

2022 MRTP Annual Report

CATEGORY: SNUS

BRAND: GENERAL SNUS

November 2021 – October 2022


Appendix 2A (4)

Direct Mail / Email / Facebook / POS / Packaging


GENERAL SNUS SOCIAL MEDIA

General Snus Nov. 2021 Facebook




11/5/21

 **General Snus**
2h · 🌟


Fall is the pinnacle for many fans who love TV sports. But with your favorite flavor of General in your pocket, you don't have to spend fall on the sidelines.



WARNING: This product is not a safe alternative to cigarettes.

 Like  Comment  Share

11/9/21


 **General Snus**
2h · 🌟

We have a winner! 1st place goes to MINT. The victorious classic edged out Original.




2nd – Original. No school like the old school.

3rd – Wintergreen. The perennial favorite.


4th – White. Those who know, know.



WARNING: This product is not a safe alternative to cigarettes.




 Like  Comment  Share

11/10/21




 **General Snus**
2h · 🌟


As avid outdoor adventurers, we can't help but be a little sad the colorful fall leaves are leaving.

Before they go, we want to know—which fall foliage is your favorite?

 **A. MAPLE**  **B. ASPEN**  **C. SUMAC**


WARNING: This product is not a safe alternative to cigarettes.

 Like  Comment  Share

See file:  11-5-21_GEN_Social_Sports.mp4

General Snus Nov. 2021 Facebook

11/13/21



General Snus

2h · 🌐

...

Today is [#WorldKindnessDay](#). So, if there was ever a day to lighten up and share your snus, this is it. (Back to normal tomorrow! 😊)




WARNING: This product is not a safe alternative to cigarettes.

👍 Like

💬 Comment

➦ Share

11/14/21




General Snus

2h · 🌐

...

When it comes to quality, nature has the highest standards of all. That's why we work with ingredients derived from nature to ensure the highest quality tobacco experience possible.

Learn more about what goes into making the Original Swedish Snus at [GeneralSnus.com/OurProcess](#)




WARNING: This product is not a safe alternative to cigarettes.

👍 Like

💬 Comment

➦ Share

See file:  11-14-21_GEN_FB Social_MeaningfulMotion.mp4



General Snus Nov. 2021 Facebook

11/16/21



General Snus
Published by Rachel Kuerz · November 16, 2021 ·

Looking for a good read? On Elevated Stories, we're into the Swedish sport Bandy — a beloved blend of ice hockey and field sports. Check out our latest article here:
<https://www.generalsnus.com/ElevatedStories/Bandy/>



WARNING: This product is not a safe alternative to cigarettes.

11/19/21



WHAT KIND OF BOTTLE
WILL YOU BE SHARING
THIS HOLIDAY?

FAVORITE WINE TOP-SHELF LIQUOR

WARNING: This product is not a safe alternative to cigarettes.

FB Story



General Snus
2h ·

What kind of bottle will you be sharing this holiday?




WARNING: This product is not a safe alternative to cigarettes.

Like Comment Share

FB Post

General Snus Nov. 2021 Facebook

11/23/21




General Snus

2h · 🌐

There's one debate we all have a stake in: Thanksgiving's best side dishes.

So, we want to know—which side do you prefer at Thanksgiving?




WARNING: This product is not a safe alternative to cigarettes.

👍 Like

💬 Comment

➦ Share

11/26/21



General Snus

2h · 🌐

What did everyone do after Thanksgiving dinner this year? Did you start any new traditions?



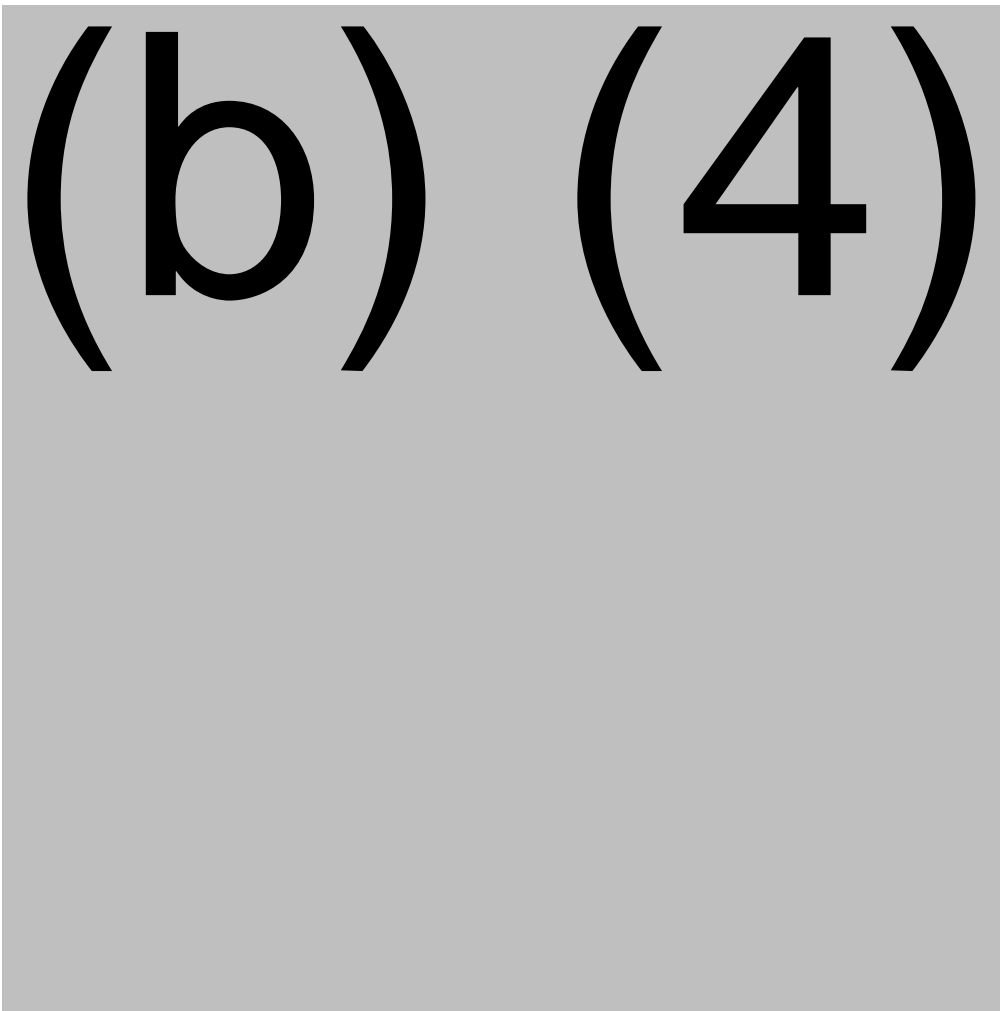
WARNING: This product is not a safe alternative to cigarettes.

👍 Like



💬 Comment

➦ Share


General Snus Nov. 2021 Facebook






11/30/21

 **General Snus**
2h · 

The first snow of autumn has a complex beauty like no other. Just like General Snus White: a flavor like no other.



WARNING: This product is not a safe alternative to cigarettes.

 Like  Comment  Share

General Snus Dec. 2021 Facebook

12/3/21



General Snus

2h · 🌐

...

Pairs perfectly with a crisp and fresh December day.




WARNING: This product is not a safe alternative to cigarettes.

👍 Like

💬 Comment

➦ Share

12/4/21




General Snus

Published by Rachel Kuerz · December 4, 2021 · 🌐

...

Here's our holiday playlist. Did we miss any of your favorites?



WARNING: This product is not a safe alternative to cigarettes.

12/7/21



General Snus

2h · 🌐

...

Long December drive getting to you? Maybe it's time to pull over for a fresh can of General for the ride. 😊



WARNING: This product is not a safe alternative to cigarettes.

👍 Like

💬 Comment

➦ Share

12/9/21



General Snus

2h · 🌐

...

Nature is the ultimate chiller.




WARNING: This product is not a safe alternative to cigarettes.

👍 Like

💬 Comment


➦ Share

See file:


 12-09-21_GEN_FB Chill.mp4

General Snus Dec. 2021 Facebook

12/10/21

General Snus
2h · 🌐

There are many special holiday traditions. What do you find most interesting?



KWANZAA **CHINESE NEW YEAR** **HANUKKAH**

General

WARNING: This product is not a safe alternative to cigarettes.

👍 Like

💬 Comment

➦ Share

12/14/21

General Snus
2h · 🌐

You'll probably want to save this one for later! Check out the full recipes for these holiday cocktails at [\[URL\]](#).



ENJOY OUR Winter COCKTAIL MENU

CHERRY BRANDY OLD FASHIONED
PAIRS WELL WITH WINTERGREEN & YOUR FAVORITE TUNES

BUTTERED APPLE CIDER
SO RELAXING WITH ORIGINAL & OLD FRIENDS

HOT GINGER TODDY
GOES NATURALLY WITH MINT & A BOASTING FIRE

PEPPERMINT WHITE RUSSIAN
ALONG WITH WHITE, ANYTHING FEELS RIGHT

HOT SPICED SANGRIA
PERFECT WITH COOL MINT & WARM CONVERSATION


WARNING: This product is not a safe alternative to cigarettes.

👍 Like

💬 Comment

➦ Share

See file:

 12-14-21_GEN_FB Cocktails.mp4

12/16/21

General Snus
2h · 🌐

Remember to collect your belongings. ✈️




WARNING: This product is not a safe alternative to cigarettes.

👍 Like

💬 Comment

➦ Share

See file:

 12-16-21_GEN_FB AirportSecurity.mp4

General Snus Dec. 2021 Facebook

12/21/21

General Snus
2h · 🌐

Tag a friend who knows “Yippee-ki-yay...” means “Happy Holidays.”




WARNING: This product is not a safe alternative to cigarettes.

👍 Like

💬 Comment


➦ Share

12/23/21

General Snus
2h · 🌐

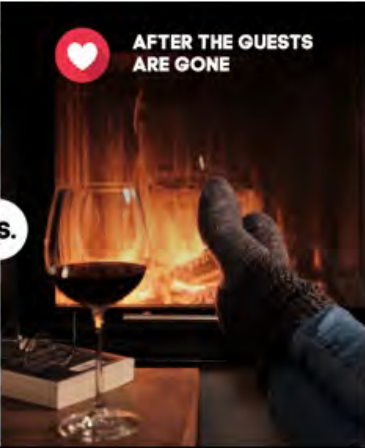
When does General Snus taste best?

AFTER THE PRESENTS ARE WRAPPED



vs.

AFTER THE GUESTS ARE GONE




WARNING: This product is not a safe alternative to cigarettes.

👍 Like


💬 Comment

➦ Share

12/24/21

General Snus
2h · 🌐

Santa’s helpers need treats, too.



WARNING: This product is not a safe alternative to cigarettes.

👍 Like

💬 Comment

➦ Share


Swedish Match

Swedish Match PMTA MRTP Annual Rpt 2022 Page 523 of 763

10

General Snus Dec. 2021 Facebook

12/25/21

General Snus
2h · 🌟

...And to all a good night!




WARNING: This product is not a safe alternative to cigarettes.

👍 Like


💬 Comment

➦ Share

12/28/21

General Snus
2h · 🌟

Solitude and quiet. The gift you give yourself.




WARNING: This product is not a safe alternative to cigarettes.

👍 Like


💬 Comment

➦ Share

12/30/21

General Snus
2h · 🌟

Finish this statement. This year I will...



WARNING: This product is not a safe alternative to cigarettes.

👍 Like

💬 Comment

➦ Share

Q1 '22 General Snus Facebook Cover Image



General Snus January '22 Facebook Posts

1-1-22



General Snus

2h · 🌐

Happy New Year from the Original Swedish Snus!



WARNING: Smokeless tobacco is addictive.

 Like

 Comment

 Share

1-7-22



General Snus

2h · 🌐

We fixed America's Top 3 New Year's Resolutions 😊




WARNING: Smokeless tobacco is addictive.

 Like

 Comment

 Share

See FB media file:

 01-07-22_GEN FB WeFixedIt.mp4

General Snus January '22 Facebook Posts

1/9/22



See FB media file:

01-9-22_GEN FB IfYouHaveAGift_Uselt.mp4

1/11/22



See FB media file:

01-11-22_GEN FB_MRTP_Explainer_Final.mp4

1/14/22



General Snus January '22 Facebook Posts

1/17/22

 **General Snus**
2h · 🌐

Today, America celebrates a man who challenged our country to elevate all of its people—no matter their color, class or creed. Did you know, in 1964, Dr. Martin Luther King Jr. accepted the Nobel Peace Prize, an award endowed by **Swedish** inventor Alfred Nobel?



WARNING: Smokeless tobacco is addictive.

👍 Like 💬 Comment ➦ Share

1/18/22

 **General Snus**
2h · 🌐

General Snus, yes. But coffee first. How do you take your morning coffee? Reply with a photo of your cup, mug or thermos!




WARNING: Smokeless tobacco is addictive.

👍 Like 💬 Comment ➦ Share

General Snus January '22 Facebook Posts

1/20/22



General Snus

2h · 🔒

Fika is the Swedish custom of taking a daily break with friends and coworkers—over toasty drinks and tasty pastries—to talk and relax. Tag someone (21+) who's the perfect fika friend.

A DELUXE, HIGHLY SOCIAL COFFEE BREAK

FIKA

/FEE-KA/




WARNING: Smokeless tobacco is addictive.

Like

Comment

Share


1/21/22



General Snus

2h · 🔒


It's the perfect time to think about ways to elevate the new year. So, General Snus has created a Bucket List Calendar to help. Check these great buckets! [\[Links to Elevated Stories\]](#).



1

DO A POLAR BEAR PLUNGE

1



WARNING: Smokeless tobacco is addictive.


Like

Comment

Share


General Snus January '22 Facebook Posts


1/26/22



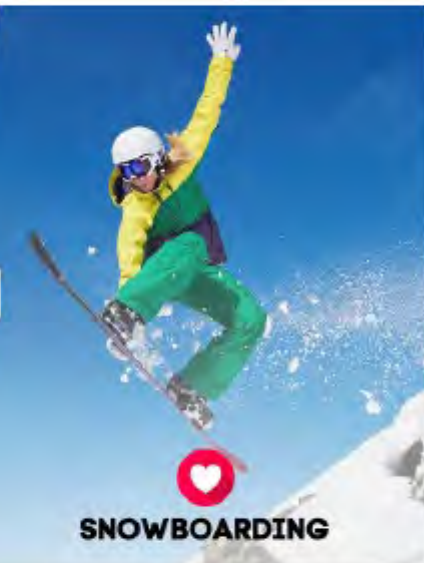
General Snus
2h · 🌐


The king of the mountain is...







SKIING

VS.




SNOWBOARDING

WARNING: Smokeless tobacco is addictive.

 Like  Comment  Share

1/28/22



General Snus
2h · 🌐

Interesting fact—in Sweden, 13.6% of people use snus daily. 😊 That's 1.4 million smart Swedes!




SWEDEN *General*

WARNING: Smokeless tobacco is addictive.

 Like  Comment  Share

See FB media file:

 01-28-22_GEN FB Social_InterestingFact.mp4

General Snus February '22 Facebook Posts

2/2/22



Perfection isn't achieved by "finishing touches." It starts from the ground up — literally, in the case of General Snus. Everything from soil temperature to nutrient content to the position of each tobacco leaf is painstakingly monitored to ensure every plant enjoys optimum growing conditions.

The result? A tobacco experience that's superior on a cellular level.



2/4/22



Enjoy a cool touch of mint.



See FB media file:

02-4-22_Gen FB WithAFlavor.mp4



General Snus February '22 Facebook Posts

2/8/22

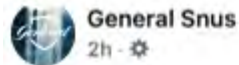


The lengths we go to...



WARNING: Smokeless tobacco is addictive.

2/11/22



Goes with *whatever* situation you find yourself in during Valentine's weekend



WARNING: Smokeless tobacco is addictive.

Directions: Muddle cane sugar, lime juice and all but 2 of the raspberries in a shaker. Add rum. Add ice to above the level of the liquid. Shake. Strain into rocks glass over large ice cubes. Garnish with mint leaves, lime wedge and 2 raspberries.

General Snus February '22 Facebook Posts

2/13/22



See FB media file:

02-13-22_GEN FB TheBigGame.mp4

Swedish Match

2/15/22



2/17/22



General Snus February '22 Facebook Posts

2/18/22



General Snus
2h · 🌐

You asked, and we heard you. Stay tuned here and on [GeneralSnus.com](https://www.generalsnus.com), we've got a big announcement coming in these next few weeks!



SOMETHING *Chill* IS COMING...

WARNING: Smokeless tobacco is addictive.

2/23/22



General Snus
2h · 🌐

Do your own thing. Be an Original.



General

WARNING: Smokeless tobacco is addictive.

 Like  Comment  Share

2/28/22




General Snus
2h · 🌐

When it's bitterly cold outside, but everybody is still planning to hang out, you're going to need indoor options.



WARNING: Smokeless tobacco is addictive.

See FB media file:

 02-28-22_GEN FB TheGreatIndoors.mp4

General Snus Facebook February cover photo



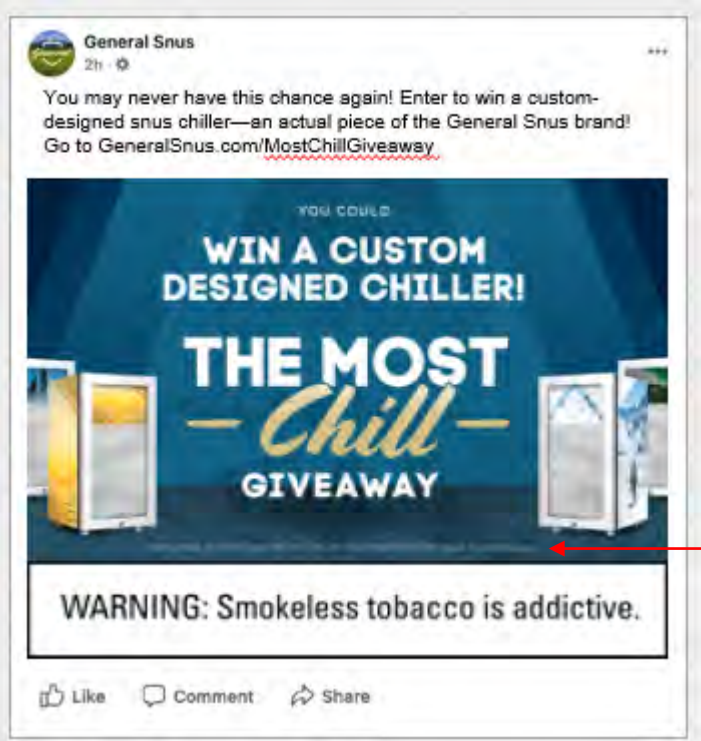
General Snus Facebook March – May 27 cover photo



NoPurchNec. 50 US/DC (excl. MA, MI & VA). 21+. Ends 11AM ET 5/27/22. Rules: GeneralSnus.com

General Snus March '22 Facebook Posts

3-1-22



See FB media file:

03-1-22_GEN FB TMC Social_Announcement.mp4

3-4-22




General Snus March '22 Facebook Posts

3-9-22



See FB media file:

 03-9-22_GEN FB Found Snus.mp4

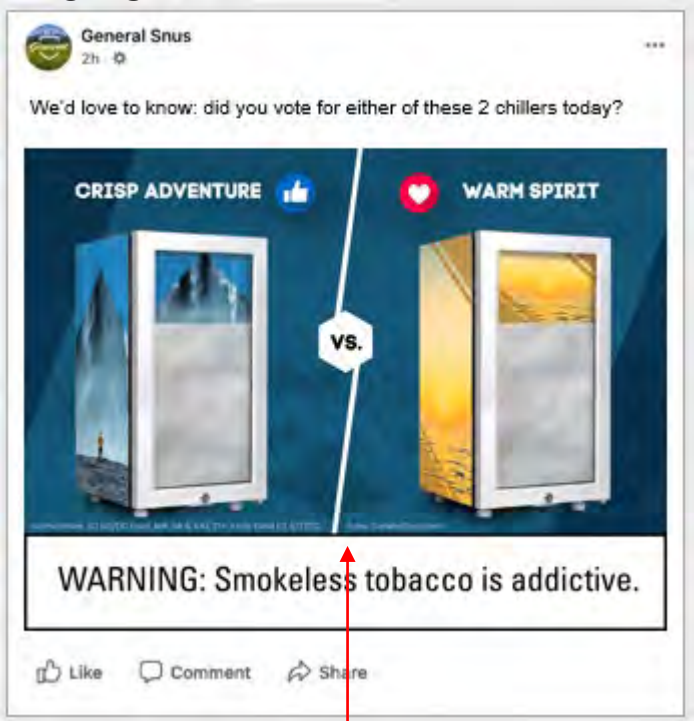


3-11-22



General Snus March '22 Facebook Posts

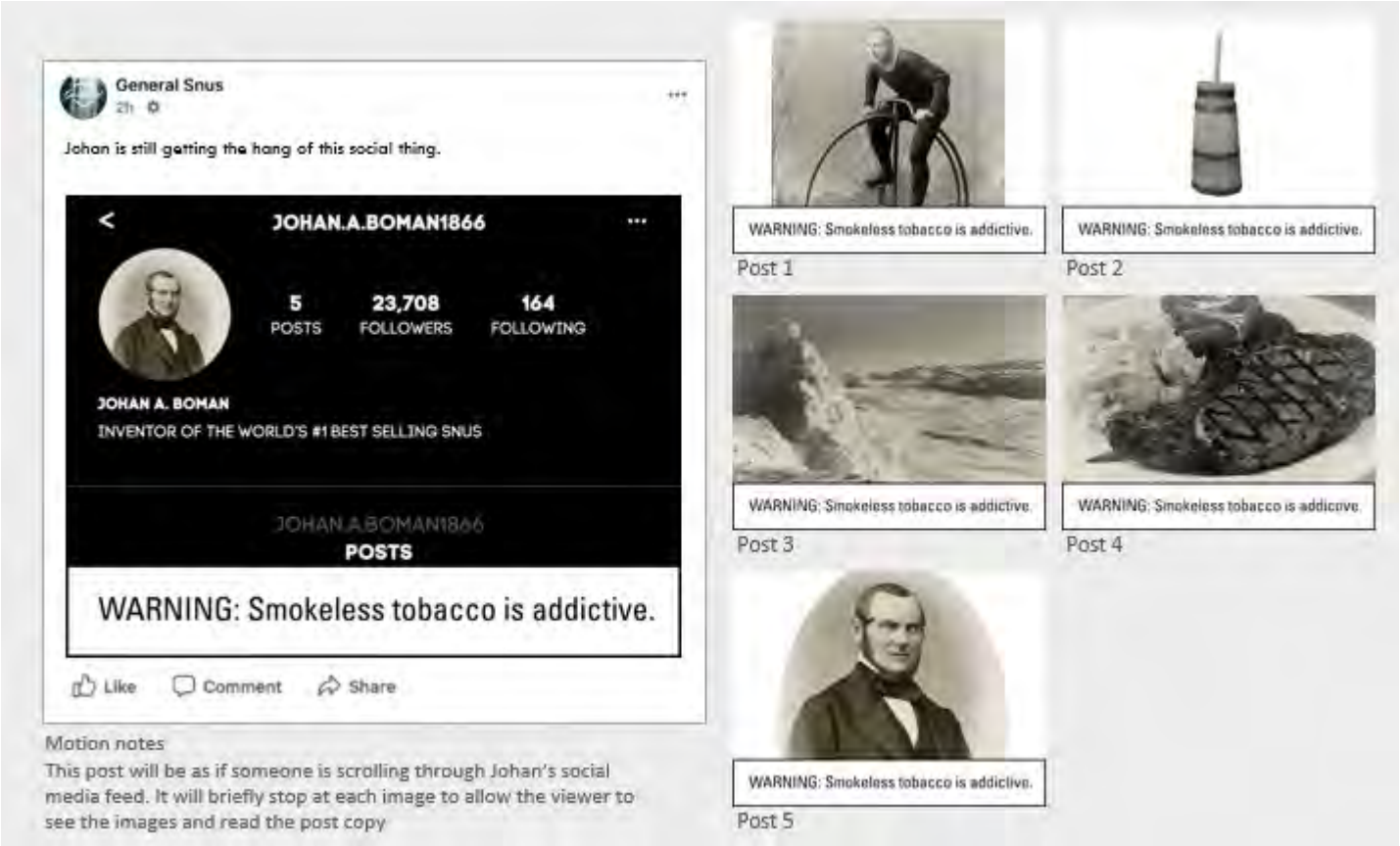
3-15-22



NoPurchNec. 50 US/DC (excl. MA, MI & VA), 21+. Ends 11AM ET 5/27/22. Rules: GeneralSnus.com

Swedish Match

3-16-22

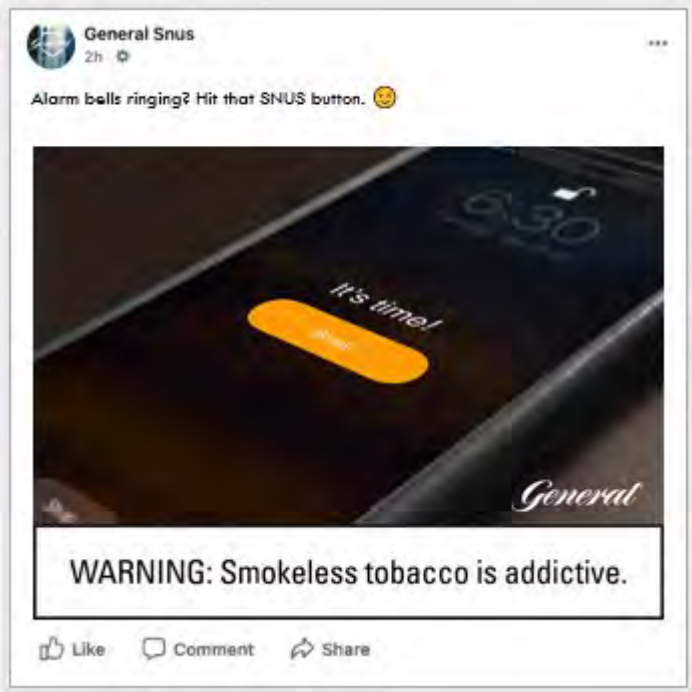


See FB media file:

03-16-22_GEN FB Johan's Feed.mp4

General Snus March '22 Facebook Posts

3-22-22



3-29-22




NoPurchNec. 50 US/DG (excl. MA, MI & VA), 21+. Ends 11AM ET 5/27/22. Rules: GeneralSnus.com

See FB media file:

03-29-22_GEN FB TMCG_Social_WhereWouldYouPutIt.mp4

General Snus April '22 Facebook Posts


4-1-22



General Snus

2h · 🌐

THIS JUST IN: On June 1, General Snus Original will be replaced by “Swedish Meatball.” Pairs well with lingonberry preserves and boiled potatoes!



WARNING: This product can cause mouth cancer.

👍 Like

💬 Comment

➦ Share


4-6-22



General Snus

2h · 🌐

Yet another thing only the Original Swedish Snus can say.



WARNING: This product can cause mouth cancer.

👍 Like

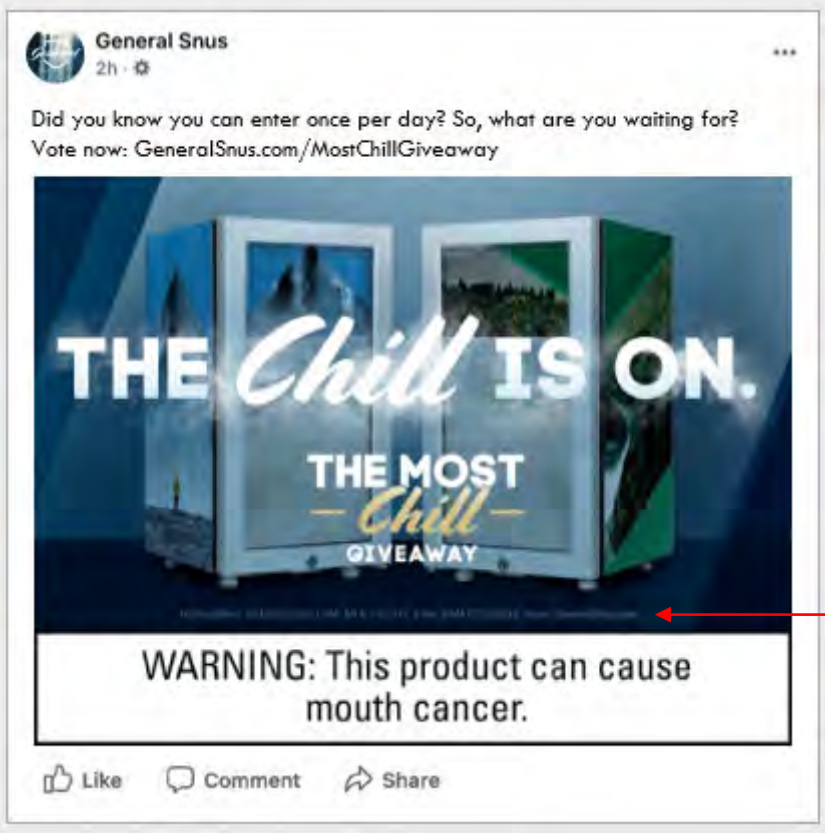
💬 Comment

➦ Share

Swedish Match

General Snus April '22 Facebook Posts

4-12-22



See FB media file:

04-12-22_GEN FB TMCg Reminder.mp4

4-13-22



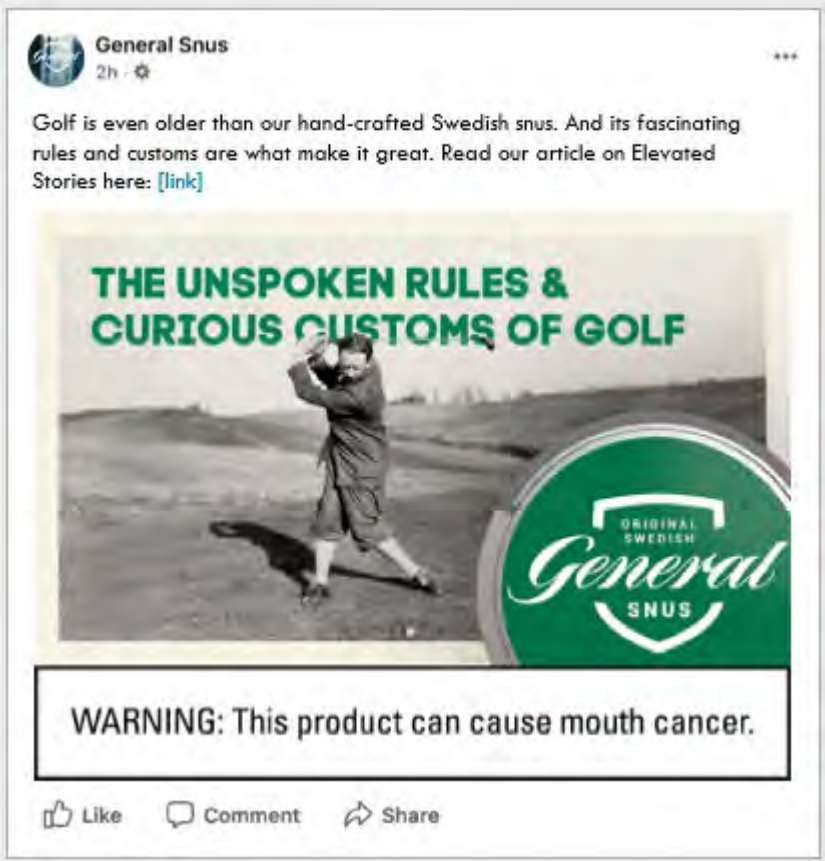
See FB media file:

04-13-22_GEN FB PKWS.mp4

Swedish Match

General Snus April '22 Facebook Posts

4-20-22



See FB media file:

04-20-22_GEN FB Rules of Golf.mp4

4-26-22



No Patch Nec. 50 US/DC (w/col. MA, MI & VA), 2H+ Ends 11AM ET 5/27/22 Rules: GeneralSnus.com



General Snus April '22 Facebook Posts

4-27-22



General Snus Facebook May - June cover photo




General Snus May '22 Facebook Posts

5-4-22

General Snus
2h · 🌐

Tag a friend (21+) who is *already* the most chill.
Vote to enter today at GeneralSnus.com/MostChillGiveaway



THE MOST Chill GIVEAWAY
NoPurchNec. 50 US/DC (excl. MA, MI & VA), 21+. Ends 11AM ET 5/27/22. Rules: GeneralSnus.com

WARNING: This product can cause mouth cancer.

👍 Like 💬 Comment ➦ Share

NoPurchNec. 50 US/DC (excl. MA, MI & VA), 21+. Ends 11AM ET 5/27/22. Rules: GeneralSnus.com

5-6-22

General Snus
2h · 🌐

They say, "Necessity is the mother of invention." In 1862, Johan A. Boman decided that *his* necessity was an elevated tobacco experience. Four years later, he introduced the world to... [See More](#)



General

WARNING: This product can cause mouth cancer.

👍 Like 💬 Comment ➦ Share

See FB media file:

📄 05-06-22_GEN FB MotherOfInvention.mp4

5-10-22

General Snus
2h · 🌐

Johan's imagination has given the world some amazing things.



WARNING: This product can cause mouth cancer.

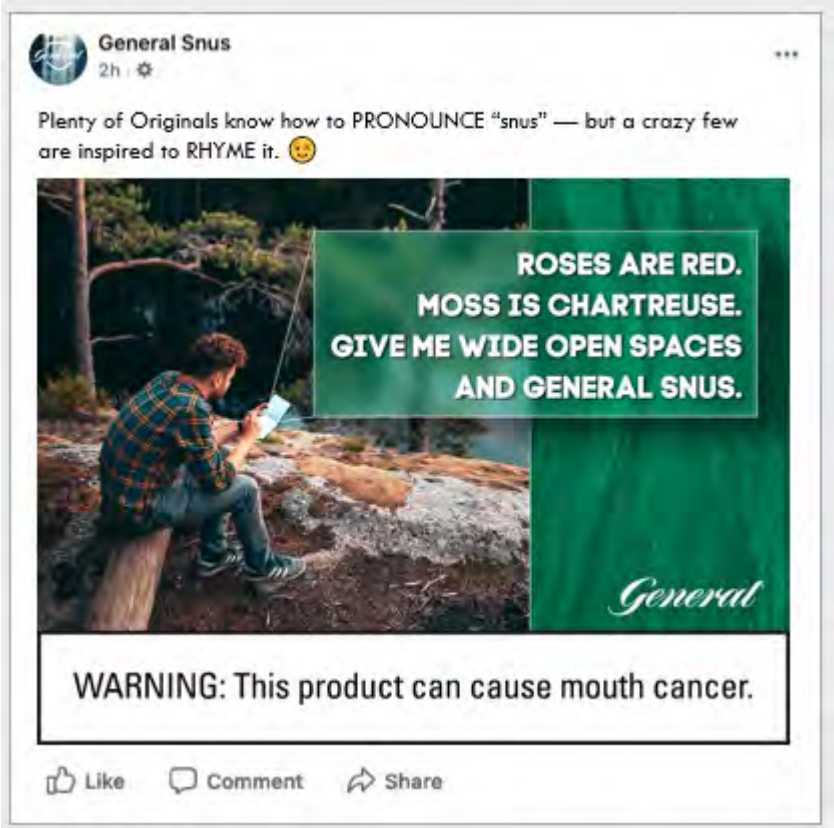
👍 Like 💬 Comment ➦ Share

See FB media file:

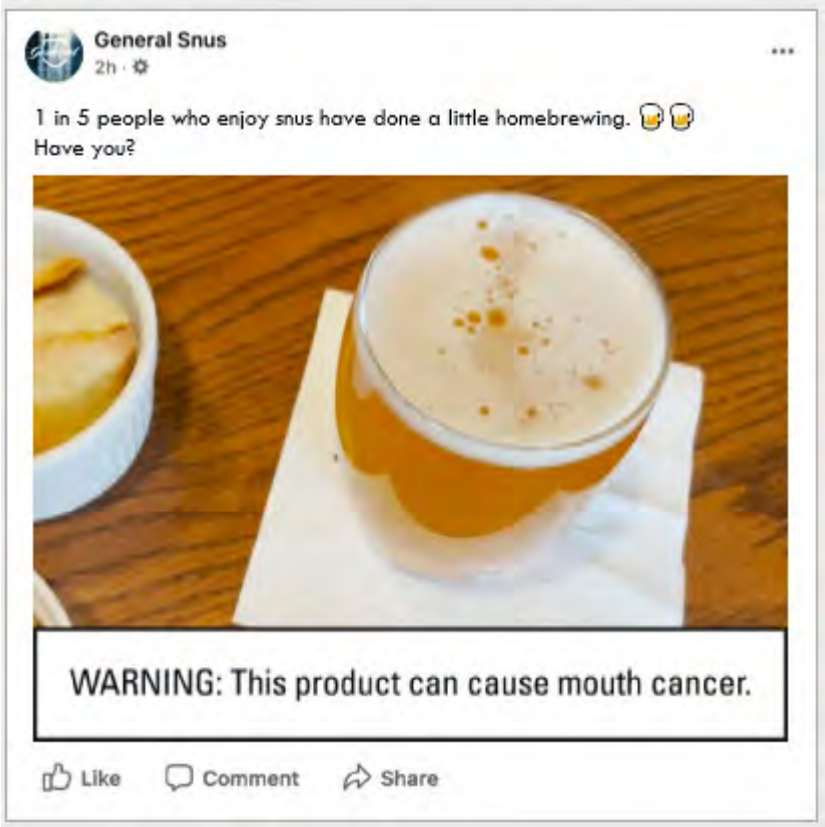
📄 05-10-22 GEN FB JohanDayDream.mp4

General Snus May '22 Facebook Posts

5-11-22



5-13-22



See FB media file:

📄 05-13-22_GEN FB SnusStats.mp4

General Snus May '22 Facebook Posts

5-17-22



See FB media file:

05-17-22_GEN_FB Wintergreen.mp4

5-19-22



See FB media file:


05-19-22_GEN FB DM Coupons.mp4

General Snus May '22 Facebook Posts

5-20-22

General Snus
2h · 🌐

May 27 is your last chance to vote in The Most Chill Giveaway...and to earn a chance to win an authentic piece of our brand story. Enter at GeneralSnus.com/MostChillGiveaway



LAST CHANCE TO Chill

THE MOST Chill GIVEAWAY

No Purch Nec. 30 US/DC (excl. MA, MI & VA), 21+. Ends 11AM ET 5/27/22. [Prizes.GeneralSnus.com](https://GeneralSnus.com)

WARNING: This product can cause mouth cancer.

👍 Like 💬 Comment ➦ Share

5-24-22

General Snus
2h · 🌐

On a scale of 'E' to 'Freaking Now,' how ready are you for a summer road trip? Whether you're staying in Colorado or heading north, south, east or west—you're gonna need tunes. Watch this feed for our upcoming Summer Road Trip Playlist!



WARNING: This product can cause mouth cancer.

👍 Like 💬 Comment ➦ Share


See FB media file:

📎 05-24-22_GEN FB SummerRoadTripPrep.mp4

5-27-22

General Snus
2h · 🌐

Perfect on its own, plays well with citrus.



WARNING: This product can cause mouth cancer.

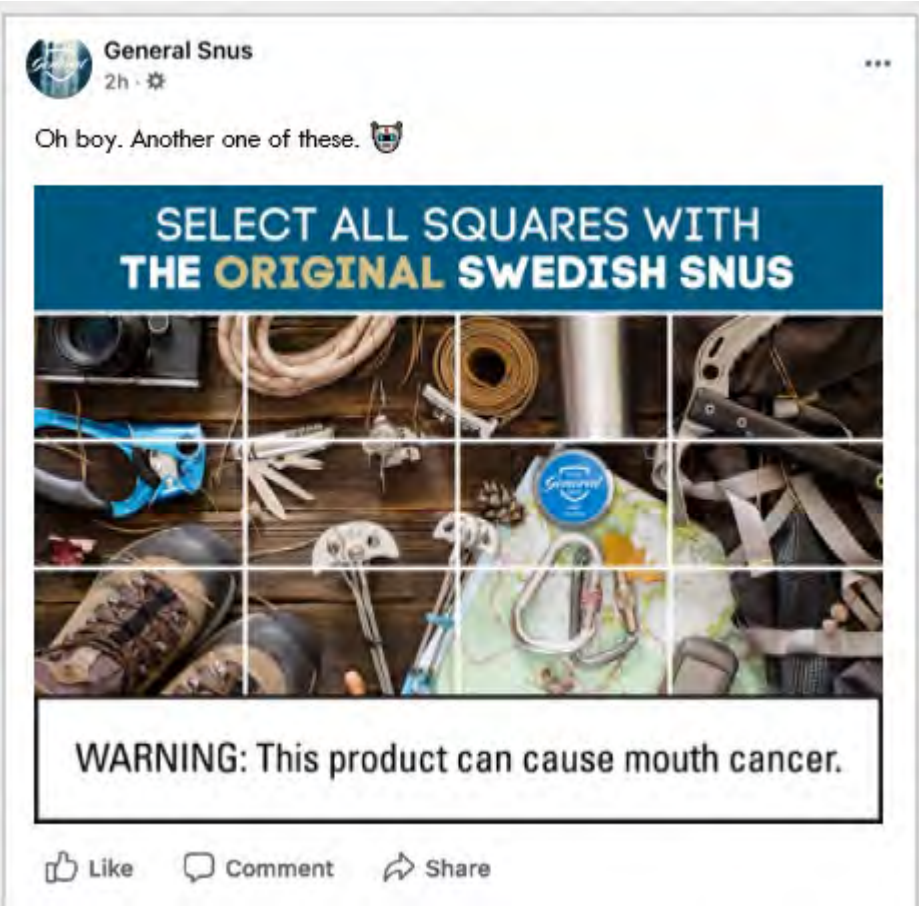
👍 Like 💬 Comment ➦ Share


General Snus Facebook May 28 – June cover photo



General Snus June '22 Facebook Posts

6-1-22



See FB media file:  06-1-22_GEN FB Squares with General Snus.mp4

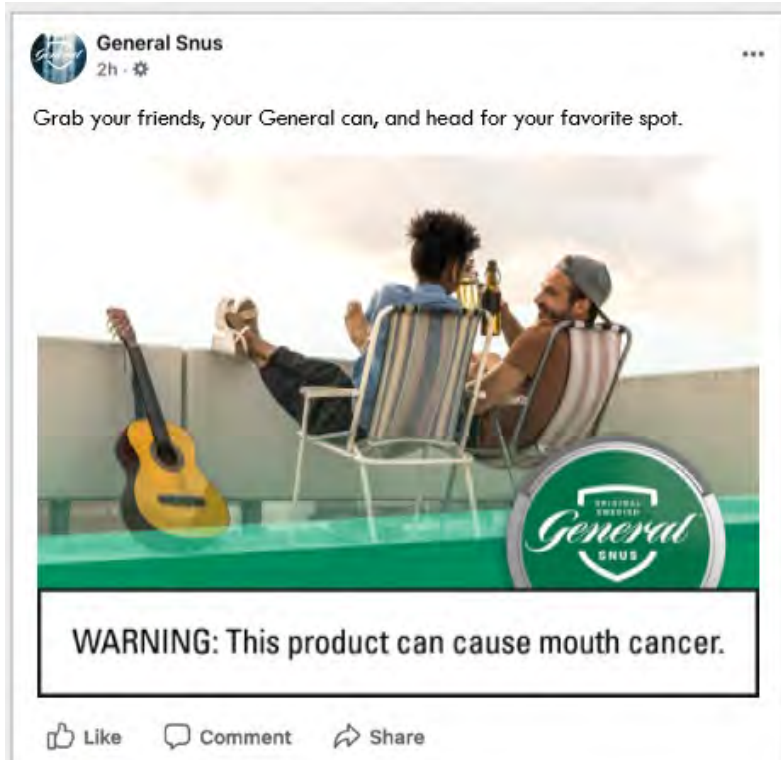


6-3-22



General Snus June '22 Facebook Posts

6/6/22



See FB media file:

06-6-22_GEN FB Grab a can to your favorite spot.mp4

6/8/22



General Snus June '22 Facebook Posts

6/10/22

General Snus
2h · 🌐

Give it up for the nature lovers among us 🍌🍌🍌



WARNING: This product can cause mouth cancer.

👍 Like

💬 Comment

➦ Share

6/14/22

General Snus
2h · ⚙️

Your votes are in—check out the winning chiller design! And see who won a grand prize or a weekly custom-poster prize! Visit: GeneralSnus.com/MostChillWinners



WARNING: This product can cause mouth cancer.

👍 Like

💬 Comment

➦ Share

General Snus June '22 Facebook Posts

6/15/22



General Snus

2h · 🌐

...

It's summertime, which means Johan is taking the train to the seashore. Check out Johan's travel tips before you start your own vacation.




JOHAN'S
SUMMER
TRAVEL
TIPS 📌

WARNING: This product can cause mouth cancer.

👍 Like

💬 Comment

➦ Share

See FB media file:  06-15-22_GEN FB Johans Summer Travel Tips.mp4



6/17/22



General Snus

2h · 🌐

...

Here's a little pop-song fact. At 70 mph, you can peel off fifty miles of highway in about the time it takes to play 9 songs. Which is why this summer, we're putting together a 90s-inspired, 9-song road trip playlist. Let us know your picks in the comments below.



COMING SOON
NINE
FROM THE
90s
OUR SUMMER '22 ROAD TRIP PLAYLIST

WARNING: This product can cause mouth cancer.

👍 Like

💬 Comment

➦ Share

General Snus June '22 Facebook Posts

6/21/22



General Snus

2h · 🌐

If you're gonna be an active, fun-loving Original, softball is the perfect summer pastime. And nobody does softball better than Chicago. So, give it up for our fellow snusers in the Windy City. (And watch this feed for more Made for Originals tributes down the road!)



WARNING: This product can cause mouth cancer.

 Like

 Comment

 Share

6/22/22



General Snus

2h · 🌐

How do you pronounce SNUS? If you're going to say it like a Swede, here are a few English words that rhyme with the Original Swedish Sn—well, you know.



WARNING: This product can cause mouth cancer.

 Like

 Comment

 Share

Posted as an album




WARNING: This product can cause mouth cancer.




WARNING: This product can cause mouth cancer.

General Snus June '22 Facebook Posts

6/24/22

General Snus
2h · 🌐

Hey, it's "Your Break." 🎱 The Y.B. is a fresh twist on the gin spritzer. Takes a bit of prep, but it pairs well with friends old and new. Find the recipe in the Comments below. Serves two!



WARNING: This product can cause mouth cancer.

👍 Like

💬 Comment

➦ Share

Comment 1:
INGREDIENTS
2 c. water • 2 c. sugar • 5 c. cantaloupe cubes or balls •
4 oz. melon simple syrup • 3 oz. gin • 2 oz. seltzer water
• cucumber slices • fresh mint • ice


INSTRUCTIONS
In a saucepan, bring water and sugar to a boil. Let boil for 30 seconds, remove from heat, and let cool completely. Once cooled, blend with 4 c. cantaloupe cubes/balls until smooth (setting aside 1 c. cantaloupe).

Shake each cocktail singly. Combine ice, mint leaf, 2 oz. simple syrup and gin in shaker and and shake for 30 seconds. Add ice, a few melon balls, and cucumber slices to a tall glass, then pour in the content of the shaker. Top with seltzer, stir, and garnish with mint. Repeat for the second drink.


See FB media file:

📄 06-24-22_GEN FB Summer Cocktail Playing Pool.mp4

6/28/22

General Snus
2h · 🌐

We're proud of our 150-year legacy. But the General Snus story doesn't begin and end with Johan A. Boman. Read about the principles that set General Snus apart: [\[link\]](#)



WARNING: This product can cause mouth cancer.

👍 Like

💬 Comment

➦ Share

General Snus July '22 Facebook Posts

7/1/22



See FB media file:

📎 07-1-22 GEN FB All American Cocktail Recipe.mp4

1st comment:

RED, WHITE & BOURBON SMASH

INGREDIENTS

1 ½ oz. bourbon

½ oz. lemon juice

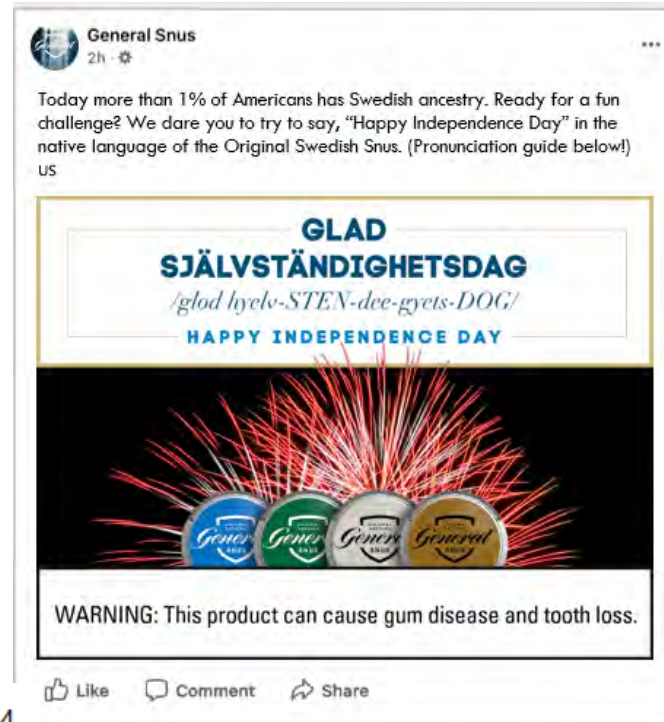
2-3 maraschino cherries

Cola on top

DIRECTIONS

Muddle cherries and lemon juice in a cocktail shaker. Add your favorite bourbon and ice; shake until chilled. Strain into a highball glass, top with cola and give it a stir. Add a classic American garnish. Sip and stay cool. US

7/4/22



7/6/22



General Snus July '22 Facebook Posts

7/8/22

General Snus
2h · 🌐

Sure, it's an acquired taste. So are you.



THE
ORIGINAL
SWEDISH SNUS

General
SNUS


WARNING: This product can cause gum disease and tooth loss.

👍 Like


💬 Comment

➦ Share


See FB media file:

 07-8-22 GEN FB Acquired Taste (Original).mp4

7/11/22

General Snus
2h · 🌐

You could just get from point A to point B. But where's the originality in that?



STAY
ORIGINAL

General

WARNING: This product can cause gum disease and tooth loss.

👍 Like

💬 Comment

➦ Share

7/13/22

General Snus
2h · 🌐

Want to earn a \$5 coupon? Shoot a selfie video with your phone and post to the comments below, telling us WHY YOU PREFER GENERAL SNUS TO OTHER TOBACCO PRODUCTS. Offer ends July 16, 2022.



POST A SELFIE VIDEO
GET A **\$5 COUPON**

WARNING: This product can cause gum disease and tooth loss.

👍 Like

💬 Comment

➦ Share

General Snus July '22 Facebook Posts

7/15/22



Posted as an album (no video)

7/19/22



See FB media file:

07-19-22_GEN FB Original Choices (White).mp4

General Snus July '22 Facebook Posts

7/22/22



General Snus

2h · 🔒

...

One of these things pairs perfectly with everything known to humankind. And the other one... also does.



ORIGINAL SWEDISH
General
SNUS
WINTERGREEN
34 PORTIONS

BACON
SALTY + RICH

WARNING: This product can cause gum disease and tooth loss.

👍 Like

💬 Comment

➦ Share

7/26/22



General Snus

2h · 🔒

...

True originals know the real history.



**A BRIEF HISTORY
OF SNUS**
- 1866 -
**JOHAN
INVENTS
GENERAL SNUS**

WARNING: This product can cause gum disease and tooth loss.

👍 Like

💬 Comment

➦ Share

See FB media file:

📄 07-26-22_GEN FB History of Snus.mp4

7/27/22




General Snus

2h · 🔒

...

Hot-sauce ale or keylime-pie IPA? In Denver—another metro made for Originals—over 200 different beers are brewed every day. Let's be honest, if you're gonna sip a PB&J lager, you're 100% Original.



**MADE FOR
ORIGINALS
NO. 2**
**DENVER'S
CREATIVE
BREWS**

WARNING: This product can cause gum disease and tooth loss.


👍 Like

💬 Comment

➦ Share


General Snus July '22 Facebook Posts

7/29/22




 **General Snus**
2h · 🌞

Being the total original in your group of friends can be a lot of fun. Who doesn't love being the rebel or the maverick? At the same time, being original sort of makes you a leader, too.

All we can say is—from one Original to another—that's not a bad way to live. Bravo. 👏



WARNING: This product can cause gum disease and tooth loss.

 Like  Comment  Share

General Snus August '22 Facebook Posts

8/2/22



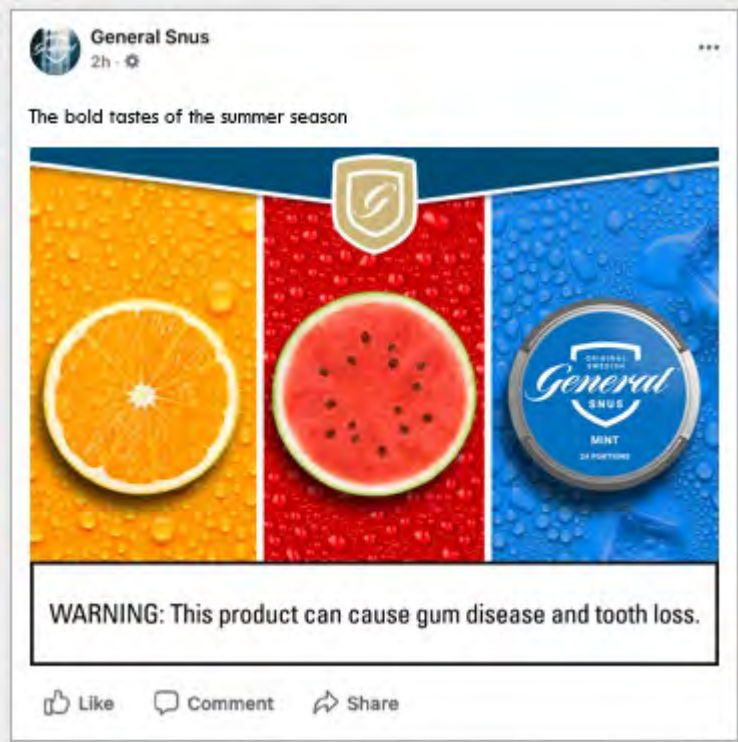
8/5/22



See FB media file:

08-05-22_GEN FB Lineup Poster.mp4

8/9/22




General Snus August '22 Facebook Posts

8/10/22



See FB media file:


 08-10-22_GEN FBGreatness is Ready.mp4

Swedish Match

8/12/22




See FB media file:

 08-12-22_GEN FB Daydream.mp4

8/17/22




See FB media file:

 08-17-22_GEN FB Evolution of Beards.mp4

General Snus August '22 Facebook Posts

8/19/22

General Snus
2h · 🌐

Find a scrap of shade for you (and your snus).



WARNING: This product can cause gum disease and tooth loss.

👍 Like

💬 Comment

➦ Share

8/23/22

General Snus
2h · 🌐

Let's hear it for another city Made for Originals: Tampa. From the world's longest ocean-front sidewalk to its heart-stopping bridge vistas, Tampa's got some amazing looks.



WARNING: This product can cause gum disease and tooth loss.


👍 Like

💬 Comment

➦ Share

General Snus August '22 Facebook Posts


8/26/22



General Snus

2h · 🌐

The old you probably explored every trend in tobacco satisfaction. But the new you knows better.



General


WARNING: This product can cause gum disease and tooth loss.

👍 Like

💬 Comment

➦ Share


8/30/22



General Snus

2h · 🌐

Good news! More stores are stocking the Original Swedish Snus. In some locations, retailers are selling General from a shelf display, thanks to our tight-fit side labels that preserve freshness. Of course, many stores are still using chillers. No matter where you buy it, the world's best-selling snus still stands apart.




WARNING: This product can cause gum disease and tooth loss.

👍 Like

💬 Comment

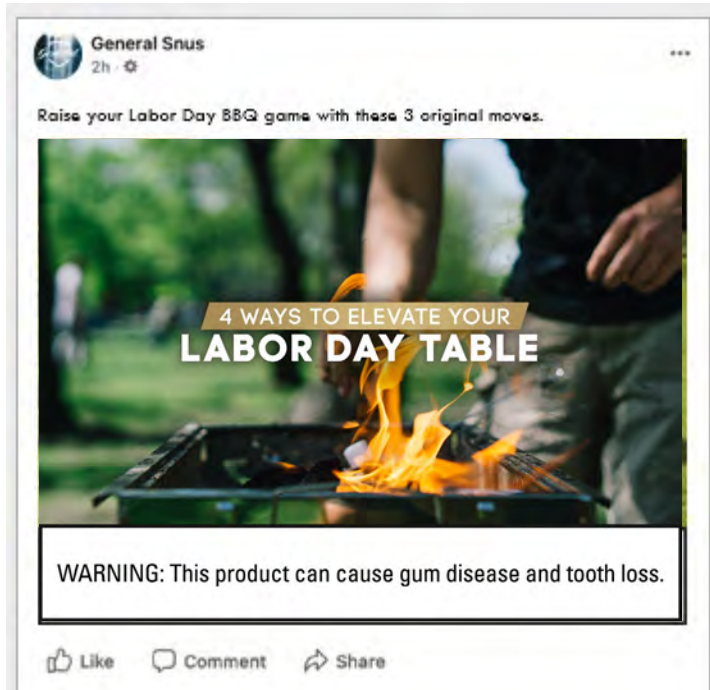
➦ Share

See FB media file:

 08-30-22_GEN FB Easier To Find.mp4

General Snus September '22 Facebook Posts

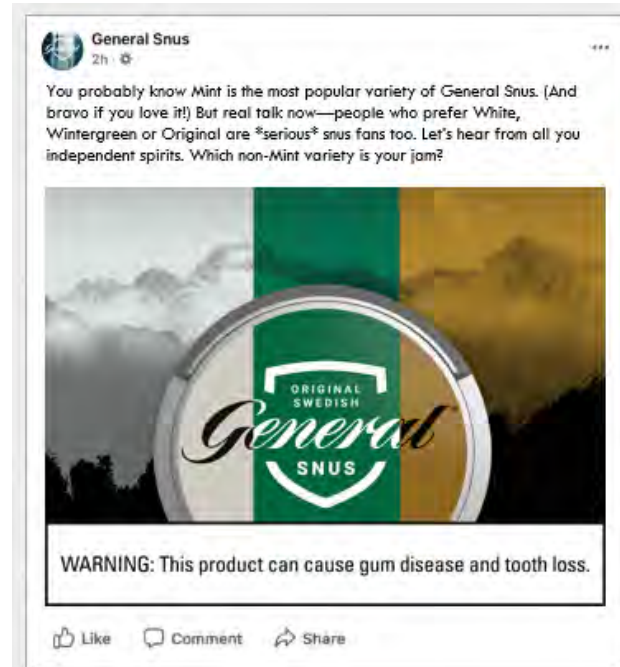
9/2/22



See FB media file:

📎 09-2-22_GEN FB Labor Day.mp4

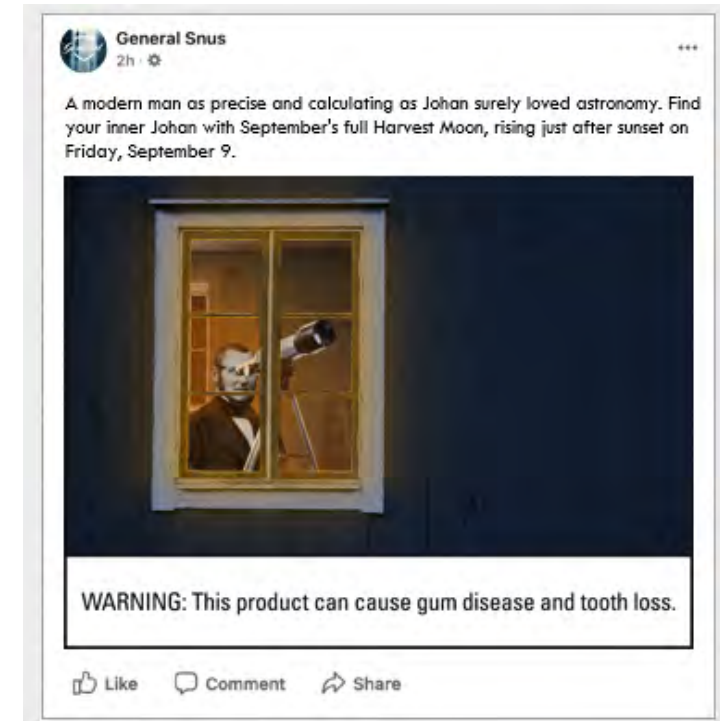
9/6/22



See FB media file:

📎 09-6-22_GEN FB Variety Showdown.mp4

9/9/22



See FB media file:

📎 09-9-22_GEN FB Johan Harvest Moom.mp4

General Snus September '22 Facebook Posts

9/13/22



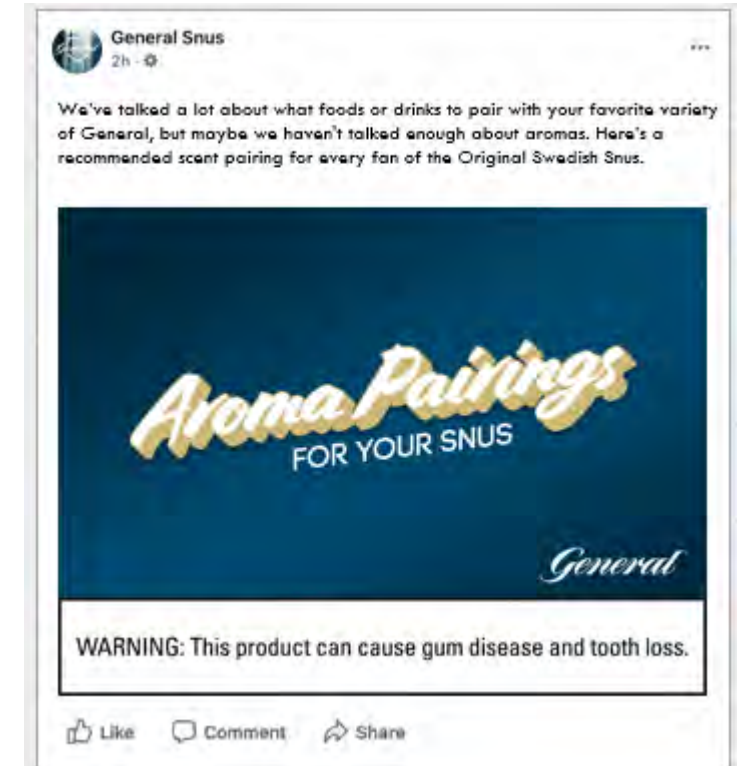
See FB media file:

📎 09-13-22_GEN FB Snus Starter Pack.mp4

9/15/22



9/20/22



See FB media file:

📎 09-20-22_GEN FB Aroma Pairing WTG.mp4

Swedish Match

General Snus September '22 Facebook Posts

9/22/22

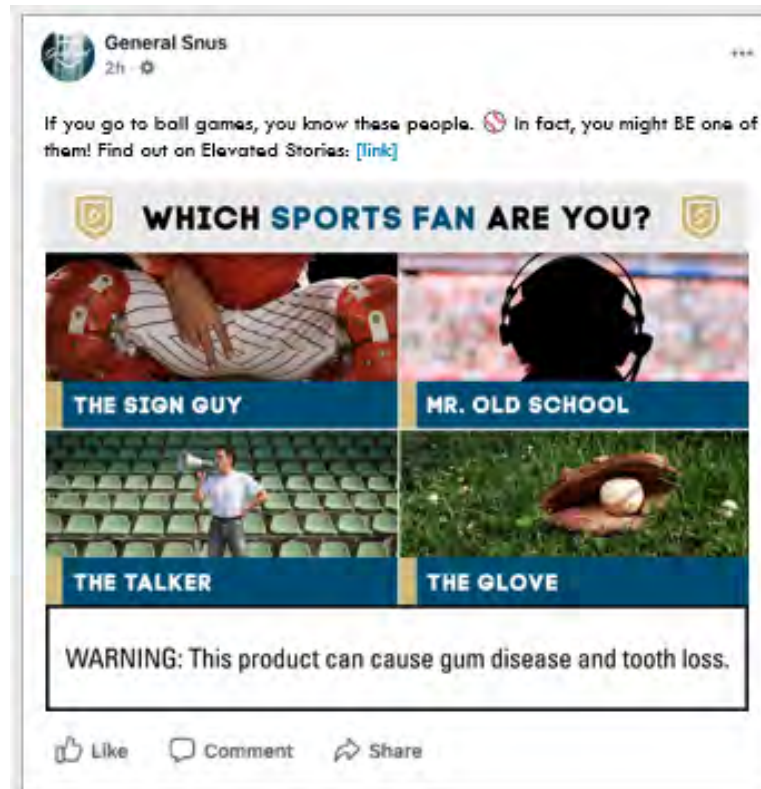


See FB media file:

📎 09-22-22_GEN FB Autumn Equinox.mp4

Swedish Match

9/27/22



General Snus September '22 Facebook Posts

9/28/22



General Snus

2h · 🌐

...

Pair your first autumn adventure with the variety that complements it.



WARNING: This product can cause gum disease and tooth loss.

👍 Like

💬 Comment

➦ Share

9/30/22



General Snus

2h · 🌐

...

Here's a color swatch every Mint fan can appreciate.



WARNING: This product can cause gum disease and tooth loss.

👍 Like

💬 Comment

➦ Share



General Snus Facebook September '22 cover photo



General Snus October '22 Facebook Posts

10/4/22

 **General Snus**
2h · 🌐

Let's shout out a civic tradition made for Originals: the balloon festivals of Albuquerque. Whether you're enjoying from the ground or soaring through stunning New Mexico skies, this annual spectacle is the perfect occasion for you and your favorite snus.




MADE FOR ORIGINALS NO. 5
ALBUQUERQUE'S BALLOON CELEBRATIONS


WARNING: This product is not a safe alternative to cigarettes.

 Like  Comment  Share

10/7/22




 **General Snus**
2h · 🌐

A color swatch made for those who know some leaves never change. Because the Wintergreen of the deep forest stays hardy and strong.



WINTERGREEN
Authentic Since 1866

WARNING: This product is not a safe alternative to cigarettes.

 Like  Comment  Share


10/11/22

 **General Snus**
2h · 🌐


October is THE month for scary movies and horror classics. What are your jump-scare faves? Let us know in the comments!



WARNING: This product is not a safe alternative to cigarettes.

 Like  Comment  Share

See FB media file:

 10-11-22_GEN_FB Halloween.mp4

General Snus October '22 Facebook Posts

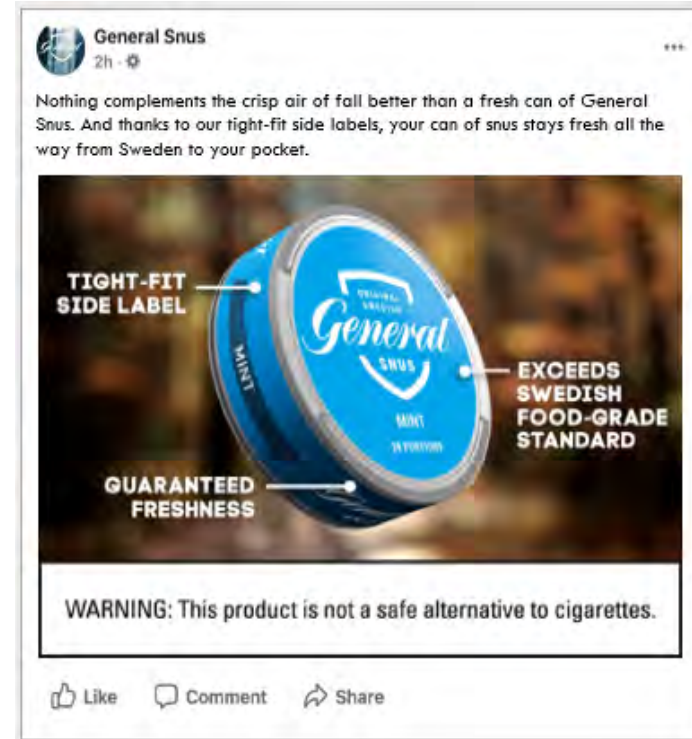
10/14/22



See FB media file:

10-14-22_GEN FB Scratch Off.mp4

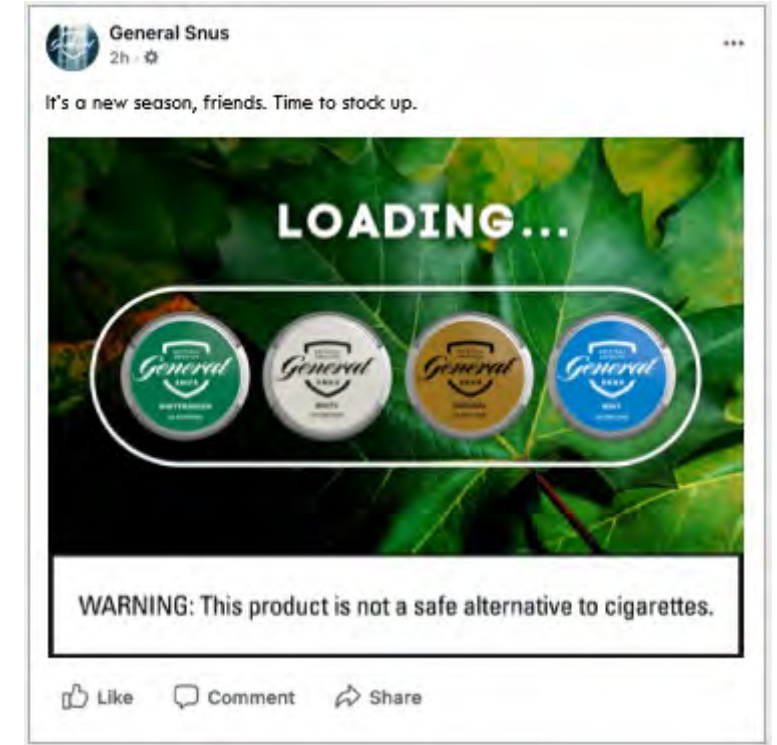
10/18/22



See FB media file:

10-18-22_GEN FB Fresh Fall.mp4

10/21/22



See FB media file:

10-21-22_GEN FB Loading Screen WITH AMBIENT AUDIO.mp4

Swedish Match

General Snus October '22 Facebook Posts

10/25/22



1st comment:

Here's how you do it: 1.) Hollow out a real pumpkin. Remove the guts but leave the thick rind intact. 2.) Add a beer tap or push-style spigot, the kind with a nut you can tighten from the inside. 3.) Open the top and fill the pumpkin with sweet stout, oatmeal stout or—of course—pumpkin ale.

10/26/22



See FB media file:



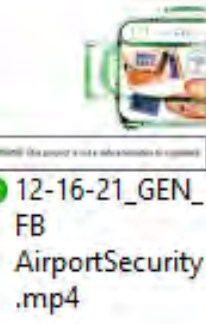
📎 10-26-22_GEN FB Aroma Pairing Original.mp4

Nov. '21 General Snus Facebook .mp4 File Guide

<u>.mp4 Image</u>	<u>.mp4 File Name and Length</u>	<u>.mp4 Descripton</u>
	 11-5-21_GEN_Social_Sports.mp4 00:00:18	
	 11-14-21_GEN_FB Social_MeaningfulMotion.mp4 00:00:20	

(b) (4)

Dec. '21 General Snus Facebook .mp4 File Guide

<u>.mp4 Image</u>	<u>.mp4 File Name and Length</u>	<u>.mp4 Description</u>
	<div>12-09-21_GEN_FB Chill.mp4</div> <div>00:00:07</div>	Shows four cans of general on icy background with snow falling
	<div>12-14-21_GEN_FB Cocktails.mp4</div> <div>00:00:33</div>	Provides different winter cocktail menu ideas
	<div>12-16-21_GEN_FB AirportSecurity.mp4</div> <div>00:00:10</div>	

(b) (4)

Jan. '22 General Snus Facebook .mp4 File Guide

.mp4 Image

.mp4 File Name and Length

.mp4 Description



✓ 1-07_GEN_January2022-Social_WeFixedIt.mp4

01-07-22_GEN FB WeFixedIt.mp4

00:00:25

Lists top 3 resolutions: Exercise More, Eat better, Enjoy family & friends.



✓ 1-9_GEN_January_IfYouHaveAGift_Uselt.mp4

01-09-22_GEN FB IfYouHaveAGift_Uselt.mp4

00:00:15

Shows a person unwrapping a gift.



✓ 1-11_General_MRTP_Explainer_Final.mp4

01-11-22_GEN FB_MRTP_Explainer_Final.mp4

00:00:21









✓ 1-28_GEN_January2022-Social_InterestingFact.mp4

01-28-22_GEN FB Social_InterestingFact.mp4

00:00:10

(b) (4)

Feb. '22 General Snus Facebook .mp4 File Guide

<u>.mp4 Image</u>	<u>.mp4 File Name and Length</u>	<u>.mp4 Description</u>
 2-4_Gen_Feb_Elevate2022_WithAFlavor.mp4	 02-4-22_Gen FB WithAFlavor.mp4 00:00:10	States “elevate with flavor” and shows a barrage of General Mint cans.
 2-13_GEN_February2022-Social_TheBigGame.mp4	 02-13-22_GEN FB TheBigGame.mp4 00:00:37	Lists stats about the Super Bowl (does not state the name “Super Bowl”).
 2-28_GEN_Feb_Social_TheGreatIndoors.mp4	 02-28-22_GEN FB TheGreatIndoors.mp4 00:00:30	Shows ideas for inside winter activities: board games, painting party, movie night.

March '22 General Snus Facebook .mp4 File Guide

.mp4 Image

.mp4 File Name and Length

.mp4 Descripton



3-1_GEN_TMC
G_Social_Anno
uncement,mp
4

03-1-22_GEN FB TMC Social Announcement.mp4

00:00:06

Introduces The Most Chill Giveaway, to win a custom designed chiller.



3-9-22 Found
Snus FB.mp4

03-9-22_GEN FB Found Snus.mp4

00:00:11

Shows a person posting a sign that their can of snus has been found.



3-16-22
Johan's Feed
FB.mp4

03-16-22_GEN FB Johan's Feed.mp4

00:00:19

Shows what Johan Boman's Facebook feed would be:









3-29_GEN_TM
CG_Social_Wh
ereWouldYouP
utIt.mp4

03-29-22_GEN FB TMC Social WhereWouldYouPutIt.mp4

00:00:17

Asks the question where consumers would put a chiller if they won via The Most Chill Giveaway. Shows places to put a chiller.

April '22 General Snus Facebook .mp4 File Guide

<u>.mp4 Image</u>	<u>.mp4 File Name and Length</u>	<u>.mp4 Descripton</u>
 4-12-22 FB TMCg Reminder.mp4	 04-12-22_GEN FB TMCg Reminder.mp4 00:00:06	Reminder to enter The Most Chill Giveaway and when it ends.
 4-13-22 FB PKWS.mp4	 04-13-22_GEN FB PKWS.mp4 00:00:05	Shows items to remember to keep with you: phone, keys, wallet, can of General Snus
 4-20-22 Rules of Golf FB.mp4	 04-20-22_GEN FB Rules of Golf.mp4 00:00:03	States “unspoken rules of golf” and shows a man swinging a golf club.

May '22 General Snus Facebook .mp4 File Guide

.mp4 Image

.mp4 File Name and Length

.mp4 Description



05-06-22_GEN FB MotherOfInvention.mp4
00:00:07

Shows images of old pictures that include one of Johan Boman.

✓ Gen_5-6-22_Mother's Day FB.mp4



05-10-22 GEN FB JohanDayDream.mp4
00:00:09

Shows a picture of Johan Boman, with a can of General Snus white popping out of his head.

✓ Gen_5-10_Johan's Daydream FB.mp4



05-13-22_GEN FB SnusStats.mp4
00:00:08

Shows a person taking a drink and a note underneath stating four of their friends would be happy to help them drink it.

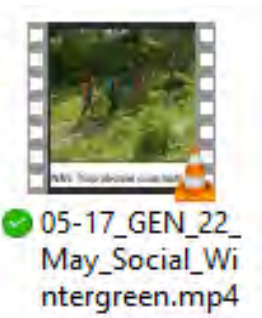
✓ Gen_5-13-22_Homebrewing FB.mp4

May '22 General Snus Facebook .mp4 File Guide con't

.mp4 Image

.mp4 File Name and Length

.mp4 Descripton



05-17-22_GEN_FB Wintergreen.mp4
00:00:09

Shows group of people walking through nature.



05-19-22_GEN FB DM Coupons.mp4
00:00:12

(b) (4)



05-24-22_GEN FB SummerRoadTripPrep.mp4
00:00:04

Shows a can of General Snus original with a tachometer going to full.

June '22 General Snus Facebook .mp4 File Guide

.mp4 Image

.mp4 File Name and Length

.mp4 Description



✓ GEN_6-1-22_FB
Squares with
General
Snus.mp4

06-1-22_GEN FB Squares with General Snus.mp4

00:00:08

Squares remove to show General Snus (open can) of Mint



✓ GEN_6-6-22_FB
_Grab a can to
your favorite
spot.mp4

06-6-22_GEN FB Grab a can to your favorite spot.mp4

00:00:04



✓ GEN_6-15-22_F
B_Johans
Summer Travel
Tips.mp4

06-15-22_GEN FB Johans Summer Travel Tips.mp4

00:00:30



✓ GEN_6-24-22_F
B Summer
Cocktail
Playing Pool....

06-24-22_GEN FB Summer Cocktail Playing Pool.mp4

00:00:11

(b) (4)

July '22 General Snus Facebook .mp4 File Guide

.mp4 Image

.mp4 File Name and Length

.mp4 Description



07-1-22 GEN FB All American Cocktail Recipe.mp4
00:00:06

Shows a drink sliding on a bar then states a drink recipe.

✓ FB 7-1-22 All American Cocktail Recipe.mp4



07-8-22 GEN FB Acquired Taste (Original).mp4
00:00:04

Shows a can of General Original and states “the original Swedish snus”.

✓ FB 7-8-22 Acquired Taste (Original).mp4



07-19-22_GEN FB Original Choices (White).mp4
00:00:08

Shows open can of General White, states “You’re not like anyone else.”


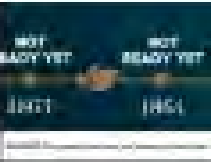



✓ FB 7-19 Original Choices (White).mp4



07-26-22_GEN FB History of Snus.mp4
00:00:21

(b) (4)

Aug '22 General Snus Facebook .mp4 File Guide

<u>.mp4 Image</u>	<u>.mp4 File Name and Length</u>	<u>.mp4 Description</u>
	08-05-22_GEN FB Lineup Poster.mp4 00:00:08	Moving image of concert-like poster for summer tour 2022. Shows four cans of General, variety names.
	08-10-22_GEN FB Greatness is Ready.mp4 00:00:09	(b) (4)
	08-12-22_GEN FB Daydream.mp4 00:00:30	(b) (4)
	08-17-22_GEN FB Evolution of Beards.mp4 00:00:20	(b) (4)
	08-30-22_GEN FB Easier To Find.mp4 00:00:11	(b) (4)

September '22 General Snus Facebook .mp4 File Guide

.mp4 Image

.mp4 File Name and Length

.mp4 Description



09-2-22_GEN FB Labor Day.mp4

00:00:20



09-6-22_GEN FB Variety Showdown.mp4

00:00:11



09-9-22_GEN FB Johan Harvest Moom.mp4

00:00:06



09-13-22_GEN FB Snus Starter Pack.mp4

00:00:17



09-20-22_GEN FB Aroma Pairing WTG.mp4

00:00:12








09-22-22_GEN FB Autumn Equinox.mp4

00:00:03

(b) (4)

October '22 General Snus Facebook .mp4 File Guide

<u>.mp4 Image</u>	<u>.mp4 File Name and Length</u>	<u>.mp4 Description</u>
	10-11_GEN_FB Halloween.mp4 00:00:07	
	10-14_GEN FB Scratch Off.mp4 00:00:08	
	10-18_GEN FB Fresh Fall.mp4 00:00:07	
	10-21_GEN FB Loading Screen WITH AMBIENT AUDIO.mp4 00:00:08	
	10-26_GEN FB Aroma Pairing Original.mp4 00:00:12	

(b) (4)

General Snus Facebook Analytics: Nov. 1, 2021 – Oct. 1, 2022

(b) (4)

(b) (4)

General Snus Facebook Analytics: Nov. 1, 2021 – Oct. 1, 2022

(b) (4)

(b) (4)

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Every can of General Snus is crafted to meet your unwavering standards for greatness. Created in Sweden by entrepreneur and tobacco pioneer Johan Boman more than 150 years ago, today's General delivers on our founder's relentless pursuit of perfecting the tobacco experience. It is uncommonly satisfying for those who are never satisfied. General Snus, a smokeless and spitless upper lip tobacco, is the #1 snus brand in the world. So, if it's a distinctive and flavorful tobacco you seek, you deserve one that delivers a level of character that matches your own. Elevate your tobacco experience with General Snus.

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General Snus November '21 EM2



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General Snus November '21 EM3



LET'S TALK TURKEY



Hope this finds you warm and relaxed. Over on Facebook today, we're talking turkey about the "serious" subject of side dishes. Happy Thanksgiving!

 JOIN THE CONVERSATION
/GENERAL SNUS



EXCLUSIVE COUPONS

SAVE \$8 ON GENERAL

CLAIM COUPONS NOW ➔



FIND GENERAL SNUS

STORE LOCATOR ➔



Questions or want to report concerns about General Snus?

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General Snus December '21 EM1

4

REASONS SNUS
IS BEST FOR
THE HOLIDAYS

1

 Refreshing as stepping outdoors

2

 Each portion elevates the season

3

 More chill shopping sprees

4

 Pairs well with wrapping, too

DISCOVER GENERAL ▶

General Snus

General Snus

General Snus

General Snus

EXCLUSIVE COUPONS

SAVE \$9 ON GENERAL

CLAIM COUPONS NOW ▶



THE 1ST PRODUCT TO OBTAIN A
MODIFIED RISK TOBACCO PRODUCT ORDER

LEARN MORE ▶



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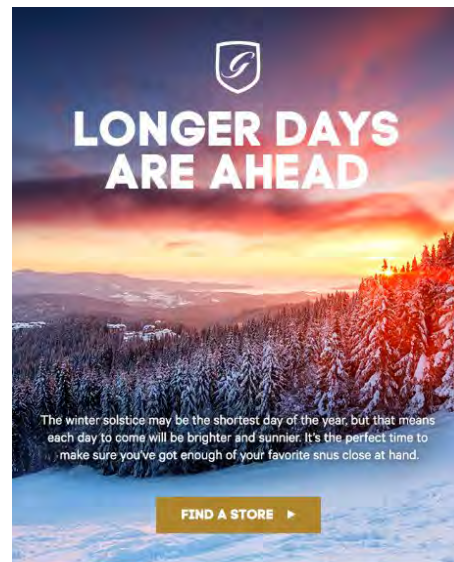
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General Snus December '21 EM2



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General Snus January EM1

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General Snus January EM2



"SHINE YOUR OWN LIGHT. FOLLOW YOUR OWN PATH."
— ANONYMOUS

The Northern Lights have helped inspire us to elevate the level of everything we create.

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General Snus February EM1

Chilling with the Olympics is a perfect snus occasion. But do you have enough snus on hand for all 17 days of games? Maybe it's time to stock up!

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General Snus February EM2

Read our article at Elevated Stories about some smart and crafty ways Swedes warm up the icy chill of winter.



Read our article at Elevated Stories about some smart and crafty ways Swedes warm up the icy chill of winter.

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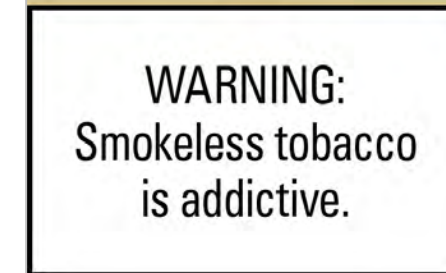
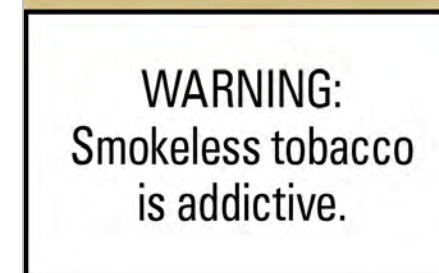
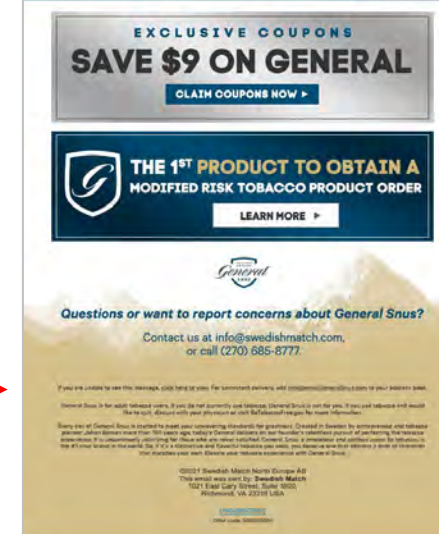
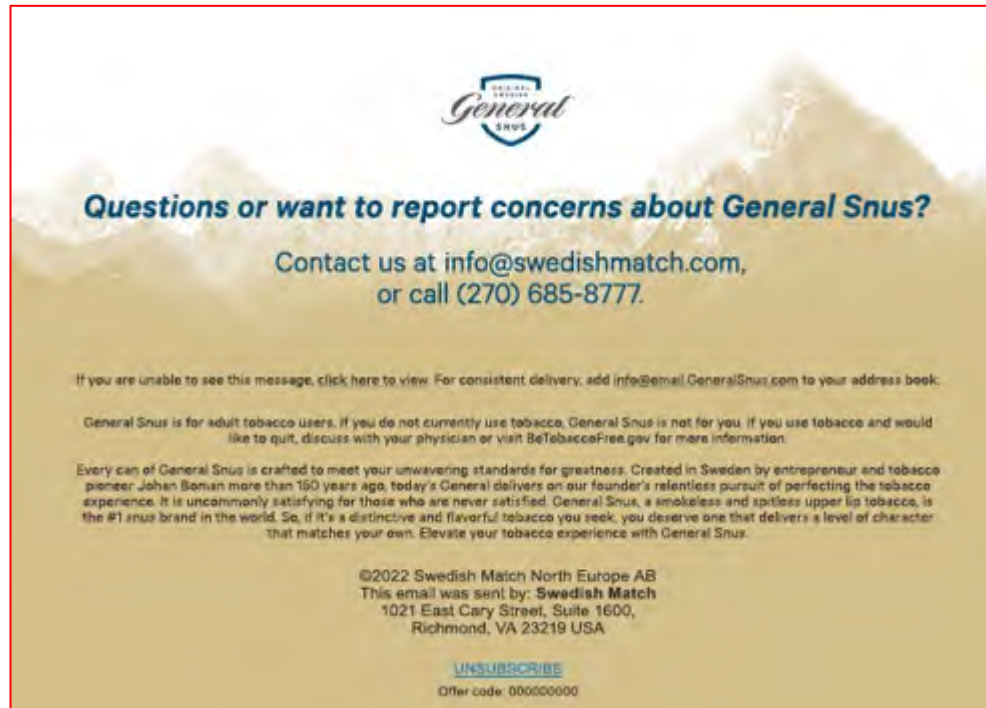
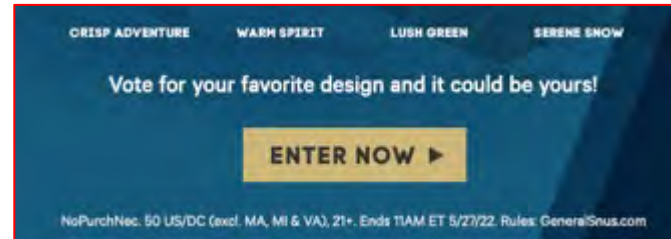
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General Snus March EM1



General Snus March EM2

The Swedes have a tradition of regular decluttering in order to live a stress-free life. On Elevated Stories, we'll help you jumpstart a plan of action.

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ORGANIZE YOUR SPACE

SWEDISH STYLE



The Swedes have traditions of simplicity, organization and decluttering in order to live a stress-free life. On Elevated Stories, we'll help you jumpstart a plan of action.


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General Snus April EM1

- 1. Woodworking in the garage
- 2. Fly fishing for your next catch
- 3. Writing a new song
- 4. Schedule your 2v2 b-ball league
- 5. ...or anything, really.


GENERAL
IS UP FOR ANY
DOWNTIME

- 1. Woodworking in the garage
- 2. Fly fishing your favorite spot
- 3. Writing a new song
- 4. Schedule your 2v2 b-ball league
- 5. ...or anything, really.



OUR LINEUP ▶

See email media file:

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General Snus April EM 2

Like snus, golf has its own fascinating traditions—from house rules to plaid pants to the Amen Corner.



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General Snus May EM 1

- 1. Clean the bike.
- 2. Check the cables.
- 3. Check the wheels.
- 4. Check the gears and brakes.
- 5. Inspect & lubricate the drivechain.
- 6. Tighten everything up.

BICYCLE TUNE-UP CHECKLIST



DISCOVER GENERAL ▶

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General Snus May EM 2

Swedes don't talk about "beating around the bush," but they will mention "walking like a cat on hot porridge." Learn why at Elevated Stories.

5 FUNNY SWEDISH SAYINGS
Swedes don't talk about "beating around the bush," but they will mention "walking like a cat on hot porridge." Learn why at Elevated Stories.



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General Snus June EM1



It's summertime! Which means activities practically invented for your discreet enjoyment of the Original Swedish Snus. Make sure you're stocked up for every happy hour, cookout, ball game and float trip on your calendar.



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General Snus June EM2

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SEE WHO WON! ▶



NoPurchNec. 50 US/DC (excl. MA, MI & VA), 21+. Ends 11AM ET 5/27/22. Rules: GeneralSnus.com

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General Snus July EM2

If General Snus is the pinnacle of discreet tobacco enjoyment...where and when exactly CAN'T you enjoy it? Scuba diving? During a harmonica solo? A hot dog eating contest? This month on Elevated Stories, we're taking a fun look at a short list of no-snus zones.



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General Snus August EM1

- 1. Lower-alcohol beer goes under the ice
- 2. Higher-alcohol sticks out of the ice
- 3. Lay very dark beers on top of the ice (right by your snus if you like it chilled)
- 4. Overall — the lighter the beer, the lower it goes

4 NO-FAIL COOLER TIPS FOR LAGERS AND ALES



- 1. Lower-alcohol beer goes under the ice
- 2. Higher-alcohol sticks out of the ice
- 3. Lay very dark beers on top of the ice (right by your snus if you like it chilled)
- 4. Overall — the lighter the beer, the lower it goes

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General Snus August EM2

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General Snus August EM3

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General Snus September EM1

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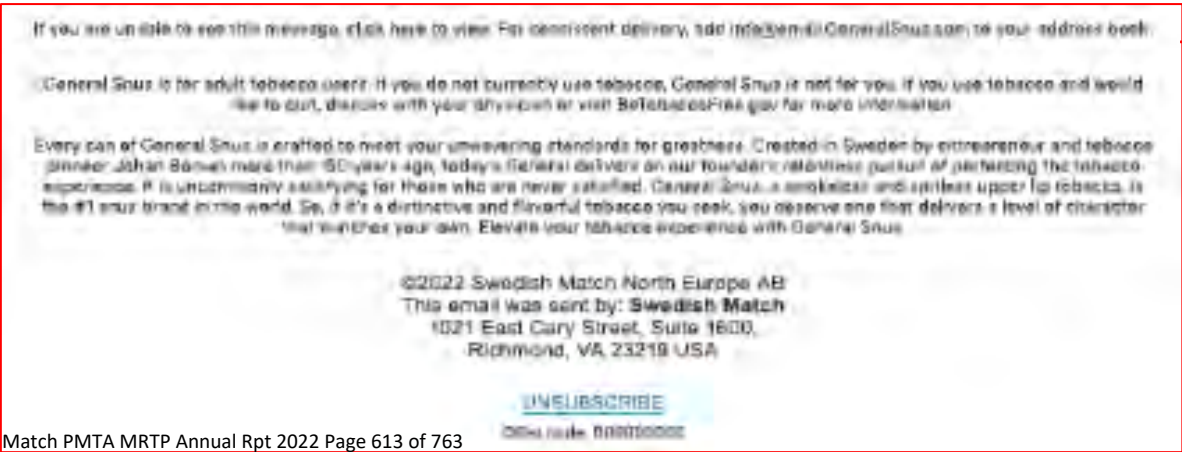
General Snus was born from the belief that there was a better way to enjoy tobacco. Check out our exciting new video about what it means to be an original.



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THE SCIENCE OF ORIGINALITY



This month's Elevated Story looks at the science behind why an original or distinctive quality — like a red paint job — changes how we see something.

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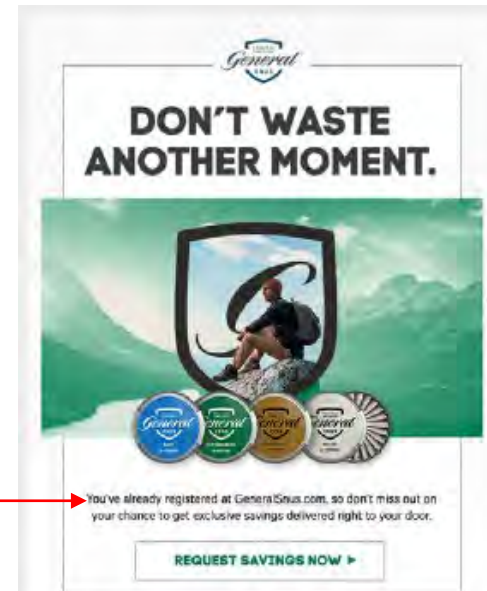
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Removed MRTPT teaser and replaced with “OUR PATH TO PERFECTION” teaser

It's official: You're now a part of something very special.

*To get exclusive monthly savings,
make sure you're signed up to
receive our direct mail.*

If you are unable to see this message, [click to view in browser](#). For consistent delivery, add info@GeneralSnus.com to your address book.

General Snus is for adult tobacco users. If you do not currently use tobacco, General Snus is not for you. If you use tobacco and would like to quit, discuss with your physician or visit BeTobaccoFree.gov for more information.

Every can of General Snus is crafted to meet your unwavering standards for greatness. Created in Sweden by entrepreneur and tobacco pioneer Johan Boman more than 150 years ago, today's General delivers on our founder's relentless pursuit of perfecting the tobacco experience. It is uncommonly satisfying for those who are never satisfied. General Snus, a smokeless and spitless upper lip tobacco, is the #1 snus brand in the world. So, if it's a distinctive and flavorful tobacco you seek, you deserve one that delivers a level of character that matches your own. Elevate your tobacco experience with General Snus.

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Swedish Match PMTA MRTP Annual Rpt 2022 Page 619 of 763

live: 1/1/22 - 3/16/22

live: 3/16/22 – current

**WE'RE
GLAD
YOU'RE
HERE.**

It's official: You're now a part of something very special. We can't wait for you to come explore with us.



**THE 1ST PRODUCT TO OBTAIN A
MODIFIED RISK TOBACCO PRODUCT ORDER**

LEARN MORE ▶



Questions or want to report concerns about General Snus?

Contact us at info@swedishmatch.com,
or call (270) 685-8777.

If you are unable to read the message, click here to view the same text version: Wing@msn.com Send this to your address too

Steve says? "I don't think it's really that surprising that people in Canada's theatre or arts sector are heavily greened," says Steve. "I don't think it's really that surprising that people in the theatre or arts sector are heavily greened." I don't think it's really that surprising that people in the theatre or arts sector are heavily greened.

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This email was sent by Swedish Match
1221 First Gary Street, Suite 1000
Richmond, VA 23179-1354

Abstract

100

WARNING:
Smokeless tobacco
is addictive.

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YOU'RE
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OUR PATH TO PERFECTION

Combining cutting-edge science with old-world craft.

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or call (770) 885-8777.

Early career research focus is on the role of social networks in the development of entrepreneurial intentions and the role of social networks in the development of entrepreneurial intentions.

Wynn's Gambler's Month Party Europe 2011
Wynn's Gambler's Month Party Europe 2011 is a 10-day event that will take place in the heart of the city of London, England. The event will feature a variety of activities, including live music, dancing, and gaming. The event will also feature a variety of food and drink, including live cooking demonstrations and a variety of beverages. The event will be held at the Wynn's Casino, which is located in the heart of the city of London, England. The event will be held from September 1st to September 10th, 2011. The event will be held at the Wynn's Casino, which is located in the heart of the city of London, England. The event will be held from September 1st to September 10th, 2011.

1031 East Cary Street, Suite 1001
Roanoke, VA 24015-2006

Keywords: child sexual abuse; disclosure; help-seeking; mental health

WARNING:
Smokeless tobacco
is addictive.

ONGOING EMAIL: WELCOME, NOT OPTED IN FOR DM

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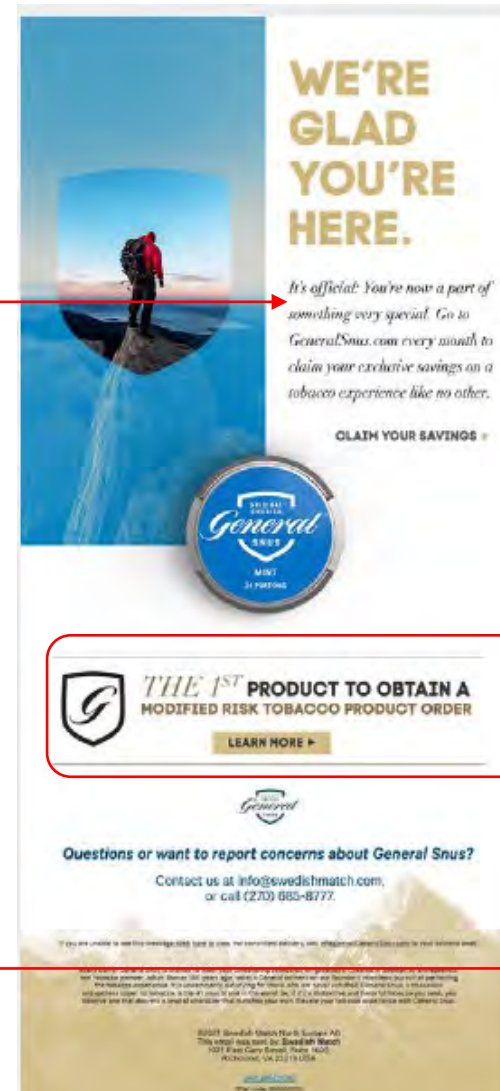
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live: 1/1/22 - 3/16/22



live: 3/16/22 – current



ONGOING EMAIL: BIRTHDAY, COUPONS NOT ALLOWED

live: 1/1/22 - 3/16/22

live: 3/16/22 – current

Here's to everything you did, made, and accomplished in the past year. We're so glad we could be on this journey with you.

Removed MRTP teaser and replaced with “OUR PATH TO PERFECTION” teaser

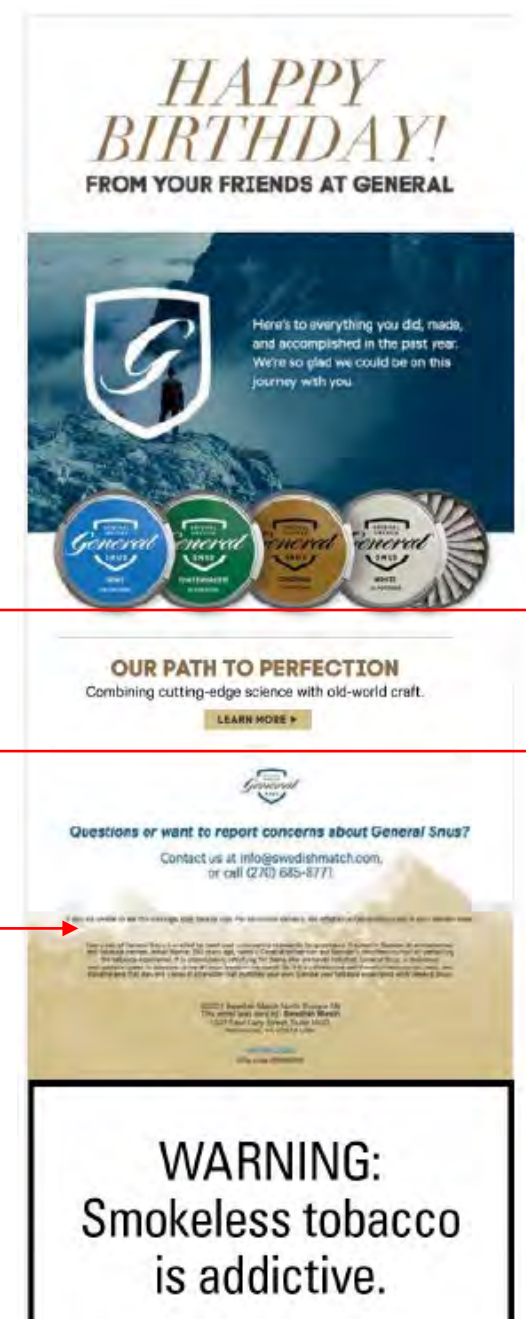
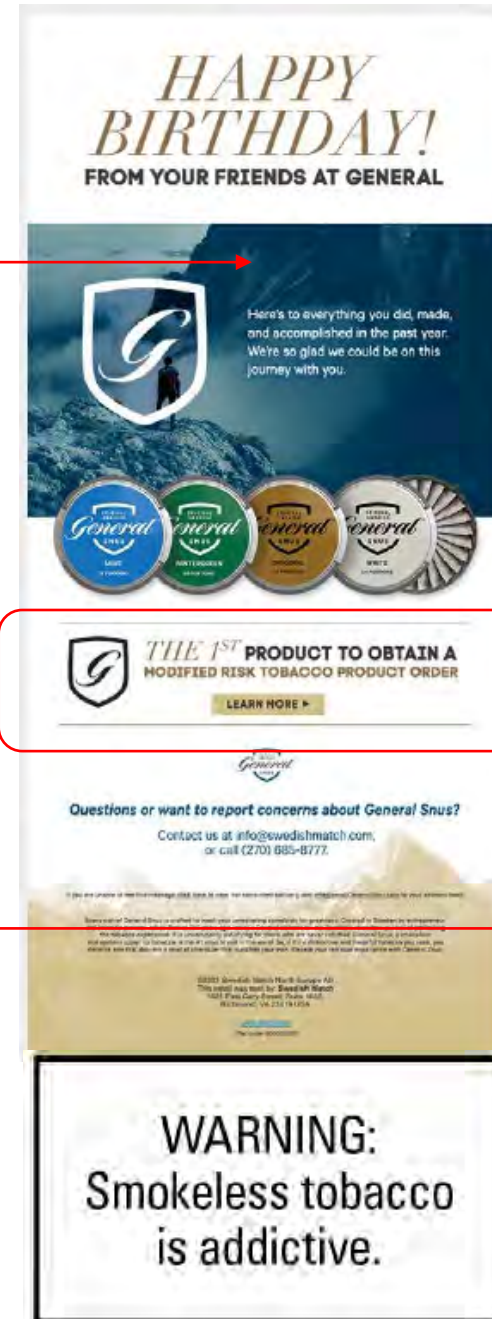
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ONGOING EMAIL: BIRTHDAY, NOT OPTED-IN FOR DIRECT MAIL

live: 1/1/22 - 3/16/22

live: 3/16/22 – current

Here's to everything you did, made, and accomplished in the past year.

To collect your special birthday savings, make sure you're signed up to receive our direct mail.

Removed MRTP teaser and replaced with “OUR PATH TO PERFECTION” teaser

Questions or want to report concerns about General Snus?

Contact us at info@swedishmatch.com, or call (270) 685-8777.

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HAPPY BIRTHDAY!
FROM YOUR FRIENDS AT GENERAL

Here's to everything you did, made, and accomplished in the past year. Get my can for \$1 and celebrate your birthday with a tobacco that elevates every occasion.

[CLAIM YOUR BIRTHDAY SAVINGS >](#)

THE 1ST PRODUCT TO OBTAIN A MODIFIED RISK TOBACCO PRODUCT ORDER

[LEARN MORE >](#)

Questions or want to report concerns about General Snus?
Contact us at info@swedishmatch.com, or call (270) 685-8777.

WARNING:
Smokeless tobacco is addictive.

HAPPY BIRTHDAY!
FROM YOUR FRIENDS AT GENERAL

Here's to everything you did, made, and accomplished in the past year. To collect your special birthday savings, make sure you're signed up to receive our direct mail.

[CLAIM YOUR BIRTHDAY SAVINGS >](#)

OUR PATH TO PERFECTION
Combining cutting-edge science with old-world craft.

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ONGOING EMAIL: NEW STORE NEAR YOU

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live: 1/1/22 - 3/16/22

THE #1 SELLING SNUS IS LESS THAN 5 MILES AWAY.

General Snus
MINT
CIGARETTE HUB
4726 Finlay St
Henrico, VA 23231
804-238-2867

[MAP IT](#)

EXCLUSIVE COUPON
GET ANY CAN OF GENERAL SNUS FOR \$1

THE 1ST PRODUCT TO OBTAIN A MODIFIED RISK TOBACCO PRODUCT ORDER
[LEARN MORE](#)

Questions or want to report concerns about General Snus?
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WARNING:
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live: 3/16/22 – current

THE #1 SELLING SNUS IS LESS THAN 5 MILES AWAY.

General Snus
MINT
STORE NAME
Address Line 1
Arlington, MD 22205
(301) 555-5555

[MAP IT](#)

EXCLUSIVE COUPON
GET ANY CAN OF GENERAL SNUS FOR \$1

OUR PATH TO PERFECTION
Combining cutting-edge science with old-world craft.
[LEARN MORE](#)

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WARNING:
Smokeless tobacco
is addictive.

General Snus Meijer Express Targeted EM

October 2022

Introduced in 1866, the authentic Swedish snus has provided an elevated smoke-free, spit-free tobacco experience. Thanks to our tight-fit side labels, you can find the superior tasting original on a shelf display or in a chiller.

**Look for it at select retailers —
including your local Meijer Express.**

If you are unable to see this message, [click to view in browser](#). For consistent delivery, add info@GeneralSnus.com to your address book.

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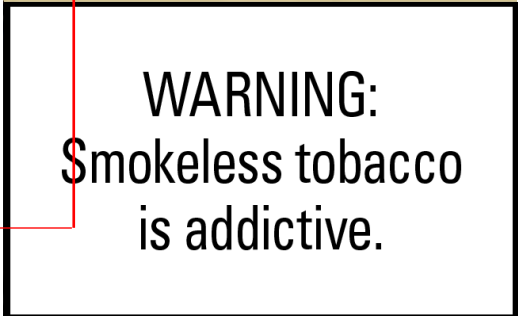
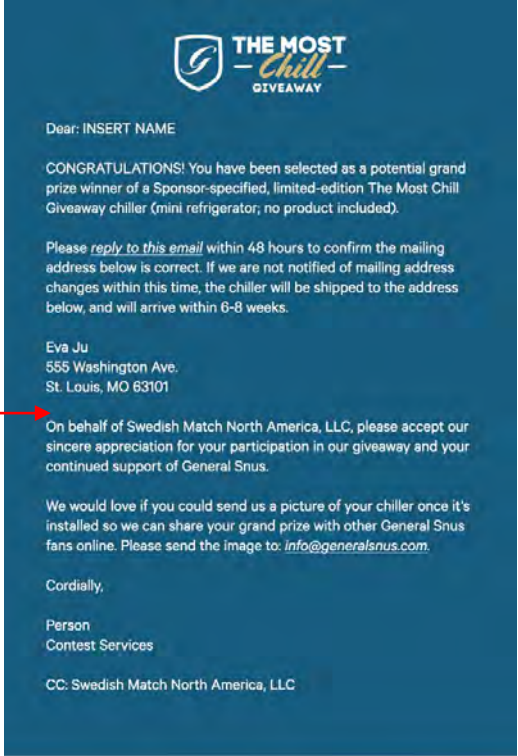
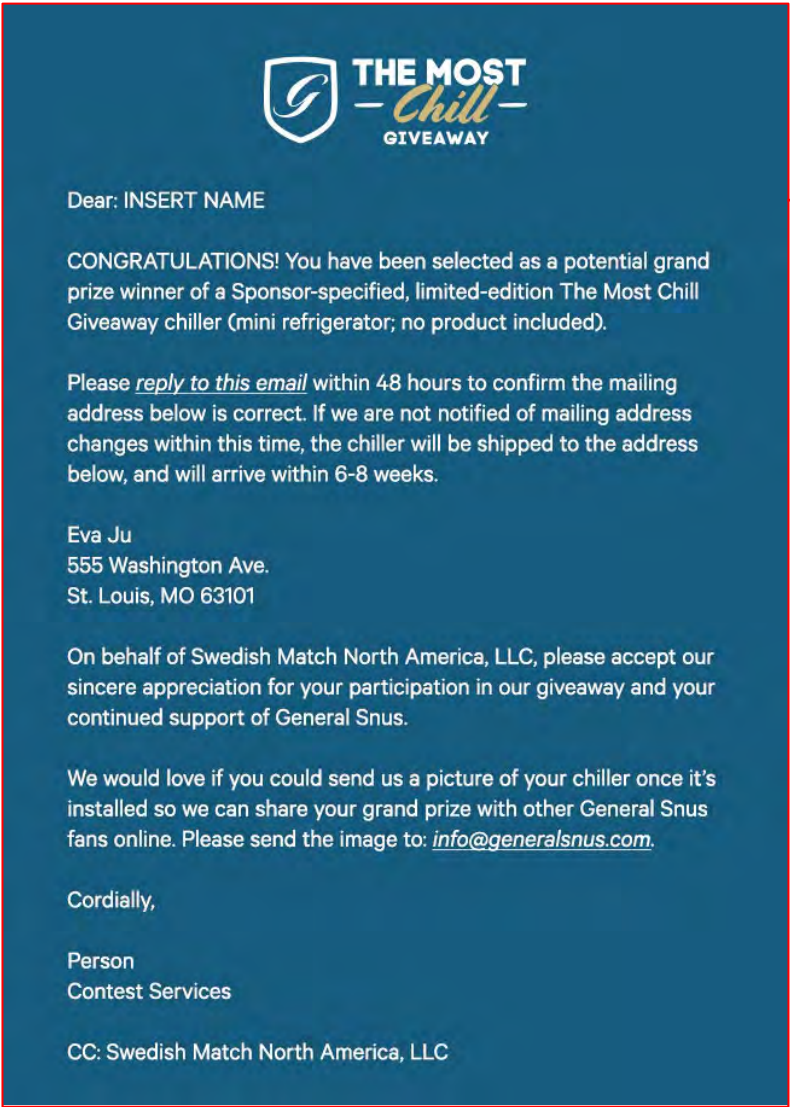
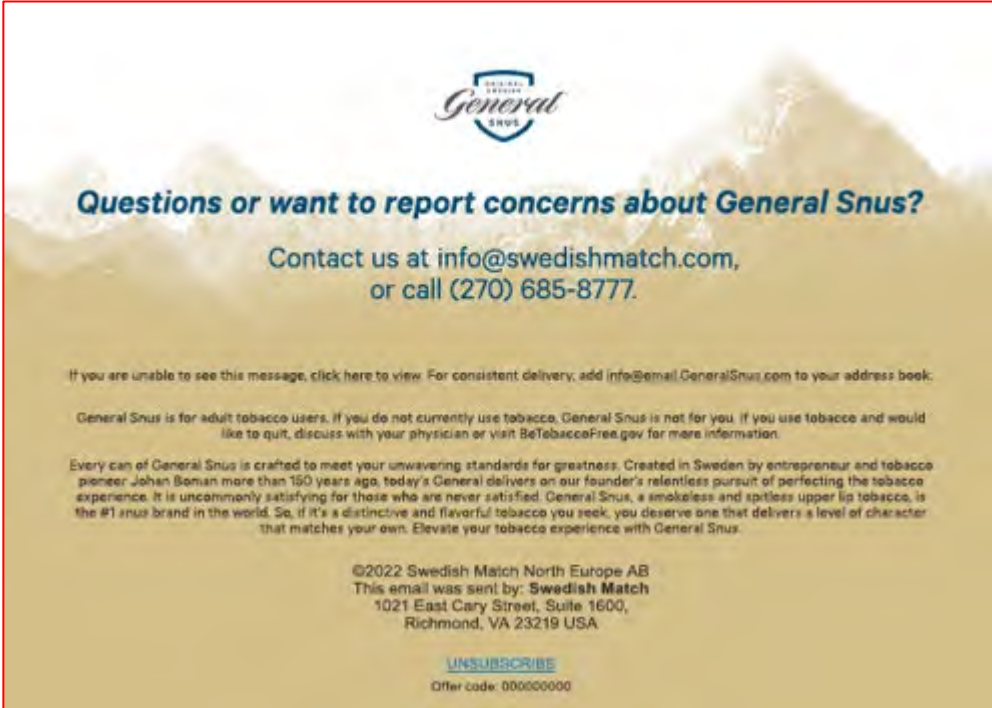


**WARNING: This product
is not a safe alternative
to cigarettes.**

Swedish Match


General Snus The Most Chill Giveaway Grand Prize Winner Confirmation E-Mail

3/10/22 – 6/14/22



General Snus The Most Chill Giveaway Weekly Prize Winner Confirmation E-Mail

3/10/22 – 6/14/22



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or call (270) 685-8777.


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This email was sent by: **Swedish Match**
1021 East Cary Street, Suite 1600,
Richmond, VA 23219 USA

[UNSUBSCRIBE](#)
Offer code: 000000000



Dear: INSERT NAME

CONGRATULATIONS! You have been selected as a potential winner of a weekly prize of a Sponsor-specified limited-edition The Most Chill Giveaway poster.

Please reply to this email within 48 hours to confirm the mailing address below is correct. If we are not notified of mailing address changes within this time, the poster will be shipped to the address below, and will arrive within 6-8 weeks.


Eva Ju
555 Washington Ave.
St. Louis, MO 63101

On behalf of Swedish Match North America, LLC, please accept our sincere appreciation for your participation in our giveaway and your continued support of General Snus.

Cordially,

Person
Contest Services

CC: Swedish Match North America, LLC



Dear: INSERT NAME

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555 Washington Ave.
St. Louis, MO 63101

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Cordially,

Person
Contest Services

CC: Swedish Match North America, LLC



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or call (270) 685-8777.

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Richmond, VA 23219 USA

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Offer code: 000000000


WARNING:
Smokeless tobacco
is addictive.



General Snus Freshness Survey Invitation EM

March 2022





On behalf of General SNUS, M/A/R/C® Research invites you to participate in a survey about the SNUS products you purchase. The survey should take no longer than 15 minutes to complete.

Your opinions will help us understand your perceptions of SNUS products you purchase, as well as other tobacco/nicotine products on the market.

To qualify for our survey **you must be at least 21 years of age**.

Our survey is **limited to the first 150 qualified consumers**; therefore, we ask that you take the survey as soon as possible.

Be sure to keep this email until you have completed the survey. If for any reason you are disconnected or need to leave and return to the survey, you will need your personalized link below.

If you **qualify and complete the survey**, you will receive a **\$5.00 Amazon electronic gift card**.

Begin Survey

Thank you for your help with our research!

General Snus

If you are unable to see this message, [click to view in browser](#). For consistent delivery, add info@generalsnus.com to your address book.

General Snus is not affiliated, endorsed, connected to or associated with Amazon.

General Snus is for adult tobacco users. If you do not currently use tobacco, General Snus is not for you. If you use tobacco and would like to quit, discuss with your physician or visit BeTobaccoFree.gov for more information.

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PO Box 998 Owensboro, KY 42302

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Offer code: 000009908

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General Snus PMSS Wave 4 Survey Email

Subject: General Snus User Study
Reply-To: invite@decipherinc.com

Dear General Snus User/Study Participant,

As you may recall, you recently agreed to participate in ongoing marketing research surveys about your use of tobacco/nicotine products.

Thank you very much for your time participating in this research.

Below are instructions to complete the second follow up survey.

You will receive \$40.00 for completing each follow up survey. Your reward will be provided in the form of an e-certificate which can be redeemed for online gift cards from a variety of places, such as Amazon, Walmart, Target, Starbucks and Gap. You will receive an additional \$50 bonus after the third survey if you complete all 3 of them.

Please click on the link included in the email to be taken to the online survey.

<https://surveys.lifepointspanel.com/survey/selfserve/kh/v3/91237824/w4?source=QoDgJRTouJ>

If you have questions, would like to update your contact information or withdraw from the study, please contact us at GeneralSnusOpinions@Kantar.com









Thank you very much for your continued participation,

General Snus

Note: General Snus is not affiliated, endorsed, connected to or associated with proprietors such as Amazon, Walmart, Target, Starbucks or Gap.



General Snus E-Mail .mp4 File Guide

<u>.mp4 Image</u>	<u>.mp4 File Name and Length</u>	<u>.mp4 Descripton</u>
 GEN_January-Email_MRTP_Focused_Area.mp4	 GEN_January-Email_MRTP_Focused_Area.mp4 00:00:01	Animated landscape
 GEN_22_March-Email_Downtime.mp4	 GEN_22_April-Email_Downtime.mp4 00:00:10	Shows man doing DIY and other projects
 GEN_22_September_Email_TrueOriginal_FocusArea.mp4	 GEN_22_September_Email_TrueOriginal_FocusArea.mp4 00:00:04	Animated landscape with General Snus shield
 GEN_22_October-Email_Scary-Movies_Spiders.mp4	 GEN_22_October-Email_Scary-Movies_Spiders.mp4 00:00:02	Spiders animating down focus area

General Snus EMail Reporting – By Email – Nov. '21 – Oct. '22

(b) (4)

General Snus EMail Reporting – By State – Nov. '21 – Oct. '22

(b) (4) (b) (4)



General Snus EMail Reporting – By Age – Nov. '21 – Oct. '22

(b) (4)

GENERAL SNUS DIRECT MAIL

General Snus Welcome Direct Mailer

Nov. 2021 – March 2022



To opt out of future promotional mailings and be removed from our mailing list, please contact the Consumer Call Center at (270) 685-8777.

NOTE: General Snus is for adult tobacco users. If you do not currently use tobacco, General Snus is not for you. If you use tobacco and would like to quit, discuss with your physician or visit BeTobaccoFree.gov for more information.

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JOIN US ON FACEBOOK AT
[FACEBOOK.COM/GENERALSNUSS](https://www.facebook.com/Generalsnus)

**QUESTIONS OR WANT TO REPORT
CONCERNS ABOUT GENERAL SNUS?**

Contact us at: info@swedishmatch.com
(270) 685-8777 | [Generalsnus.com](https://www.Generalsnus.com)

(b) (4)

- Over 155 years of unequalled quality
- Simple, high-grade ingredients
- Smokeless and spitless
- Adheres to strict food-grade manufacturing process

MANUFACTURER'S COUPON EXPIRES 03/31/23

RETAILER: Subtract \$1.00 from your normal retail price including applicable sales tax. Write that amount (your price minus \$1) in the space provided.

RETAILER: Swedish Match LLC, will pay you the face value of this coupon plus \$.08 handling provided you accept the coupon from a consumer in exchange for specified package purchase. Retailer must submit on request invoices proving purchases of sufficient stock within normal redemption cycle to cover the coupons presented for redemption. This coupon is non-transferable. Void where prohibited, taxed or otherwise restricted. Cash redemption value 1/20 of \$.01. LIMIT ONE COUPON PER PURCHASE. ANY USE NOT CONSISTENT WITH THESE TERMS CONSTITUTES FRAUD. For coupon inquiries, call the Retailer Hotline: 1-800-285-7602. EXPIRATION DATE: 3/31/23. CONSUMER: By submitting this coupon, I hereby certify that I am 21 years of age or older as may be specified by state law, and am a current consumer of tobacco products. Distribution of product prohibited to persons under 21. THIS COUPON CANNOT BE COMBINED WITH ANY OTHER OFFERS OR COUPONS. MAIL TO: Retailer Brand Solutions Dept. 70195 Mr Rcv Office 801 UNION PACIFIC BLVD STE 5 LAREDO TX 78045-9475



(b) (4)



General Snus Welcome Direct Mailer

March 2022 – October 31, 2022

- Over 150 years of unequalled quality
- Simple, high-grade ingredients
- Smokeless and spitless
- Adheres to strict food-grade manufacturing process

FOR THOSE WHO KNOW





You've joined a select community that knows that the pinnacle of tobacco satisfaction can only be reached by combining precise Swedish craft with an impeccable technique over 150 years in the making.

WE'RE GLAD YOU'RE HERE.

BENEFITS OF GENERAL SNUS

- Over 150 years of unequalled quality
- Simple, high-grade ingredients
- Smokeless and spitless
- Adheres to strict food-grade manufacturing process

QUESTIONS OR WANT TO REPORT CONCERNS ABOUT GENERAL SNUS?

Contact us at:
info@swedishmatch.com
(214) 685-8777
GeneralSnus.com

WARNING: This product is not a safe alternative to cigarettes.

GET ANY CAN OF General Snus FOR \$1



MANUFACTURER'S COUPON EXPIRES 03/31/23

RETAILER: Subtract \$1.00 from your normal retail price including applicable sales tax. Write that amount (your price minus \$1) in the space provided.

1-800-285-7602

109249 17000

WARNING: This product is not a safe alternative to cigarettes.

MANUFACTURER'S COUPON EXPIRES 03/31/23

RETAILER: Subtract \$1.00 from your normal retail price including applicable sales tax. Write that amount (your price minus \$1) in the space provided.

RETAILER: Swedish Match LLC, will pay you the face value of this coupon plus \$.08 handling provided you accept the coupon from a consumer in exchange for specified package purchase. Retailer must submit on request invoices proving purchases of sufficient stock within normal redemption cycle to cover the coupons presented for redemption. This coupon is non-transferable. Void where prohibited, taxed or otherwise restricted. Cash redemption value 1/20 of \$.01. LIMIT ONE COUPON PER PURCHASE. ANY USE NOT CONSISTENT WITH THESE TERMS CONSTITUTES FRAUD. For coupon inquiries, call the Retailer Hotline: 1-800-285-7602. EXPIRATION DATE: 3/31/23. CONSUMER: By submitting this coupon, I hereby certify that I am 21 years of age or older as may be specified by state law, and am a current consumer of tobacco products. Distribution of product prohibited to persons under 21. THIS COUPON CANNOT BE COMBINED WITH ANY OTHER OFFERS OR COUPONS. Mail to: Inmar Brand Solutions Dept. 70195 Mfr Rcv Office 801 UNION PACIFIC BLVD STE 5 LAREDO TX 78045-9475

General Snus Welcome Direct Mailer

Nov. 2022 - current

OUTSIDE

To opt out of future promotional mailings and be removed from our mailing list, please contact Consumer Care at (270) 685-8777.

NOTE: General Snus is for adult tobacco users. If you do not currently use tobacco, General Snus is not for you. If you use tobacco and would like to quit, discuss with your physician or visit BeTobaccoFree.gov for more information.

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GN322001

JOIN US ON FACEBOOK AT
[FACEBOOK.COM/GENERALSNU](https://www.facebook.com/generalsnus)

WARNING: This product is not
a safe alternative to cigarettes.

PACK THIS COUPON
BEFORE YOUR NEXT
ADVENTURE

WARNING: This product is not a safe alternative to cigarettes.

INSIDE

FOR THOSE WHO KNOW

General SNUS

You've joined a select community that knows that the pinnacle of tobacco satisfaction can only be reached by combining precise Swedish craft with an impeccable technique over 150 years in the making.

WE'RE GLAD YOU'RE HERE.

BENEFITS OF GENERAL SNUS

- Over 150 years of unequaled quality
- Simple, high-grade ingredients
- Smokeless and spitless
- Adheres to strict food-grade manufacturing process

QUESTIONS OR WANT TO REPORT CONCERNS ABOUT GENERAL SNUS?

Contact us at:
info@swedishmatch.com
(270) 685-8777
GeneralSnus.com

WARNING: This product is not a safe alternative to cigarettes.

GET ANY CAN OF General Snus FOR \$1

MANUFACTURER'S COUPON EXPIRES 03/31/23

RETAILER: Subtract \$1.00 from your normal retail price including applicable sales tax. Write that amount (your price minus \$1) in the space provided.

WARNING: This product is not a safe alternative to cigarettes.

RETAILER: Swedish Match North America LLC, will pay you the face value of this coupon plus \$.08 handling provided you accept the coupon from a consumer in exchange for specified package purchase. Retailer must submit on request invoices proving purchases of sufficient stock within normal redemption cycle to cover the coupons presented for redemption. This coupon is non-transferable. Void where prohibited, taxed or otherwise restricted. Cash redemption value 1/20 of \$.01. LIMIT ONE COUPON PER PURCHASE. ANY USE NOT CONSISTENT WITH THESE TERMS CONSTITUTES FRAUD. For coupon inquiries, call the Retailer Hotline: 1-800-285-7602. EXPIRATION DATE: 3/31/23. CONSUMER: By submitting this coupon, I hereby certify that I am 21 years of age or older as may be specified by state law, and am a current consumer of tobacco products. Distribution of product prohibited to persons under 21. THIS COUPON CANNOT BE COMBINED WITH ANY OTHER OFFERS OR COUPONS. Mail to: Inmar Brand Solutions Dept. 70195 Mr Rcv Office 801 UNION PACIFIC BLVD STE 5 LAREDO TX 78045-9475

General Snus Monthly Direct Mailer (requested via EM)

Nov. 2021 – June 2022

FOR THOSE WHO
REACH NEW HEIGHTS



THANK YOU
We hope you know how much we appreciate your interest in these exclusive offers.

THANK YOU

We hope you know how much we appreciate your interest in these exclusive offers.

QUESTIONS OR WANT TO REPORT
CONCERNS ABOUT GENERAL SNUS?
CONTACT US AT

info@swedishmatch.com | (270) 685-8777
You can also learn more at GeneralSnus.com

To opt out of future promotional mailings and be removed from our mailing list, please contact the Consumer Call Center at (270) 685-8777.

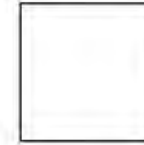
WARNING: Smokeless tobacco is addictive.

MANUFACTURER'S COUPON EXPIRES 03/31/23

RETAILER: Subtract \$1.00 from your normal retail price including applicable sales tax. Write that amount (your price minus \$1.00) in the space provided.

RETAILER: Swedish Match LLC, will pay you the face value of this coupon plus \$.08 handling provided you accept the coupon from a consumer in exchange for specified package purchase. Retailer must submit on request invoices proving purchases of sufficient stock within normal redemption cycle to cover the coupons presented for redemption. This coupon is non-transferable. Void where prohibited, taxed or otherwise restricted. Cash redemption value 1/20 of \$.01. LIMIT ONE COUPON PER PURCHASE. ANY USE NOT CONSISTENT WITH THESE TERMS CONSTITUTES FRAUD. For coupon inquiries, call the Retailer Hotline: 1-800-285-7602. EXPIRATION DATE: 3/31/23. CONSUMER: By submitting this coupon, I hereby certify that I am 21 years of age or older as may be specified by state law, and am a current consumer of tobacco products. Distribution of product prohibited to persons under 21. THIS COUPON CANNOT BE COMBINED WITH ANY OTHER OFFERS OR COUPONS. Mail to: Inmar Brand Solutions Dept. 70195 Mfr Rev

Swedish Match PWT A MRP Annual Rpt 2022 Page 637 of 768



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06/22/2022

QUESTIONS OR WANT TO REPORT
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You can also learn more at GeneralSnus.com

To opt out of future promotional mailings and be removed from our mailing list, please contact the Consumer Call Center at (270) 685-8777.

\$3 OFF 2 CANS OF General Snus MANUFACTURER'S COUPON EXPIRES 03/31/23

RETAILER: Swedish Match LLC, will pay you the face value of this coupon plus \$.08 handling provided you accept the coupon from a consumer in exchange for specified package purchase. Retailer must submit on request invoices proving purchases of sufficient stock within normal redemption cycle to cover the coupons presented for redemption. This coupon is non-transferable. Void where prohibited, taxed or otherwise restricted. Cash redemption value 1/20 of \$.01. LIMIT ONE COUPON PER PURCHASE. ANY USE NOT CONSISTENT WITH THESE TERMS CONSTITUTES FRAUD. For coupon inquiries, call the Retailer Hotline: 1-800-285-7602. EXPIRATION DATE: 3/31/23. CONSUMER: By submitting this coupon, I hereby certify that I am 21 years of age or older as may be specified by state law, and am a current consumer of tobacco products. Distribution of product prohibited to persons under 21. THIS COUPON CANNOT BE COMBINED WITH ANY OTHER OFFERS OR COUPONS. Mail to: Inmar Brand Solutions Dept. 70195 Mfr Rev

5 09249 10008 8 0609249-877093

WARNING: Smokeless tobacco is addictive.

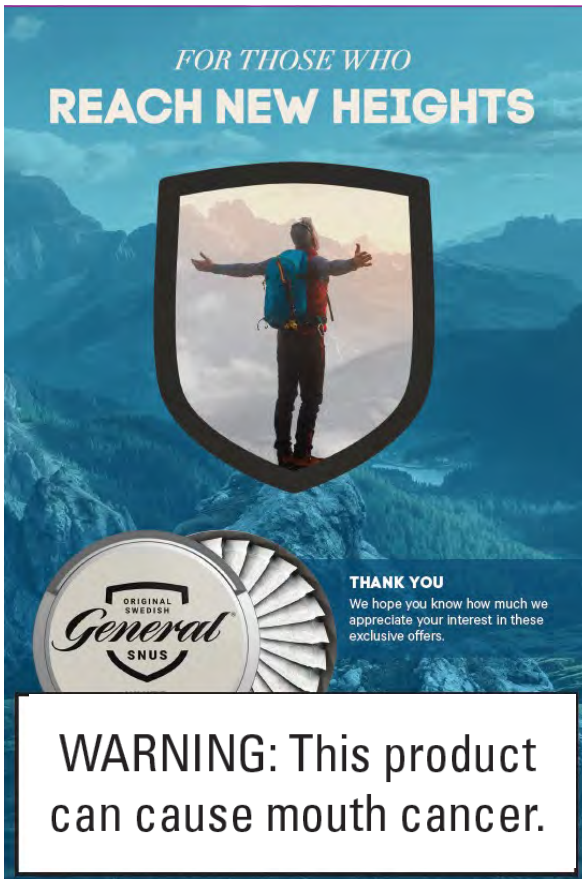
\$5 OFF 3 CANS OF General Snus MANUFACTURER'S COUPON EXPIRES 03/31/23

RETAILER: Swedish Match LLC, will pay you the face value of this coupon plus \$.08 handling provided you accept the coupon from a consumer in exchange for specified package purchase. Retailer must submit on request invoices proving purchases of sufficient stock within normal redemption cycle to cover the coupons presented for redemption. This coupon is non-transferable. Void where prohibited, taxed or otherwise restricted. Cash redemption value 1/20 of \$.01. LIMIT ONE COUPON PER PURCHASE. ANY USE NOT CONSISTENT WITH THESE TERMS CONSTITUTES FRAUD. For coupon inquiries, call the Retailer Hotline: 1-800-285-7602. EXPIRATION DATE: 3/31/23. CONSUMER: By submitting this coupon, I hereby certify that I am 21 years of age or older as may be specified by state law, and am a current consumer of tobacco products. Distribution of product prohibited to persons under 21. THIS COUPON CANNOT BE COMBINED WITH ANY OTHER OFFERS OR COUPONS. Mail to: Inmar Brand Solutions Dept. 70195 Mfr Rev

5 09249 10074 3 0609249-877092

WARNING: Smokeless tobacco is addictive.

General Snus Monthly Direct Mailer (requested via EM) June 2022-current



QUESTIONS OR WANT TO REPORT
CONCERNS ABOUT GENERAL SNUS?
CONTACT US AT

info@swedishmatch.com | (270) 685-8777
You can also learn more at GeneralSnus.com

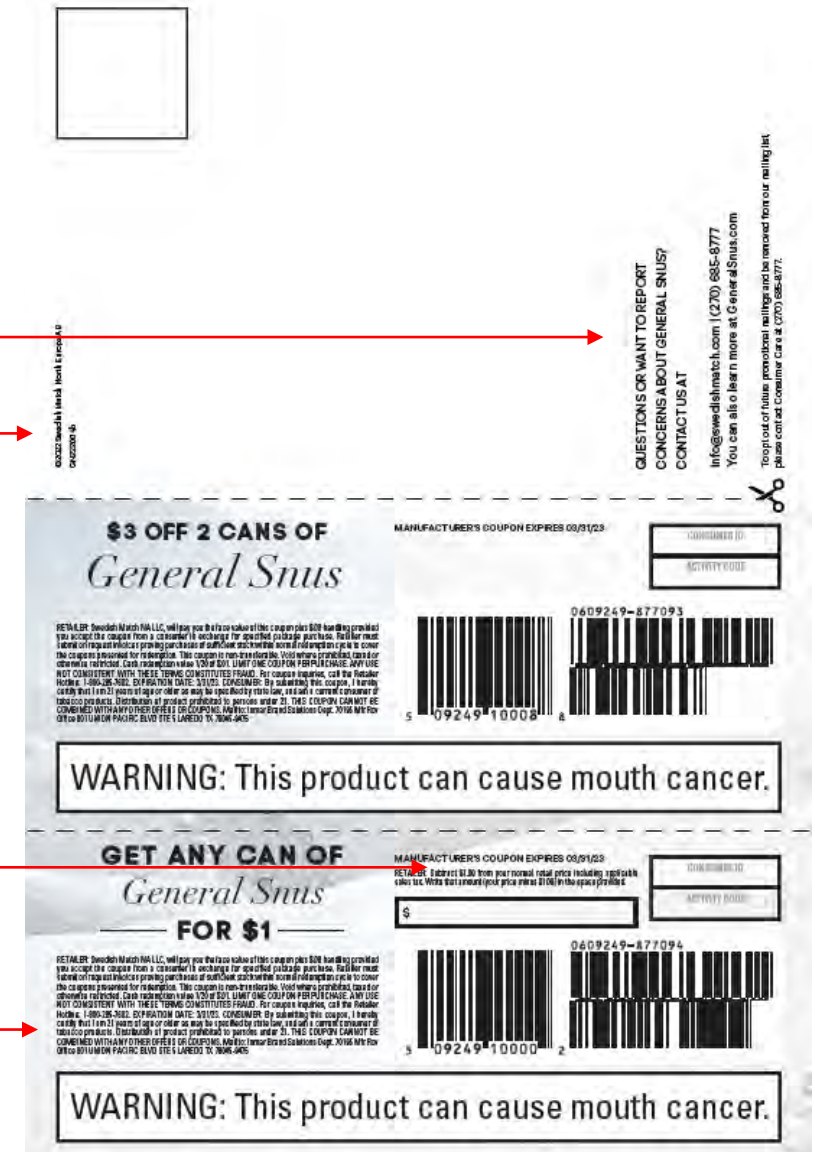
To opt out of future promotional mailings and be removed from our mailing list,
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GN222004a

THANK YOU
We hope you know how much we appreciate your interest in these exclusive offers.

MANUFACTURER'S COUPON EXPIRES 03/31/23
RETAILER: Subtract \$1.00 from your normal retail price including applicable sales tax. Write that amount (your price minus \$1.00) in the space provided.

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General Snus Monthly Direct Mailer (requested via EM) Nov. 2021 - current



We hope you know how much we appreciate your interest in these exclusive offers.

QUESTIONS OR WANT TO REPORT CONCERNS ABOUT GENERAL SNUS? CONTACT US AT

info@swedishmatch.com | (270) 685-8777
You can also learn more at GeneralSnus.com

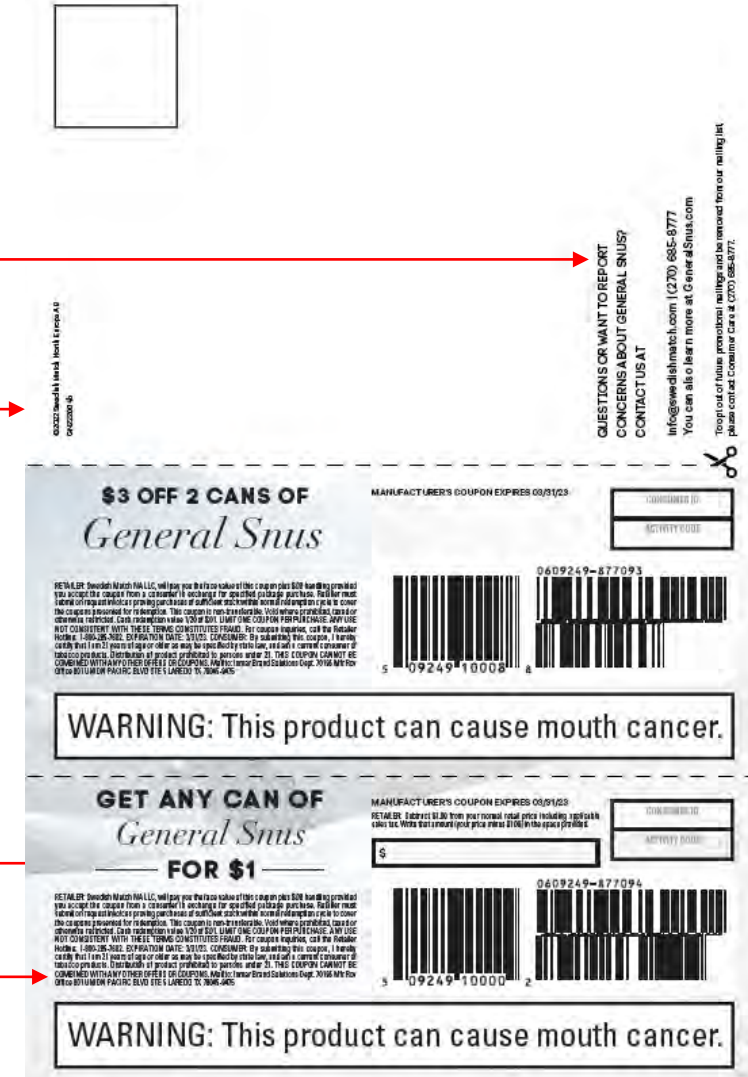
To opt out of future promotional mailings and be removed from our mailing list, please contact Consumer Care at (270) 685-8777.

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MANUFACTURER'S COUPON EXPIRES 03/31/23

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General Snus Monthly Direct Mailer (requested via EM) Nov. 2021 - current



THE
PINNACLE
OF
FLAVOR

THANK YOU
We hope you know how much we appreciate
your interest in these exclusive offers.

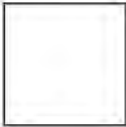
WARNING: This product
can cause mouth cancer.

QUESTIONS OR WANT TO REPORT
CONCERNS ABOUT GENERAL SNUS?
CONTACT US AT

info@swedishmatch.com | (270) 685-8777
You can also learn more at GeneralSnus.com

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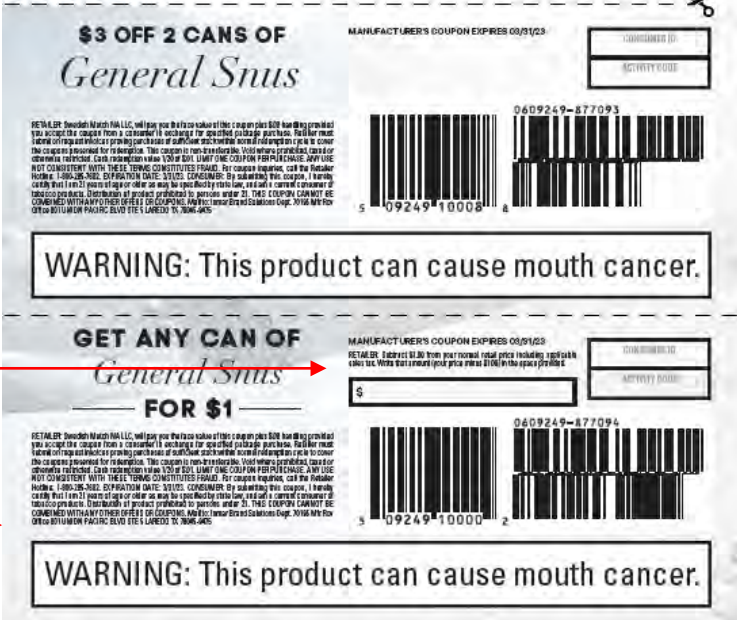
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MANUFACTURER'S COUPON EXPIRES 03/31/23

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RETAILER: Swedish Match LLC, will pay you the face value of this coupon plus \$.08 handling provided you accept the coupon from a consumer in exchange for specified package purchase. Retailer must submit on request invoices proving purchases of sufficient stock within normal redemption cycle to cover the coupons presented for redemption. This coupon is non-transferable. Void where prohibited, taxed or otherwise restricted. Cash redemption value 1/20 of \$.01. LIMIT ONE COUPON PER PURCHASE. ANY USE NOT CONSISTENT WITH THESE TERMS CONSTITUTES FRAUD. For coupon inquiries, call the Retailer Hotline: 1-800-285-7602. EXPIRATION DATE: 3/31/23. CONSUMER: By submitting this coupon, I hereby certify that I am 21 years of age or older as may be specified by state law, and am a current consumer of tobacco products. Distribution of product prohibited to persons under 21. THIS COUPON CANNOT BE COMBINED WITH ANY OTHER OFFERS OR COUPONS. Mail to: Inmar Brand Solutions Dept. 70195 Mfr Rcv Office 601 UNION PACIFIC BLVD STE 3 LAREDO TX 78045-9475

Warning reflects when mailer re-ordered



General Snus Monthly Direct Mailer (requested via website) Nov. 2021 - current

JOIN OUR COMMUNITY AT [FACEBOOK.COM/GENERALSNU](https://facebook.com/generalsnus)

**YOU
ALREADY
KNOW**

THIS IS A TOBACCO EXPERIENCE
LIKE NO OTHER.



JOIN OUR COMMUNITY AT [FACEBOOK.COM/GENERALSNU](https://facebook.com/generalsnus)

WARNING: Smokeless tobacco is addictive.

To opt out of future promotional mailings and be removed from our mailing list, please contact the Consumer Call Center at (270) 685-8777.

NOTE: General Snus is for adult tobacco users. If you do not currently use tobacco, General Snus is not for you. If you use tobacco and would like to quit, discuss with your physician or visit BeTobaccoFree.gov for more information.

**\$4 OFF 2 CANS OF
General Snus**

MANUFACTURER'S
COUPON EXPIRES
03/31/23

0609249-877102

09249-17093

RETAILER: Swedish Match LLC, will pay you the face value of this coupon plus \$0.08 handling provided you accept the coupon from a consumer in exchange for specified package purchase. Retailer must submit on request invoices proving purchases of sufficient stock within normal redemption cycle to cover the coupons presented for redemption. This coupon is non-transferable. Void where prohibited, taxed or otherwise restricted. Cash redemption value 1/20 of \$0.01. LIMIT ONE COUPON PER PURCHASE. ANY USE NOT CONSISTENT WITH THESE TERMS CONSTITUTES FRAUD. For coupon inquiries, call the Retailer Hotline: 1-800-285-7602. EXPIRATION DATE: 3/31/23. CONSUMER: By submitting this coupon, I hereby certify that I am 21 years of age or older as may be specified by state law, and am a current consumer of tobacco products. Distribution of product prohibited to persons under 21. THIS COUPON CANNOT BE COMBINED WITH ANY OTHER OFFERS OR COUPONS. Mail to: Inmar Brand Solutions Dept. 70195 Mfr Rev Office 801 UNION PACIFIC BLVD STE 5 LAREDO TX 78045-9475

WARNING: Smokeless tobacco is addictive.

QUESTIONS OR WANT TO REPORT
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CONTACT US AT
info@swedishmatch.com | (270) 685-8777
You can also learn more at GeneralSnus.com

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GN122001

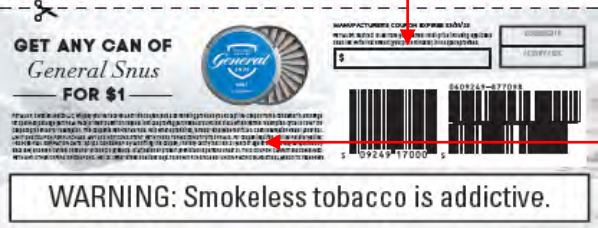
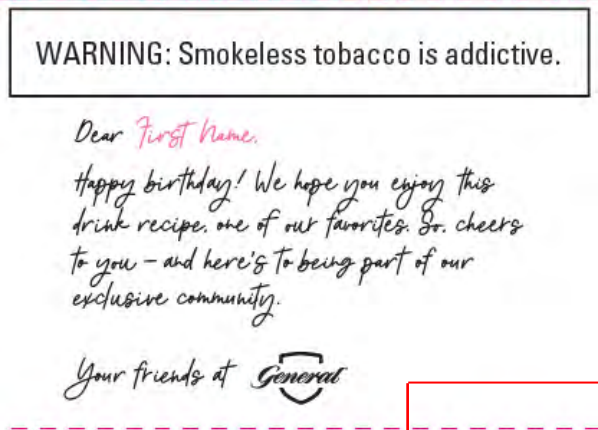
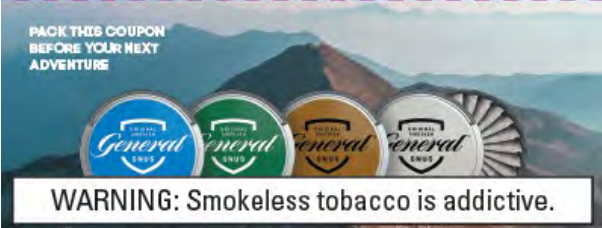
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General Snus B-Day Direct Mailer

Nov. 2021 - current



To opt out of future promotional mailings and be removed from our mailing list, please contact the Consumer Call Center at (270) 685-8777.

NOTE: General Snus is for adult tobacco users. If you do not currently use tobacco, General Snus is not for you. If you use tobacco and would like to quit, discuss with your physician or visit BeTobaccoFree.gov for more information.

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GN422001

THE SWEDISH HORSEMAN

2oz SWEDISH VODKA
2 DASHES ANGOSTURA BITTERS
4oz CHILLED GINGER ALE
2 LEMON SLICES
HANDFUL FRESH MINT LEAVES
ICE CUBES

Combine vodka and Angostura bitters in an ice-filled glass. Slowly add the ginger ale, and gently stir. Garnish with mint and lemon slices.

MANUFACTURER'S COUPON EXPIRES 03/31/23
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RETAILER: Swedish Match LLC, will pay you the face value of this coupon plus \$.08 handling provided you accept the coupon from a consumer in exchange for specified package purchase. Retailer must submit on request invoices proving purchases of sufficient stock within normal redemption cycle to cover the coupons presented for redemption. This coupon is non-transferable. Void where prohibited, taxed or otherwise restricted. Cash redemption value 1/20 of \$.01. LIMIT ONE COUPON PER PURCHASE. ANY USE NOT CONSISTENT WITH THESE TERMS CONSTITUTES FRAUD. For coupon inquiries, call the Retailer Hotline: 1-800-285-7602. EXPIRATION DATE: 3/31/23. CONSUMER: By submitting this coupon, I hereby certify that I am 21 years of age or older as may be specified by state law, and am a current consumer of tobacco products. Distribution of product prohibited to persons under 21. THIS COUPON CANNOT BE COMBINED WITH ANY OTHER OFFERS OR COUPONS. Mail to: Inmar Brand Solutions Dept. 70195 Mfr Rcv Office 801 UNION PACIFIC BLVD STE 5 LAREDO TX 78045-9475

Warning reflects when mailer re-ordered

General Snus Specialty Direct Mailer (In-Home 3/1/22) - folded



**HERE'S YOUR
CHANCE TO WIN**
A CUSTOM CHILLER

See inside for details on how to win.
PLUS EXCLUSIVE SAVINGS!

To opt out of future promotional mailings and be removed from our mailing list, please contact the Consumer Call Center at (270) 685-8777.
©2022 Swedish Match North Europe AB GN522010



Gift Sticker Included
SPECS
4.75 x 4.75in



General Snus Specialty Direct Mailer (In-Home 3/1/22) - unfolded

RETAILER: Swedish Match LLC, will pay you the face value of this coupon plus \$08 handling provided you accept the coupon from a consumer in exchange for speci-ed package purchase. Retailer must submit on request invoices proving purchases of suf-cient stock within normal redemption cycle to cover the coupons presented for redemption. This coupon is non-transferable. Void where prohibited, taxed or otherwise restricted. Cash redemption value 1/20 of \$01. LIMIT ONE COUPON PER PURCHASE. ANY USE NOT CONSISTENT WITH THESE TERMS CONSTITUTES FRAUD. For coupon inquiries, call the Retailer Hotline: 1-800-285-7602. EXPIRATION DATE: 3/31/23. CONSUMER: By submitting this coupon, I hereby certify that I am 21 years of age or older as may be speci-ed by state law, and am a current consumer of tobacco products. Distribution of product prohibited to persons under 21. THIS COUPON CANNOT BE COMBINED WITH ANY OTHER OFFERS OR COUPONS. Mail to: Inmar Brand Solutions Dept. 70195 Mfr Rev Ofce 801 UNION PACIFIC BLVD STE 5 LAREDO TX 78045-9475

WAYS TO WIN

- Vote each day to increase your chances to win.
- We're awarding 13 chiller grand prizes.
- 7 weekly prizes – General poster series, with a different theme each month.

To opt out of future promotional mailings and be removed from our mailing list, please contact the Consumer Call Center at (270) 685-8777.
©2022 Swedish Match North Europe AB

SAVE \$5 ON A CAN OF
General Snus

WARNING: Smokeless tobacco is addictive.

INTRODUCING

THE MOST Chill GIVEAWAY

YOU COULD WIN A CUSTOM CHILLER. OR A WEEKLY PRIZE!

CHOOSE THE MOST CHILL CHILLER

VOTE FOR YOUR FAVORITE DESIGN AND YOU COULD WIN.

ORCHAD ADVENTURE

NARROW BRIDGE

LUMINOUS BEACH

ICEBERG BEACH

VOTING BEGINS MARCH 1
[GENERALSNU.COM/MOSTCHILLGIVEAWAY](https://www.generalsnus.com/mostchillgiveaway)

WAYS TO WIN

- Vote each day to increase your chances to win.
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- 7 weekly prizes – General poster series, with a different theme each month.

ENTER HERE

WARNING: Smokeless tobacco is addictive.

MAILER - Inside

Display Area: 71.5 sq. in.
Warning Size Needed for 30% = 14.3 sq. in.
Warning Size Area = 6 in.
Actual Warning Size % =
Text is 31 pt. Univers LT.

KEEP THINGS CHILL.

Turn over for details

SAVE \$5 ON A CAN OF
General Snus

GIFT STICKER INSIDE

A SMALL WAY TO SHOW THE WORLD HOW CHILL YOU REALLY ARE

THE MOST Chill GIVEAWAY

WE'RE GIVING AWAY PRIZES FOR

13 WEEKS

HERE'S YOUR CHANCE TO WIN A CUSTOM CHILLER

PLUS EXCLUSIVE SAVINGS!

See inside for details on how to win.

Outside

No purchase necessary. Open only to legal residents of, and currently residing in, the 50 U.S. and D.C. (excluding residents of MA, MI & VA), who are tobacco consumers, 21 & older. Void in MA, MI, VA and where prohibited. Begins 11:00 am. ET on 3/1/22 and ends 11:00 am. ET on 5/27/22. The Most Chill Giveaway is sponsored by Swedish Match North America, LLC. For complete details, see Official Rules at GeneralSnus.com.

QUESTIONS OR WANT TO REPORT CONCERNS ABOUT GENERAL SNUS? CONTACT US AT Info@swedishmatch.com or (270) 685-8777. You can also learn more at GeneralSnus.com.

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General Snus Specialty Direct Mailer (In-Home 3/1/22) – folded CO ONLY

Includes full rules

SPECS

Folded: 6 x 4in

Soft touch treatment for the paper



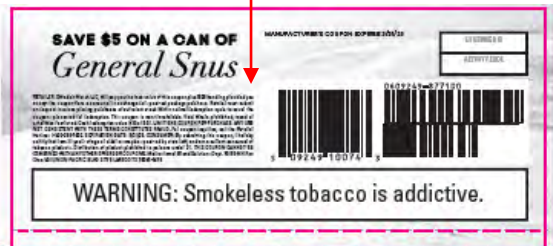
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General Snus Specialty Direct Mailer (In-Home 3/1/22) – unfolded

CO ONLY

Includes full rules



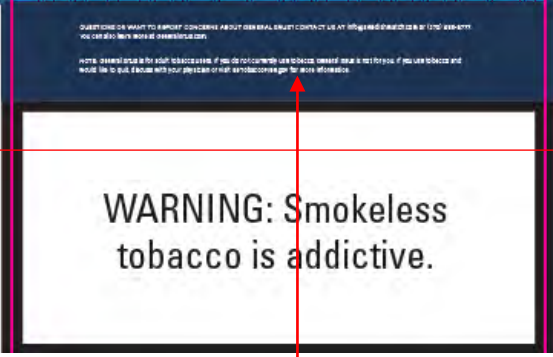
Consumer Disclosure: This is an offer and does not imply that you have won a prize. No purchase necessary to enter or win. Purchasing will not increase your chances of winning. Void where prohibited. Starts 11:00 am. ET on 3/1/22. Ends 11:00 am. ET on 5/27/22. Odds of winning a Prize depend upon the number of eligible Entries received for each Weekly drawing and overall. See insert for Official Rules and complete details. (13) Grand Prizes: A Sponsor-specified limited edition chiller. ERV = \$200/each. (91) First Prizes: A Sponsor-specified Poster. ERV = \$10/each. Sponsored by Swedish Match North America, LLC.

RETAILER: Swedish Match LLC, will pay you the face value of this coupon plus \$.08 handling provided you accept the coupon from a consumer in exchange for speci-ed package purchase. Retailer must submit on request invoices proving purchases of suf-cient stock within normal redemption cycle to cover the coupons presented for redemption. This coupon is non-transferable. Void where prohibited, taxed or otherwise restricted. Cash redemption value 1/20 of \$.01. LIMIT ONE COUPON PER PURCHASE. ANY USE NOT CONSISTENT WITH THESE TERMS CONSTITUTES FRAUD. For coupon inquiries, call the Retailer Hotline: 1-800-285-7602. EXPIRATION DATE: 3/31/23. CONSUMER: By submitting this coupon, I hereby certify that I am 21 years of age or older as may be speci-ed by state law, and am a current consumer of tobacco products. Distribution of product prohibited to persons under 21. THIS COUPON CANNOT BE COMBINED WITH ANY OTHER OFFERS OR COUPONS. Mail to: Inmar Brand Solutions Dept. 70195 Mfr Rcv Ofce 801 UNION PACIFIC BLVD STE 5 LAREDO TX 78045-9475



Turn over for details

KEEP THINGS CHILL. JUST AS THE SWEDES INTENDED.



WAYS TO WIN

- Vote each day to increase your chances to win.
- We're awarding 13 chiller grand prizes.
- 7 weekly prizes – General poster series, with a different theme each month.



Outside

No purchase necessary. Open only to legal residents of, and currently residing in, the 50 U.S. and D.C. (excluding residents of MA, MI & VA), who are tobacco consumers, 21 & older. Void in MA, MI, VA and where prohibited. Begins 11:00 am. ET on 3/1/22 and ends 11:00 am. ET on 5/27/22. The Most Chill Giveaway is sponsored by Swedish Match North America, LLC. For complete details, see Official Rules at GeneralSnus.com.

QUESTIONS OR WANT TO REPORT CONCERNS ABOUT GENERAL SNUS? CONTACT US AT info@swedishmatch.com or (270) 685-8777. You can also learn more at GeneralSnus.com.


NOTE: General Snus is for adult tobacco users. If you do not currently use tobacco, General Snus is not for you. If you use tobacco and would like to quit, please consult your physician or visit BeTobaccoFree.gov for more information.

To opt out of future promotional mailings and be removed from our mailing list, please contact the Consumer Call Center at (270) 685-8777.


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General Snus – Meijer Express (In-Home October 2022)

STILL THE ORIGINAL
EASY TO FIND NEAR YOU

General SNUS x 

Our tight fit side labels are designed to keep your authentic Swedish snus fresh. So now you can find General Snus in a cooler or on the shelf at select retailers near you, including your local Meijer Express.



WARNING: This product is not a safe alternative to cigarettes.



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GN522014

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You can also learn more at GeneralSnus.com

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Our tight fit side labels are designed to keep your authentic Swedish snus fresh. So now you can find General Snus in a cooler or on the shelf at select retailers near you, including your local Meijer Express.

RETAILER: Swedish Match NA LLC, will pay you the face value of this coupon plus \$.08 handling provided you accept the coupon from a consumer in exchange for specified package purchase. Retailer must submit on request invoices proving purchases of sufficient stock within normal redemption cycle to cover the coupons presented for redemption. This coupon is non-transferable. Void where prohibited, taxed or otherwise restricted. Cash redemption value 1/20 of \$.01. LIMIT ONE COUPON PER PURCHASE. ANY USE NOT CONSISTENT WITH THESE TERMS CONSTITUTES FRAUD. For coupon inquiries, call the Retailer Hotline: 1-800-285-7602. EXPIRATION DATE: 3/31/23. CONSUMER: By submitting this coupon, I hereby certify that I am 21 years of age or older as may be specified by state law, and am a current consumer of tobacco products. Distribution of product prohibited to persons under 21. THIS COUPON CANNOT BE COMBINED WITH ANY OTHER OFFERS OR COUPONS. Mail to: Inmar Brand Solutions Dept. 70195 Mfr Rcv Office 801 UNION PACIFIC BLVD STE 5 LAREDO TX 78045-9475

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\$3 OFF ANY CAN OF
General Snus

MANUFACTURER'S COUPON EXPIRES 03/31/23

CONSUMER ID: _____
ACTIVITY CODE: _____

9409249-877104

3 09249 10087 3

WARNING: This product is not a safe alternative to cigarettes.

General Snus Direct Mail Reporting – By Direct Mailer – Nov. '21 – Oct. '22

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General Snus Direct Mail Reporting – By State – Nov. 21 – Oct. 22

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General Snus Direct Mail Reporting – By Age – Nov. ‘21 – Oct. ‘22

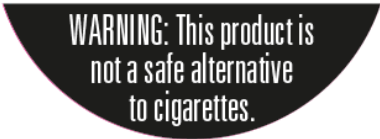
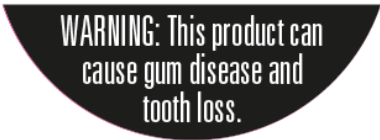
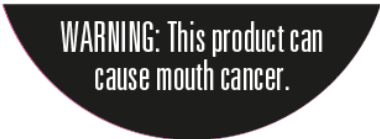
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GENERAL SNUS PACKAGING

General Packaging – Mint – November 2021 – October 2022



ORIGINAL | 24 PORTIONS

WARNING: This product can cause gum disease and tooth loss.

GENERAL® ORIGINAL

24 Portions Swedish Snus
Sale Only Allowed in the United States
100% Premium Imported Tobacco
Net. Wt. 0.85 oz. (24 g)
Manufactured in Sweden and Distributed by:
© Swedish Match NA, LLC, Richmond, VA 23219. U.S.A.
Customer Call Center: (270) 685-8777
or visit GeneralSnus.com

Best Before:

6 09249 60000 4

Ingredients: Water, Tobacco, Humectant (Propylene Glycol), Taste Enhancer (Salt), pH Adjuster (Sodium Carbonate), Natural and Artificial Flavors including Artificial Smoke Flavor

WARNING: This product can cause mouth cancer.

WARNING: This product can cause gum disease and tooth loss.

WARNING: This product is not a safe alternative to cigarettes.

WARNING: Smokeless tobacco is addictive.

Swedish Match PMTA MRTP Annual Rpt 2022 Page 653 of 763



General Packaging Update – White – November 2021 – October 2022



WARNING: This product can cause mouth cancer.

WARNING: This product can cause gum disease and tooth loss.

WARNING: This product is not a safe alternative to cigarettes.

WARNING: Smokeless tobacco is addictive.



General Packaging Update – Wintergreen –November 2021 – October 2022

WARNING: This product can cause mouth cancer.

WARNING: This product can cause gum disease and tooth loss.

WARNING: This product is not a safe alternative to cigarettes.

WARNING: Smokeless tobacco is addictive.

GENERAL® WINTERGREEN

24 Portions Swedish Snus
Sale Only Allowed in the United States
100% Premium Imported Tobacco
Net. Wt. 0.85 oz. (24 g)
Manufactured in Sweden and Distributed by:
© Swedish Match NA, LLC, Richmond, VA 23219. U.S.A.
Customer Call Center: (270) 685-8777
or visit GeneralSnus.com

Best Before:

Ingredients: Water, Tobacco, Taste Enhancer (Salt), Natural and Artificial Flavors including Artificial Smoke Flavor, Humectant (Propylene Glycol), pH Adjuster (Sodium Carbonate) Artificial Sweetener (Acesulfam K)

Swedish Match PMTA MRTP Annual Rpt 2022 | Page 655 of 763

142



GENERAL SNUS POS

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GENERAL SNUS MERCHANDISING

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2022 MRTP Annual Report

CATEGORY: SNUS

BRAND: GENERAL SNUS

November 2021 – October 2022

Appendix 2A (7)

Trade Advertising

General Print Trade Ad: In-market Q1-2 2022

(b) (4)

General Print Trade Ad: In-market Q3 2022



GREATER PROFITS

NOW IN FULL VIEW

NEW UNREFRIGERATED DISPLAYS RAISE YOUR BOTTOM LINE.
TIGHT-FIT SIDE LABELS KEEP SNUS FRESH.

***Swedish Match.

CALL YOUR REP AT 800-774-7754
Stock the product with the 1st Modified Risk Tobacco Product order

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RAISE YOUR BOTTOM LINE. *RIGHT NOW.*

WITH THE WORLD'S #1
SELLING SNUS, THERE'S
NO COMPARISON.

**Increase velocity & grow
profits immediately**

- Displays built to
move product
- Side labels keep
snus fresh
- Strong penny profit

**CALL YOUR REP AT
800-774-7754**

Swedish Match



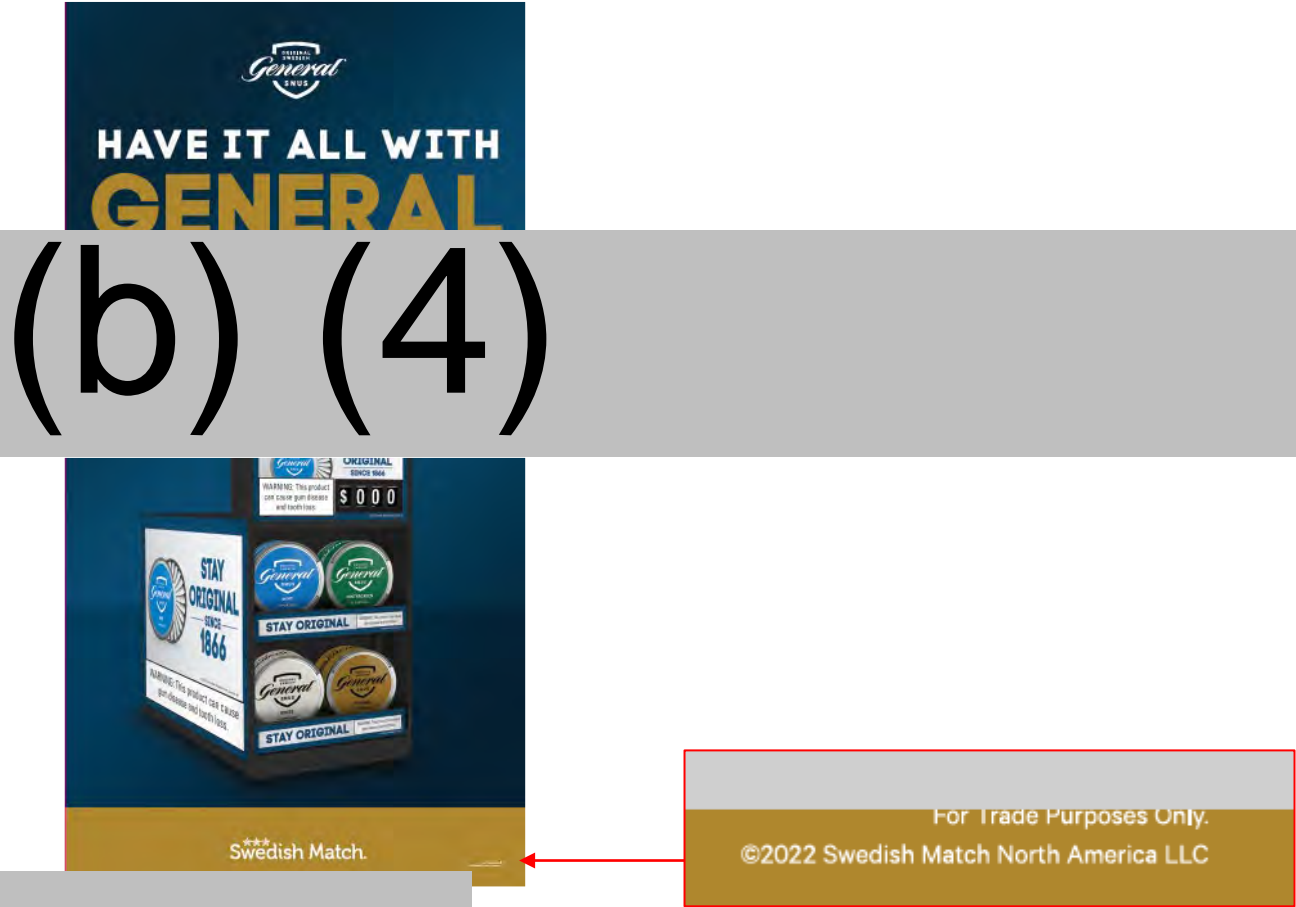
For trade purposes only.
©2022 Swedish Match North America LLC

General NACS Show Banner and Poster: In-market Q4 2022

Poster



Banner



For Trade Purposes Only.
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Swedish Match

Q4 2021 General Print Trade Ad Plan

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2022 General Print Trade Ad Plan

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2022 General Print Trade Ad Plan Q1

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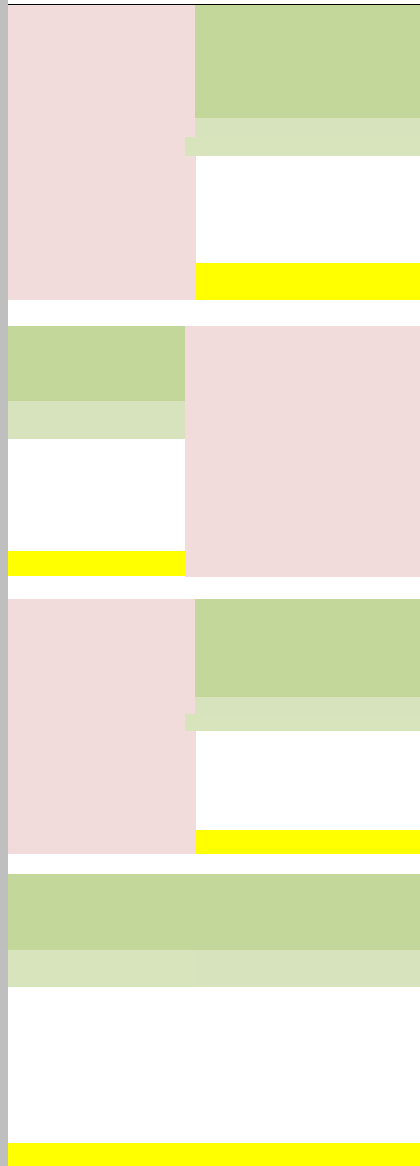
Swedish Match

2022 General Print Trade Ad Plan Q2

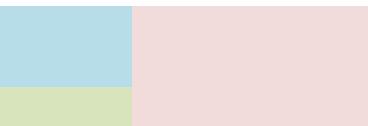
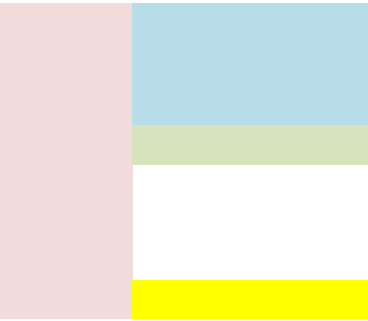


Swedish Match

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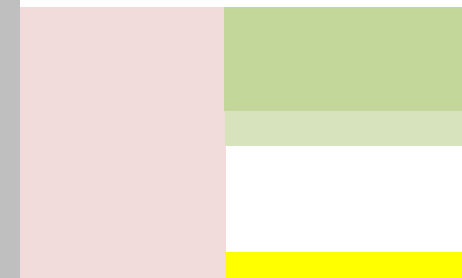
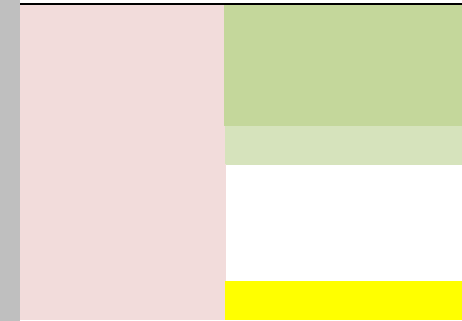


2022 General Print Trade Ad Plan Q3



Swedish Match

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2022 General Print Trade Ad Plan Q4

(b) (4)





U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

JUN 7 - 2018

RECEIVED
LEGAL OPS

June 01, 2018

GENERAL CORRESPONDENCE

Swedish Match North America, Inc.
Attention: Gerard Roerty, Jr., Vice President, General Counsel & Secretary
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219

FDA Submission Tracking Numbers (STN(s)): MULTIPLE STNs, See Below

Dear Mr. Roerty:

Please refer to your Postmarket Periodic reports for the Premarket Tobacco Applications (PMTAs) received on October 27, 2017 and November 22, 2017, submitted under section 910(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for the following tobacco products:

<u>Periodic Report STN</u>	<u>STN</u>	<u>TOBACCO PRODUCT NAME</u>
TC0003310	PM0000010	General Loose
TC0003024	PM0000017	General Wintergreen Portion White Large
TC0003025	PM0000011	General Dry Mint Portion Original Mini
TC0003026	PM0000012	General Portion Original Large
TC0003028	PM0000014	General Mint Portion White Large
TC0003030	PM0000016	General Portion White Large

Based on our review of your 2017 Periodic reports, we have identified the following issues for which we believe additional information or clarification will be helpful to FDA in performing a complete substantive review of **subsequent** Periodic Reports.

1. For all products, you submitted summary information on the (b) (4) (b) (4). It appears that these two studies are ongoing. The (b) (4) study appears to be comprised of tobacco users and non-users, however details on the study population are not provided. In subsequent post-market Periodic reports, clearly indicate for all studies if they are ongoing or complete. Including details on the sample populations for all studies along with summary information by key demographic variables such as tobacco use status, age, and gender would assist FDA in evaluating the study.
2. For all products, you submitted summary information about the (b) (4) (b) (4). On slide 2 of the PowerPoint slide deck you indicate that the (b) (4) was conducted between April and September 2016, and terminated on January 1, 2017. However, slide 16 suggests that data was collected for this

Page 2,TC0003310, TC0003024-TC0003026, TC0003028, TC0003030

study from 2014 through 2016, presenting conflicting information.(b) (4)

(b) (4)

(b) (4) In order to assess the potential impact of these products on public health, it is important for FDA to review information from studies that have been completed about the products. In your next Periodic report, clarify the dates that referenced studies were completed. In addition, we recommend you provide complete summaries of all study data for completed studies relevant to these tobacco products to assist FDA evaluation of the study.

3. For all of the products you provide a table of publications identified through a literature search. In this post-market report (b) (4) publications were identified. However, (b) (4) publications in the table did not include complete information (citations #13 and 16). In subsequent reports, include a complete citation for the publications identified including full title, author names, publications date, and publisher so that FDA can easily identify the referenced publication.

4. For all products, you submitted information (b) (4)

(b) (4)

(b) (4)

(b) (4)

. In subsequent reports, provide summary information including point estimates, confidence intervals, and denominators which will allow FDA to fully evaluate the study data.

5. For all products, you provided sales data for each product specific to this post-market review including a summary of total US distribution by units (cans and pounds) and dollars, by US census region, retail markets and channels.(b) (4)

(b) (4)

(b) (4)

. The survey information does not provide direct information about the tobacco products specific to this post-market review.

On the September 7, 2017 teleconference FDA recommended you provide data separated by product along with a summary of the prevalence of your product's use by key demographic variables (e.g., tobacco use status, age, gender). In this report, you state (b) (4)

(b) (4)

(b) (4) Studies suggest that information on user of the products associated with this report has been collected. In subsequent reports, we recommend that you provide complete summaries for studies relevant to the products associated with this review, including product use information by tobacco use status, age, and gender so the FDA can fully evaluate the study information.

Page 3,TC0003310, TC0003024-TC0003026, TC0003028, TC0003030

We remind you that all regulatory correspondence can be submitted via the FDA Electronic Submission Gateway (www.fda.gov/esg) using eSubmitter or mailed to :

Food and Drug Administration
Center for Tobacco Products
Document Control Center (DCC)
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We are unable to accept regulatory submissions by electronic mail.

If you have any questions, please contact Shireen Ahmad, MS, Regulatory Health Project Manager, at (240) 402 – 0435 or at Shireen.Ahmad@fda.hhs.gov.

Sincerely,

Ilun C. Murphy -S

2018.06.01 13:12:30 -04'00'

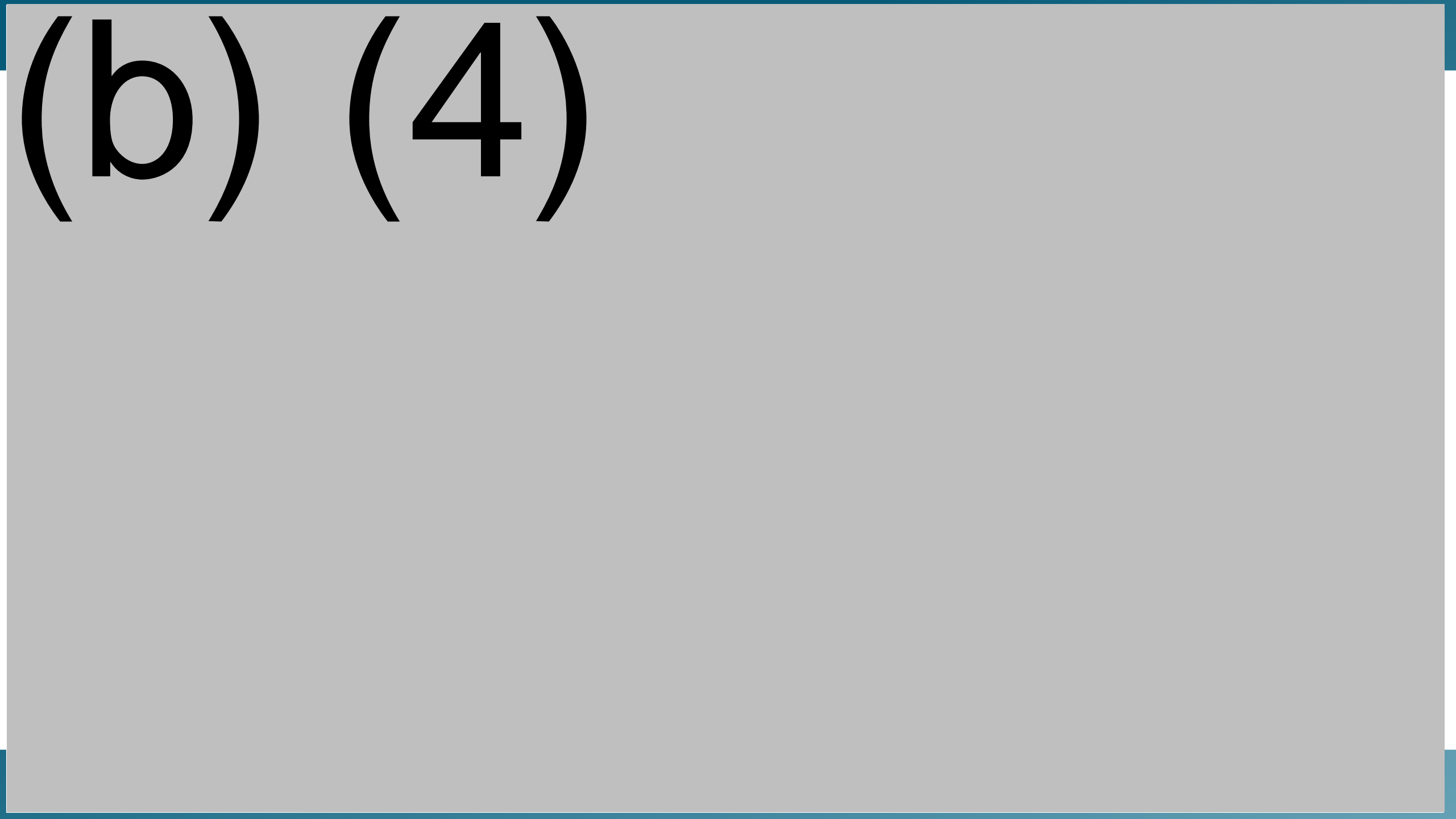
Ilun Murphy, M.D.
Director, Division of Individual Health Science
Office of Science
Center for Tobacco Products

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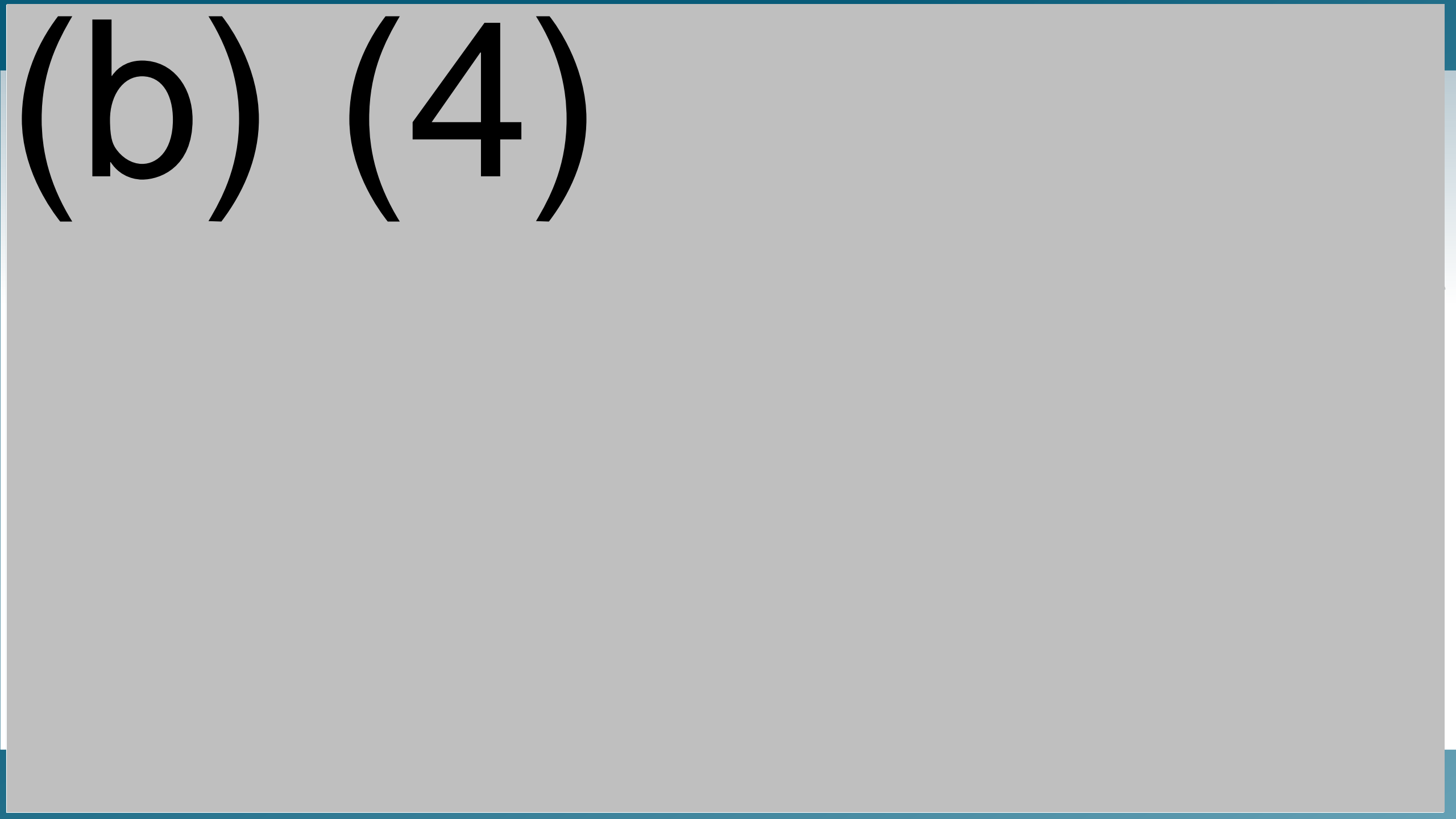


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QUESTIONS OR COMMENTS?

(b) (4)

Editorial

Method Development and Applications for Reduced-Risk Products

Fadi Aldeek * and Mohamadi A. Sarkar

Altria Client Services LLC, 601 East Jackson Street, Richmond, VA 23219, USA; mohamadi.a.sakar@altria.com

* Correspondence: fadi.aldeek@altria.com

1. Introduction

Cigarette smoking remains the leading cause of preventable premature death and disease in the U.S. There is an overwhelming scientific consensus that cigarette smoking is addictive and causes lung cancer, heart disease, chronic obstructive pulmonary disease, and other serious diseases [1]. While there are thousands of constituents in cigarette smoke, ref. [2] certain representative classes of chemicals characterized as harmful and potentially harmful constituents (HPHCs) have been studied extensively and attributed to the harm caused by the inhaled smoke of combusted tobacco [3]. Many people in the public health sector have acknowledged that a continuum of risk exists among tobacco products, with conventional combustible cigarettes at the highest end of that spectrum, and non-combustible products on the lower end [4–6]. In recent years, there has been rapid growth in the availability of innovative, non-combustible products, including oral tobacco-derived nicotine (OTDN) products, heated tobacco products (HTPs), and electronic cigarettes (also referred to as e-vapor products; EVPs). Because they are non-combustible, such products contain far fewer combustion-related HPHCs [7–9]. As a result, substantial reduction in the biomarkers for exposure to HPHCs have been reported among adult smokers who completely switch to such products [10,11]. Such large reductions in exposure to HPHCs are accompanied with favorable changes in biomarkers indicative of smoking-related disease outcomes [12]. Consequently, there is a growing body of evidence suggesting that such products likely present a substantial reduction in disease risks [13], and many people in the public health sector recognize the potential of such non-combustible products for reducing harm [6,14,15]. Therefore, switching to non-combustible alternatives presents a significant opportunity to decrease the burden of disease associated with smoking combustible cigarettes, particularly among adult smokers who are unable or unwilling to quit.

There is a growing body of research dedicated to characterizing non-combustible products. Many researchers from industry, academia, and government are working to develop and validate analytical methods to extract, separate, identify, and quantitate a variety of analytes from innovative tobacco products using a wide range of analytical techniques. Understanding the basic properties of these products is important to better characterize innovative oral and inhalable tobacco products. The oral non-combustible categories include traditional smokeless tobacco and OTDN products. Traditional smokeless tobacco products contain tobacco leaves and exist in three different forms including chewing tobacco (loose leaf, plug, or twist); snuff (finely ground tobacco that can be dry, moist, or packaged in pouches (e.g., snus)); and dissolvable (finely ground tobacco pressed into shapes such as tablets, sticks, or strips) products [16]. OTDN products, on the other hand, are tobacco-leaf free and are available in various forms including nicotine pouches, lozenges, gums, and dissolvable products [17,18]. These products may contain a number of ingredients that include tobacco-derived nicotine, pH adjusters (e.g., sodium carbonates), filler materials (e.g., modified cellulose, microcrystalline cellulose), sweeteners, stabilizers, and flavorings.



Citation: Aldeek, F.; Sarkar, M.A. Method Development and Applications for Reduced-Risk Products. *Separations* **2022**, *9*, 78. <https://doi.org/10.3390/separations9030078>

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Inhalable non-combustible products including EVPs and HTPs are compositionally different than cigarettes. Unlike traditional cigarettes, EVPs do not contain tobacco plant material or paper. They are mainly composed of a mixture of propylene glycol and glycerol in various ratios and flavors, and may or may not contain nicotine. In contrast, HTPs contain tobacco leaves but the tobacco is heated instead of burned, thereby lowering the temperature from $>900\text{ }^{\circ}\text{C}$ to $\sim 500\text{ }^{\circ}\text{C}$. Due to the absence of tobacco leaves and paper in EVPs and the process of heating the tobacco in HTPs, many of the HPHCs in mainstream smoke are either not present or are present at significantly lower levels than smoking cigarettes [19,20].

The accurate determination and quantitation of constituents and chemicals in these products is needed for guiding product design, determining relative product performance, ensuring consistency during the manufacturing process, informing toxicological risk assessment, and regulatory reporting. This also allows for the characterization of inherent risks of innovative products, which helps determine whether the use of such products is potentially less harmful than smoking cigarettes. In this Special Issue, we discuss the latest analytical methods for chemical characterization of a variety of oral and inhalable non-combustible products.

2. Summary of Published Articles

This Special Issue includes research papers which address the latest analytical methods used for the identification and characterization of a variety of constituents and analytes in innovative oral and inhalable non-combustible tobacco products, using state-of-the-art techniques and instrumentations. The various contributions presented in this Special Issue are summarized based on the type of products evaluated and related methods reported.

Recently, nicotine pouches have emerged as a new category of innovative OTDN products. In this Special Issue, we received four contributions from different groups on methods that have been developed and validated to determine the nicotine release profiles, nicotine degradants, and HPHCs from a variety of nicotine pouch products. In these contributions, the authors have systematically used the developed methods to compare OTDN to traditional smokeless tobacco products. In the first manuscript, Aldeek et al. evaluated the nicotine release from 35 nicotine pouch products that are currently marketed in seven flavors with five different nicotine levels [21]. This is an important method to characterize the nicotine release from these pouches. The authors implemented a well-established dissolution method using the U.S. Pharmacopeia flow-through cell dissolution apparatus 4 (USP-4) that the same group previously developed for the evaluation of the nicotine release from traditional smokeless tobacco products [22]. The dissolution method was used for product-to-product comparison. The percent nicotine release profiles obtained from the 35 nicotine pouches under the same experimental conditions were found to be equivalent across all nicotine levels and flavors analyzed, indicating a similar rate of nicotine release from these oral nicotine pouch products. The authors further compared the percent nicotine release profiles from these nicotine pouches to a variety of other commercially available nicotine pouches and traditional pouched smokeless tobacco products. The authors state that the differences in percent nicotine release rates within the OTDN category could be associated with the inherent product characteristics (e.g., pouch paper and ingredients).

In the second manuscript, Knopp et al. developed a biorelevant dissolution method to study the nicotine release from OTDN nicotine pouches and portioned smokeless tobacco products (e.g., pouched snus) [23]. The *in vitro* release of nicotine was investigated in biorelevant volumes of artificial saliva using a custom-made dissolution apparatus. The apparatus consisted of a sinker that was prepared by 3D printing using polylactic acid material. The nicotine released was quantitated by a validated high-pressure liquid chromatography ultra-violet spectroscopy (HPLC-UV) method. The percent nicotine release profiles obtained from the OTDN and snus pouches were found to be distinct, indicating the ability of this method to discriminate between these two product categories. Additionally,

the authors compared the *in vitro* dissolution to *in vivo* data from a previously conducted clinical study [24]. Data showed a strong *in vitro*/*in vivo* correlation, indicating that the method reported in this publication is not only sensitive enough to discriminate between nicotine pouch and snus products, but could also serve as a predictive tool for product development and/or a monograph for oral tobacco/nicotine product equivalence studies.

The stability of nicotine depends on the inherent components of the product (e.g., fillers, pH, stabilizers, other ingredients, and moisture content) as well as the external environment (e.g., exposure to light and high temperatures). Therefore, developing methods to assess the nicotine stability in these products by monitoring the nicotine degradation compounds and select impurities is very important. These methods are useful to monitor the stability of nicotine in these products and for quality control purposes (e.g., to evaluate the purity of nicotine added to the product). In the third manuscript, Avagyan et al. developed a selective, accurate, and repeatable liquid chromatography–tandem mass spectrometry (LC-MS/MS) method for the determination of seven nicotine-related degradants and impurities [25]. The seven nicotine degradants in this method were nicotine-N'-oxide, cotinine, nor nicotine, anatabine, anabasine, β -nicotyrin, and myosmine. Most of the analytes were detected in the nicotine pouch products; however, they were found to be at lower levels compared to traditional tobacco products.

In the fourth manuscript, Jablonski et al. used fully validated CORESTA recommended methods to determine 17 selected HPHCs (including tobacco-specific nitrosamines, carbonyls, benzo[a]pyrene, nitrite, and metals) from 21 nicotine pouch products [26]. The selected pouches were obtained from seven different commercially available brands at the maximum nicotine level and a variety of flavors. The authors assessed two types of pouch products described as “white powder-based pouches” and “plant-based” pouches. The white powder-based pouches were similar to those described above, whereas the plant-based pouches were made from non-tobacco plant materials with pharmaceutical grade nicotine added during the production process. HPHCs in the 21 nicotine pouches were compared to those found in four traditional smokeless tobacco products (two CORESTA reference products and two commercially available products). The authors reported that the HPHCs levels, most notably metals, in the plant-based pouches were higher than those observed in powder-based products. In some plant-based pouches, these levels were even higher than those seen in traditional pouch smokeless tobacco products. However, the overall HPHCs levels observed in these plant-based nicotine pouches were at or below those levels observed in traditional pouch smokeless tobacco products.

The presence of unique constituents in the aerosol of EVPs is an important consideration in overall risk assessment of such products and is of interest to regulators and public health researchers. EVPs include both the e-liquid (containing nicotine and other ingredients) and aerosolizing apparatus, whether sold as a unit or separately. Due to the unique parts and components of EVPs, the constituents are distinct and specific to the product type (e.g., pod-based, open system, etc.). Therefore, in addition to the HPHCs, unknown compounds in the aerosol need to be characterized. The majority of analytical work on EVPs has focused on targeting known chemicals of interest based on changes to the device, formulation, power, temperature, or sampling approaches [27]. In this Special Issue, we received three contributions highlighting the development of targeted and non-targeted analytical methods for the determination of HPHCs and unknowns in EVPs. In the first report, Jin et al. evaluated the traditional 2,4-dinitrophenylhydrazine (2,4-DNPH) derivatization and quantitation of formaldehyde in e-liquid and aerosol of EVPs [28]. Formaldehyde is an HPHC listed by the FDA as a carcinogen and a respiratory toxicant [3]. Previous reports stated that formaldehyde is often underreported in EVPs due to a possible reaction with propylene glycol and glycerin in the aerosol which causes the formation of hemiacetals [29]. The research presented in this study provided a thorough experimental design to clearly demonstrate that hemiacetals formed in the aerosol readily hydrolyze to free formaldehyde and consequently form formaldehyde hydrazone in the typical 2,4-DNPH acidic trapping solution for quantitation. This study showed that the

commonly used 2,4-DNPH method is an appropriate method for the derivatization and accurate quantitation of formaldehyde in the aerosol generated by EVPs.

In the second manuscript, Chen et al. developed a comprehensive, targeted analysis using gas chromatography coupled to mass spectrometry (GC-MS) for the determination of 53 aerosol constituents from EVPs of currently marketed products [30]. The aerosol generation was conducted using non-intense and intense puffing regimens. Only 10 out of the targeted 53 analytes were quantifiable. The authors have compared their data to constituents collected from aerosols generated by both traditional cigarettes and a commercially available HTP that has been authorized for marketing in the U.S. The aerosol generated by the evaluated EVPs had detectable levels of ten targeted analytes including known degradants of propylene glycol and glycerin (e.g., acetaldehyde and formaldehyde) and nicotine-related compounds. The majority of tobacco-related HPHCs were not detectable in the aerosols. The levels of select HPHCs (other than nicotine) measured in the EVPs were found to be 96–99% lower than the same HPHCs reported in the cigarette smoke. However, the reduction levels of these select HPHCs in the EVPs ranged from 61% to 99% when compared to the levels found in HTP aerosol. The authors attributed the low levels of HPHCs in the EVPs' aerosols to the controlled temperature used in the device which is designed to reduce byproducts of combustion.

To address the potential gaps in understanding left by targeted analysis of EVPs, Crosswhite et al. developed and optimized liquid chromatography high resolution mass spectrometry (LC-HRMS) and GC-MS semi-quantitative methods to study unknown chemicals in generated aerosols [31]. These two methods were developed to account for the different physicochemical properties of possible chemical compounds including polarity, volatility, hydrophilicity, etc. The authors used differential analyses based on nine aerosol collection replicates of each studied EVP and each collection condition (intense and non-intense puffing regimens) to characterize compounds that differed from collection blanks. They relied on statistical tools to extract relevant information from a highly complex dataset. The authors reported all compounds at or above concentrations of 0.5 µg/g which were considered related to the sample. A total of 91 compounds were identified using these two methods in both non-intense and intense puffing regimens. This number was strikingly low when compared to the number of compounds (>5000) found in cigarette smoke [32]. Of the detected compounds, 47% were confirmed using reference standards. The authors showed that the studied aerosols from EVPs were approximately 50-fold less complex when compared to cigarette smoke.

We have also received two articles describing the development of LC-MS/MS methods for the identification of biomarkers of exposure specific to EVPs and other non-combustible products. Burkhardt et al. developed an LC-MS/MS method for measuring human exposure to 1,2-propylene glycol and glycerol, the main e-liquid constituents in EVPs [33]. These constituents were analyzed in plasma and urine samples from a clinical study comparing five nicotine product user groups (users of combustible cigarettes, EVPs, HTPs, oral tobacco products, and nicotine replacement therapy (NRT) products) and a control group of non-users. The results demonstrated elevated propylene glycol levels in urine and plasma in EVPs users compared to users of other products. The data showed a correlation between the propylene glycol and nicotine equivalents in the plasma and urine of EVP users. The nicotine equivalents were calculated by measuring the levels of nicotine and ten nicotine metabolites using a method developed by Piller et al. [34]. The authors also reported a dose–response relationship between urinary and plasma propylene glycol and intensity of vaping. The authors proposed that propylene glycol can be used as a potential biomarker to monitor compliance to EVP use when assessing switching behavior among smokers.

The same group, in a second article by Rogner et al., developed and validated another highly sensitive LC-MS/MS method for the determination of 3-hydroxybenzo[a]pyrene (3-OH-BaP), a metabolite of benzo[a]pyrene (BaP), in urine samples from smokers and non-combustible products users [35]. BaP is listed by FDA as an HPHC and classified

by IARC as a human carcinogen which is formed during the incomplete combustion of tobacco [3]. The method was validated with a very low limit of quantitation (50 pg/L) to account for trace levels of 3-OH-BaP in urine samples. The detected levels of 3-OH-BaP in urine samples were found to be significantly higher in cigarette smokers compared to non-combustible product users. The data presented by the authors showed the suitability of 3-OH-BaP as a biomarker for BaP and could be applied in clinical studies evaluating innovative non-combustible tobacco products.

3. Conclusions

The nine articles published in this Special Issue covered the latest analytical methods developed and applied for the chemical characterization or exposure assessment to tobacco product constituents of innovative non-combustible products (i.e., EVPs, HTPs, and OTDN products). The developed methods included (1) characterizing the nicotine dissolution release profiles and determining nicotine degradants and HPHCs in OTDN pouches; (2) identifying HPHCs, targeted, and unknown compounds in EVPs; and (3) determining potential biomarkers at trace levels in urine and blood samples in a variety of EVPs, HTPs, and OTDN products. The contributors to this Special Issue systematically compared the amount and release characteristics of select HPHCs, degradants, and unknown compounds found in innovative non-combustible products to combustible cigarettes or traditional smokeless tobacco products. This Special Issue is representative of the importance of analytical sciences research in characterizing innovative non-combustible products for guiding product design, determining relative product performance, ensuring consistency during the manufacturing process, informing toxicological risk assessment, and enabling regulatory reporting. The current advances in the development and applications of the analytical methods reported in this Special Issue can be used to inform the harm reduction potential of innovative non-combustible products for adult smokers.

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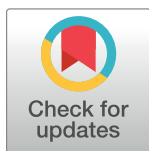
RESEARCH ARTICLE

Chronic snus use in healthy males alters endothelial function and increases arterial stiffness

Lukasz Antoniewicz^{1,2*}, Mikael Kabele³, Ulf Nilsson³, Jamshid Pourazar³, Gregory Rankin³, Jenny A. Bosson³, Magnus Lundbäck⁴

1 Division of Internal Medicine, Department of Clinical Sciences, Karolinska Institutet, Danderyd University Hospital, Stockholm, Sweden, **2** Division of Pulmonology, Department of Medicine II, Medical University of Vienna, Vienna, Austria, **3** Division of Medicine, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden, **4** Division of Cardiovascular Medicine, Department of Clinical Sciences, Karolinska Institutet, Danderyd University Hospital, Stockholm, Sweden

* lukasz.antoniewicz@meduniwien.ac.at



Abstract

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Background

Snus usage is commonly touted as a safer alternative to cigarette smoking. However, recent studies have demonstrated possible adverse cardiovascular effects in chronic snus users. The present study evaluates the effects of chronic snus use on vascular function by assessing central arterial stiffness and endothelial vasodilatory function in healthy chronic snus users as compared to matched non-users.

Methods and results

Fifty healthy males (24 snus users, 26 age-matched controls) with a mean age of 44 years were included in the study. Arterial stiffness was assessed employing both pulse wave velocity and pulse wave analysis. Endothelial vasodilatory function was measured by venous occlusion plethysmography, utilizing intra-arterial administration of acetylcholine, glyceryl trinitrate and bradykinin to further gauge endothelium-dependent and -independent vasodilatory function. Arterial stiffness was significantly higher in chronic snus users as compared to controls: pulse wave velocity [m/s]: 6.6 ± 0.8 vs 7.1 ± 0.9 resp. ($p = 0.026$), augmentation index corrected for heart rate [%]: 0.1 ± 13.2 vs 7.3 ± 7.8 resp. ($p = 0.023$). Endothelial independent vasodilation, i.e. the reaction to glyceryl trinitrate, was significantly lower in snus users as measured by venous occlusion plethysmography.

Conclusions

The results of this study show an increased arterial stiffness and an underlying endothelial dysfunction in daily snus users as compared to matched non-tobacco controls. These findings indicate that long-term use of snus may alter the function of the endothelium and

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therefore reinforces the assertion that chronic snus use is correlated to an increased risk of development of cardiovascular disease.

Introduction

Cigarette smoking causes approximately 6 million deaths each year worldwide [1]. These deaths are mainly attributed to heart and lung disease as well as various forms of cancer [2]. The clear association between cigarette smoking and impaired health has for some time now been an unquestioned fact. The last decades of increasing regulations and improved public awareness have caused a dramatic decline in cigarette sales. In response to this, large transnational tobacco companies have been searching for alternative means of marketing and merchandising their product. One such strategy is to advance the global market of Swedish moist snuff, a tobacco product placed under the lip, most commonly referred to as snus [3].

In Sweden, the use of snus is widely spread and can be traced back to the beginning of the 18th century. Currently, approximately 22% of Swedish men and more than 4% of Swedish women use snus on a daily basis. This regular usage of snus has been steadily increasing since 2010 in both sexes [4]. Although the sale of snus is prohibited within the European Union (EU), Sweden did negotiate an exemption to this rule upon joining in 1995. As a result, snus is mainly manufactured in Sweden as well as in Norway, which is not an EU member. Despite persistent and intense lobbying efforts by the tobacco industry to challenge this ban, the EU Advocate General has opted to uphold this legislation [3]. Therefore, until recently, this product has almost exclusively been found in the Scandinavian countries.

Snus was first introduced to the US market in 2006, initially only available in a handful of cities used as test markets. Since then, snus has been heavily marketed by tobacco companies towards several different potential customer groups including women, young adults as well as chewing tobacco users [5]. As the tobacco industry looks to establish these products in new markets, it has been greatly debated whether snus is a safer alternative to cigarette smoking [6].

At present, several studies have demonstrated a link between snus use and increased risk of type 2 diabetes, heart failure as well as an increased mortality following myocardial infarction (MI) and stroke [7–11]. However, there are also studies that question these associations and which tend to be dismissive of the overall risk for cardiovascular disease (CVD) [12, 13]. Mechanistic studies investigating possible pathophysiological effects following chronic snus use are scarce. Thus far, the acute biological effects found immediately following snus use are increased blood pressure and heart rate as well as endothelial dysfunction demonstrated by flow mediated dilation [14, 15]. Furthermore, daily snus users exhibit a chronically altered flow mediated dilation compared to non-users [16, 17]. These findings indicate an intrinsic association between chronic snus use and endothelial dysfunction.

Increased arterial stiffness is an independent risk factor for the development of CVD [18]. Determining central arterial stiffness by pulse wave velocity (PWV) and pulse wave analysis (PWA) is a well-established and non-invasive method. Another method for assessing vascular function is measuring forearm blood flow (FBF) with venous occlusion plethysmography, which is generally accepted as the “gold standard” for the evaluation of endothelial function [19]. Through intra-arterial administration of locally active vasodilatory drugs, venous occlusion plethysmography is used to assess endothelium-dependent and independent vasodilation in the forearm. This comprehensive technique allows for analysis of different pathways and

aspects of endothelial dysfunction as well as evaluating general vasomotor function. Venous occlusion plethysmography has previously been employed to demonstrate endothelial damage in e.g. cigarette smokers and individuals exposed to combustion emission air pollution [20, 21]. To our current knowledge, no study has been performed in chronic snus users utilizing these methods to assess central arterial stiffness or vascular function.

This study aims at investigating the effects of long-time habitual snus use with several well-established methods for measuring vascular health.

Materials and methods

Study design

Sample size analysis was performed using G*Power 3.1 for a two-tailed ANOVA with repeated measures and between factor analysis [22]. A comparable study, analyzing forearm blood flow with venous occlusion plethysmography in smokers and non-smokers was used for effect size estimation [23]. A priori calculation using an effect size f of 0.42 showed that a total sample size of 50 is needed with a statistical power of 95% at a $p < 0.05$ significance level.

Twenty-four healthy male chronic snus users (≥ 15 years of snus use) and 26 age-matched healthy controls between the age of 30 to 65 years were included in the study. Study exclusion criteria included prior smoking > 1 year, hypertension, any form of cardiovascular, metabolic or respiratory disease, BMI > 30 as well as active allergy or inflammation within four weeks prior to the study. Upon enrolment, study participants had to complete a health wellness form and were investigated with ECG, dynamic spirometry, blood pressure control and blood tests (total blood count, white blood count, Na, K, creatinine, apolipoprotein A and B, HbA1C, INR, aPTT). Length, weight and waist circumference were checked upon enrolment. Self-reported tobacco-use as well as alcohol consumption and level of physical activity was recorded. Prior to measurements, study participants had to abstain from all forms of nicotine, alcohol and caffeine for 24 hours and from vigorous physical activity for 48 hours. All measurements were performed in a quiet, temperature-controlled room with volunteers resting comfortably in a semi-supine position.

Arterial stiffness

Following 20 minutes of rest, blood pressure was measured using a semi-automated non-invasive oscillometric sphygmomanometer (Boso-Medicus, Boso, Jungingen, Germany) after which arterial stiffness measurements commenced.

In accordance with the manufacturer's instructions, pulse wave analysis was assessed at the right radial artery with applanation tonometry using a transcutaneous micromanometer (Millar Instruments, Texas, USA) employing the SphygmoCor™ system (AtCor Medical, Sydney, Australia). Briefly, pulse wave analysis obtains the radial artery pulse wave and systematically converts this to an aortic pulse pressure waveform through a validated mathematical transfer function. The waveform is composed of a forward pressure wave, originating from the ventricular contraction, and a reflected wave caused by the peripheral vascular resistance. Augmentation index (AIx), expressed as a percentage, relates how much of the pulse pressure rise is attributed to the reflected wave. As Augmentation index is inversely proportional to heart rate (HR), it is commonly normalized for a heart rate at 75bpm (AIx@75). Measurements were accepted according to the SphygmoCor™ quality control criteria.

Pulse wave velocity (PWV) was measured using the Vicorder™ system (Skidmore Medical, Bristol, UK). This well-validated, non-invasive method obtains the pulse at sensor points on two inflatable cuffs, one placed around the neck over the carotid artery and the other at the upper thigh registering the femoral artery. As the distance between these two points is

measured and recorded, PWV can then be calculated to reflect the measure of the pulse pressure wave's rate of travel.

Three independent measurements of PWA, PWV and blood pressure were obtained from each volunteer and reported as mean values, as is standard practice.

Forearm blood flow

All participants underwent cannulation of the brachial artery using a 27-standard wire gauge needle. Following 30 minutes of saline infusion, acetylcholine at 5, 10 and 20 $\mu\text{g}/\text{min}$; glyceryl trinitrate (GTN) at 4, 8 and 16 $\mu\text{g}/\text{min}$ and bradykinin at 100, 300 and 1000 pmol/min were infused for 6 minutes at each dose. All infused vasodilators were separated by 20 minutes of saline infusion and given in a randomized order. FBF was assessed in both arms (infused and non-infused) by venous occlusion plethysmography using a mercury-in-silicone gauge as previously described [19].

Statistical analysis

Statistical calculations were performed with SPSS Statistics (24.0, IBM Corporation, NY, US) and GraphPad Prism (8.0, GraphPad Software Inc., CA, US) software. Data was checked for normality applying Shapiro-Wilk test. Skewed variables were checked for outliers and were analyzed by means of a non-parametric test (Mann-Whitney U Test) and normally distributed variables were compared with independent samples T-test. Two-way ANOVA for repeated measures was performed on measurements of FBF. If Mauchly's test for sphericity was violated, Greenhouse-Geisser corrected results were presented. Skewed variables in multiple measures ANOVA were analyzed following logarithmic transformation. Multiple regression analysis (Method: Stepwise Enter) was applied for arterial stiffness measurements. Prior to analysis independent variables were checked for collinearity. p-values of <0.05 were considered to be statistically significant. Blinded investigators performed all analyses.

Ethics statement

The study was approved by the local Ethics Review Board in Umeå and performed in accordance to the Declaration of Helsinki and with the written, informed consent of all participants. The whole study was performed at Umeå University and at Umeå University Hospital, Sweden.

Results

Baseline characteristics are presented in Table 1. The loose type of snus was used by 13, and the portion form by 11 snus users (54% vs 56% resp.). In order to negate single dose size differences, snus use was classified as cans per week. The only significant factor among baseline characteristics between groups was that snus users had a significantly higher alcohol consumption compared to controls.

Arterial stiffness

Snus users had significantly higher pulse wave velocity (PWV) and augmentation index corrected for heart rate (AIx@75) compared to controls (Fig 1). There was no significant difference in systolic and diastolic blood pressure or heart rate between snus users and controls (SBP [mmHg]: 123.9 vs 123.7, DBP [mmHg]: 78.5 vs 76.1, HR [bpm]: 54.9 vs 55.5 resp.).

Waist circumference was significantly correlated with BMI, apolipoprotein ratio and vigorous physical activity (S1 Table). Age, apolipoprotein ratio, vigorous physical activity and

Table 1. Baseline characteristics.

	Snus users n = 24	Controls n = 26	p-values
Age [years]	44.8±8.5	43.4±8.6	n.s.
BMI [kg/m ²]	25.5±2.4	25±3.3	n.s.
Waist circumference [cm]	91.8±7.7	90.3±8.6	n.s.
Alcohol consumption [ml/week]	62.3±57.3	29.3±30.3	0.017
Vigorous physical activity [h/week]	2.4±1.5	2.5±1.7	n.s.
Hemoglobin [g/L]	152.8±7.5	147.3±10.3	n.s.
Leukocyte count [x10 ⁹ /L]	5.7±1.2	5.4±1.1	n.s.
Platelet count [x10 ⁹ /L]	225±29.4	219.3±45.7	n.s.
Creatinine [μmol/L]	85.8±10.2	87.7±10	n.s.
Apolipoprotein A [g/L]	1.5±0.2	1.5±0.2	n.s.
Apolipoprotein B [g/L]	1.1±0.3	0.9±0.2	n.s.
Apolipoprotein B/A ratio	0.7±0.2	0.6±0.2	n.s.
HbA1c [mmol/mol]	35.6±3.7	36.2±2.6	n.s.
Snus use [years]	29.3±8.5	0±0	n.s.
Snus use [cans/week]	5.8±2.4	0±0	n.s.

Mean values ± SD.

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alcohol consumption were significantly correlated with HbA1c. Snus use, age, alcohol consumption and waist circumference were used in multiple regression analysis to predict PWV and AIx. Age and snus consumption were the only independent variables that significantly predicted arterial stiffness:

$$\text{PWV} : 5.378 + (\text{age} \times 0.028) + (\text{snus use} : 0.491); F(2, 47) = 4.968, p = 0.011, R^2 = 0.175.$$

$$\text{AIx@75} : -29.47 + (\text{age} \times 0.681) + (\text{snus use} : 6.244) : F(2, 47) = 12.888, p < 0.001, R^2 = 0.354$$

Forearm blood flow

All vasoactive drugs caused a dose-dependent increase in FBF ($p < 0.001$) in repeated measures ANOVA. However, at the highest dose of GTN (16 μg/ml) snus users had significantly lower FBF compared to controls (Fig 2).

Discussion

The present study is the first to show elevated arterial stiffness (PWV and AIx@75) in normotensive chronic snus users as compared to age-matched healthy controls. Chronic snus users also exhibited an impaired response to the endothelium-independent vasodilator GTN in FBF measured by venous occlusion plethysmography.

This study casts new light on the continuing debate whether snus use is a modifiable risk factor for CVD, particularly in regard to myocardial infarction (MI) and stroke. Thus far, cohort studies of snus users indicate no overall increase in the risk for onset of CVD compared to non-users. However, mortality rates do appear elevated in long term snus users that in fact go on to develop MI or stroke [7, 11–13]. This was further supported by Arefalk et al. who

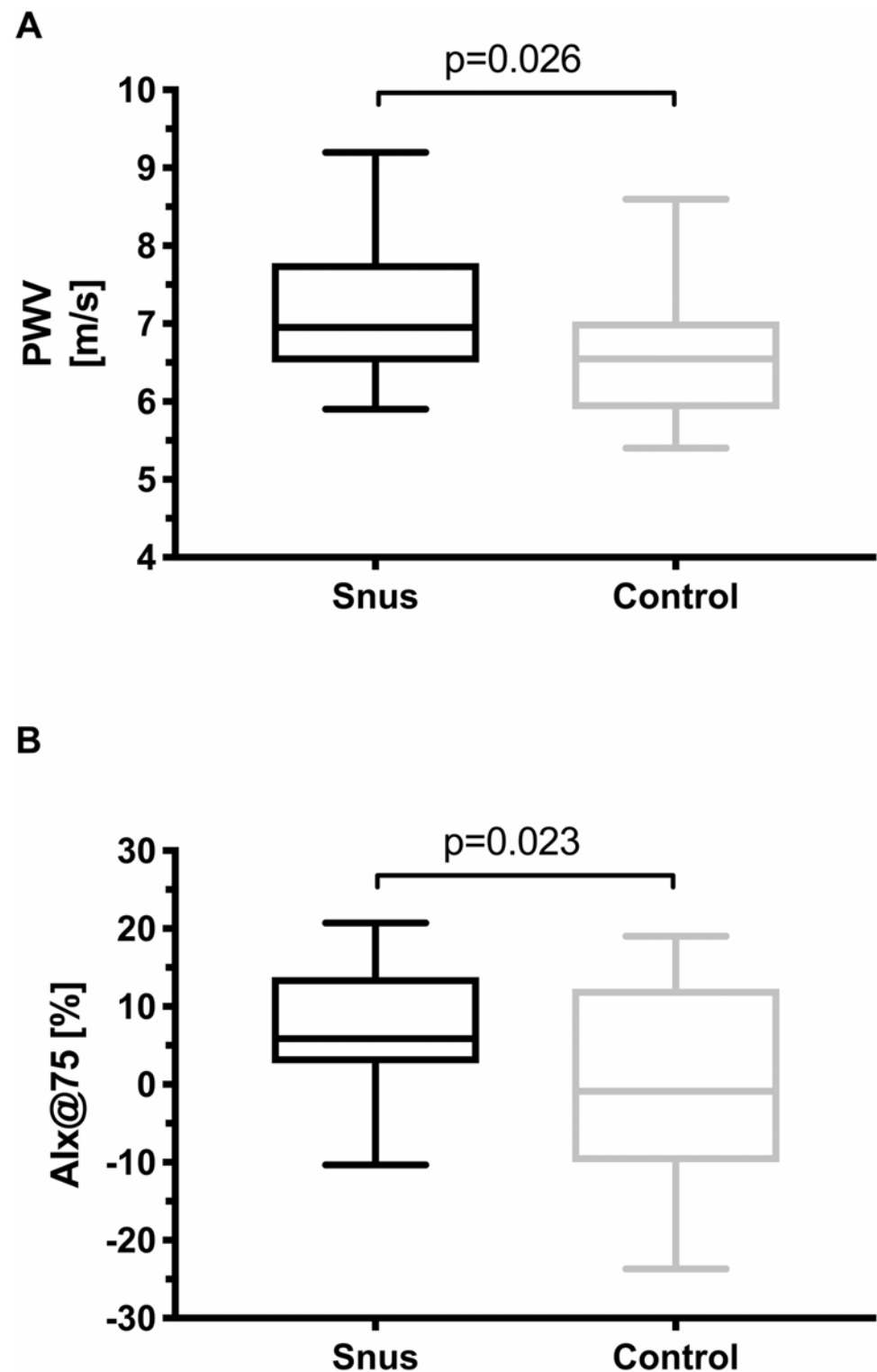


Fig 1. Arterial stiffness in chronic snus users and controls. Boxplots for (A) pulse wave velocity (PWV) and (B) heart rate corrected augmentation index (Aix@75). Whiskers represent minimum to maximum values.

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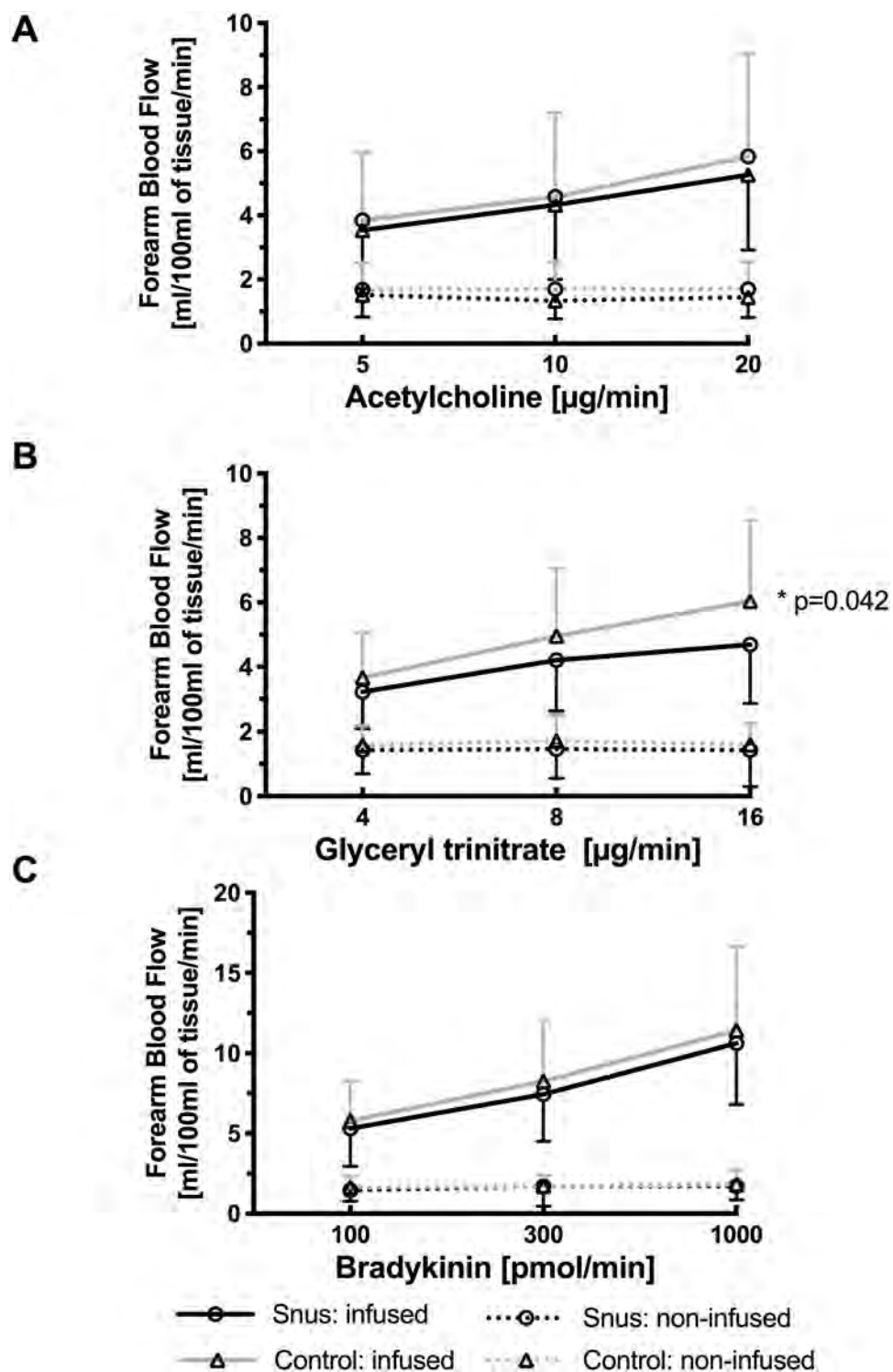


Fig 2. Vasodilatory function in chronic snus users and controls. Forearm blood flow (mean values \pm SEM) in snus users and controls during unilateral, intra-brachial infusion of vasoactive drugs in infused (solid line) and non-infused (dotted line) arms. Significant p -values are given for students T-test applied at each vasoactive drug dose.

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monitored snus users that gave up the habit compared to those who did not quit following an MI. They observed a nearly 50% reduction of mortality rates in the cessation group as compared to those that continued to use snus [10]. They also determined that the risk reduction was of the same magnitude as seen following smoking cessation post-MI. In the current study, we demonstrate that long term snus use is associated with increased arterial stiffness and impaired endothelial function, which strengthens the argument that snus use does indeed need to be considered a risk factor for CVD. The results also offer a pathophysiological explanation as to how snus use may lead to an elevated risk of death following MI or stroke.

Increased arterial stiffness is a blood pressure independent risk factor for the onset of CVD [18]. This stiffening of the arteries inversely impacts both systolic and diastolic pressure thus steadily leading to an increased workload, heightened oxygen demand of the left ventricle as well as diminishing coronary flow during diastole [24]. It is well-established that cigarette smoking leads to increased arterial stiffness as measured by PWV and AIX@75, yet the effects of snus use on arterial stiffness have not been as thoroughly investigated [25]. Regression analysis of our data demonstrates that age as well as snus use can predict an increase in arterial stiffness. Arterial stiffness has been shown to augment with age due to the physiological loss of elastic properties in the vascular tissue due to years of repeated stretching [26]. In this study we find that snus usage is comparable to an increase of AIX@75 throughout the time of 9.2 life years and 17.5 life years for PWV.

The monolayer of endothelial cells is key for sustaining systemic as well as local homeostasis. Endothelial dysfunction can affect both the macrovasculature as well as the microvasculature and has been associated with nearly every known risk factor for CVD, making it an independent and valuable predictor of cardiovascular events [27]. There are two previous studies that have shown impaired endothelial function in chronic snus users as measured by flow mediated dilation [16, 17]. However, this is currently the first study to investigate vasomotor function in chronic snus users by means of forearm venous occlusion plethysmography, recognized as the 'gold standard' method for the assessment of endothelial function [19]. We demonstrate that chronic snus users have attenuated FBF following GTN infusion as compared to the control group, yet no significant differences were found between the two groups following infusions of acetylcholine and bradykinin.

Nitric oxide (NO) is a signaling molecule released from the endothelium by the enzyme nitric oxide synthase, which generates smooth muscle relaxation and acts as a local anti-inflammatory agent [27]. Reduced bioavailability of NO is considered to be the hallmark feature of endothelial dysfunction. Acetylcholine and bradykinin are both endothelium-dependent dilators (EDD), which denotes a dependence on the function of nitric oxide synthase in the endothelium. In contrast, GTN is an endothelium-independent dilator (EID) and acts as a NO donor, and therefore is a test of NO sensitivity further along the pathway.

Our novel finding that chronic snus use is associated with impaired vasodilation following GTN infusion may offer a further explanation for the increased mortality rates seen in snus users during acute MIs as well as post-MI [7, 10]. GTN, also known as nitroglycerin, is a commonly used medication both in hospitals and as needed in daily life to prevent and treat chest pain caused by an inadequate supply of oxygen to the heart muscles, such as in angina pectoris and acute MI. It is well known that habitual, repeated usage of GTN causes nitrate tolerance and attenuated EID [28]. One hypothesis to the underlying mechanism of this is that an important enzyme in the signaling cascade for vasodilation, the cGMP-dependent protein kinase (PKG), may be diminished upon repeated GTN exposure [29]. It has been shown in rats that nicotine may also alter EID through this pathway, as chronic nicotine altered aortic muscle cell relaxation through the PKG pathway [30]. This is also supported by Halimi et al. who found that nicotine may alter the PKG pathway by demonstrating decreased urinary

excretion of cGMP after nicotine administration in non-smoking human subjects [31]. Therefore, it is possible that chronic nicotine exposure may have similar effects as recurrent GTN use on the PKG pathway resulting in a diminished vasodilation response to GTN in chronic snus users.

Lind et al. studied FBF in cigarette smokers compared to matched non-smokers, they showed an inverse correlation of the duration of smoking to impairment of EDD, with a trend seen towards reduced EID [20]. It is possible that combustion-derived compounds found in cigarette smoke are responsible for these effects on the EDD [32]. Nicotine, a key component in snus, is known to prompt a systemic sympathomimetic reaction and may induce increased arterial stiffness and endothelial dysfunction [33]. A study where rats were chronically exposed to nicotine-free cigarette smoke extract showed impaired EDD, but not EID [34]. Furthermore, due to prolonged absorption, additives that raise the product pH as well as sustained plasma levels of nicotine and its metabolites, snus users are exposed to higher nicotine levels as compared to cigarette smokers [35, 36]. Thus, the adverse effects of snus use on EID may be markedly attributable to the high circulating levels of nicotine.

Clinical experimental studies examining vascular function following exposure to nicotine or nicotine replacement therapy are scarce. Though it has been shown that the intake of a single 2mg nicotine tablet caused an acute elevation in arterial stiffness in healthy volunteers as opposed to placebo [37]. This could suggest that nicotine itself can also alter arterial stiffness, which is further supported by findings from in vitro and animal studies. Nicotine exposure in vitro has been demonstrated to decrease the elastic properties of smooth muscle cells and increase proliferation of endothelial cells [38, 39]. Furthermore, rats exposed to repeated intravenous nicotine infusions displayed aortic remodeling, a process associated with the development of hypertension [40].

Baseline characteristics in this study showed that chronic snus use was significantly associated with a higher alcohol use than in non-snus users. This finding may not be so unexpected, as tobacco use has been linked with increased alcohol consumption [41]. More importantly, the overall alcohol consumption was not at risk-behavior levels and was not correlated with arterial stiffness in regression analysis.

Study limitations

The present study investigated male subjects. Endothelial function has been demonstrated to be affected by sex hormones, several of these differences may explain the divergence of CVD presentation in women relative to men. Therefore, it is pertinent to perform these as separate studies, so as to be able to power each group in order to correctly assess the effects on vasomotor function. As snus usage among women has shown an increasing trend during the last decade, it is undoubtedly important to continue with similar studies performed in females.

We did not evaluate additional factor that furthermore may influence endothelial function: level of education, monthly income and diet [42, 43]. Instead, waist circumference, BMI and self-reported levels of physical activity were assessed which partly correlate with these factors [44, 45].

Conclusions

The present study demonstrates an impaired endothelial function as well as an increased arterial stiffness in chronic snus users as compared to matched non-tobacco controls. Both findings designate early risk factors for CVD. Furthermore, chronic snus usage significantly impacted endothelial independent dilation, resulting in a decreased vasodilatory response to GTN. This study not only aligns with the epidemiological data suggesting that chronic snus

use poses a risk factor for mortality related to CVD but also demonstrates a pathophysiological explanation for the deleterious impacts on the endothelium.

Supporting information

S1 Table. Spearman correlation of baseline characteristics. CC = Correlation Coefficient. Sig. = 2-tailed significance. * Correlation is significant at the 0.05 level. ** Correlation is significant at the 0.01 level.
(DOCX)

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Author Contributions

Conceptualization: Lukasz Antoniewicz, Jenny A. Bosson, Magnus Lundbäck.

Data curation: Lukasz Antoniewicz.

Formal analysis: Lukasz Antoniewicz.

Funding acquisition: Magnus Lundbäck.

Investigation: Lukasz Antoniewicz, Mikael Kabele, Gregory Rankin.

Methodology: Lukasz Antoniewicz, Mikael Kabele, Jamshid Pourazar, Gregory Rankin.

Project administration: Jenny A. Bosson, Magnus Lundbäck.

Resources: Ulf Nilsson, Jenny A. Bosson.

Supervision: Jamshid Pourazar, Jenny A. Bosson, Magnus Lundbäck.

Visualization: Jamshid Pourazar.

Writing – original draft: Lukasz Antoniewicz, Magnus Lundbäck.

Writing – review & editing: Lukasz Antoniewicz, Mikael Kabele, Ulf Nilsson, Jamshid Pourazar, Gregory Rankin, Jenny A. Bosson, Magnus Lundbäck.

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Original Paper

Perceptions and Discussions of Snus on Twitter: Observational Study

Jiarui Chen¹; Siyu Xue¹, BSc; Zidian Xie², PhD; Dongmei Li², PhD

¹Goergen Institute for Data Science, University of Rochester, Rochester, NY, United States

²Department of Clinical & Translational Research, University of Rochester Medical Center, Rochester, NY, United States

Corresponding Author:

Dongmei Li, PhD

Department of Clinical & Translational Research

University of Rochester Medical Center

265 Crittenden Boulevard CU 420708

Rochester, NY, 14642-0708

United States

Phone: 1 585 276 7285

Email: Dongmei_Li@urmc.rochester.edu

Abstract

Background: With the increasing popularity of snus, it is essential to understand the public perception of this oral tobacco product. Twitter—a popular social media platform that is being used to share personal experiences and opinions—provides an ideal data source for studying the public perception of snus.

Objective: This study aims to examine public perceptions and discussions of snus on Twitter.

Methods: Twitter posts (tweets) about snus were collected through the Twitter streaming application programming interface from March 11, 2021, to February 26, 2022. A temporal analysis was conducted to examine the change in number of snus-related tweets over time. A sentiment analysis was conducted to examine the sentiments of snus-related tweets. Topic modeling was applied to tweets to determine popular topics. Finally, a keyword search and hand-coding were used to understand the health symptoms mentioned in snus-related tweets.

Results: The sentiment analysis showed that the proportion of snus-related tweets with a positive sentiment was significantly higher than the proportion of negative sentiment tweets (4341/11,631, 37.32% vs 3094/11,631, 26.60%; $P < .001$). The topic modeling analysis revealed that positive tweets focused on snus's harm reduction and snus use being an alternative to smoking, while negative tweets focused on health concerns related to snus. Mouth and respiratory symptoms were the most mentioned health symptoms in snus-related tweets.

Conclusions: This study examined the public perception of snus and popular snus-related topics discussed on Twitter, thus providing a guide for policy makers with regard to the future formulation and adjustment of tobacco regulation policies.

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KEYWORDS

snus; Twitter; sentiment; topic modeling; smokeless tobacco products

Introduction

Smokeless tobacco is a type of tobacco that is neither smoked nor burnt during consumption. Examples of smokeless tobacco products include chewing tobacco, dissolvable tobacco, and oral nicotine pouches. According to the Centers for Disease Control and Prevention (CDC), in 2020, there were 5.7 million adult users of smokeless tobacco nationwide in the United States [1]. Among the smokeless tobacco products, snus is a smokeless and sometimes flavored tobacco product for oral consumption

that originated from Sweden. It is usually in the following two forms: loose ground powder and sachets. When snus is consumed, it is held behind the upper lip [2]. Although this tobacco product was banned in the member countries of the European Union, with a few exceptions such as Sweden [3], its use in the rest of the world is prevalent. By 2013 for example, 18% of adolescents had tried snus in Finland [4]. In the United States, a study conducted in 2021 by the CDC suggested that 1.2% of US high school students are current users of smokeless products, including snus [1].

Studies have found that snus use may result in oral cancer, cardiovascular diseases, respiratory diseases, diabetes, and other illnesses [5]. A cohort study on 135,036 male, Swedish construction industry employees found that the age-adjusted relative risk of dying from cardiovascular disease for smokeless tobacco users was 40% higher than that for nonusers [6]. Despite these concerns, previous studies indicated that snus use has a considerably lower health risk than cigarette smoking [2,7]. According to a review on multiple health symptoms, including oral health and cardiovascular diseases, among others, the health risk of snus is significantly lower than that of cigarettes [2].

Similar to other tobacco products, snus use results in nicotine dependence, and the perceptions toward the relationship between snus consumption and other types of nicotine consumption have been controversial [5]. The gateway hypothesis states that the use of snus may lead to more addictive smoking behaviors. On the contrary, the pathway hypothesis claims that snus use helps to prevent people from smoking [5]. Previous studies on this topic reported different conclusions. A previous study tracked 496 pairs of users and nonusers of smokeless tobacco products and concluded that there was insufficient evidence to conclude that using smokeless tobacco products leads to a higher chance of smoking [8]. Another research study on smokers in Sweden found that 76.3% of the male smokers and 71.6% of the female smokers included in the study quit smoking after they started consuming snus [9]. However, a focus group study that was performed on 66 participants in 2010 concluded that the participants believed that snus use could potentially lead to smoking [10].

With the controversial gateway and pathway hypotheses and the potential health impact of snus products, disagreements on the perception of snus product may exist among the public. As snus is becoming increasingly popular, governmental regulation plays an essential role in the relationship between snus consumption and public health. For example, the US Food and Drug Administration stipulates that for smokeless tobacco products, including snus, special warnings such as “WARNING: Smokeless tobacco is addictive” should be attached to the packages [11]. For governors and regulators to better manage the relationship between snus and public health and be more informed in policy making, it is beneficial to understand how the public truly perceives snus.

Twitter, as a popular social media platform, has been used to examine smoking behaviors and perceptions of tobacco products, such as e-cigarettes [12,13]. Although perceptions of snus have been investigated by using focus groups, the sample sizes of such focus groups are very limited [10,14]. Research that uses social media data to study the public perceptions of snus is scarce.

Our study aimed to examine the public perceptions of and popular topics regarding snus on Twitter. Our study consisted of 3 specific goals. First, we aimed to determine the sentiments of snus-related tweets via a sentiment analysis. Second, we attempted to explore specific topics related to snus. Finally, we tried to examine potential health risks that were mentioned in snus-related tweets. Through a comprehensive examination of the public perceptions and the top topics discussed about snus,

we hope to provide some insights to policy makers on regulating snus for public health protection.

Methods

Ethics Approval

We only used publicly available tweets for this study, and there was no identifying information on Twitter users in this study. In addition, this study was reviewed and approved by the Office for Human Subject Protection Research Subjects Review at the University of Rochester (study ID: STUDY00006570).

Data Collection and Preprocessing

We collected Twitter posts (tweets) related to snus from March 11, 2021, to February 26, 2022, through the Twitter streaming application programming interface by using the keyword *snus*, and we obtained a data set with 28,427 tweets. We then preprocessed the data to enhance their quality. First, all the tweets were lowercased. Afterward, by using the Regular Expression Operations Package (Python Software Foundation) [15], we removed the parts of tweets that did not contribute to the tweets' actual contents, including email addresses, new-line characters, single quotation marks, URLs, and “@” signs (used to mention other users). Next, we applied 2 sets of promotion filters to eliminate tweets that were related to the commercial promotion of snus [13]. The first filter targeted the usernames, using keywords such as *snus*, *smokeless*, *dealer*, *supply*, *nicotine*, *cigarette*, and *store*. Tweets posted by users with usernames containing any of these words were not included in this study because they might have been posted by commercial accounts. The second layer of the filter aimed to remove potentially commercial tweet content, and the keywords included *order*, *new*, *offer*, *discount*, and *free shipping*. Tweets that contained these words were highly likely to be promotional tweets. Finally, we eliminated the repetitive tweets. After preprocessing, the final data set contained 11,631 tweets.

Sentiment Analysis

Sentiment analysis is a computational method of learning the attitudes in text, and the Valence Aware Dictionary and Sentiment Reasoner (VADER) is a sentiment analysis package that is specialized for social media data [16]. By applying the VADER on each tweet, we assigned each tweet a sentiment score of between -1.0 and 1.0. To better define the sentiments, we grouped the tweets into 3 categories based on the corresponding sentiment scores; tweets with a sentiment score of ≥ 0.05 were labeled as “positive,” and tweets with a score of ≤ -0.05 were labeled as “negative.” The remaining tweets were labeled as “neutral.” The proportions of positive, neutral, and negative tweets were then calculated. The daily proportion of positive tweets was then calculated.

We performed the chi-square goodness-of-fit test by using statistical analysis software (R version 4.0.2; R Foundation for Statistical Computing) to examine the frequency distribution of different attitudes [17]. A significance level of .05 was used to determine whether the proportion of positive tweets was statistically significantly higher than the proportion of the negative tweets.

Topic Modeling

Topic modeling is a computational method of identifying major topics in text. The model we chose for our study was the latent Dirichlet allocation model, which was applied to positive tweets, neutral tweets, and negative tweets to observe the main topics that Twitter users had been discussing.

By using the *gensim* package in Python [18], we built a bigram and trigram based on our data set. Bigrams and trigrams are sequences of 2 words and 3 words, respectively. With the bigram and the trigram, we treated some of the most frequently mentioned phrases as a whole instead of 2 or 3 separate words. For example, *harm reduction* was a frequently mentioned phrase among the tweets, and we considered *harm reduction* as a single token that contributed to a topic instead of preserving *harm* and *reduction* separately.

We applied the Natural Language Toolkit to remove the stop words in the tweets [19]. Stop words include but are not limited to commonly used articles, pronouns, and prepositions, which undermine the quality of topic modeling results if kept. In addition, we used spaCy (Explore) to lemmatize the words in tweets into their dictionary forms without changing their meaning [20]. For example, *smoked* became *smoke* after lemmatization. After conversion, words like *smoked* were left unused for topic modeling, and only their dictionary forms were included. Both coherence scores and intertopic distance maps were used to determine the optimal number of topics discussed in the tweets, using the *pyLDAvis* package in Python [21].

To better interpret the results from the model, we inferred the topics based on the keyword outputs and example tweets. Two authors reviewed the tweets from each category and summarized the topics independently. The results from the two authors were

compared and discussed. Any discrepancy was resolved by a group of 4 members.

Health-Related Discussion

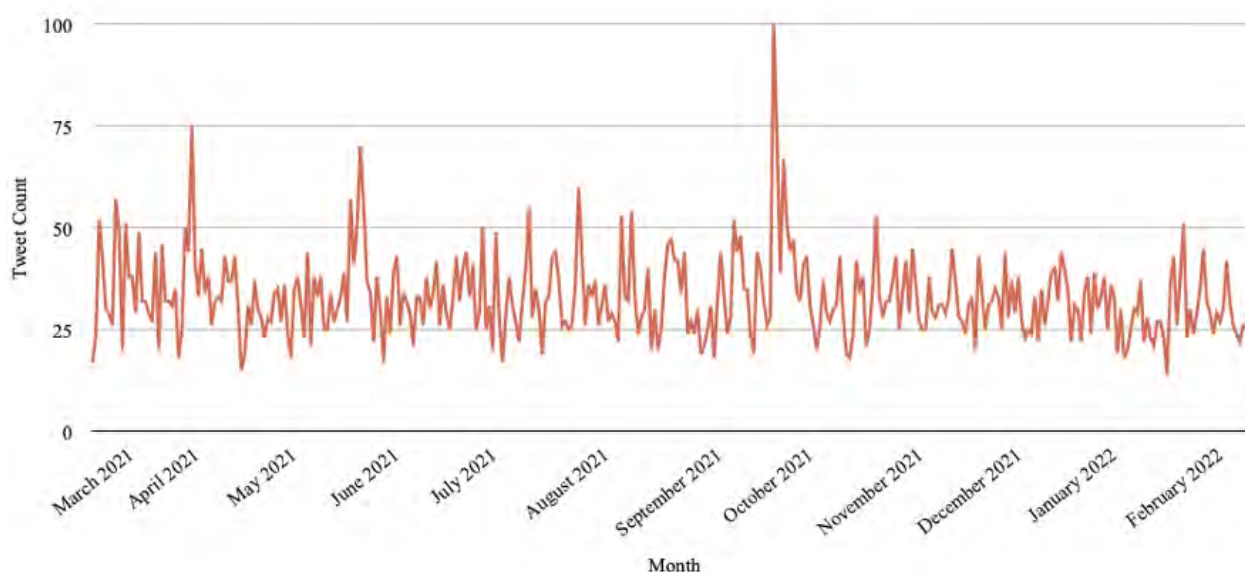
To determine the frequency of health effects that were mentioned in snus-related tweets, we filtered the data set by using a list of health-related keywords that were created in previous studies [22-24], which resulted in a set of 654 unique tweets with 1254 health-related keyword appearances. The list included the following nine major groups of health effects that are related to smoking and nicotine consumption: mouth (eg, gum, teeth, etc), respiratory (eg, lung, cough, etc), cardiovascular (eg, heart, etc), psychological (eg, stress, anxiety, etc), neurological (eg, numb, fatigue, etc), cancer (eg, lung cancer, mouth cancer, etc), throat, digestive, and other effects (eg, skin, liver, etc). For each major group of health effects, the number of occurrences of specific keywords belonging to the groups were counted. In addition, two authors hand-coded 200 randomly selected tweets to determine whether the users directly experienced the health symptoms mentioned or whether they believed that snus use might help with lowering the risk of the symptoms when compared to smoking. The Cohen κ statistic reached 0.73, indicating substantial agreement between the two coders.

Results

Temporal Analysis

To better understand the popularity of snus discussion, we examined the number of snus-related tweets over time during our study time period. As shown in Figure 1, the number of tweets per day typically oscillated between 25 and 50, with a few peaks occurring in April 10, 2021; May 31, 2021; and October 3, 2021.

Figure 1. Snus-related tweets from March 11, 2021, to February 26, 2022.



Perceptions of Snus on Twitter

To examine the public perception of snus on Twitter, we performed a sentiment analysis on tweets related to snus. The average sentiment score for 11,631 snus-related tweets was 0.080, which indicated that the overall sentiment in snus-related tweets was positive. Among these tweets, there were 4341 (37.32%) positive tweets, 3094 (26.60%) negative tweets, and 4196 (36.08%) neutral tweets. Further statistical analysis showed that the proportion of positive tweets was significantly higher than the proportion of negative tweets (4341/11,631, 37.32% vs 3094/11,631, 26.60%; $P<.001$). Our longitudinal analysis showed that there was no noticeable change in the proportion of positive tweets over time (Multimedia Appendix 1).

Topics Discussed in Snus-Related Tweets

To understand what might be responsible for different sentiments in snus-related tweets, we performed topic modeling for the tweets in the different sentiment groups. As shown in Table 1, among the positive sentiment snus-related tweets, the most popular topic was “Snus being a safer way of nicotine consumption” (1472/4341, 33.9%), followed by “Way of snus consumption” (1441/4341, 33.2%) and “Snus addiction and enjoyment” (1428/4341, 32.9%). Among the negative sentiment snus-related tweets, the top topic was “Risk comparison between snus and smoking” (1064/3094, 34.4%), followed by “Negative health impacts” (1018/3094, 32.9%) and “Other problems related to snus” (1012/3094, 32.7%). The topics for neutral sentiment snus-related tweets are included in Table S1 in Multimedia Appendix 2.

Table 1. Topics discussed in snus-related tweets with different sentiments.

Sentiment group and inferred topic	Keywords	Token percentage	Examples
Positive			
Snus addiction and enjoyment	<i>snus, good, make, time, day, love, feel, free, access, today, strong, man, back, coffee, pack, life, pretty, friend, enjoy, and week</i>	32.9	“Proper pint of bitter and a wintergreen snus. Perfect on a fair night like tonight”
Snus being a safer way of nicotine consumption	<i>pouch, vape, smoking, smoke, quit, cigarette, nicotine, safe, give, amp, year, alternative, smoker, start, risk, big, stop, switch, low, and option</i>	33.9	“For long-term nicotine use, data on safety are strongest for snus: decades of epidemiological studies. No harm. So if many people with mental health issues self-medicate with #safernicotine (they are), at least there is no harm. #qualityoflife”
Way of snus consumption	<i>snus, tobacco, product, Swedish, people, chew, work, thing, great, smokeless, put, dip, find, call, play, gum, nice, hard, flavor, and mouth</i>	33.2	“snus is a black tobacco product you chew or put on your gums. You don’t snort it or sniff it. He’s clearly closing one nostril to sniff smelling salts, which are commonly used in sports. Not rocket science.”
Negative			
Risk comparison between snus and smoking	<i>Tobacco, smoke, vape, cigarette, smoking, pouch, product, cancer, risk, low, nicotine, amp, quit, harm, gum, rate, smoker, chew, reduce, and smokeless</i>	34.4	“not just snus but the attempt to restrict and eliminate all lower risk products is astonishingly short sighted.”
Negative health impacts	<i>Snus, ban, make, stop, day, Swedish, year, give, feel, thing, death, man, start, high, mouth, kill, lose, addiction, long, and cig</i>	32.9	“not in epok which i assume is some zoomer snus? i dont know i only use odens and sometimes siberia which has no flavouring just tobacco. the nicotine content is pretty potent in those, would kill your average vaper no joke.”
Other problems related to snus	<i>snus, people, time, bad, work, put, hard, good, study, week, today, back, call, big, find, coffee, problem, and life</i>	32.7	“our big daddy is always the leader he is the familys captain and chief, but once i choked when my snus caught up in my throat cause there was our pop in the oak.”

Health Risks Mentioned in Snus-Related Tweets

To understand what health risks might be associated with snus, we explored the health symptoms mentioned in the snus-related tweets. Oral health (mouth effects) was the most mentioned health category in snus-related tweets (519/1254, 41.39%), followed by other effects (213/1254, 16.99%) and respiratory effects (182/1254, 14.51%). The other health categories had

relatively lower proportions of tweets. For example, the cancer category (cancer is a health effect that is often associated with nicotine consumption) only took up 5.34% (67/1254) of the total tweets. Further hand-coding results showed that of the 200 randomly selected tweets, 40 (20%) mentioned that the health symptoms were a direct result of snus consumption or mentioned a negative opinion about snus. In addition, 28% (56/200) of the

tweets discussed the harm reduction of snus, in terms of the health symptoms mentioned, when compared to smoking.

Discussion

Principal Findings

In our study, we showed that the proportion of snus-related tweets with a positive sentiment was significantly higher ($P < .001$) than the proportion of snus-related tweets with a negative sentiment. By using topic modeling, we observed that the positive sentiments toward snus might be the result of personal experiences and the perception that snus use is a safer alternative to smoking. In contrast, concerns about health risks might contribute to the negative sentiments in snus-related tweets. A further analysis showed that in snus-related tweets, the most popular health category was mouth effects, followed by other effects (eg, liver and skin effects) and respiratory effects.

Comparison With Previous Studies

Our temporal analysis showed an obvious peak in the number of snus-related tweets on October 3, 2021. After extracting all snus-related tweets from that day, we noticed that most of the tweets (67/100, 67%) discussed the possible use of snus by the son of a famous English former soccer player. This peak indicates the large impact of influencers on Twitter users.

Given that the top topic in snus-related tweets with a positive sentiment was related to switching from smoking to snus use, since snus was perceived as a safer option and there was no strong evidence in negative sentiment tweets indicating the gateway effect, it might be possible that Twitter users' perceptions on snus tend to lean toward the pathway hypothesis instead of the gateway hypothesis. This finding contradicts that of a focus group study, in which participants viewed snus use as a potential gateway to smoking [10]. There are 2 possible reasons for this inconsistency. First, the focus group was conducted in 2010, and the tweets used in our study were collected in 2021. It is possible that temporal differences might account for the difference in the perceptions of snus. Second, the conclusion from the focus group was based on a sample of 66 young adults who ranged in age from 18 to 26 years [10]. In comparison, our study included a broader range in terms of demographic characteristics, which may have led to the different results.

From the aspect of health risks, the health-related keywords identified in the tweets captured the majority of the potential health impact of snus. According to a report published by the Norwegian Institute of Public Health in 2019, the main potential adverse health effects of snus cover cancer, cardiovascular disease, mental disorders, and caries [25]. The health-related keyword frequency distribution from our study included these potential health effects through the oral, cardiovascular, cancer,

and psychological effect categories, demonstrating the consistency between our findings from Twitter data and previous findings on the health risks of snus.

Limitations

Our study has several limitations. Data collected from Twitter may contain some bias. A study on tourist attraction visit sentiment data sourced from Twitter suggested that the tourists' sentiments could be affected by factors other than the tourist attraction itself, including the number of attraction sites that are visited in 1 day and whether the tourists are local visitors, out-of-state visitors, or international visitors [26]. Another study in 2012 suggested that the demographic distributions of Twitter users are different from those of the general population [27]. For example, around 31% of young adults who ranged in age from 18 to 24 years used Twitter, while this proportion was only 17% for adults aged between 25 and 34 years [27]. Therefore, our findings, which are based on Twitter data, may not represent the general population.

With regard to data collection and preprocessing, the keyword set we used may not have been comprehensive. For example, when collecting the data, we only included *snus* as the single keyword, which may have resulted in us missing some relevant tweets in our study. Additionally, in the processed data set, there might have still been some bot accounts, which can automatically deliver messages. This may have introduced some bias in our results. With regard to topic modeling, inferences based on keywords involve subjective judgments, even with the support of example tweets. In addition, the mentioning of health symptoms in snus-related tweets does not imply any causal relationship between snus and health risks. Our hand-coding results further validated this notion. Moreover, our study did not include the demographic information of Twitter users. Different demographic groups might perceive snus differently.

Conclusion

Our study showed more positive sentiments in snus-related tweets from Twitter users, which might have been due to the relative safety of snus when compared to that of smoking. Our study provided an efficient measurement of the public perceptions of snus among a relatively large sample by using social media data. According to the health belief model, the perceived susceptibility, seriousness, benefits, and barriers of actions explain health-related behaviors [28]. Therefore, these perceptions of snus are possibly a predictor of the public's snus consumption patterns. Our study will help policy makers better anticipate consumption behavior changes and make necessary policy changes. The results from our study will provide insights to policy makers on further regulations for snus. Future studies could take demographic and geographic factors into consideration to explore potential disparities in snus-related perceptions and discussions.

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Data Availability

The data and scripts used for analysis and for creating the figures are available on request from the corresponding author (DL).

Authors' Contributions

ZX and DL conceived and designed this study. JC and SX analyzed the data. JC wrote the manuscript. ZX and DL assisted with the interpretation of analyses and edited the manuscript. All authors have approved the final article.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Proportion of snus-related positive tweets over time.

[[PNG File , 149 KB-Multimedia Appendix 1](#)]

Multimedia Appendix 2

Table S1. Topics mentioned in snus-related tweets with a neutral sentiment.

[[DOCX File , 15 KB-Multimedia Appendix 2](#)]

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Abbreviations

CDC: Centers for Disease Control and Prevention
FDA: Food and Drug Administration
NIH: National Institutes of Health
VADER: Valence Aware Dictionary and Sentiment Reasoner

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Article

Online Tobacco Advertising and Current Chew, Dip, Snuff and Snus Use among Youth and Young Adults, 2018–2019

Megan C. Diaz ^{1,*} , Elexis C. Kierstead ¹ , Domonique Edwards ¹, Yoonsang Kim ² , Shyanika W. Rose ³, Sherry Emery ² , Bushraa Khatib ¹, Michael Liu ¹ and Ganna Kostygina ²

¹ Schroeder Institute, Truth Initiative, Washington, DC 20001, USA; lkierstead@truthinitiative.org (E.C.K.); domonique.dae@gmail.com (D.E.); bkhatib@truthinitiative.org (B.K.); mliu@truthinitiative.org (M.L.)

² NORC at the University of Chicago, Chicago, IL 60637, USA; kim-yoonsang@norc.org (Y.K.); emery-sherry@norc.org (S.E.); kostygina-anna@norc.org (G.K.)

³ College of Medicine, Department of Behavioral Science, Center for Health Equity Transformation, University of Kentucky, Lexington, KY 40506, USA; s.rose@uky.edu

* Correspondence: mdiaz@truthinitiative.org

Abstract: Objective: To understand the relationship between exposure to online tobacco advertising and current smokeless tobacco use in the context of tobacco control policies. Methods: Three waves of a national probability-based sample of ($n = 15,985$) youth and young adults were used. Analysis consisted of GEE logistic models controlling for social media use, demographics, tobacco use, average price of smokeless tobacco inclusive of taxes, smoke-free indoor air laws (SFIA) and state tobacco control expenditures. Results: Frequent exposure to tobacco advertising on social media is associated with greater odds of current smokeless use (aOR: 2.05, 95% CI: 1.62, 2.60). Higher prices and SFIA coverage were associated with reduced current smokeless use when examined separately from other tobacco policy variables (aOR: 0.79, CI: 0.73, 0.85; aOR: 0.44, CI: 0.28, 0.70). Conclusions: Greater exposure to tobacco advertising online is associated with greater odds of smokeless use among surveyed youth and young adults. This effect of social media marketing exposure on smokeless use outweighs the mitigating impact of existing tobacco control policies. The findings underscore the need for strong advertising regulation of evolving tobacco products, including smokeless products, on social media and surveillance of digital marketing tactics to young people.

Keywords: smokeless tobacco; tobacco advertising; social media; policy



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1. Introduction

Despite declining cigarette use and the rapid rise of e-cigarette use among young people, youth use rates of smokeless tobacco products, specifically chew, dip, snuff and snus, have remained stable in the United States (U.S.) in the past decade. As of 2020, 5% of 8th, 10th and 12th graders used smokeless tobacco products [1]. Smokeless tobacco use is highest among White males living in rural areas, and the product has been historically marketed to cigarette users as a non-combustible tobacco alternative for use where combustible tobacco is restricted but is now being leveraged to youth who may no longer be attracted to combustible cigarettes [2].

Tobacco companies are increasingly marketing their products on social media platforms most popular with young customers [3]. Their extensive reach among youth [4] make social media platforms a powerful tool for communicating social norms and influencing risk behaviors among youth [5,6]. A 2015 study found that 52.5% of youth reported exposure to tobacco imagery via social media in the past month and a 2019 study found that 21% of youth reported actively engaging with at least one form of online tobacco marketing [7]. Youth who had engaged with online tobacco marketing were more likely to initiate tobacco, use tobacco more frequently, use multiple tobacco products and were less likely to later

quit [8]. Additionally, youth who reported two or more forms of online tobacco marketing engagement were more likely to use smokeless tobacco products a year later [9].

Research shows that engaging with promotional messages on social media is linked to increased tobacco product susceptibility among never users, emphasizing the impact of tobacco advertising via online platforms [7]. These promotional messages can include content created and distributed by the company, paid influencers and product users. Exposure to product placements in social media feeds may also directly influence knowledge, attitudes and beliefs or could strengthen the relationship between such beliefs and tobacco-related behaviors [7,10,11]. With the recent rise of social media use, tobacco companies are leveraging social media that is popular among youth to cultivate a younger customer base addicted to alternative tobacco products [3,12].

Despite its pervasive impact, tobacco advertising on social media is under-regulated, creating space to present products like smokeless tobacco to young audiences. Social media was not present when either the 1998 Smokeless Tobacco Master Settlement Agreement or the 2009 Tobacco Control Act were passed, restricting tobacco advertising to outdoor and transit advertising, or distribution of apparel or merchandise [13–16]. Although many social media platforms ban paid tobacco advertising, to varying degrees of enforcement, product promotions circulated by branded social media accounts and paid product influencers are less regulated [11,17], prompting tobacco companies to take advantage of patchwork regulation to raise brand visibility and engagement [18,19].

Despite evidence of the power of social media tobacco marketing, more research is needed to understand the direct effect of exposure on tobacco use behaviors—specifically on smokeless tobacco use. This study aimed to explore the relationship between self-reported digital tobacco marketing exposure and current smokeless tobacco use, using data from a nationally representative, longitudinal sample of U.S. youth and young adults. We also aimed to understand to what extent tobacco control policies including prices, smoke-free indoor air laws (SFIA) and tobacco control expenditures modify the relationship between self-reported digital tobacco marketing exposure and smokeless tobacco use.

2. Materials and Methods

2.1. Sample

Data were obtained from the Truth Longitudinal Cohort (TLC), a national probability-based youth and young adult cohort (ages 15–21 at recruitment) established to evaluate the tobacco prevention media campaign, “truth®”. Participants were primarily recruited via address-based sampling from a customized panel from GfK KnowledgePanel, with follow-up online surveys every six months to one year. In most survey waves, new participants were recruited, spanning anywhere from 400–1300 individuals, to reduce bias due to attrition and help cross-sectional representation of the sample. Wave 7 was fielded from 15 February to 29 May 2018; Wave 8 was fielded from 10 February to 20 May 2019; and Wave 9 was fielded from 26 August to 16 December 2019. In Wave 7, questions were added to examine awareness of tobacco advertising. We included all participants at Wave 7 ($n = 14,377$), Wave 8 ($n = 12,113$) and Wave 9 ($n = 10,902$) to maximize our number of observations. Sampling methods are described elsewhere [20–22]. Survey retention rates were 72.7% for Wave 7, 67.5% for Wave 8 and 66.4% for Wave 9.

2.2. Measures

Respondents who had ever used chewing tobacco, dip, snuff and snus were asked on how many of the past 30 days they used these products. Participants were considered current users if they reported use on 1–30 days and non-current users if they responded with “0 days” or had never used smokeless tobacco. Smokeless tobacco use served as the primary outcome.

Tobacco advertising exposure on websites and social media was the primary independent variable. For Waves 7 and 8 participants were asked “How often do you remember seeing or hearing about tobacco advertising or promotions on websites or social media in

the past 30 days?" For Wave 9, tobacco advertising exposure in the past 30 days on websites and social media was evaluated using two separate questions (for websites and social media, respectively). To account for this data difference, we used the maximum response for either question to match the response categories used for Waves 7 and 8. Response options were categorized: never, sometimes and often/very often.

In our models we controlled for a series of independent variables suggested by the literature to affect smokeless tobacco use. We started by controlling for time spent on social media to account for the possibility that the intensity of social media use may confound the relationship between an individual's tobacco advertising exposure, their memory of this exposure and smokeless product use. Participants were asked how much time they spent on social media on an average day. Response options included: none, less than 1 h, 1 to less than 3 h and 3 h or more.

We also controlled for: respondent age at each wave, gender (female, male), race/ethnicity (any non-White race/ethnicity combined, non-Hispanic White), highest educational attainment of either parent (less than high school education, high school graduate, some college or associates degree, college graduate or more) and non-metropolitan residence determined if an individual's home address was located in a non-metropolitan statistical area as classified by the United States Census Bureau (non-metropolitan, metropolitan).

To control for the respondent's tobacco environment we included own poly-tobacco use, any household tobacco use and peer cigarette smoking. Own poly-tobacco use was defined as "yes" if participants used cigarettes, large cigars or cigarillos and/or electronic cigarettes in the past 30 days, and "no" if they had not. Household tobacco use was defined as "yes" if those living in the same household as the survey participant used cigarettes, large cigars or cigarillos, hookah or e-cigarettes, and "no" if no household members used any of the previously listed tobacco products. To assess peer cigarette smoking, participants were asked how many of their four closest friends smoked cigarettes; response options were treated categorically in the model.

As sensation-seeking tendencies are known to affect tobacco use [23], we included a validated sensation-seeking index constructed from eight survey items with a five-point Likert scale (strongly disagree to strongly agree) [24]. A description of this measure is published elsewhere [24]. The mean score of the scale items was calculated and treated as a continuous measure with a range of (1–5); the measure was assessed upon entry to the cohort and is time-invariant in our models.

In addition to demographic variables, it has been proven that tobacco control policies impact smokeless tobacco use [25]. Thus, we controlled for the policy environment by including three state-level measures as time-varying covariates: (a) price of smokeless tobacco, (b) share of the population covered by indoor smoking restrictions, and (c) state tobacco control expenditures. Tobacco control expenditure data were aggregated at the calendar year. Data from 2018 were assigned to Wave 7, and data from 2019 were assigned to Waves 8 and 9. First, we used Nielsen retail scanner data to estimate the price of one ounce of smokeless tobacco in each state. We summed the total dollar sales and total ounces sold for the ten most popular brands based on total dollar sales. We then calculated the sales weighted average price of one ounce of smokeless tobacco in each state where the participant resided for the four-week period in which they submitted the survey. State-level sales data were available for the 48 continental states. We adjusted for inflation (2019 dollars) using the United States Bureau of Labor Statistics Consumer Price Index [26]. This price measure is inclusive of all taxes levied.

Secondly, we summed to the state level the share of the population in each county covered by smoke-free indoor air laws (SFIA) for private workplaces, restaurants and bars. These data have been used elsewhere [27], and weights SFIA applying to bars, restaurants and private workplaces equally, while partial SFIA are weighted by half.

Thirdly, we constructed a per capita measure of state tobacco control expenditures adjusted for inflation (2019 dollars) and based on the American Lung Association's annual State of Tobacco Control report. We assigned aggregated fiscal year data from 2018 to

Wave 7, data from fiscal year 2019 to Wave 8 and data from fiscal year 2020 to Wave 9. This report includes spending for each state from tobacco excise tax revenues earmarked for tobacco control, Master Settlement Agreement funds, individual state settlements with the tobacco industry earmarked for tobacco control, other state funds appropriated for tobacco control programs, and Federal funding to states allocated for tobacco control [28,29]. We used the United States Census decennial estimates to calculate per capita figures.

2.3. Analysis

Characteristics of respondents were summarized for each wave. Frequency and percentage were reported for categorical variables; mean and standard deviation were reported for continuous variables. Characteristics included tobacco advertising exposure, current smokeless use, social media use, demographic and psychosocial characteristics, and tobacco policy measures.

We used a generalized estimating equation (GEE) for logistic regressions to evaluate the relationship between self-reported tobacco advertising exposure on websites and social media and current smokeless use. GEE regression models account for lack of independent outcomes across waves within participants [30]. We used an exchangeable correlation structure in our models to account for correlated errors across waves within participants, and calculated robust standard errors using the method developed by Huber [31]. We did not account for complex survey design because there is no readily available software to correctly calculate standard errors while simultaneously accounting for the survey design and correlated errors nested within participants.

We estimated five alternative models. Model 1 controlled for social media exposure, age, gender, parental education, race, sensation-seeking tendencies, residence in a non-metropolitan statistical area, own poly-tobacco use, household tobacco use and peer cigarette smoking. To understand to what extent tobacco control policies modify the relationship between self-reported tobacco marketing exposure and smokeless tobacco use, Models 2 through 4 included all aforementioned variables and each of the state-level policy measures individually. These three measures were moderately correlated from 0.28–0.47 and thus included in separate models to minimize collinearity. However, omitting these variables could result in biased estimates of the effect of tobacco advertising exposure on current smokeless tobacco use; therefore, Model 5 included all covariates. We present alternative models in this manner to exemplify the trade-off between multicollinearity and potential omitted variable bias. We present four additional models in a supplemental table. Model 6, our simplest model, only includes our primary outcome, exposure to tobacco advertising and wave fixed effects. We subsequently include social media use (Model 7), and our demographic and psychosocial characteristics (Model 8). We also include a model with all covariates and state fixed effects (Model 9). All analyses were conducted using Stata version 15.1.

3. Results

3.1. Sample

There were 15,985 unique respondents across the three waves, 23% ($n = 3675$) had data for one wave only, 20% ($n = 3213$) had data for two waves and 57% ($n = 9097$) had data in all three waves.

Across the three waves, respondents were on average 23 years old (spanning in age from 15–36), less than half were male, 64–65% were non-Hispanic White and 58–59% of parents completed some college education or more (Table 1).

Table 1. Categorical sample characteristics across Waves 7, 8 and 9 of the national Truth Longitudinal Cohort.

	Wave 7 February–May 2018 Response Rate: 72.7%		Wave 8 February–May 2019 Response Rate: 67.5%		Wave 9 September–December 2019 Response Rate: 66.4%		Wave 7–9	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Current Smokeless Use								
Yes	281	2.0	225	1.9	211	1.9	717	1.9
No	14,084	98.0	11,887	98.1	10,691	98.1	36,662	98.1
Tobacco Advertising Exposure	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Never	9399	66.0	8099	67.4	6415	59.0	23,913	64.4
Sometimes	3890	27.3	3253	27.1	3669	33.7	10,812	29.1
Often, Very often	956	6.7	657	5.5	796	7.3	2409	6.5
Social Media Use	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
None	970	6.8	878	7.3	772	7.1	2620	7.0
Less than 1 h	4325	30.3	3004	24.9	2749	25.3	10,078	27.1
1 to 3 h	6150	43.1	5271	43.6	4774	43.9	16,195	43.5
3 or more h	2840	19.9	2935	24.3	2585	23.8	8360	22.4
Gender	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Male	6233	43.4	5208	43.0	4636	42.5	16,077	43.0
Female	8144	56.7	6905	57.0	6266	57.5	21,315	57.0
Parental Education	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
LT high school	673	4.8	514	4.3	468	4.4	1655	4.5
High school graduate	1860	13.2	1504	12.7	1380	12.9	4744	12.9
Some college/AA degree	3414	24.2	2822	23.7	2529	23.6	8765	23.9
College graduate or more	8142	57.8	7051	59.3	6347	59.2	21,540	58.7
Race/Ethnicity	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Non-Hispanic White	9220	64.2	7860	64.9	7011	64.3	24,091	64.4
Any other race	5152	35.9	4250	35.1	3891	35.7	13,273	35.6
Metropolitan Residence	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Metropolitan	10,987	88.8	10,797	89.1	9738	89.3	31,522	89.1
Non-metropolitan	1385	11.2	1316	10.9	1164	10.7	3865	10.9
Own Poly-Tobacco Use	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
None	11,455	79.7	9372	77.4	8614	79.0	29,441	78.8
Any (cigarette, cigar, ENDS)	2922	20.3	2737	22.6	2285	21.0	7944	21.2
Household Tobacco Use	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
None	8722	61.1	9424	78.7	8688	79.8	26,834	72.3
Any	5549	38.9	2557	21.3	2199	20.2	10,305	27.8
Peer Smoking	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
None	9523	67.0	8357	69.9	7548	69.4	25,428	68.6
1	2701	19.0	2156	18.0	2019	18.6	6876	18.6
2	1179	8.3	923	7.7	817	7.5	2919	7.9
3	457	3.2	314	2.6	300	2.8	1071	2.9
4	356	2.5	213	1.8	188	1.7	757	2.0

Any household tobacco use changed over time, decreasing from 39% in Wave 7 to 20% in Wave 9, while own poly-tobacco use and peer cigarette use remained steady. For 67–70% of participants, none of their four closest peers smoked cigarettes, while 18–19% reported that one of their friends smoked, about 8% reported two of their friends smoked, about 3% reported three of their friends smoked and 2–3% reported four of their friends smoked (Table 1).

3.2. Smokeless Tobacco Use, Tobacco Advertising Exposure and Social Media Use

Across the survey waves, about 2% of the respondents used smokeless tobacco products in the past 30 days. Regarding their exposure to tobacco advertising on websites and social media, 27–34% reported they were sometimes exposed and 6–7% said they were

often or very often exposed. About 32–37% of the respondents reported being on social media not at all or <1 h a day, 43–44% reported spending 1–3 h a day and 20–24% reported spending 3+ h a day (Table 1).

3.3. Policy Environment

Across the waves 83–84% of participants were covered by SFIA (Table 1). Real price of smokeless tobacco products was USD 4.57–4.89 per ounce, and state tobacco control expenditure was on average USD 2.25 per capita (Table 2).

Table 2. Continuous sample characteristics across Waves 7, 8 and 9 of the national Truth Longitudinal Cohort.

	Wave 7 February–May 2018 Response Rate: 72.7%		Wave 8 February–May 2019 Response Rate: 67.5%		Wave 9 September–December 2019 Response Rate: 66.4%		Wave 7–9	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	22.2	4.2	23.0	4.0	23.6	4.1	22.9	4.1
Sensation Seeking	2.9	0.8	2.9	0.8	2.9	0.8	2.9	0.8
Real Weighted Avg Price of Smokeless Tobacco (USD/one oz) *	\$4.57	1.44	\$4.75	1.51	\$4.89	1.56	\$4.72	1.5
Smoke-Free Indoor Air Laws (% population)	83.3%	20.7	83.5%	20.5	83.9%	20.5	83.5%	20.6
Real State Tobacco Control Expenditure (USD/capita) *	\$2.41	2.52	\$2.15	\$1.93	\$2.16	1.94	\$2.25	2.18

* Adjusted for inflation to 2019 dollars.

3.4. Modeling

Self-reported exposure to tobacco advertising on websites and social media was significantly associated with current smokeless tobacco use across all five models with an adjusted odds ratio (aOR) of 2.05–2.07 (Table 3). Additionally, compared to individuals who use social media 3+ h a day, those who reported no daily social media use had significantly lower odds of current smokeless tobacco use (aOR: 0.65–0.66) (Table 3). The stability of these effects across each model strongly indicates that the effects are independent of other variables and not the result of confounding. Without including our covariates, the adjusted odds ratio is 2.47 (Supplementary Table S1, Model 6).

Respondents living in a non-metropolitan statistical area (aOR: 1.90–2.09) had higher odds of current smokeless tobacco use. Conversely, respondents who are non-Hispanic White (aOR: 1.73–1.79), male (aOR: 5.51–5.56), poly-tobacco users (aOR: 2.98–3.00), living with a tobacco user (aOR: 1.27) and have higher sensation-seeking tendencies (aOR: 1.41–1.43) had greater odds of current smokeless tobacco use. Further, respondents with peers who smoke cigarettes had greater odds of smokeless use, and the odds of current smokeless use increased with the number of peers who smoked cigarettes; for those with two or more peers smoking cigarettes, the odds were almost two and a half times that of those with no friends who smoked cigarettes.

The three state-level policy measures showed varying effects across the models. When price of smokeless tobacco was included as the sole policy variable (Model 2) and amongst the other policy variables (Model 5), the odds of current smokeless tobacco use were 31% lower with one dollar increase in price. The odds were 56% lower for those residing in a state with SFIA policies, compared to those without (Model 3). State tobacco control expenditure, however, was not significantly associated with current smokeless tobacco use (Model 4). When all policy variables were included in the model (Model 5), the effects of SFIA policies and state tobacco control expenditures were insignificant. The lack of significance of these variables is possibly due to multicollinearity. To test this, we calculated

mean variance inflation factors (VIFs). Mean VIFs for Models 1–5 was 1.2, suggesting that multicollinearity is not an issue. Wave fixed effects were also included in all models; there was no significant change in the current smokeless tobacco use over waves. We also examined a model where we included state fixed effects; however, we present these results in our supplemental table due to high multicollinearity. The results from this model are consistent with all five models presented.

Table 3. Current smokeless tobacco use modeled against tobacco advertising expenditure, social media use, sociodemographic characteristics and policy variables using Waves 7,8 and 9 (2017–2019) of the national Truth Longitudinal Cohort Study.

	Model 1	Model 2	Model 3	Model 4	Model 5
	OR	OR	OR	OR	OR
	95% CI	95% CI	95% CI	95% CI	95% CI
Tobacco Advertising Exposure (REF: Never)					
Sometimes	1.03 (0.87, 1.23)	1.03 (0.87, 1.23)	1.03 (0.87, 1.22)	1.03 (0.87, 1.23)	1.03 (0.87, 1.23)
Often, Very often	2.07 *** (1.63, 2.62)	2.05 *** (1.61, 2.60)	2.07 *** (1.63, 2.63)	2.06 *** (1.63, 2.62)	2.05 *** (1.62, 2.60)
Social Media Use (REF: 3 or more h)					
None	0.65 * (0.44, 0.97)	0.65 * (0.44, 0.98)	0.66 * (0.44, 0.98)	0.65 * (0.44, 0.98)	0.66 * (0.44, 0.98)
Less than 1 h	0.96 (0.77, 1.19)	0.95 (0.76, 1.19)	0.96 (0.77, 1.21)	0.96 (0.77, 1.20)	0.95 (0.76, 1.19)
1 to 3 h	0.99 (0.81, 1.19)	0.98 (0.81, 1.19)	1 (0.82, 1.21)	0.99 (0.82, 1.20)	0.98 (0.81, 1.19)
Age	1.02 (0.99, 1.05)	1.02 (0.99, 1.05)	1.02 (0.99, 1.05)	1.02 (0.99, 1.05)	1.02 (0.99, 1.05)
Gender (REF: Female)					
Male	5.54 *** (4.31, 7.14)	5.52 *** (4.28, 7.12)	5.55 *** (4.31, 7.15)	5.56 *** (4.31, 7.16)	5.51 *** (4.28, 7.11)
Parental Education (REF: College Graduate or More)					
Less than high school	1.25 (0.75, 2.10)	1.31 (0.78, 2.20)	1.26 (0.75, 2.11)	1.25 (0.75, 2.10)	1.31 (0.78, 2.20)
High school graduate	1.17 (0.85, 1.60)	1.13 (0.82, 1.55)	1.15 (0.84, 1.57)	1.16 (0.85, 1.59)	1.13 (0.82, 1.55)
Some college/AA degree	1.27 (1.00, 1.61)	1.23 (0.97, 1.56)	1.25 (0.99, 1.59)	1.27 (0.99, 1.61)	1.23 (0.97, 1.56)
Race/Ethnicity (REF: Any Other Race)					
Non-Hispanic White	1.75 *** (1.39, 2.21)	1.73 *** (1.37, 2.19)	1.79 *** (1.37, 2.19)	1.75 *** (1.36, 2.16)	1.76 *** (1.40, 2.21)
Metropolitan Residence (REF: Metropolitan)					
Non-metropolitan	2.09 *** (1.62, 2.70)	1.92 *** (1.48, 2.48)	1.92 *** (1.42, 2.26)	2.09 *** (1.62, 2.69)	1.90 *** (1.47, 2.46)
Sensation Seeking	1.41 *** (1.24, 1.60)	1.43 *** (1.26, 1.63)	1.43 *** (1.25, 1.62)	1.41 *** (1.24, 1.60)	1.43 *** (1.26, 1.63)
Own Poly-Tobacco Use (REF: None)					
Any	3.00 *** (2.47, 3.65)	2.98 *** (2.46, 3.63)	2.99 *** (2.46, 3.64)	3.00 *** (2.47, 3.64)	2.98 *** (2.46, 3.63)
Household Tobacco Use (REF: None)					
Any	1.27 ** (1.08, 1.50)	1.27 ** (1.08, 1.50)	1.27 ** (1.08, 1.50)	1.27 ** (1.08, 1.50)	1.27 ** (1.08, 1.50)

Table 3. Cont.

	Model 1	Model 2	Model 3	Model 4	Model 5
	OR	OR	OR	OR	OR
	95% CI	95% CI	95% CI	95% CI	95% CI
Peer Smoking (REF: None)					
1	1.70 *** (1.38, 2.08)	1.67 *** (1.36, 2.06)	1.69 *** (1.37, 2.08)	1.69 *** (1.38, 2.08)	1.67 *** (1.36, 2.06)
2	2.49 *** (1.97, 3.15)	2.41 *** (1.91, 3.05)	2.47 *** (1.95, 3.12)	2.48 *** (1.96, 3.14)	2.41 *** (1.91, 3.05)
3	2.36 *** (1.70, 3.29)	2.29 *** (1.64, 3.20)	2.33 *** (1.67, 3.24)	2.36 *** (1.69, 3.28)	2.29 *** (1.64, 3.19)
4	1.97 ** (1.34, 2.88)	1.84 ** (1.26, 2.69)	1.94 ** (1.32, 2.84)	1.96 ** (1.33, 2.87)	1.84 ** (1.26, 2.69)
Real Weighted Avg Price of Smokeless Tobacco (USD per one ounce)		0.79 *** (0.73, 0.85)			0.79 *** (0.72, 0.87)
Smoke-Free Indoor Air Laws (% population)			0.44 ** (0.28, 0.70)		0.85 (0.50, 1.45)
Real State Tobacco Control Expenditure (USD per capita)				0.96 (0.81, 1.10)	1.02 (0.97, 1.08)
Wave					
8	0.94 (0.81, 1.10)	0.98 (0.84, 1.14)	0.94 (0.81, 1.10)	0.94 (0.81, 1.10)	0.98 (0.84, 1.15)
9	0.98 (0.82, 1.16)	1.04 (0.87, 1.24)	0.98 (0.82, 1.16)	0.97 (0.82, 1.15)	1.04 (0.87, 1.24)
State Fixed Effects Included	No	No	No	No	No
Model Number of Observations	34,201	34,121	34,201	34,201	34,121
Model Number of Survey Participants	15,089	15,056	15,089	15,089	15,056
Model Mean VIF	1.20	1.20	1.20	1.20	1.22

Notes: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, 95% confidence intervals are shown in parenthesis. A GEE logistic regression modeling technique was used.

4. Discussion

Youth and young adults in this study often or very often exposed to tobacco advertising on websites and social media had more than double the odds of being current smokeless users compared to those who were not exposed. Although not statistically significant, the odds were 3% greater for those who were sometimes exposed to tobacco advertising than those who were not exposed. Trends persisted when accounting for social media use, demographics, psychosocial and tobacco use characteristics, as well as each policy variable of interest individually. These findings are consistent with prior literature, as increased exposure to online tobacco advertising is associated with increased initiation and use of tobacco and nicotine products among youth [8,32–36]. Also consistent with the literature, White male participants living in rural areas and those using multiple tobacco products had greater odds of smokeless tobacco use [2,8,37]. While national studies find that smokeless use is highest in the 25–44 age group [38], we focused on youth and young adults as an at-risk population for establishing patterns of smokeless tobacco use and susceptibility to social media advertising. In our study, marketing exposure and smokeless tobacco use were measured within each wave over time allowing for the possibility that those using smokeless tobacco may seek out marketing. However, we believe this may not be the case, as prior research on other forms of marketing suggests that marketing exposure is cumulative over time. As an example, youth receiving tobacco coupons at baseline and one year later were more likely to use smokeless at follow-up and these effects were stronger for those who were not using at baseline [9].

Our findings suggest that the amount of time spent on social media matters. Youth and young adults in this study who spent three or more hours per day on social media had 51% greater odds of smokeless tobacco use than those who did not spend any time on social media.

Smokeless tobacco use among youth and young adults remains a growing concern. As youth lean away from cigarettes, some are using a diverse array of new nicotine products [12,39] such as Zyn, a novel smokeless product touted as “tobacco-free” [40,41]. Zyn sales increased by 470% in the first six months of 2020 [42]. Products like Zyn should be monitored, specifically among youth and young adults, as their emergence indicates an industry interest to expand the market for alternative non-combustible products or as an alternative to quitting [43].

In addition to expanding their product market, tobacco companies are increasingly dedicating resources to promote smokeless products on smartphone-optimized websites, apps and social media [34,44]. This is concerning given that youth and young adults use social media at disproportionately high rates [4], as well as the pre-existing findings that tobacco advertising on social media encourages product use [18,19], and the direct relationship between tobacco promotion and smokeless use observed in this study.

Our results also confirm that tobacco control policies curb youth and young adult smokeless use. Higher prices and SFIA laws were independently associated with lower odds of smokeless tobacco use. Prior research has shown the relationship between smokeless price and product use and has identified that SFIA laws are indicative of a stronger tobacco regulatory environment, decreasing the likelihood of tobacco use [45,46]. With the adjustment of tobacco control policies in the models, exposure to tobacco advertising still had a significant effect on smokeless use, emphasizing the significant power of tobacco advertising on social media. These findings underscore the need for strong policies banning online tobacco marketing to youth and young adult populations—akin to historic bans on cigarette marketing—to meaningfully reverse trends in smokeless tobacco product use.

5. Limitations

Although this study has many strengths, it is not without limitations. The data available with our measures of interest were limited to a time span of a year and a half, restricting our ability to observe the relationship over time. Second, the survey design involved multistage sampling and over-sampling of sub-populations, normally accounted for using sample weights. We did not account for sampling weights in the GEE logistic models as there is no readily available statistical software to correctly estimate the standard errors of odds ratios from logistic regression while simultaneously accounting for complex survey design and correlated errors nested within respondents. To reduce the bias, we controlled for respondents’ demographic characteristics that were related with survey sampling and weighting and applied robust standard errors [31]. We acknowledge that the magnitudes of odds ratios may not be generalizable to the U.S. youth and young adult population; however, the positive relationship found between exposure to tobacco advertising and smokeless tobacco use still holds. Additionally, our study used self-reported measures of tobacco advertising exposure on websites and social media, which could be subject to recall bias. The validity of this measure requires respondents to see an advertisement, recognize it as a tobacco ad, encode the image in memory and then retrieve the image from memory when prompted by a survey question [47]. Further, the self-reported exposure measure may suffer from endogeneity: respondents who are or are interested in using smokeless tobacco will have greater opportunities to be exposed to online tobacco advertisements due to their online search behavior [48]. Therefore, it would be ideal to use self-reported recall measures in conjunction with exogenous and objective assessment of the level of exposure in a given geographic region and time period. Lastly, our survey question pertaining to tobacco advertising exposure was not specific to smokeless tobacco products.

6. Conclusions

The strong relationship between exposure to online tobacco marketing and smokeless tobacco use emphasizes the importance of social media and websites as a key promotional arena for tobacco companies, particularly when considering the expansion of the alternative,

non-combustible tobacco product market in recent years. Findings underscore the need for stronger regulation of tobacco product marketing on digital platforms to curtail the impact of these promotional activities on young people.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/ijerph19084786/s1>, Table S1: Current smokeless tobacco use modeled against tobacco advertising expenditure, social media use, sociodemographic characteristics and policy variables with state and wave fixed effects using Waves 7, 8 and 9 (2017–2019) of the national Truth Longitudinal Cohort Study.

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OPEN ACCESS

Characterising advertising strategies and expenditures for conventional and newer smokeless tobacco products

Sherry L Emery ,¹ Steven Binns ,¹ Chandler C Carter,¹ Shyanika W Rose ,² Ganna Kostygina ¹

¹Public Health, NORC, Chicago, Illinois, USA

²Behavioral Science, University of Kentucky College of Medicine, Lexington, Kentucky, USA

Correspondence to

Dr Ganna Kostygina, Public Health, NORC, Chicago, IL 60603, USA; kostygina-anna@norc.org

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ABSTRACT

Objective Nicotine pouch products are an emerging and rapidly growing smokeless tobacco (ST) category in the USA. Little is known about the promotional strategies and media channels used to advertise this ST category or the extent to which the marketing strategies differ from strategies used to promote 'conventional' smokeless products (eg, snuff). We describe the nature, timing of and expenditures related to conventional, snus and newer ST product advertising on print, broadcast and internet media.

Methods Advertising expenditures were collected using Kantar Media's 'Strategy' tool, which provides advertising data including dollars spent promoting specific products across various media channels, including print magazines and newspapers, broadcast television and radio, outdoor posters and billboards, and internet. We identified 306 smokeless products within Kantar database and collected ad expenditures retrospectively for January 2018–April 2020. Promotional expenditures were aggregated by product category, by month and by designated market area (DMA).

Results Kantar data analysis returned 28 conventional ST, 22 oral nicotine and 3 snus products (53 total) advertised during the period of observation, with over \$71 million spent collectively on ST promotion. Across categories, more advertising dollars were spent on conventional ST products (63%) than newer oral nicotine products (25%) or snus (12%). However, during the later 9-month period from August 2019 to April 2020, oral nicotine products accounted for the majority of monthly ad spending. Most ad spending was placed in the national market (\$66.5 million), with Atlanta (\$1.1 million), Houston (\$1 million) and Las Vegas (\$0.8 million) as the top three local DMAs for expenditures.

Discussion Advertising expenditures for nicotine pouches have recently exceeded conventional ST product advertising and nicotine pouches are being promoted nationally. Marketing surveillance as well as understanding consumer appeal, perceptions and consumption are critical next steps in tracking potential uptake of these new products.

INTRODUCTION

Nicotine pouches are a rapidly growing smokeless tobacco (ST) category in the USA. Similar to snuff (dry or moist tobacco leaf in packets) or snus (a variant of pouched dry snuff originating from Sweden), these products are portioned in pouches, but instead of containing tobacco leaf they hold

KEY MESSAGES

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Smokeless tobacco product landscape is rapidly changing with the emergence of newer oral nicotine pouch products on the US market.

WHAT THIS STUDY ADDS

- ⇒ We examined the amount and nature of conventional and newer smokeless tobacco product advertising expenditures on print, broadcast and internet media.
- ⇒ We found that promotional spending for smokeless tobacco shifted from conventional products (eg, moist snuff) to newer nicotine pouches during the study period.
- ⇒ Nicotine pouches were predominantly advertised on television, likely due to the lack of regulation of broadcast media promotion of tobacco-free nicotine products.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Marketing surveillance as well as understanding consumer appeal, perceptions and consumption are critical next steps in tracking potential uptake of these new products.
- ⇒ Stronger marketing regulations can curb exposure to smokeless product advertisement among novices and young people.

nicotine powder.¹ Prominent brands in the USA are produced by major cigarette and cigar product manufacturers, including Velo (RJ Reynolds), Zyn (Swedish Match), Rogue (Swisher International) and On! (Altria).^{2,3} Other emerging brands introduced by independent manufacturers are NIIN (or 'Nicotine Innovated'), Rush, Nic-S, Lucy, Black Buffalo and Fre.^{2,4} These products come in a variety of flavours (eg, mint, fruit and candy flavours) and contain different amounts of nicotine. For instance, Zyn products range from 3 mg to 6 mg of nicotine; Velo pouches are available in 2 mg, 4 mg and 7 mg nicotine strength options.² Some brands feature as much as 12 mg (Fre) and 20 mg (Faro) of nicotine per pouch. Additionally, several brands (eg, Fre, NIIN) indicate that they use synthetic nicotine in their pouch products, with claims that their products are formulated to remove such known carcinogens as tobacco-specific nitrosamines.⁵

The 'tobacco-free nicotine', 'non-tobacco' and 'synthetic nicotine' claims and potential reduced



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risk statements used by brands, vendors and marketers to promote newer ST products have not been verified by the US Food and Drug Administration (FDA) and may be misleading.^{6,7} It is unclear whether any newer smokeless brands have submitted an application to receive modified risk tobacco product (MRTP) status from FDA, that is, a designation that tobacco product poses lower health risks to individual users and the population as a whole when compared with existing products on the market.⁸ While switching to newer ST could reduce morbidity and mortality among smokers who are unable to quit, the products also have potential to attract and addict a new generation to tobacco. In particular, the availability of flavours, high nicotine content and 'tobacco free' claims are likely to be appealing to youth.^{9,10}

Nicotine pouches, which were introduced in 2016, grew to 4.0% in market share by 2019.¹¹ While this market is rapidly growing, nicotine pouches are also competing in an increasingly diverse nicotine product landscape. New product categories and brands of smokeless and nicotine products (eg, nicotine gums, lozenges, sticks) continue to emerge despite FDA actions to limit the sales of flavoured products.^{12–14}

Furthermore, the FDA recently approved modified risk claims for several General snus products indicating that use of those brands results in lower harm of various tobacco-related illness compared with cigarette use.¹⁵ These MRTP marketing orders may affect consumers' perceptions of other oral nicotine products, such as nicotine pouches. The growth and diversification within the smokeless market have raised both regulatory questions and health concerns, particularly as they relate to youth who are using tobacco and nicotine products, including flavoured varieties.¹⁶

Use of these products may encourage dual or poly-tobacco product use. Indeed, evidence suggests that youth never-tobacco users who try ST products are more likely to try cigarettes and e-cigarettes 1 year later¹⁷ and nearly two-thirds of youth who reported using ST products also used at least one other tobacco product.¹⁸

The transformation of the ST product landscape coincided with changes in the tobacco regulatory environment. The 2009 Family Smoking Prevention and Tobacco Control Act required ST packages and advertisements to have larger and more visible warning labels.¹⁹ In recent years, some localities in states such as California and Massachusetts banned all flavoured tobacco products, including ST products.²⁰ The way in which ST products are taxed has also shifted, resulting in reduced taxes for consumers of these products.^{11,21} These regulatory changes likely have affected how tobacco companies market ST products.

Understanding where and how the industry is promoting newer oral tobacco products is important to predict population uptake and public health impact. The latest Federal Trade Commission (FTC) report that tracks industry spending for ST marketing does not include these products.²² Our analyses describe the nature, timing of and expenditures for 'conventional'/older (eg, snuff), snus and newer ST product categories on print, broadcast and internet media. Comparative analysis of the marketing expenditures for conventional, snus and newer smokeless products can help shed light on unique strategies used to promote each of these ST categories and elucidate whether the channels used to promote newer products differ from the traditionally used channels and potentially reach a new audience to help expand the consumer base.

METHODS

Data collection

We employed Kantar Media's 'Strategy' tool to estimate US advertising expenditures for ST products from January 2018 to April 2020. Kantar's estimates are based on rate cards provided by publishers, television (TV) and radio networks, and advertising agencies to forecast the cost of advertising placement. We searched the Strategy database using ST-related terms (such as nicotine, nic, snus, pouch, gum, stick, lozenge, pellet, strip, dissolvables), established brand names (such as Copenhagen, Grizzly and Skoal) and emerging ST brand names (such as Velo, Zyn and On!). We also reviewed all products falling under the same Kantar Strategy categories as the products we used in our initial searches based on the established brand names. Relevant product categories included 'cigar & tobacco' and 'smoking deterrents' categories, which yielded additional ST products. We identified 297 smokeless products in the Kantar database and collected ad expenditures retrospectively for the time period from January 2018 through April 2020.

Analysis

Marketing expenditures were aggregated by month and media type: TV (local and national), print (local and national magazines and newspapers, in English and Spanish), radio (local and national), internet (standard web and mobile device types) and outdoor (billboard, poster, etc). Promotional expenditures were also aggregated by designated market area (DMA) and product category: conventional ST (eg, dip, moist and dry snuff, chewing tobacco), snus (an established variant of pouched dry snuff) and newer oral nicotine ST products (eg, nicotine pouches and lozenges). Finally, within each product category we reviewed the specific products with highest advertising expenditures.

RESULTS

There were 53 ST products advertised during the period of observation, with a total of \$71.7 million in advertising expenditures collectively. Among ST categories, conventional ST products accounted for 63% (\$45.2 million) of the total (\$71.1 million), followed by newer oral nicotine products (25%, \$18 million) and snus (12%, \$8.5 million). Of the 22 oral nicotine products (ie, nicotine pouches, toothpicks, gums, sprays, tablets and lozenges), 5 pouch products accounted for 97% (\$17.4 million) of oral nicotine expenditures (\$18 million). Most ad spending was placed in the national market (\$66.5 million or 92.7%), with Atlanta (\$1.1 million), Houston (\$1 million) and Las Vegas (\$0.8 million) emerging as the top three DMAs for localised expenditures.

Figure 1 shows the monthly expenditures for ST marketing by product category across time, from January 2018 through April 2020. Notably, all product categories approached zero ad spending in January and February of 2019 and overall spending remained relatively low through August of that year. However, during the 9 months between August 2019 and April 2020, overall ST expenditures increased, with newer oral nicotine products largely replacing conventional ST advertisement spending.

Figure 2 shows the proportion of advertising for each product category by media type. Over 96% of advertising dollars for both conventional ST and snus were spent on print advertising. However, the majority (61%) of the spending on oral nicotine ST promotion was for TV advertising. Almost a quarter (23%) of oral nicotine ST promotion dollars were spent on radio and

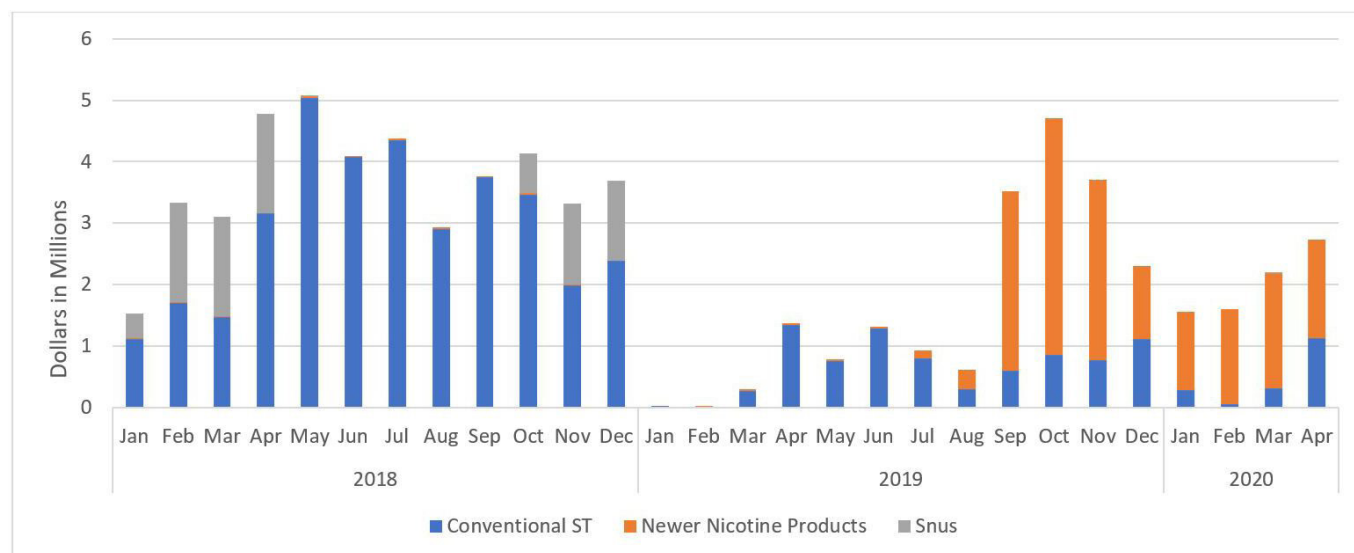


Figure 1 Amount of smokeless tobacco (ST) marketing expenditures by product category from January 2018 to April 2020. Each stacked bar shows the proportion of expenditures by product category.

the remaining dollars were spent on internet ads (8%), print ads (4%) and outdoor ads (4%).

Top advertisers of conventional ST products included U.S. Smokeless Tobacco Company (USSTC, Altria subsidiary), which spent more than \$14 million advertising a prominent moist snuff brand. The second, third and fourth highest levels of ad expenditures for specific conventional ST product brands ranged between \$4.8 and \$5.6 million during the same period. RJ Reynolds spent the most among newer tobacco product manufacturers (\$16.6 million), distantly followed by Swedish Match (\$0.67 million). This vast discrepancy is likely because the RJ Reynolds product was introduced to the market in 2019, while the Swedish Match product was introduced earlier in 2016 and was already a market leader.^{23 24}

DISCUSSION

Advertising expenditures for nicotine pouches have recently exceeded those for conventional ST and account for the majority of spending for newer nicotine product marketing. Five nicotine pouch products accounted for 97% of expenditure for oral nicotine (ie, pouches, toothpicks, gum, spray, tablets and lozenges). It is noteworthy that while most ad spending was placed in the

national market, Atlanta, Houston and Las Vegas emerged as the top three DMAs based on the amount of expenditures, which may be due to the fact that these areas were test markets for oral nicotine products (eg, Velo).²⁵ Both newer and conventional smokeless products were promoted on media channels easily accessible to youth. Namely, while the majority of conventional and snus advertisement expenditures were placed on print media, over 60% of spending on nicotine pouch promotion was allocated for TV advertising. There is a robust body of evidence that exposure to tobacco product marketing is associated with youth initiation, across a variety of products.^{26–29} Thus, there is no reason to expect that promotion of newer ST products would be an exception. Further, marketing of these products may encourage dual or poly-use since youth who try ST products are more likely to try combustible and e-cigarette products.^{17 18}

Despite potentially lower health risks compared with combustible products, newer smokeless products also have potential to addict a new generation to tobacco. Testing of newer smokeless products finds high levels of nicotine which may be associated with increased risk of dependence.³⁰ The FDA should evaluate the reduced risk claims of ST products, including newer oral tobacco products, to help ensure that young users are not misled. Furthermore, if any nicotine pouch products are approved for modified risk, the FDA should ensure that these products are not marketed using strategies that appeal to youth. Public health and tobacco control professionals can contribute to the effort to reduce youth tobacco and nicotine use by educating parents and children about the tobacco industry's role in developing newer products to attract new users.

Limitations

The study is not without limitations. Kantar expenditures data capture mass media and outdoor ads, but not point-of-sale marketing, direct-to-consumer mail or email marketing, or social media marketing. Other research demonstrates that direct mail ST marketing (including for newer products) was prevalent in 2018–2020, with 38 million pieces of newer smokeless direct mail advertisements sent to US consumers during the time period from March 2018 to August 2020.^{6 31} In addition, while the Kantar database includes internet advertising data, it cannot

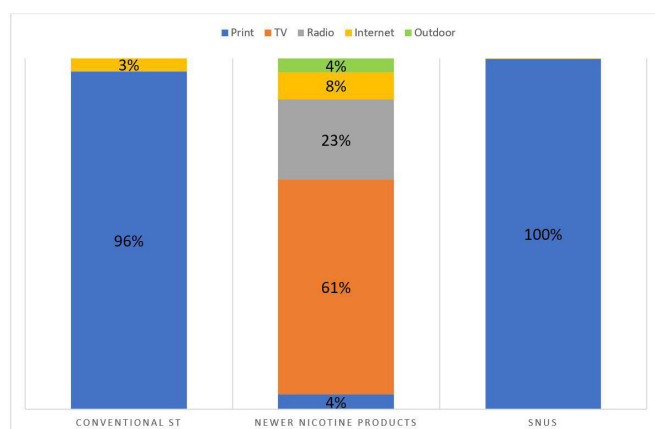


Figure 2 Proportion of smokeless tobacco advertising expenditures by product category by media type. ST, smokeless tobacco; TV, television.

capture some important types of online marketing—influencer partnerships or social media campaigns that do not pay to promote posts, for example.

Our findings revealed that there was a retrenchment in ST advertising in January–February 2019, and while we are unsure what caused the spending decline these results are in line with estimates from the FTC Smokeless Tobacco report which shows a 12.5% reduction in advertising and promotional expenditures from 2018 to 2019.³² Despite limitations, this paper provides needed data on newer ST marketing practices beyond what is publicly available in FTC reports.

CONCLUSIONS

This analysis provides early surveillance of the introduction of a nicotine pouch product to the market. Promotional spending for ST shifted from conventional products and snus in 2018 to primarily newer oral nicotine pouches towards the end of 2019 and into early 2020. Newer ST products are not regulated in the same way as conventional ST products. While it is unlawful to advertise conventional ST on TV, newer ST products, which claim to be ‘tobacco-free’, have evaded regulation thus far. Thus, TV audiences recently saw ads for ST products for the first time since 1986.^{33 34} Continued marketing surveillance as well as research to understand consumer appeal, perceptions, sales and consumption are critical next steps in tracking potential uptake and the public health impact of these new products.

Twitter Sherry L Emery @sherryemery and Shyanika W Rose @ShyanikaRose

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ORCID iDs

Sherry L Emery <http://orcid.org/0000-0001-9278-9990>

Steven Binns <http://orcid.org/0000-0001-8573-107X>

Shyanika W Rose <http://orcid.org/0000-0002-4200-1197>

Ganna Kostygina <http://orcid.org/0000-0002-8416-6168>

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Article

Introducing a Novel Biorelevant In Vitro Dissolution Method for the Assessment of Nicotine Release from Oral Tobacco-Derived Nicotine (OTDN) and Snus Products

Matthias M. Knopp ^{1,*}, Nikolai K. Kiil-Nielsen ¹, Anna E. Masser ²  and Mikael Staaf ²

¹ Bioneer: FARMA, Department of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen, Denmark; nkn@bioneer.dk

² Swedish Match North Europe AB, Regulatory & Scientific Affairs, P.O. Box 17037, S-104 62 Stockholm, Sweden; anna.masser@swedishmatch.com (A.E.M.); mikael.staaf@swedishmatch.com (M.S.)

* Correspondence: mmk@bioneer.dk

Abstract: The rate at which oral tobacco-derived nicotine (OTDN) and snus pouches release nicotine into saliva is crucial to determine product performance. As no standardized method is available for this purpose, this study sought to develop a biorelevant dissolution method that could both discriminate between different products and predict in vivo behavior. Using a μ DISS Profiler™ as a surrogate for the US Pharmacopoeia standard apparatuses and a custom-made sinker, nicotine release from an OTDN pouch product (ZYN® Dry Smooth) and a snus product (General® Pouched Snus White Portion Large) was determined in biorelevant volumes (10 mL) of artificial saliva. In addition, nicotine extraction in vivo was measured for both products. Strikingly, the method showed distinct dissolution curves for OTDN and snus pouches, and the nicotine release observed in vitro did not significantly differ from the nicotine extracted in vivo. The custom-made sinker was designed to accommodate both loose and pouched oral tobacco/nicotine products, and thus the proposed in vitro dissolution method is suitable to assess nicotine release from OTDN and snus pouches. Apart from providing individual dissolution curves, the method was also able to predict in vivo nicotine extraction. Thus, this method could serve as a (biorelevant) monograph for product equivalence studies.

Keywords: oral tobacco derived nicotine (OTDN) pouches; snus; nicotine release; nicotine dissolution; nicotine extraction; equivalence



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1. Introduction

Oral tobacco-derived nicotine (OTDN) pouch products are growing in popularity, but cigarettes remain the most common tobacco product worldwide [1]. Cigarettes are a huge health burden in terms of tobacco-related morbidity and mortality, and smoking tobacco is the factor contributing to most preventable deaths worldwide [2]. The hazards of cigarettes are a result of the inhaled combustion products formed during smoking and have less to do with their tobacco and nicotine content [3]. Still, nicotine is the addictive substance sustaining cigarette dependence. Smokeless tobacco products (STPs) expose the user to no combustion products and epidemiological data on the STP Swedish snus have shown the use of Swedish snus to be significantly less harmful, in terms of morbidity and mortality, compared to cigarettes [4–6]. Little data are available on OTDN pouches, but current literature indicate that they contain less (potentially) harmful constituents and are less toxic in vitro, compared to cigarettes [7,8]. OTDN pouches are therefore an enticing alternative to traditional tobacco-based products, in terms of harm reduction.

OTDN pouches come in small, white sachets that are intended to be placed between the gum and upper lip where nicotine is released into the surrounding saliva from which it permeates the buccal mucosa, and subsequently enters systemic circulation. Thus, the

performance of these products depends on the rate at which nicotine is released. However, despite growing attention among regulatory agencies and tobacco researchers, a standardized method to evaluate the nicotine release from OTDN pouches is yet to be established.

In vitro, nicotine release can be measured by dissolution testing, a method commonly used for pharmaceuticals. Therefore, it would be logical to glance at pharmaceutical guidance's and monographs when developing a novel dissolution method. In the United States (US), STPs and OTDN pouches are regulated by the Food and Drug Administration (FDA) Center for Tobacco Products, which requires that dissolution testing is carried out on novel nicotine products as well as to demonstrate product equivalence [9].

For STPs, such as snus and moist snuff, only limited literature on development of dissolution methods that are designed to discriminate between OTDN products or simulate in vivo nicotine release is available [10–15]. One of these studies utilizing the US Pharmacopeia type 4 apparatus (USP-4) (flow-through cell) method was able to discriminate between moist snuff and OTDN pouches [15]. However, this method saw a 77% nicotine release from a Swedish-style snus pouch after 30 min, which greatly differs from the in vivo situation where only 31–46% nicotine extraction from the same product is reported after 1 h [13,16–18]. As the amount of agitation on the products in the USP-4 is minimal, this inconsistency could be due to the amount of flow/volume of artificial saliva used in this method (4 mL/min) which is almost 10-fold higher than the unstimulated saliva flow rate (0.5 mL/min) [19].

Other methods utilizing the USP-1 and USP-2 (basket and paddle, respectively) were able to discriminate between the dissolution curves for moist snuff and Swedish snus. The authors pointed out the benefits of using USP-1 (and USP-2) being that they are the most used apparatuses, come at a lower cost than USP-4 and their ease of use [20]. Slower rates of nicotine release were shown, although still significantly faster than in vivo, probably also due to the large amount (500 mL) of artificial saliva used. Moreover, it is unclear if these methods could also discriminate between moist snuff/snus and OTDN pouches.

In this study, the in vitro release of nicotine from the OTDN pouch product ZYN[®] Dry Smooth and General[®] Pouched Snus White Portion Large (PSWL) was investigated in biorelevant volumes of artificial saliva using a μ DISS Profiler[™] dissolution method. The in vitro release data (i.e., biorelevance of the proposed dissolution method) was verified through in vivo nicotine extraction studies on the same products.

2. Materials and Methods

2.1. Investigational Products, Standards, and Reagents

General PSWL is a Swedish snus product containing 8 mg of nicotine. It comes in a rectangular pouch measuring 18 × 33 mm that weighs 1.0 g with a moisture content of 53.5% and a pH of 8.7. The pouch contains ground, air-cured tobacco, water, sodium chloride, sodium carbonate, humidifying agents, and food-grade flavorings.

ZYN Dry Smooth is an OTDN pouch product containing 6 mg of nicotine. The pouch measures 14 × 28 mm, weighs 0.4 g, contains 3% moisture, and has a pH of 8.3. The pouch contains fillers (maltitol and microcrystalline cellulose), a stabilizer (hydroxypropyl cellulose), pH adjusters (sodium carbonate and sodium bicarbonate), nicotine salt, food-grade flavorings, and a sweetener (acesulfame K).

Both products were provided by the manufacturer Swedish Match North Europe AB.

2.2. Standards and Reagents

A nicotine reference standard (>99.9%) was sourced from Łukasiewicz IPO (Warsaw, Poland). Saliva Orthana[®] (artificial saliva) containing (per 100 mL aqueous solution): porcine gastric mucin 3500 mg, methyl-4-hydroxybenzoate 100 mg, benzalkonium chloride 2 mg, EDTA disodium salt. H₂O (E386) 50 mg, H₂O₂ 250 ppm, xylitol 2000 mg, peppermint oil 5 mg, spearmint oil 5 mg, NaCl 45 mg, KCl 63 mg, CaCl₂ 30 mg, K₂HPO₄ 10 mg, KOH 76 mg with a neutral pH, was purchased from Biofac A/S (Kastrup, Denmark).

2.3. Sinkers Preparation

As there is no suitable sinker commercially available, a custom-made sinker was prepared by 3D printing a 12 mm tall, hollow tube with an outside diameter of 21 mm and a wall thickness of 2 mm using polylactic acid (PLA). The structure was designed by computer aided design (CAD) using the online platform Tinkercad from Autodesk (San Rafael, CA, USA), exported as .stl files and converted to a readable file for the printer using the Cura software (version 3.6.0) from Ultimaker (Geldermase, The Netherlands). An Ultimaker 3 extended from Ultimaker (Geldermalsen, The Netherlands) was used to print the tube structures from a 2.85 mm PLA 3D printer filament (Innofil3D BV, Emmen, Netherlands) using a printing temperature of 200 °C and a layer height of 50 µm. After printing, the tube was fitted with a 20-mesh stainless steel sieve (0.84 mm sieve opening) by molding it into the PLA tube at 200 °C using a hot-plate. A picture of the final product loaded with an OTDN pouch can be seen in Figure 1A.

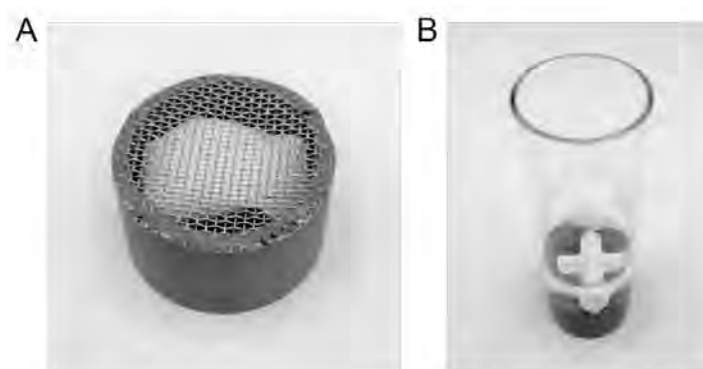


Figure 1. Details of the µDISS Profiler™ experimental setup. (A) An OTDN pouch loaded in the custom-made sinker, 3D printed using polylactic acid (PLA) and fitted with a 20-mesh stainless steel sieve. The sinker measures 12 mm in height and 21 mm in width. (B) A snus pouch loaded in the custom-made sinker and placed on the bottom of the standard 20 mL µDISS Profiler™ dissolution vessel containing 10 mL of artificial saliva with a 20 mm cross-shaped magnetic stirrer on top.

2.4. In Vitro Nicotine Release

The nicotine release experiments were carried out using a µDISS Profiler™ (Pion Inc., Billerica, MA, USA) with six channels without the in-line UV probes connected. The snus/OTDN pouches were weighed individually, loaded in the sinkers, and placed on the bottom (mesh up) of the standard 20 mL dissolution vessels with 20 mm cross-shaped magnetic stirrers on top. A picture of the experimental setup is shown in Figure 1B. The magnetic stirrers were set to operate at 100 rpm and the minibath temperature was set to 37 °C. The experiment was initiated by addition of 10 mL of artificial saliva (preheated to 37 °C) to each of the six dissolution vessels. Samples of 250 µL were taken at $t = 5, 10, 15, 30, 45, 60, 90,$ and 120 min and replaced with 250 µL of preheated artificial saliva. The samples were diluted immediately with 375 µL acetonitrile and 375 µL ethanol in a 1.5 mL Eppendorf centrifuge tube to precipitate proteins from the saliva and avoid potential precipitation of the nicotine upon cooling. Diluted samples were centrifuged at 10,000 rpm for 10 min at room temperature and the resulting supernatant was analyzed for nicotine content using high-performance liquid chromatography (HPLC). The dissolution testing was performed on 12 dosage units of each formulation in accordance with regulatory guidelines [21].

2.5. Quantitative Analysis

Nicotine released in vitro was quantified by HPLC-UV using an Ultimate 3000 HPLC system (Dionex, Sunnyvale, CA, USA). A reverse phase Kinetex Evo C18 100A column (4.6 × 100 mm, 2.6 µm) (Phenomenex, Værløse, Denmark) was used for the separation and the mobile phases consisted of (A) 15 mM ammonium formate adjusted to pH 10.5 using

triethylamine and (B) acetonitrile, which were pumped isocratically at 75% A and 25% B. A volume of 10 µL was injected and eluted at a flow rate of 0.5 mL/min, and the effluent was detected at a wavelength of 260 nm with a retention time of approximately 4.3 min. The concentration of nicotine in the samples was calculated using the mean value of the peak areas obtained from a calibration standard curve prepared in triplicate. Representative chromatograms are shown in Supplemental Figure S1. The method was validated for linearity, accuracy (recovery), range, precision (repeatability), limit of detection (LOD) and limit of quantification (LOQ) prior to use. The triplicate standard curve for nicotine was linear with an $r^2 = 0.9998$ over the range 1.95–500 µg/mL and a y-intercept at 0.86% of the target concentration response (200 µg/mL). At 50%, 100%, and 150% of the target concentration response, the recovery of nicotine was 98.95–99.62%. The precision of the retention time, peak area and peak height for nicotine was 0.12–0.50%. The LOD and LOQ for nicotine was 0.23 µg/mL and 0.75 µg/mL, respectively.

2.6. In Vivo Nicotine Extraction

A non-blinded, crossover, single-dose administration study was conducted to obtain the in vivo nicotine extraction data [22]. The study enrolled healthy male and female snus users aged ≥ 19 years, willing and able to give written informed consent. The study was carried out in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonization (ICH)/Good Clinical Practice (GCP), European Union Clinical Trials Directive, and applicable local regulatory requirements. The study was approved by the Swedish Ethical Review Authority and registered on the ISRCTN registry (ISRCTN44913332). The 18 subjects kept the pouch still between the upper lip and gum. Each used pouch, 18 replicates per product and time point (15 and 60 min), was collected and frozen (-20°C) pending nicotine analysis. Unused pouches, 10 replicates per product, were collected and frozen (-20°C) for analysis as references in the calculations of extracted doses. The concentration of nicotine in pouches was determined using a Gas Chromatography/Mass Spectrometry (GC/MS) system (Agilent 7890A GC, 7693A autosampler and 5975C MS) using an Agilent Innnowax, 60 m \times 0.25 mm ID column with a 0.25 µm film.

2.7. Data Analysis

Results from the in vitro and in vivo studies are expressed as mean \pm standard deviation (SD). Statistical analysis was performed in SigmaPlot 14.0 from Systat Software Inc. (Chicago, IL, USA). A Student's t-test was performed on untransformed data to identify significant differences between in vitro and in vivo nicotine release after 15 min and 60 min.

A mathematical approach recognized by the US FDA was used to compare the similarities and differences in dissolution profiles [21,23]. The difference factor (f_1) was used to calculate the percent difference between two curves at each time point, which measures the absolute relative error between the two points. The similarity factor (f_2) measures the similarity in the percent dissolution between two curves. The two factors were calculated using the following equations:

$$f_1 = \left(\frac{\sum_{t=1}^n |R_t - T_t|}{\sum_{t=1}^n R_t} \right) * 100$$

$$f_2 = 50 * \log \left(100 * \left(1 + \frac{\sum_{t=1}^n (R_t - T_t)^2}{n} \right)^{-\frac{1}{2}} \right)$$

R_t and T_t are the cumulative percentage dissolved of reference product and test product at time t , respectively, and n is the number of timepoints. Curves are considered similar for f_1 values close to 0, and f_2 values close to 100. Generally, dissolution profiles are judged to be equivalent if f_1 values are below 15 and if f_2 values are greater than 50.

3. Results and Discussion

Several different *in vitro* nicotine release methods have been proposed that are able to discriminate between different STPs, but common for these methods is that they all seem to substantially overpredict the nicotine release *in vivo* [13,20]. Therefore, this work sought to develop a discriminative and biorelevant *in vitro* method for nicotine release/dissolution from OTDN pouches and snus products and validate this with *in vivo* nicotine extraction data. To determine what volumes are biorelevant a reasoning made by the FDA in their memorandum regarding dissolution testing were followed [9]. There, usage time and salivary flow at the site where the pouch is placed were taken into consideration. No data on average usage time for ZYN Dry are available, but for pouched snus 65 min has been reported [24]. Both ZYN Dry and snus are placed under the upper lip where the parotid glands secrete saliva into the mouth. The resting and stimulated flow rate of saliva from the parotid glands are 0.1 mL/min and 1.05 mL/min, respectively [25,26]. Assuming that the pouch is kept for 60 min, the average flow of saliva from both parotid glands would vary between 6–63 mL, depending on degree of stimuli. As the pouch is kept on one side of the mouth, and therefore is mainly in contact with saliva from one of the glands, 3–33 mL can be considered biorelevant. Here, 10 mL of test medium was chosen, and the μ DISS Profiler™ was used as a surrogate for the USP standard dissolution apparatuses, to allow for the low volume. As there is no standard simulated saliva fluid recipe described in the US Pharmacopeia, we chose a commercially available artificial saliva as dissolution medium as opposed to less viscous buffer systems. Finally, a custom-made sinker was designed to prevent floating and pouch/material discharge during the experiments, and to accommodate both loose and pouched products (Figure 1A).

Using the novel dissolution method, nicotine release profiles for ZYN Dry Smooth and General PSWL were obtained (Figure 2). The average nicotine release profiles are plotted as percentage of dose, to account for differences in nicotine dose due to pouch filling/weight variance. After 15 min and 60 min, the nicotine release from General PSWL was $9.2 \pm 4.7\%$ and $29.9 \pm 11.2\%$, respectively. For ZYN Dry Smooth, the nicotine release after 15 min and 60 min, was $15.3 \pm 7.2\%$ and $50.1 \pm 14.5\%$, respectively.

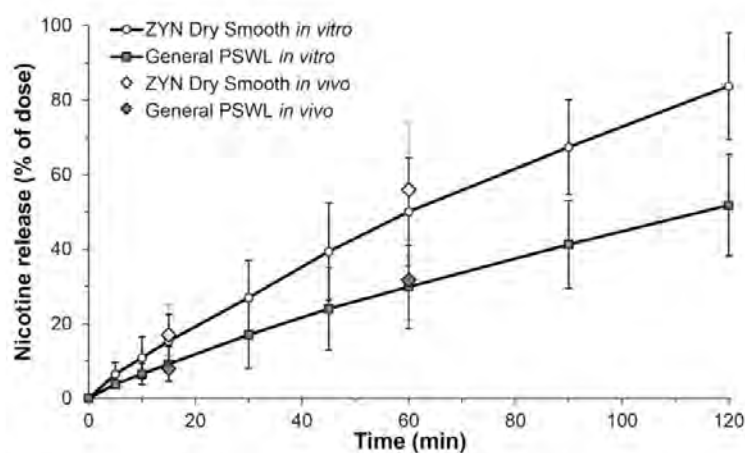


Figure 2. *In vitro* and *in vivo* nicotine release from ZYN Dry Smooth and General Pouched Snus White Portion Large (PSWL) as a function of time. Nicotine *in vitro* release profiles from General PSWL (dark gray squares, black error bars) and ZYN Dry Smooth (white circles, black error bars) in artificial saliva as % of dose \pm standard deviation (SD) ($n = 12$). Based on calculations of the difference (f_1) and similarity factor (f_2) the curves are distinct ($f_1 = 63.6$, $f_2 = 38.8$). *In vivo* nicotine extraction after 15 min and 60 min for ZYN Dry Smooth (white diamonds, grey error bars) and General PSWL (dark grey diamonds, grey error bars) is added for comparison as % of dose \pm SD ($n = 18$). No significant differences were seen at 15 and 60 min between *in vitro* and *in vivo* conditions for both products, respectively.

To investigate if the in vitro dissolution method reflected on actual in vivo conditions the results were compared to a previously conducted clinical study. The study enrolled 18 daily snus users aged ≥ 19 years which kept one pouch at a time still between the upper lip and gum. The in vivo extracted fraction of nicotine from General PSWL, after 15 and 60 min, was $8.0 \pm 3.3\%$ and $31.8 \pm 10.8\%$, respectively. For ZYN Dry Smooth, the in vivo extracted fraction of nicotine, after 15 and 60 min, was $17.1 \pm 7.8\%$ and $56.0 \pm 18.1\%$, respectively (Figure 2). General PSWL contains 33% more nicotine per pouch than ZYN Dry Smooth does. However, the absolute nicotine release was 32% higher in ZYN Dry Smooth because of a higher extracted fraction of nicotine. The results are in line with previously published data on Swedish snus and ZYN Dry Smooth [16–18,27]. The large difference in extracted fractions between both products are likely an effect of their diverse characteristics, in terms of nicotine source (ground tobacco leaves vs. nicotine salt), moisture, pH, and pouch geometry.

A critical feature of any dissolution method is that it should be able to distinguish between different products, here an OTDN and a snus pouch product. To compare the similarities and differences in dissolution profiles a mathematical approach recognized by the US FDA were used [21,23]. Based on this method, curves are considered similar for f_1 values close to 0, and f_2 values close to 100. In contrast, dissolution profiles are judged to be distinct if f_1 values are above 15 and if f_2 values are smaller than 50. We obtained f_1 and f_2 values of 63.6 and 38.8, respectively, showing that the curves for ZYN Dry Smooth and General PSWL are distinct.

A second feature of dissolution testing is that it can be used to predict the in vivo behavior of a product. A Student's t-test was used to verify similarities and differences between in vitro and in vivo conditions. Strikingly, no significant differences ($p > 0.05$) were seen for both products, at the two time points tested. As earlier studies have used much higher media volumes [13,20], it seems that the volume of saliva is of great importance when comparing nicotine release from OTDN and snus products.

In summary, this indicates that not only is the proposed in vitro nicotine release method able to discriminate between products from two different product categories, but it is also predictive of in vivo nicotine release, at least for the products tested. Thus, this method could serve as a predictive tool for product development and/or a monograph for oral tobacco/nicotine product equivalence studies.

4. Conclusions

In this work, a novel dissolution method was developed and the nicotine extraction from an OTDN pouch product (ZYN Dry Smooth) and a snus product (General PSWL) was determined. Calculations of the difference and similarity factor showed distinct nicotine-release curves for the two different products, verifying that the method can discriminate between different product categories. To investigate if the in vitro method could predict in vivo behavior, in vivo nicotine extraction was measured for both products and both time points. No significant differences could be seen within products when comparing in vitro and in vivo data after 15 min and 60 min.

Consequently, this method is to the best of our knowledge the first method developed that is both sensitive enough to discriminate between a product containing purified nicotine (ZYN Dry Smooth) and a product containing tobacco (General PSWL), as well as to be able to predict in vivo behavior.

Finally, the custom-made sinker was designed to accommodate both loose and pouched snus/snuff material. Thus, the proposed in vitro dissolution method could potentially be applied to assess the nicotine release from other oral nicotine/tobacco products e.g., moist snuff, dry snuff, and dissolvables.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/separations9020052/s1>.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Swedish Ethical Review Authority (protocol code Dnr 2017/318 approved 13 September 2017).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to company policies.

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Conflicts of Interest: A.E.M. and M.S. are employees of Swedish Match North Europe AB who markets the ZYN and general products described in the article. M.M.K. has received funding from Swedish Match North Europe AB.

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Development and Validation Of A Discriminatory Dissolution Method for Portioned Moist Snuff and Snus

ZiYaur Rahman¹, Eman M. Mohamed^{1,2}, Sathish Dharani¹, Tahir Khuroo¹, Mimy Young³, Charles Feng³, Todd Cecil³, Mansoor A. Khan^{1,*}¹ Irma Lerma Rangel College of Pharmacy, Texas A&M Health Science Center, Texas A&M University, College Station, TX 77843, USA² Department of Pharmaceutics, Faculty of Pharmacy, Beni-Suef University, Egypt³ Division of Product Science, Office of Science, Center for Tobacco Products, Food and Drug Administration, Silver Spring, MD, USA

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ABSTRACT

Portioned moist snuff and snus, two subcategories of smokeless tobacco products (STP) were dissolution tested as a quality control test. A USP Apparatus 4 was employed to develop and validate the method. The method was assessed based on time to reach nicotine dissolution plateau, percentage difference between two profiles at each time point, relative standard deviation (RSD), and f_1 (similarity) and f_2 (dissimilarity) values. Based on these criteria, 200 ml volume and 8 ml/min flow were found to be discriminatory. The amount of nicotine dissolved from the nine products varied widely (2.0–3.4, 2.1–4.1, 3.3–4.6, 5.5–6.6, 6.9–9.1, 11.5–14.2, 12.5–14.6, 14.0–15.5, and 15.5–19.6 mg/pouch at 60 min). RSDs of the dissolution ranges were more than 20% at earlier time points and less than 20% at later timepoints. The developed method produced distinct profiles for all the tested products, which was further confirmed by $f_1 > 15$ and $f_2 < 50$ values. In conclusion, the developed method was discriminatory and can be employed as a quality control test and to differentiate among moist snuff and snus products.

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Introduction

Smokeless tobacco products (STPs), in general, are oral use tobacco products. Users place these products between the gum and cheek or lip, suck on the tobacco, and spit out or swallow the juice. Most STPs are broadly classified into chewing tobacco, snuff (also called “dip”), and snus. Chewing tobacco is cured tobacco in the form of loose leaf, plug or twist. Snuff is a finely ground tobacco product that is sold in a moist or dry form. Dry snuff contains fire-cured, finely cut powdered tobacco, and is typically sniffed through nostril. Unlike other category of STPs, dry snuff is not placed in gum or cheek. Moist snuff typically contains air-cured and fire-cured tobaccos that are blended and fermented, and available in both portioned and loose package. Snus is similar to moist snuff but typically contains air-cured or sun-cured tobacco. It is also available in loose or a portioned package.^{1–2} Other STPs products include dissolvable products in the form of tablets, lozenges, orbs, sticks or strips that contain finely ground tobacco.^{3–5} Published literature has extensively reported compositional (chemical and physical) differences among different types of STPs.^{6–7} For example, American and Swedish snus differs in water,

pH, total and unionized nicotine content, and portion sizes, which may impact nicotine release rate and absorption. Nicotine dosing from STPs is determined by the amount of nicotine in the product, product pH, and the size of tobacco leaf cutting.⁸ Nicotine is a basic molecule that exists mostly in unionized form at high pH. Unionized nicotine is quickly absorbed from the biological membrane. It is possible to achieve higher buccal absorption of nicotine from Swedish snus compared to American snus due to Swedish snus’s higher pH and higher levels of unionized nicotine.⁹

In-vitro methods such as dialysis and mouth model systems have been used to measure nicotine release for STPs.^{10–11} However, these are not standardized methods or accepted by regulatory bodies. Nicotine release rate from STPs can also be measured by USP dissolution methods. Dissolution testing, a method that measures the extent and rate of an active ingredient’s release from a solid substance dose into a solution, is widely employed to characterize and control the quality of various drug dosage forms, and is also used as a surrogate of in vivo behavior of various dosage forms.^{12–13} The U.S. Food and Drug Administration (FDA) Center for Tobacco Products recommended dissolution testing of STPs for substantial equivalence determination between products.² Similarly, it can be employed as a one of the quality control tests for STPs. Literature reported USP apparatus 4 for dissolution testing of STP reference products.¹⁴ In this study, we developed and validated a discriminatory nicotine

* Corresponding author at: Texas A&M University, Rangel College of Pharmacy, Reynolds Medical Building, Suite 159 College Station, Texas 77843-1114, USA.

E-mail address: mkhan@tamu.edu (M.A. Khan).

dissolution method that can be used to test portioned moist snuff and snus products.

Materials and Methods

Materials

Materials used included nicotine bitartrate USP (USP, Rockville, MD), methanol, magnesium chloride, potassium hydrogen phosphate anhydrous, sodium chloride, potassium chloride, calcium chloride dihydrate, hydrochloric acid, and ammonium acetate (Fisher Scientific, Asheville, NC). Millipore water (18 M Ω) was collected from an in-house facility (Millipore Milli-Q Gradient A-10 water purification system). Portioned moist snuff and snus products were obtained from Northerner Scandinavia Inc., Mechanicsburg, PA (Table 1). The products were selected based on product composition such as physical size of pouch, weight of leave, pH, nicotine content etc. CORESTA CRP1.1 Swedish style snus pouch (CRP, reference standard product of snus pouch category) was obtained from Cooperation Centre for Scientific Research Relative to Tobacco, Paris, France. Products were purchased in Jan to Feb 2019, stored at room temperature (22–23 °C) and analyzed in Feb–July 2019.

Methods

Ultra-Performance Liquid Chromatography (UPLC)

UPLC equipment consisted of an Acquity H-Class with Acquity PDA, QDa quaternary pump, online degasser, column heater, auto sampler, and UV detector (Waters, Milford, WV, US). The literature reported analytical method of nicotine analysis was modified and validated as per ICH guidelines.^{15,16} Separation of nicotine was achieved on a Poroshell-120, C18, 4.6 × 50 mm, 2.7 μ m (Agilent Technologies, Wilmington, DE, US) column and a C18, 2.1 × 4.6 mm (<3 μ m packing) SecurityGuard™ Ultra cartridge (Phenomenex, Torrance, CA, USA). The flow rate of mobile phase A (5 mM ammonium acetate pH 5.5) and mobile phase B (methanol) was 0.45 ml/min. The gradient conditions were as follows: 0–0.25 min, mobile phase A: mobile phase B 98:02; 0.25–5.25 min, mobile phase A: mobile phase B 02:98; 5.25–6.25 min, mobile phase A: mobile phase B 02:98; and 6.25–6.50 min, mobile phase A: mobile phase B 98:02. Sample volume of 10 μ L was injected and detected at a wavelength of 260 nm. Data collection and analysis were performed using Empower 3 software (Waters, Milford, WV, USA). Analytical range, limit of detection, limit

of quantification, accuracy, and precision of the method were 3.255–32.548 μ g/ml, 0.66 μ g/ml, 2.64 μ g/mL, <4.3%, and <1%, respectively.

Dissolution

A USP Apparatus 4 (flow-through cells) in closed loop configuration was used for discriminatory dissolution method development (CE 7 smart, Sotax Corp, Westborough, MA, USA). Artificial saliva pH 6.8 was used as a dissolution medium.¹⁷ A 22.6 mm polymethyl methacrylate cell was used for holding 1 mm glass beads and the pouch, and 5 mm ruby beads were used as a check valve. The cell inlet was covered with the ruby beads followed by packing with one scoop of glass beads. The glass beads provide laminar flow of the dissolution medium. The pouch was placed on top of the glass beads; one scoop of the glass covered the pouch to prevent floating. The flow cells were placed in the jacket that was filled with water to maintain a medium temperature of 37°C. The media bottles were placed on a temperature-controlled magnetic stirrer (42 °C). Camel Snus Large Robust (CRT) and Skoal Classic Wintergreen Pouches (SWG) were used as reference products as per FDA recommendation for dissolution method development. Discriminatory dissolution method was developed by changing flow rate and dissolution media volume.^{18–22} The dissolution test was performed at flow rates of 2, 4, 6, 8 and 10 ml/min and at a dissolution medium volume of 100 and 200 ml. A 1 mL sample was collected at a specified time and analyzed by a validated UPLC method to measure dissolved nicotine. The products (SWG and CRT) were tested in three replicates in method development, and either 72 or 120 replicates in validation.

Extraction

Nicotine extraction from each pouch was performed in 0.1 N HCl (hydrochloric acid). Briefly, the portioned moist snuff or snus pouch was opened, and the content and wrapper were transferred into 200 ml solvent bottles containing 100 ml of 0.1 N HCl.²³ The bottles were capped and shaken in a horizontal water-bath shaker maintained at 100 rpm and 70°C for 4 hours. The extract was centrifuged at 4500 rpm for 15 min. The extract was then diluted 25–50 times with water and analyzed by UPLC to determine the nicotine present in the sample. The extraction experiment was performed in five replicates for each product.

Physicochemical Characterization

The products were tested for physical and chemical parameters. The parameters included dimension, weight of pouch, weight of

Table 1
Physicochemical Characteristics of Portioned Moist Snuff and Snus.

Product	Weight (mg)	Dimension (length × breadth) mm	Loss on drying	pH	Assay (mg/gm)	Particle size (D ₉₀ , μ m)
Camel Snus Large Robust (CRT)	Weight of pouch and content - 802.4±22.7 mg Content - 737±25.2 mg	37.4 × 14.9	13.78±0.1	7.23	10.1±0.4	74.6±3.6
Skoal Classic Wintergreen Pouches (SWG)	Weight of pouch and content - 1459.7±36.7 mg Content - 1349.7±33.4 mg	38.5 × 17.3	51.43±0.7	7.17	12.7±0.5	15.6±2.3
CORESTA CRP1.1 Reference product (Swedish style snus pouch) (CRP)	Weight of pouch and content - 971.3±19.5 mg Content - 891.7±17.5 mg	34.7 × 18.3	50.94±2.2	8.09	8.5±0.6	115.7±10.2
Camel Snus Large Frost (CFT)	Weight of pouch and content - 960.6±46.9 mg Content - 876±49.7 mg	37.6 × 16.4	25.87±0.5	7.43	7.7±0.5	84.6±0.9
Camel Snus Mellow (CML)	Weight of pouch and content - 499.2±35.8 mg Content - 435.7±39.1 mg	37.7 × 11.6	13.63±0.4	7.32	7.3±0.4	100.2±1.1
Camel Snus Mint (CMT)	Weight of pouch and content - 493.7±1.2 mg Content - 454.3±17.1 mg	37.4 × 11.4	16.93±1.0	7.47	10.2±1.2	80.4±5.7
Skoal Wintergreen Xtra Pouches (SWX)	Weight of pouch and content - 1616.5± mg Content - 1206.3± mg	38.5 × 17.3	52.59±0.5	6.84	12.7±0.6	12.6±2.0
Skoal Smooth Mint Pouches (SSM)	Weight of pouch and content - 1066.3±45.9 mg Content - 933.3±36.9 mg	38.5 × 17.0	22.52±0.8	5.91	14.8±0.7	34.3±9.2
Timber Wolf Mint Pouches (TWM)	Weight of pouch and content - 1483.5±30.0 mg Content - 1332.5±37.6 mg	39.7 × 17.3	49.33±0.2	6.98	10.5±0.3	40.4±6.4

pouch content, weight of empty pouch, and weight loss on drying (105°C) (Intelligent XM 60, Lab Precisa, Switzerland); pH (dispensing the content in 10 ml water and measuring the pH, Model H260G, Hach Company, Loveland, CO, USA) and particle size measurements by laser diffraction (PSA 1190, Anton Paar, Ashland, VA, USA).

Statistical Analysis

Dissolution profiles were compared by analysis of variance (ANOVA) analysis (SAS software, SAS Institute, Cary, NC). The profiles were considered statistically significant different at $p \leq 0.05$.

Results and Discussion

Physicochemical Characterization

The nine products differed significantly in physical and chemical attributes (Table 1). The products can be divided into three groups based on pouch and nicotine content; group I: content of pouch <500 mg, nicotine content <5 mg; group II: content of pouch ≥500 and <900 mg, nicotine content ≥5 and <9 mg; and group III: content of pouch >900 mg, nicotine content >12 mg. Products included in group I were Camel Snus Mellow (CML) and Camel Snus Mint (CMT); products included in group II were CRT, CRP, and Camel Snus Large Frost (CFT); and products included in group III were SWG, Skoal Wintergreen Xtra Pouches (SWX), Skoal Smooth Mint Pouches (SSM), and Timber Wolf Mint Pouches (TWM). A positive correlation of 0.896 was observed between pouch weight and nicotine content.

Product pH was approximately 7 or 7–8, except for SSM (pH 5.9). Products pH may determine relative proportion of the ionized and unionized forms of the nicotine, which may influence extent of buccal absorption. Previous research has reported almost no buccal absorption from cigarettes containing flue-cured tobacco (pH ~5.5) even when held in the mouth.²⁴ On the other hand, good buccal absorption has been observed from air-cured tobacco (pH >6.5).²⁵ Efficient absorption of nicotine at pH >6.5 is probably due to the presence of a high proportion of the unionized nicotine form of nicotine, since is a weak base; a

unionized form of a molecule is absorbed more quickly than its ionized form.²⁶ Higher nicotine buccal absorption can be expected from CRP due to the product's high pH, which may have a higher portion of unionized nicotine. Similarly, SSM is expected to have lower nicotine buccal absorption due to its low pH. Mean water content varied from 13.63 ± 0.4 to $52.59 \pm 0.5\%$ among products. SWG, CRP, SWX, and TWM contained close to 50% or greater water content, while CRT, CFT, CML, CMT and SSM contained less than 26% water.

Particle size distribution is expressed by D_{90} . Products can be classified into two categories based on particle size: group I D_{90} ranged from 70–120 μm and group II D_{90} ranged from 10–45 size μm . Group I included Camel and reference products (CRT, CFT, CMT, CML and CRP) and group II included Skoal and Timber Wolf products (SWG, SWX, SSM and TWM). Particle size distribution may impact nicotine dissolution from the products as dissolution is directly proportional to surface area, according to the Noyes-Whitney equation.^{27–28}

Method Development

SWG and CRT were used as reference products for dissolution method development; these two products were selected based on their physical and chemical differences. SWG had bigger pouch size, higher pouch weight and nicotine content, and smaller particle size distribution compared to CRT (Table 1). The products' dissolution data at various flow rates and volumes are shown in Fig. 1, and 2. The amount of nicotine dissolved from the two products varied widely as a function of dissolution test conditions. For example, the amount of SWG nicotine dissolved in 60 min was 11.1 ± 0.7 – 14.2 ± 0.2 and 12.1 ± 0.4 – 15.3 ± 0.5 mg/g in 100 and 200 ml dissolution volumes, respectively, at various flow rates. Similarly, the amount of CRT nicotine dissolved in 60 min was 6.4 ± 0.4 – 9.9 ± 0.7 and 7.2 ± 0.2 – 10.8 ± 0.3 mg/g in 100 and 200 ml dissolution volumes, respectively, at various flow rates. Higher volume and higher flow rate resulted in higher nicotine dissolution compared to dissolution at smaller volumes and lower flow rates. Specifically, nicotine amounts of 13.3 ± 0.6 and 15.3 ± 0.5 mg/g were dissolved in SWG at 2 ml/min and 10 ml/min, in 200 ml volume at 60 min, respectively. Similarly, nicotine amounts of

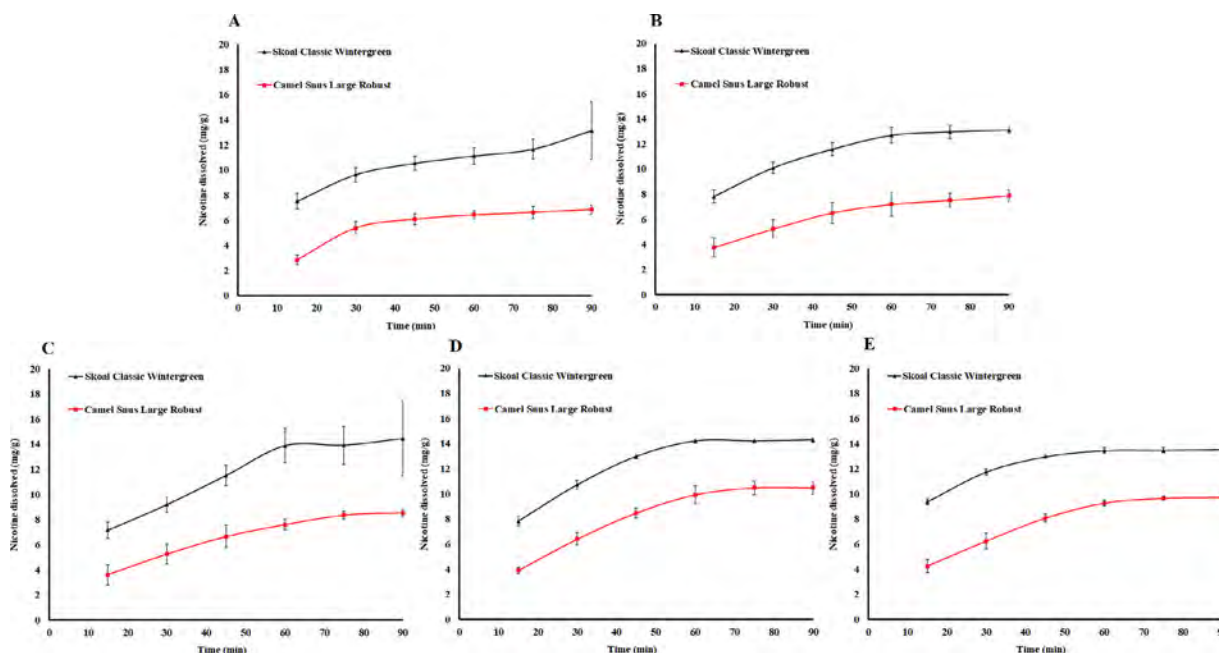


Figure 1. Nicotine released from Skoal Classic Wintergreen Pouches and Camel Snus Large Robust in 100 ml dissolution at A) 2 ml/min, B) 4 ml/min, C) 6 ml/min, D) 8 ml/min and E) 10 ml/min flow rate. Data is presented as mean \pm standard deviation ($n=3$).

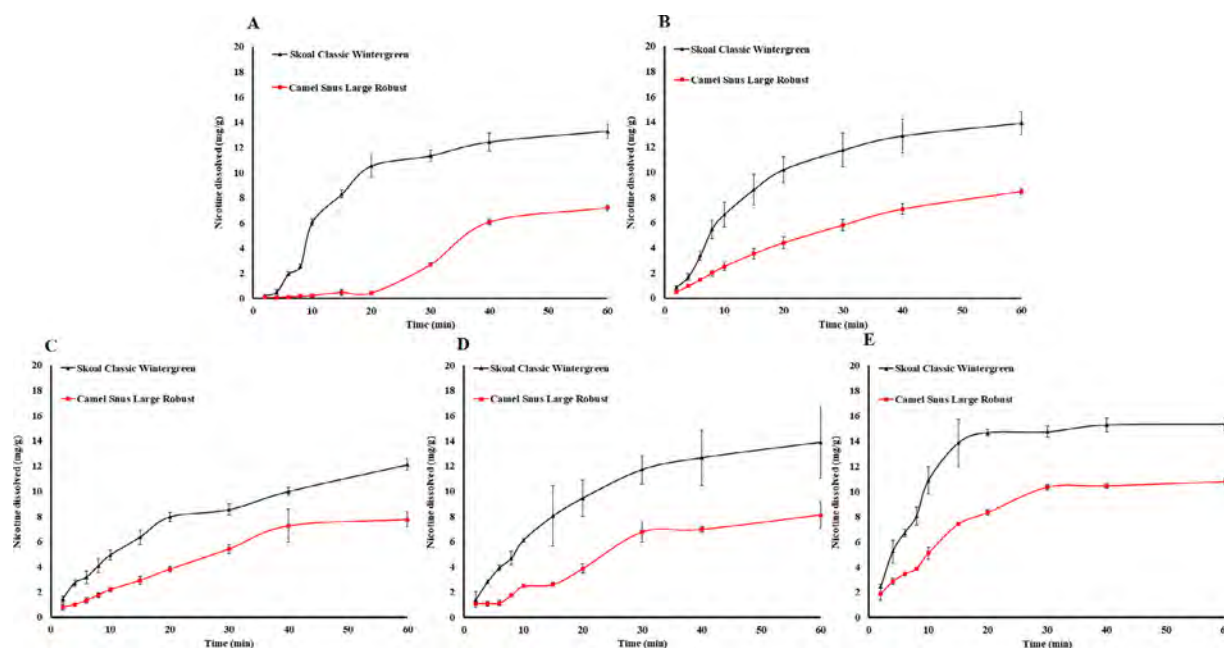


Figure 2. Nicotine released from Skoal Classic Wintergreen Pouches and Camel Snus Large Robust in 200 ml dissolution at A) 2 ml/min, B) 4 ml/min, C) 6 ml/min, D) 8 ml/min and E) 10 ml/min flow rate. Data is presented as mean±standard deviation (n=3).

7.2±0.2 and 10.8±0.3 mg/g were dissolved in CRT at 2 ml/min and 10 ml/min, respectively, in 200 ml volume at 60 min.

Notably, the volume of the dissolution medium had a statistically significant ($p < 0.05$) effect on the amount of nicotine dissolved from SWG: when dissolution was performed in 100 ml volume rather than 200 ml volume, the nicotine dissolved from SWG decreased by 18–32%. On the other hand, no significant difference was observed in the amount of CRT nicotine dissolved when the volume was reduced to 100 ml.

Furthermore, the dissolution rate and extent were higher in SWG compared to CRT. This was probably related to SWG's higher nicotine content. A difference of 15% nicotine dissolved between dissolution time points was used as a criterion for determining time to reach a dissolution plateau. Time to achieve a dissolution plateau varied between two products depending upon dissolution testing conditions. A dissolution plateau was achieved in ≤60 min for both the products when tested in 100 ml dissolution medium at all flow rates except 2 ml/min. Time to achieve dissolution plateau varied with flow rate in 200 ml dissolution medium as well. For both products, the plateau was achieved in ≤40 min at 2, 4 and 6 ml/min, and ≤30 min at 8 and 10 ml/min. Quicker achievement of a dissolution plateau in 200 ml compared to 100 ml volume occurred because more volume was available in which nicotine could dissolve. Similarly, a higher flow rate also causes faster nicotine dissolution due to faster exchange of the dissolution medium between cells and medium bottles.^{29–30}

The dissolution profiles were compared by calculating the nicotine percentage dissolved at various time points. Percentage nicotine dissolved from CRT and SWG tested products were 21.0–33.6%, 23.0–26.6%, 19.0–32.0%, 5.2–22.0% and 8.0–30.6% at 2, 4, 6, 8 and 10 ml/min in 100 ml dissolution medium volume, respectively. Similarly, differences in nicotine dissolved were 0.9–78.4%, 1.6–35.6%, 3.1–24.0%, 0.1–36.7% and 0.2–33.7% at 2, 4, 6, 8 and 10 ml/min in 200 ml medium volume, respectively. At 200 ml medium volume, differences in nicotine dissolved were smaller at earlier time points but higher at the middle and later time points. On the other hand, at 100 ml medium volume, differences in nicotine dissolved were higher at 15–45 min but smaller at earlier and later time points.

FDA guidance on “Immediate release solid oral dosage forms” provides recommendation for comparing dissolution profiles of two immediate release drug products. This guidance can also be applied to STPs for dissolution profiles comparison by using f_1 (similarity) and f_2 (dissimilarity) factors. The two profiles are considered similar if $f_1 < 15$ and $f_2 > 50$.³¹ FDA document provides guidance on methods and test criteria to compare dissolution profiles of products. The f_1 and f_2 values were ≥11.6 and ≤41.7 at various flow rates in 100 ml dissolution medium (Table 2). The profiles can be considered dissimilar at all tested flow rates except the 8 ml flow rate, where f_1 was <15. Similarly, f_1 and f_2 values were ≥22.3 and ≤41.5 at various flow rates in 200 ml dissolution medium (Table 2). The dissolution profiles in 200 ml at 2–10 ml/min flow rates met f_1 and f_2 criteria of profiles dissimilarity. Dissimilarity of profiles was high at low flow rates in 200 ml compared to 100 ml dissolution medium. As flow rate increased, similarity decreased due to faster nicotine dissolution and faster exchange of volume between the cells and bottles.^{29–30} Furthermore, ANOVA analysis of the profiles indicated significant statistical ($p \leq 0.001$) differences between two reference products.

Data variability was measured by relative standard deviation (RSD). FDA guidance on dissolution of immediate release dosage forms recommends an RSD <20% at earlier time points and RSD <10% RSD at later time points.³¹ In this study, RSD was >20% at earlier time points and <20% at later time points of dissolution profiles. Possible sources of variability in the data may be (1) the use of tobacco, a botanical product, which is heterogeneous in nature, and (2)

Table 2
Dissimilarity (f_1) and Similarity (f_2) Factors Values of Dissolution Data of Skoal Classic Wintergreen Pouches and Camel Snus Large Robust.

Factors	Volume	Flow rate				
		2 ml/min	4 ml/min	6 ml/min	8 ml/min	10 ml/min
f_1	100 ml	25.4	23.5	18.6	11.6	15.7
f_2	100 ml	29.4	30.1	34.4	41.7	34.8
f_1	200 ml	66.5	37.3	28	38.1	22.3
f_2	200 ml	18.3	30.1	41.5	30.4	33.3

heterogeneity of the pouch membrane, which provides another barrier to nicotine dissolution.^{32–33}

All the tested dissolution conditions could be considered discriminatory except 8 ml/min in 100 ml medium, based on f_1 and f_2 values. However, dissolution testing in 200 ml at 10 ml/min was selected for method validation. The reason for selecting these conditions was based on values of f_1 and f_2 , time to reach plateau, and RSD of the data. The dissolution plateau was achieved in 20 and 30 min for SWG and CRT, respectively. Similarly, the dissolution method was discriminatory in 200 ml at an 8 ml/min flow rate, based on similar f_1 and f_2 values and dissolution plateau time. However, a higher RSD of up to 20.6% was obtained at later phases of dissolution in 200 ml at 8 ml flow rate. At 2, 4 and 6 ml/min in 200 ml medium volume, the time to achieve plateau was longer compared to 8 and 10 ml flow rates. Similarly, time to achieve plateau was longer (60 min), f_1 values were smaller, and f_2 values were higher in 100 ml dissolution medium compared to 200 ml dissolution medium (Table 2).

Product Dissolution Testing

Dissolution testing was conducted in all products using the selected discriminatory method (i.e., 200 ml dissolution medium volume at 10 ml/min flow rate) to validate the method. The products were tested in multiple replicates to determine data variability. Ten containers each of CRT and SWG were tested; six containers of each of the other products were tested. Products were tested in twelve pouches/container (Table 1). In total, 72 replicates of CRP, CFT, CML, CMT, SMM, SWX and TWM and 120 replicates of CRT and SWG products were tested.

The dissolution profiles of individual containers and means are shown in Figs. 3–8. The amount of nicotine dissolved from CRT, SWG, CRP, CFT, CML, CMT, SMM, SWX and TWM varied considerably (8.5–10.5, 10.9–15.7, 6.1–9.2, 4.0–7.3, 3.9–6.8, 4.5–8.9, 14.9–18.9, 12.0–14.8 and 9.2–12.2 mg/g in 60 min, respectively). The percentage of nicotine dissolved from CRP was 71.4–85.7%, which was slightly lower than the value reported by Miller et al. However, the amount of nicotine dissolved on a mg/g basis was similar to the value reported by

Miller et al. This discrepancy can be attributed to a difference in the assay value of CRP. Furthermore, Miller et al reported data from 12 CRP replicates, while we performed dissolution testing in 72 replicates.¹⁷ The differences in maximum and minimum percentages of nicotine dissolved at specific time points varied widely among products. The differences were lower in bigger pouches, which had a higher nicotine content compared to smaller pouches. Furthermore, differences in nicotine dissolved were higher at earlier time points compared to later time points. The differences in maximum and minimum percentages of nicotine dissolved at 60 min were 23.8, 30.9, 33.9, 45.9, 41.9, 48.9, 21.3, 19.0 and 23.9% for CRT, SWG, CRP, CFT, CML, CMT, SMM, SWX and TWM, respectively. Similarly, differences in maximum and minimum percentage of nicotine dissolved at 5 min were 62.2, 64.3, 61.2, 58.4, 58.7, 69.3, 47.3, 54.2 and 50.2% for CRT, SWG, CRP, CFT, CML, CMT, SMM, SWX and TWM, respectively. Data variability in container of products are represented by RSD. RSD values were 3.8–34.1, 2.6–29.8, 5.3–27.8, 9.5–23.4, 4.3–25.6, 5.5–25.4, 2.7–20.6, 1.4–16.9 and 4.7–15.9% for CRT, SWG, CRP, CFT, CML, CMT, SMM, SWX and TWM, respectively. RSD was high at earlier time points of the dissolution profile and decreased as time elapsed. RSD >20% at earlier time points but <20% at later time points. The products do not meet FDA dissolution profile criteria of RSD <20% at earlier time points <10% at later time points.³¹ Unlike dosage forms of small molecules from products that are relatively homogenous^{1–2}, tobacco products are heterogeneous, suggesting that widening of dissolution profile RSD criteria is reasonable (for example 20–30% at earlier time points and 15–20% at later phases).

Time to reach dissolution plateau varied among products. Plateau was achieved in 20 min in SSM and SWX, 30 min in SWG, CRP, TWM and SSM, 45 min in CRT, and 60 min in CFT, CMT and CML. The variation in plateau time was related to nicotine content per normalized weight of pouch content after subtracting weight of water content. The nicotine content per normalized weight of pouch content was 11.4, 26.2, 17.3, 10.4, 8.4, 12.3, 26.7, 19.2 and 20.8 mg/g in CRT, SWG, CRP, CFT, CML, CMT, SMM, SWX and TWM, respectively. Lower nicotine means a higher matrix-to-nicotine ratio. Possibly, a higher matrix weight may prolong nicotine diffusion.

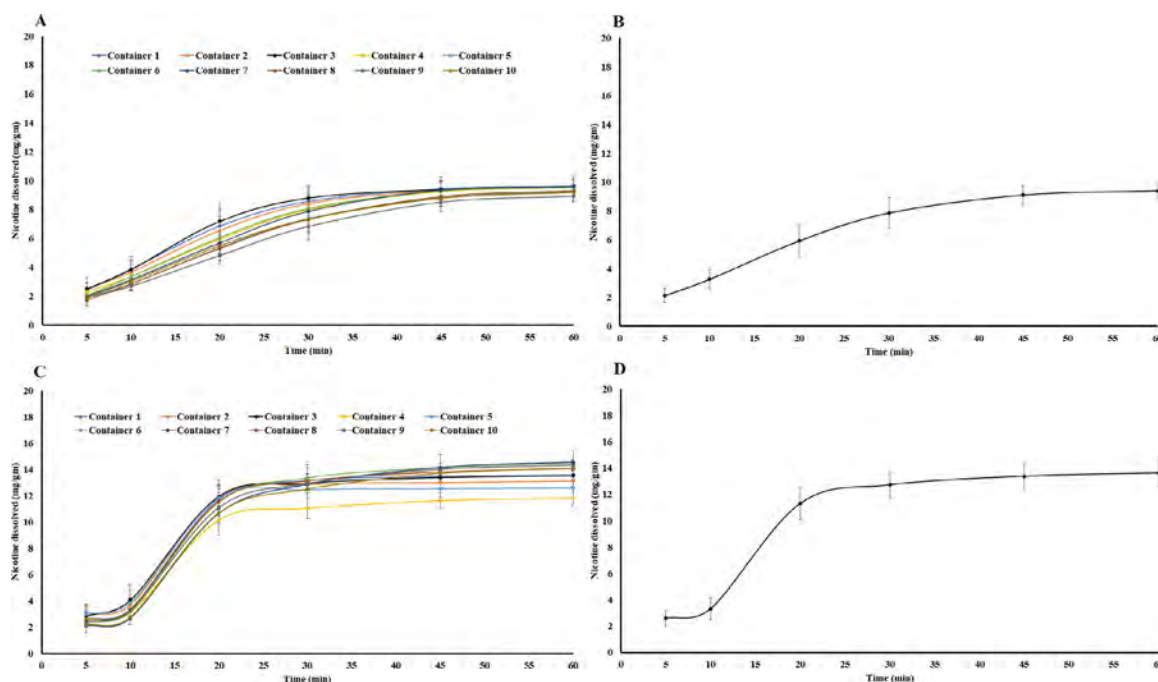


Figure 3. Dissolution profiles of Camel Snus Large Robust A) individual container (12 pouch/container) and B) average container (10 containers) data, and Skoal Classic Wintergreen Pouches C) individual container (12 pouch/container) and D) average container (10 containers) data. Data is presented as mean \pm standard deviation ($n=120$).

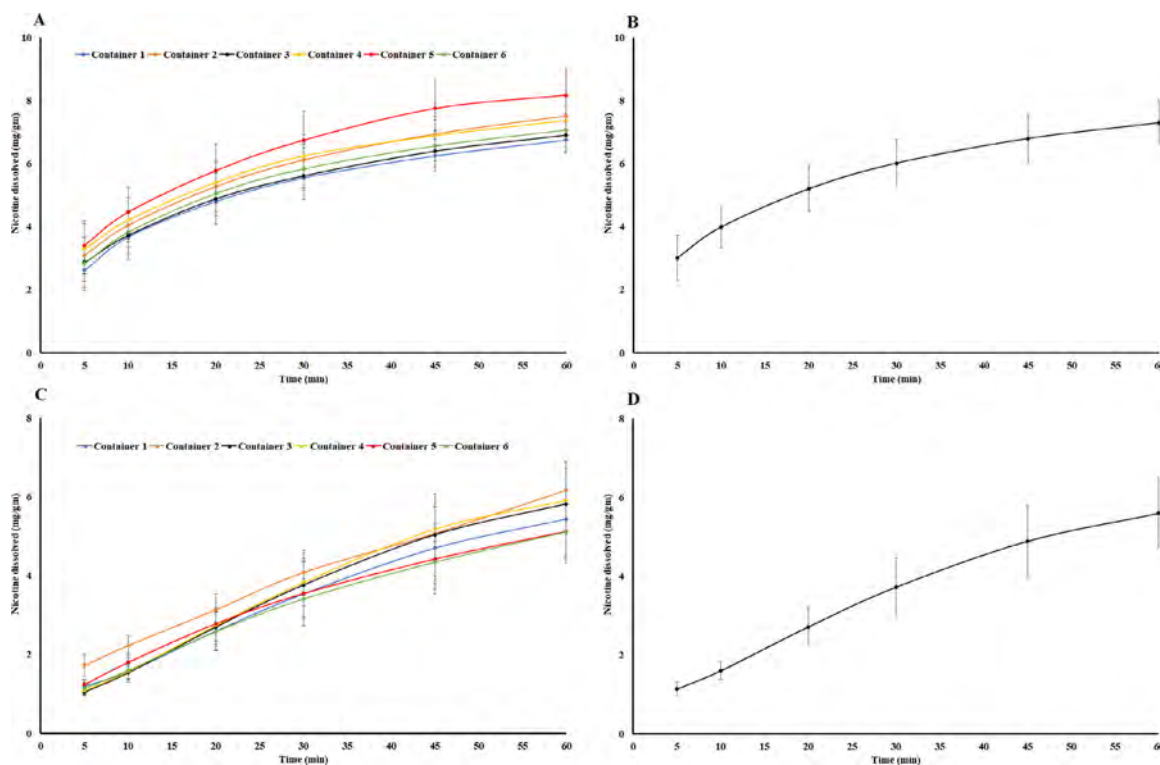


Figure 4. Dissolution profiles of CORESTA CRP1.1 A) individual container (12 pouch/container) and B) average container (6 containers) data, and Camel Snus Large Frost C) individual container (12 pouch/container) and D) average container (6 containers) data. Data is presented as mean \pm standard deviation ($n=72$).

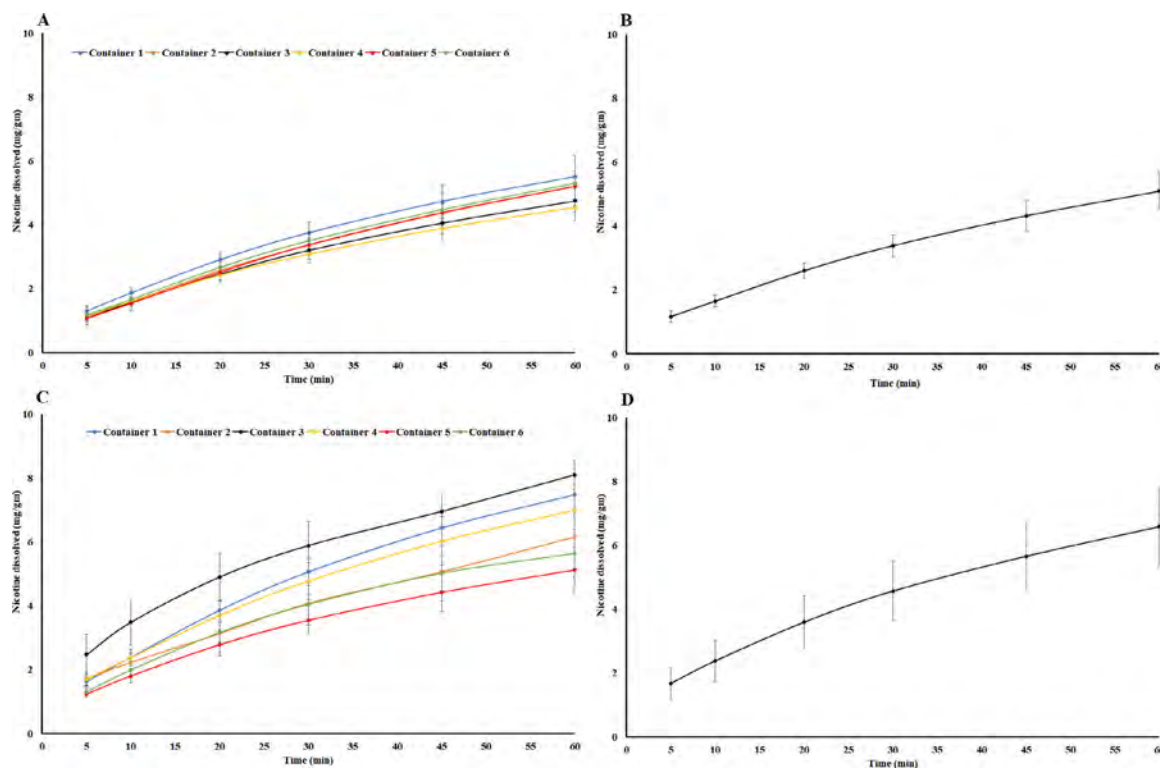


Figure 5. Dissolution profiles of Camel Snus Mellow A) individual container (12 pouch/container) and B) average container (6 containers) data, and Camel Snus Mint C) individual container (12 pouch/container) and D) average container (6 containers) data. Data is presented as mean \pm standard deviation ($n=72$).

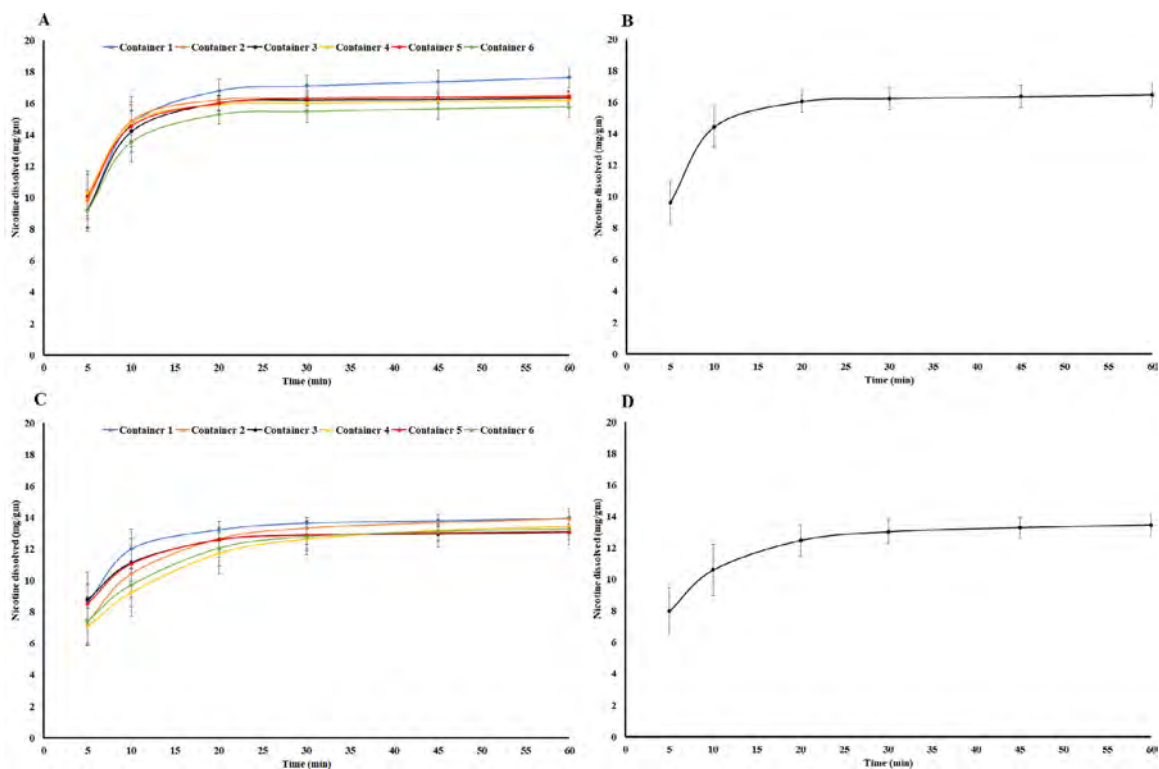


Figure 6. Dissolution profiles of Skoal Smooth Mint Pouches A) individual container (12 pouch/container) and B) average container (6 containers) data, and Skoal Wintergreen Xtra Pouches C) individual container (12 pouch/container) and D) average container (6 containers) data. Data is presented as mean \pm standard deviation ($n=72$).

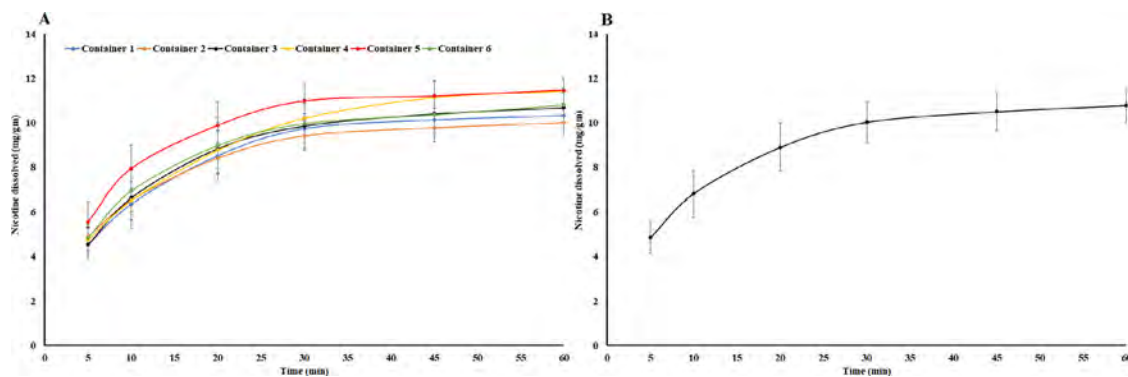


Figure 7. Dissolution profiles of Timber Wolf Mint Pouches A) individual container (12 pouch/container) and B) average container (6 containers) data. Data is presented as mean \pm standard deviation ($n=72$).

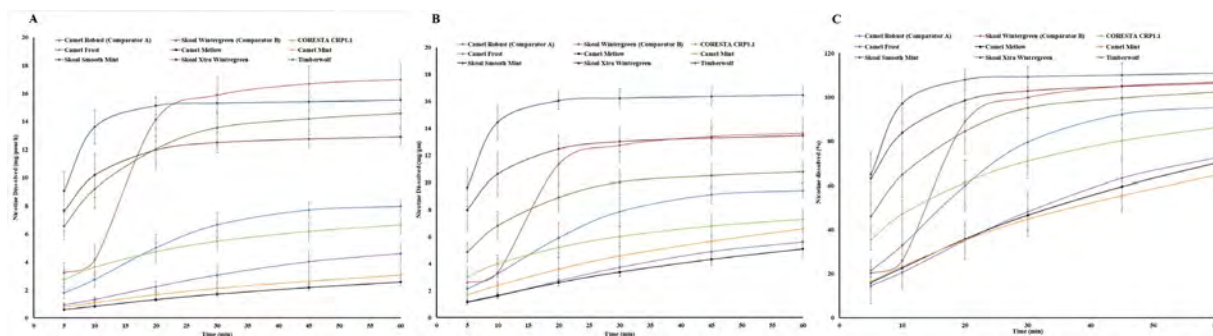


Figure 8. Portioned moist snuff and snus products data in A) mg/pouch, B) mg/g and C) percent of nicotine dissolved.

Table 3
Dissimilarity (f_1) and Similarity (f_2) Factors Values of Dissolution Data of Products.

Reference Product	Camel Snus Large Robust		Skoal Wintergreen Classic Pouches		COREST CRP1.1		Camel Snus Large Frost		Camel Snus Mellow		Camel Snus Mint		Skoal Smooth Mint Pouches		Skoal Wintergreen Xtra Pouches		Timber Wolf Mint Pouches	
Factor	f_2	f_1	f_2	f_1	f_2	f_1	f_2	f_1	f_2	f_1	f_2	f_1	f_2	f_1	f_2	f_1	f_2	f_1
Camel Snus Large Robust	-	-	39.4	14.9	48.2	12.3	31.9	35.9	30.8	37.3	28.8	41.7	19.7	31.2	23.9	27	34.2	18.7
Skoal Wintergreen Classic Pouches	39.4	16.9	-	-	31.4	28.7	21.2	54.3	20.5	55.9	19.3	60.9	22.5	21.9	26.4	17.3	35.6	14.1
CORESTA CRP1.1	48.2	12.3	31.4	25.3	-	-	33.2	35.8	32.8	37.2	31.2	41.6	21.2	31.2	25.9	27	36	18.7
Camel Frost	31.9	26.4	21.2	35.2	33.2	26.4	-	-	81.4	3.3	65.1	6.9	11.4	49.4	14.2	46.3	19.7	40.2
Camel Mellow	30.8	27.2	20.5	35.9	32.8	27.1	81.4	3.2	-	-	75.4	3.9	11.3	49.9	14.1	46.8	19.4	40.8
Camel Mint	28.8	29.4	19.3	37.8	31.2	29.4	65.1	6.6	75.4	3.7	-	-	10.7	51.4	13.5	48.4	18.5	42.6
Skoal Smooth Mint Pouches	19.7	45.4	22.5	28	21.2	45.4	11.4	97.6	11.3	99.6	10.7	105.9	-	-	55.4	6.2	35.2	18.2
Skoal Xtra Wintergreen Pouches	23.9	36.9	26.4	20.8	25.9	37	14.2	86.1	14.1	88	13.5	94	55.4	5.8	-	-	45	11.3
Timberwolf Mint Pouches	34.2	23	35.6	15.3	36	23.1	19.7	67.2	19.4	68.9	18.5	74.3	35.2	15.4	45	10.1	-	-

Product dissolution profiles were compared using FDA f_1 and f_2 criteria; data is shown in Table 3.²⁶ All the products served as both the reference products and the test products for f_1 and f_2 calculation (Table 3). All product profiles were dissimilar when CRT, SWG, CRP or TWM were used as reference products based on $f_1 > 15$ and $f_2 < 50$ criteria. On the other hand, CFT, CMT and CML profiles were similar when CFT, CMT or CML were used as reference products. However, profiles were different when tested against CRT, SWG, CRP, SSM, SWX and TWM. Nicotine content per pouch in CFT, CMT and CML was lower than the other tested products. Furthermore, nicotine content per pouch, particle size distribution, and pH were very similar in CFT, CMT and CML, which may account for similar dissolution profiles (Table 3). Similarly, profiles of SSM and SWX were similar based on the f_1 and f_2 values. Nicotine content per pouch was similar in SWG, SWX, SSM and TWM. However, only SWX and SSM dissolution profiles were similar based on f_1 and f_2 values; this may be due to similar nicotine content in the products. On the other hand, dissimilarity of SWG and TWM dissolution profiles may be related to particle size distribution of the formulations (i.e., TWM particle size distribution is greater), which may influence nicotine dissolution despite similar nicotine content (Table 1). Furthermore, ANOVA analysis of dissolution profiles indicated that dissolution profiles of the products were statistically significant ($p \leq 0.03$) when compared to each other except CML and CMT. CML and CMT profiles were statistically significant ($p \leq 0.03$) from all the products except CFT and CML, respectively.

Product dissolution profiles can be presented in mg/pouch, mg/g, or percentage of nicotine dissolved with time (Fig. 8). Data presentation as mg/pouch will overestimate or underestimate nicotine dissolution, since pouch weight differs widely among products. Normalizing dissolution data with respect to weight of pouch content or nicotine allows for more accurate product comparison. Data can be normalized as mg/g or percentage of nicotine present in the pouch. However, some products have similar pouch weight content but differ in nicotine content. In such a scenario, presenting data in mg/g will also overestimate or underestimate nicotine dissolution; moreover, it will not indicate whether the dissolution method is discriminatory. Presenting data as percentage of nicotine dissolved provides the most accurate picture of nicotine dissolution and provides information regarding whether the dissolution method is discriminatory. Furthermore, presenting dissolution data in as a percentage of nicotine dissolved is recommended by FDA, since these data can also be used in f_1 and f_2 calculations.^{2,31}

Conclusion

Portioned moist snuff and snus differ in terms of pouch content, moisture, pH, and nicotine content. In general, Camel Snus products

(Robust, Frost, Mellow, Mint) have smaller pouches, lower moisture and less nicotine compared to Skoal and Timber Wolf products (Classic Wintergreen, Xtra Wintergreen, Smooth Mint). These differences may influence user acceptability. Discriminatory dissolution method was developed by changing flow rate and volume of dissolution medium of USP apparatus 4 based on f_1 and f_2 , and statistical criteria. The products can be differentiated by a developed dissolution method based on USP 4 in 200 ml artificial saliva pH 6.8 at 10 ml flow rate, which produced distinct dissolution profiles. The Skoal products can be differentiated from Camel, Timber Wolf and reference (CORESTA) products as well as among themselves. However, this is not true for Camel products, which can be differentiated from other products but not among themselves, especially Mint, Mellow and Frost, which produced overlapping dissolution profiles. Overlapping dissolution profiles of Camel products might be related to nicotine content or other differences in the formulations. This was further confirmed by f_1 and f_2 values of > 15 and < 50 when Camel Robust, Skoal Classic Wintergreen, CORESTA CRP1.1 and Timber Wolf Mint were used as reference products. In general, the developed method was discriminatory and can be employed as a quality control test and to differentiate among moist snuff and snus products. However, nicotine dissolution kinetic may change if additional components is added to the products. e.g. pH modifier or filler etc.

Competing Interests

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Food and Drug Administration. Also, certain commercial equipment, instruments, or laboratory are identified in this paper in order to specify the experimental procedure adequately. Such identification is not intended to imply recommendation or endorsement by FDA/CTP.

Acknowledgement

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Summary of All Manufacturing Deviations

Product:	General Dry Mint Portion Original Mini
SKU Number:	4800
FDA Tracking number:	PM0000011
Reporting Period:	October 1, 2021 to September 30, 2022

Deviation Number	Type of Manufacturing Deviation	Production Date (YYYY-MM-DD)	Description of Deviation	Design Feature	Deviation May Affect the Characteristics of the Final Product (Yes/No)	Product With Deviation Distributed at Retail Level (Yes/No)
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Justification; why product that reached retail would not affect public health

---	No manufacturing deviations to report.
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--- = Not applicable.

Summary of All Manufacturing Deviations

Product:	General Portion Original Large
SKU Number:	4880
FDA Tracking number:	PM0000012
Reporting Period:	October 1, 2021 to September 30, 2022

Deviation Number	Type of Manufacturing Deviation	Production Date (YYYY-MM-DD)	Description of Deviation	Design Feature	Deviation May Affect the Characteristics of the Final Product (Yes/No)	Product With Deviation Distributed at Retail Level (Yes/No)
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Justification; why product that reached retail would not affect public health

---	No manufacturing deviations to report.
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--- = Not applicable.

Summary of All Manufacturing Deviations

Product:	General Mint Portion White Large
SKU Number:	4352
FDA Tracking number:	PM0000014
Reporting Period:	October 1, 2021 to September 30, 2022

Deviation Number	Type of Manufacturing Deviation	Production Date (YYYY-MM-DD)	Description of Deviation	Design Feature	Deviation May Affect the Characteristics of the Final Product (Yes/No)	Product With Deviation Distributed at Retail Level (Yes/No)
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Justification; why product that reached retail would not affect public health

---	No manufacturing deviations to report.
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--- = Not applicable.

Summary of All Manufacturing Deviations

Product:	General Portion White Large
SKU Number:	4881
FDA Tracking number:	PM0000016
Reporting Period:	October 1, 2021 to September 30, 2022

Deviation Number	Type of Manufacturing Deviation	Production Date (YYYY-MM-DD)	Description of Deviation	Design Feature	Deviation May Affect the Characteristics of the Final Product (Yes/No)	Product With Deviation Distributed at Retail Level (Yes/No)
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Justification; why product that reached retail would not affect public health

---	No manufacturing deviations to report.
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--- = Not applicable.

Summary of All Manufacturing Deviations

Product:	General Wintergreen Portion White Large
SKU Number:	4882
FDA Tracking number:	PM0000017
Reporting Period:	October 1, 2021 to September 30, 2022

Deviation Number	Type of Manufacturing Deviation	Production Date (YYYY-MM-DD)	Description of Deviation	Design Feature	Deviation May Affect the Characteristics of the Final Product (Yes/No)	Product With Deviation Distributed at Retail Level (Yes/No)
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Justification; why product that reached retail would not affect public health

---	No manufacturing deviations to report.
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--- = Not applicable.