* at 44849-50. The agency, therefore, asserted that it had jurisdiction under the FD&C Act to regulate cigarettes and smokeless tobacco products. *Id.* at 44628-29.

A group of tobacco manufacturers, retailers, and advertisers challenged the regulations. *See Coyne Beahm, Inc. v. FDA*, 966 F. Supp. 1374 (M.D.N.C. 1997). After the district court upheld FDA's jurisdiction to issue the rule, the Court of Appeals for the Fourth Circuit reversed, holding that Congress had not granted FDA jurisdiction to regulate cigarettes and smokeless tobacco products. *See FDA v. Brown & Williamson Tobacco Corp.*, 153 F.3d 155 (4th Cir. 1998).

The Supreme Court affirmed the decision of the Court of Appeals. 529 U.S. at 126. In a five-four decision, the Court held that FDA exceeded its statutory authority in promulgating the Final Rule. The Court held that although the problem of nicotine addiction and tobacco use were among the most "troubling public health problems facing our Nation," the regulatory scheme of the FD&C Act and the tobacco-specific legislation enacted by Congress subsequent to the FD&C Act precluded FDA's assertion of jurisdiction over the products covered by such legislation. *Id.* at 125-26. Although FDA's judgments about the scope of its jurisdiction are entitled to deference under *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), because Congress "clearly" and "unambiguously" expressed its intent that FDA not regulate cigarettes and smokeless tobacco products, the Court concluded that FDA's attempt to exercise jurisdiction over those products could not stand. *Brown & Williamson*, 529 U.S. at 126.

The Court expressly based its opinion on the fact that Congress had established an alternative regulatory system for cigarettes and smokeless tobacco products. *Id.* at 137-39, 142-43, 155-56. In fact, the Court stated that in order to assess whether FDA had jurisdiction over cigarettes and smokeless tobacco products, the Court was required to "consider in greater detail the tobacco-specific legislation that Congress has enacted over the past 35 years." *Id.* at 143. During that time period, Congress had enacted several statutes specifically addressing the problem of cigarette and smokeless tobacco use. *See id.* at 143-44. The Court extensively discussed both the Federal Cigarette Labeling and Advertising Act (FCLAA), Pub. L. No. 89-92, 15 U.S.C. §§ 1331 *et seq.*, and the Comprehensive Smokeless Tobacco Health Education Act (CSTHEA), Pub. L. No. 98-474 (1986), 15 U.S.C. §§ 4401 *et seq.* Among other provisions, those statutes provided that cigarettes and smokeless tobacco products must bear certain warnings for users. *Id.* §§ 1331, 4402. The statutes also prohibited the advertisement of tobacco products through "any medium of electronic communication" subject to regulation by the Federal Communications Commission. *Id.* §§ 1335, 4402(f).

The Court noted that the very products that FDA sought to regulate under the FD&C Act had been specifically addressed in the FCLAA and CSTHEA. In the Court's view, those statutes demonstrated that Congress had made a specific choice to allow cigarettes and smokeless tobacco products to be legally marketed, subject to certain disclosures and obligations; however, were FDA to regulate cigarettes and smokeless tobacco products, the agency would be forced to ban them because they could not meet the FD&C Act's safety, effectiveness, and labeling requirements. *Brown & Williamson*, 529 U.S. at 142-43. Because "Congress ... has foreclosed the removal of tobacco products from the market," the Court stated, "a ban would contradict Congress' clear intent as expressed in its more recent, tobacco-specific legislation," including FCLAA and CSTHEA *Id.* at 137, 143. The fact that Congress had enacted an alternative regulatory system specifically for cigarettes and smokeless tobacco conflicted with FDA's assertion that it could regulate such products under the FD&C Act. *Id.* at 149, 155-57. According to the Court, "[i]f they cannot be used safely for any therapeutic purpose, and yet they cannot be banned, they simply do not fit." *Id.* at 143.

The Court concluded, therefore, that cigarettes and smokeless tobacco as customarily marketed do not fall within FDA's jurisdiction.

**B. Brown & Williamson Has No Application to Nicogel**

As noted, the *Brown & Williamson* decision was limited to the specific products at issue in that case. Neither the holding nor the reasoning of the case extends to Nicogel, a gel intended to be rubbed on the skin and absorbed transdermally.

First, the express scope of *Brown & Williamson* clearly does not encompass Nicogel. FDA's Final Rule was directed at traditional tobacco products, including cigarettes and smokeless tobacco products intended to be placed in the oral cavity. *See* 61 Fed. Reg. at 44616. Nicogel USA has characterized Nicogel as an innovative product, unlike any previously marketed tobacco product in the United States. Ref. 7 at 7; Ref. 8 at 3. FDA's Final Rule did

not encompass products analogous to Nicogel,<sup>20</sup> and thus the Court's decision invalidating that rule is not applicable to Nicogel.

Second, even assuming that Nicogel is, as you contend, a customarily marketed tobacco product, a point we do not concede (see section II.B. above), unlike the products at issue in *Brown & Williamson*, there are no statutes regulating Nicogel that would conflict with the agency's exercise of jurisdiction. Congress has never passed legislation indicating that it intends a topically applied product such as Nicogel to remain on the market or to be free of FDA regulation. In fact, the statute primarily cited by Nicogel USA is the CSTHEA, which does not apply to Nicogel, as Nicogel USA concedes. *See Ref. 7 at 39* (import hearing transcript) (statement by Mr. Branding) (Nicogel "does not technically fit the definition of smokeless tobacco as it's currently written . . .").

The CSTHEA applies to smokeless tobacco products, which are expressly defined as "any finely cut, ground, powdered, or leaf tobacco that is intended to be placed in the oral cavity." 15 U.S.C. § 4408. Nicogel is not comprised of cut, ground, or powdered tobacco. Rather, by the company's own description, Nicogel is "made using liquefied tobacco." *See Ref. 6 at 2; Ref. 7 at 7* ("It is liquified tobacco in a water-soluble gel with the plant fiber and the stem removed"). The product is manufactured by removing and discarding the fiber of the tobacco plant. Ref. 6 at 2. The fact that plant material at a microscopic level may persist in the product, *see Ref. 16 at 3*, appears to be only an unintended consequence of the company's manufacturing process. *See Ref. 7 at 15*. FDA does not believe that these trace amounts of plant material in Nicogel meet the definition of finely cut, ground or powdered tobacco within the meaning of the CSTHEA. *See 15 U.S.C. § 4408*. But even if the product were considered to be comprised of cut, ground, or powdered tobacco, the product is clearly not "intended to be placed in the oral cavity," as is required by the CSTHEA. *Id.* Instead, Nicogel is expressly marketed as a hand gel. It is intended to be rubbed on the skin and absorbed transdermally into the bloodstream. *See Ref. 1 at 8; Ref. 3 at 4, 6* (product directions). For these reasons, the product clearly falls outside the bounds of the CSTHEA.

By its terms, therefore, the CSTHEA cannot and does not apply to Nicogel, and Nicogel USA concedes this point. *See Ref. 7 at 39; see also Ref. 6 at 5-7*. Instead, Nicogel USA argues that the definition of smokeless tobacco in the CSTHEA should be "expanded to include current innovative, topically applied smokeless tobacco products such as Nicogel." *See Ref. 6 at 6*. The company asserts that "Nicogel should be subject solely to the [CSTHEA]," and not the FD&C Act. *Id.* But whether Nicogel *should* be subject to the CSTHEA is a matter for Congress, not FDA. Cf. *United States v. 9/1 Kg. Containers . . . of an Article of Drug*, 854 F.2d 173, 179 (7th

<sup>20</sup> Although the Final Rule occasionally used the general term "tobacco products," the scope of the rule was expressly limited to cigarettes and smokeless tobacco products. *See 61 Fed. Reg. at 44616* ("This part sets out the restrictions under the [FD&C Act] on the sale, distribution, and use of cigarettes and smokeless tobacco that contain nicotine."). The rule defined "cigarettes" as "any product which contains nicotine, is intended to be burned under ordinary conditions of use, and consists of . . . any roll of tobacco . . ." and "smokeless tobacco" as "any product that consists of cut, ground, powdered, or leaf tobacco that contains nicotine and that is intended to be placed in the oral cavity." *Id.* FDA's Final Rule, therefore, would not have applied to Nicogel.

Cir. 1988) ("Judge's role is to decipher and enforce the existing [statutory] scheme, whatever they think of its wisdom."). The fact is that Nicogel is *not* subject to the CSTHEA, and there is, therefore, no conflict with FDA asserting jurisdiction over the product.

Nicogel USA also urges FDA to speculate that had Nicogel, or some similar product, been on the market when Congress passed the CSTHEA, it would have included that product in the CSTHEA. The company claims that Nicogel "fits within Congress' express rationale" in enacting the CSTHEA and, therefore, FDA should refrain from exercising its jurisdiction. *See* Ref. 6 at 7. Even if this were an appropriate basis for FDA to decline jurisdiction, the agency would have no basis for doing so here. In the CSTHEA, Congress established a regulatory scheme for a specific type of product: *orally applied* tobacco products *containing finely cut, ground, powdered, or leaf tobacco*. Nicogel is not such a product. Congress made the decision that smokeless tobacco products (as defined in the statute) should remain on the market, so long as specific warnings were provided and manufacturers complied with other elements of the law. But Congress has made no such determination with respect to Nicogel, which, as a topically applied product, may present different health and safety concerns and other public policy considerations than do the smokeless tobacco products that fall within the CSTHEA. Transdermal absorption of tobacco constituents, including nicotine, may have very different health effects than *oral administration*. Moreover, Nicogel contains a large (42%) concentration of DGME, a chemical specifically added to facilitate the *absorption* of Nicogel into the body. *See* Ref. 16 at 1-2; Ref. 7 at 16 (import hearing transcript) (Bill Whalen stating that DGME is added to Nicogel to facilitate absorption). Accordingly, there is no reason to speculate that Congress would have included Nicogel in the CSTHEA.

FDA concludes, therefore, that the *Brown & Williamson* decision is not applicable to Nicogel and that the case does not undermine the agency's assertion of jurisdiction here.

**C. Jurisdiction over Nicogel is Not Foreclosed by FDA's Past Regulation of Tobacco and Nicotine**

Nicogel USA states that FDA historically has not asserted jurisdiction over tobacco products and claims that the agency is thus "obliged to decline jurisdiction over Nicogel." *See* Ref. 6 at 4. We disagree. The agency asserted jurisdiction over cigarettes and smokeless tobacco products in its 1996 Final Rule, as discussed above. Although the Supreme Court concluded that jurisdiction over traditional tobacco products was foreclosed by other Congressional acts, the *Brown & Williamson* decision did not invalidate the agency's scientific and policy conclusions about tobacco products. Even ignoring the 1996 Final Rule, all of the statements cited by Nicogel USA concern traditional tobacco products, such as cigarettes, cigars, and smokeless tobacco intended to be placed in the oral cavity. *See* Ref. 6 at 4. Nicogel USA has produced no evidence that FDA has ever disclaimed jurisdiction over topically applied products containing nicotine.

Nicogel USA also argues that because the agency concluded that it did not have jurisdiction over Ariva, a smokeless tobacco product, it should decline to regulate Nicogel. *See* Ref. 6 at 3. Ariva is a tablet form of tobacco made from compressed powdered tobacco that is

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intended to be placed in the oral cavity. See Ref. 6 Exh. E at 2-3. FDA received a citizen petition asking the agency to, among other things, regulate Ariva as a drug. Because Ariva met the definition of smokeless tobacco in the CSTHEA and appeared to be a “customarily marketed” tobacco product under *Brown & Williamson*, FDA denied the petitioners’ request to regulate the product. *Id.* at 3. As discussed, Nicogel is not a smokeless tobacco product as defined in the CSTHEA, and thus the Ariva decision provides no precedent for FDA’s action here.

In contrast, FDA has asserted jurisdiction over products analogous to Nicogel. For example, in 1987, the agency asserted jurisdiction over a nicotine product marketed as “Favor Smokeless Cigarettes.” See Ref. 28. The Favor product was comprised of a plastic tube containing a plug impregnated with nicotine solution that allowed the user to inhale nicotine vapor. The product was marketed as providing “cigarette satisfaction without smoke.” See, e.g., Ref. 29 at 1. The marketing materials also claimed that Favor could be used “in places where smoking is not permitted or just doesn’t fit in” and could provide “full tobacco pleasure and satisfaction.” See Ref. 29 at 3. Like the detained Nicogel, Favor made no claims regarding smoking cessation, and in its Form 10-K (annual report) filed with the Securities and Exchange Commission in 1984, the company claimed that it would “market the Smokeless Cigarette as a pleasurable nicotine product and not as a product intended to discourage or reduce smoking or to have therapeutic benefits.” See Ref. 30 at 2, 4-5. Favor would not have met the definition of either a cigarette or a smokeless tobacco product under the FDA’s Final Rule, nor would it qualify under either FCLAA or the CSTHEA.

Accordingly, FDA’s regulation of Nicogel is not foreclosed by the agency’s regulatory history.

#### **IV. The Tariff Classification for Nicogel is Not Relevant to FDA’s Jurisdiction**

Nicogel USA cites the “international community’s” classification of Nicogel as a tobacco product “for importation and Customs purposes” in support of its position that Nicogel should be considered a tobacco product that is outside FDA’s jurisdiction. Ref. 6 at 7. In particular, Nicogel USA states that under the Harmonized Commodity Description and Coding System (“Harmonized System”), Nicogel has been classified as a “tobacco product.” The company asserts that Nicogel’s harmonized tariff code is 2403.99.20.90<sup>21</sup> and contends that because the United States is a “Contracting Party” to the International Convention that established the Harmonized System, “FDA is obliged to accept Nicogel’s classification as a tobacco product,” and should therefore “refrain from any regulation of NicoGel under the [FD&C Act] . . . .” Ref. 6 at 8. For the reasons discussed below, we do not agree that the tariff classification for Nicogel has any bearing on whether that product is subject to regulation under the FD&C Act.

<sup>21</sup> Chapter 24 of the Harmonized System is for “Tobacco and manufactured tobacco substitutes.” Ref. 31. Heading 2403 is “Other manufactured tobacco and manufactured tobacco substitutes; ‘homogenized’ or ‘reconstituted’ tobacco; tobacco extracts and essences.” Subheading 99 is “Other” and its subheading 20 is “[p]repared for marketing to the ultimate consumer in the identical form and package in which it is imported.” See Ref. 31.

The Harmonized System is an internationally standardized system of names and numbers for classifying traded products that was developed by the World Customs Organization, an independent intergovernmental organization focused on Customs matters. *See Ref. 32 at 1.* It reflects the “culmination of an international effort to create a single commodity coding system (tariff classification system) across nations.” *Cummins Inc. v. United States*, 377 F. Supp. 2d 1365, 1368 (Ct. Int’l Trade 2005), *aff’d* 454 F.3d 1361 (Fed. Cir. 2006). Under the Harmonized System, products are defined to a certain level of specificity (the six-digit level) at the international level, and each nation can establish further subdivisions beyond that level. *Id.*

The Harmonized System has a relatively narrow and altogether different purpose than the FD&C Act. It is used by more than 120 countries to facilitate the assessment of tariffs and for the collection of trade statistics. Ref. 6 Exh. V; Ref. 6 Exh. U at 4 (Preamble to the International Convention) (explaining that parties to the Harmonized System desire to, for example, “facilitate international trade”; “reduce the expense incurred by redescribing, reclassifying and recoding goods as they move from one classification system to another in the course of international trade . . . ”; and “promote as close a correlation as possible between import and export trade statistics and production statistics.”). The Harmonized System’s “essential purposes” include “(1) facilitat[ing] the computation of trade statistics and (2) establish[ing] a standard product descriptor to provide a basis for trade concessions and predictability for international commerce.” *Cummins*, 377 F. Supp. 2d at 1368. In stark contrast, the FD&C Act’s core purpose is promoting and protecting the public health. *See* 21 U.S.C. § 393(b); *United States v. An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 798 (1969).

Contrary to Nicogel USA’s suggestion, the United States’ obligations as a Contracting Party<sup>22</sup> do not require it to apply the Harmonized System’s classifications when interpreting and applying the FD&C Act (or any other statute). Indeed, the International Convention includes a narrow list of “Obligations of Contracting Parties.” *See* Ref. 6 Exh. U at 7. They include (i) using “Customs tariff and statistical nomenclatures” that are “in conformity with the Harmonized System,” including “the headings and subheadings of the Harmonized System without addition or modification, together with their related numerical codes,” applying “the General Rules for the interpretation of the Harmonized System and all the Section, Chapter and Subheading Notes,” and following the “numerical sequence of the Harmonized System”; and (ii) making publicly available the Contracting Party’s “import and export trade statistics in conformity with the six-digit codes of the Harmonized System.” *Id.* Nothing in the International Convention suggests that the Harmonized System is to be used to inform the interpretations of the member countries’ public health and safety statutes. *See id. passim.*

Nicogel USA has not cited any authority in support of its assertion that FDA must classify Nicogel, for regulatory purposes, in a manner that is consistent with that product’s classification under the Harmonized System or, for that matter, any precedent where a product’s classification under the Harmonized System was considered in determining its status under the FD&C Act. Moreover, the United States Court of International Trade has repeatedly and

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<sup>22</sup> The United States became a Contracting Party in 1988. *See* 19 U.S.C. § 3003(a). The tariff laws of the United States are generally codified in the Harmonized Tariff Schedule of the United States. *Cummins*, 377 F. Supp. 2d at 1368.

consistently rejected the notion that FDA's classification of products dictates how a product should be classified under the Harmonized System. *See, e.g., Bestfoods v. United States*, 342 F. Supp. 2d 1312, 1316 (Ct. Int'l Trade 2004) (FDA standards of identity are "helpful" but "not controlling" in determining classification under the Harmonized System) (internal citation omitted); *Nestle Refrigerated Food Co. v. United States*, 18 C.I.T. 661, 665-66, 1994 Ct. Int'l Trade LEXIS 141 (Ct. Int'l Trade 1994) ("The government errs in arguing that if the Malpica product satisfies FDA standards for canned tomatoes it therefore must be classified as tomatoes in pieces . . . [I]t is well established that *statutes, regulations, and administrative interpretations not related to tariff purposes are not determinative of customs classification disputes.*"") (emphasis added); *Cf. Marubeni Am. Corp. v. United States*, 35 F.3d 530, 537 (Fed. Cir. 1994) ("non-tariff regulations (NHTSA and EPA regulations) are not dispositive for purposes of tariff classification."); *Inabata Specialty Chemicals v. United States*, 366 F. Supp. 2d 1358, 1363 (Ct. Intl. Trade 2005) ("Whatever FDA labeling or marketing regulation restricts the manner in which [chondroitin sulfate] preparations are sold does not control for tariff purposes. Further, definitions and classifications of other agencies do not control tariff classifications.") (internal citations omitted), *appeal dismissed*, 143 Fed. Appx. 358 (Fed. Cir. 2005).

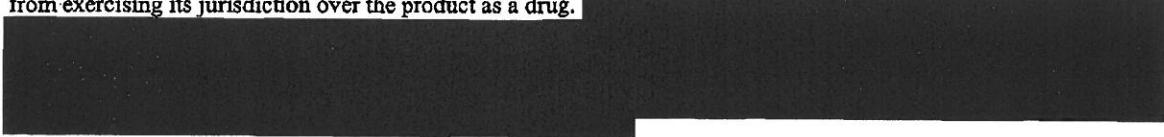
In short, Nicogel's nomenclature under the Harmonized System has no bearing on its regulatory status under the FD&C Act.<sup>23</sup>

#### V. Conclusion

For the reasons set forth above, Nicogel appears to be an unapproved new drug, and FDA intends to refuse admission to Entry No. 112-7769262-2 pursuant to 21 U.S.C. § 381(a)(3). In your September 21st letter, you stated that if FDA concludes there are statements or other representations "over which the company has control and is presently unaware" that might "comprise or imply a health, smoking cessation, nicotine replacement or any other drug claim," Nicogel USA requests authorization to relabel the detained product or to perform other action to bring it into compliance with the FD&C Act or render it other than a product regulated by FDA. Ref. 6 at 1.

The owner or consignee of the detained shipment can submit an application for authorization to relabel or perform other action to bring an entry into compliance with the FD&C Act or render it other than a food, drug, device, or cosmetic. *See* 21 C.F.R. §§ 1.94, 1.95. As discussed above, Nicogel USA has not submitted documentation showing that it is the owner or consignee of the detained entry. FDA will defer issuing a notice of refusal for Entry No. 112-

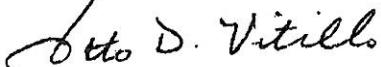
<sup>23</sup> Nicogel USA also claims that some states tax Nicogel as a tobacco product and that the United States Department of Treasury's Alcohol and Tobacco Tax and Trade Bureau ("TTB") is currently reviewing Nicogel for taxation as a tobacco product. Ref. 6 at 2. Even if some states or the TTB were to classify the product as a tobacco product, the classification of Nicogel under other statutes for *taxation* purposes would not obligate FDA to refrain from exercising its jurisdiction over the product as a drug.



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7769262-2 until the date specified in the accompanying Notice of FDA Action in order to provide the owner or consignee with an opportunity to submit a proposal to relabel or otherwise bring the detained products into compliance. If such a proposal is submitted by Nicogel USA, it should also include documentation to support Nicogel USA's assertion that it is the owner or consignee of the import entry.

Sincerely,



Otto D. Vitillo  
District Director  
New York District Office

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