CREATIVE CHEMISTRY: ADDRESSING INDUSTRY EVASION AND SYNTHETIC NICOTINE
LEGAL TECHNICAL ASSISTANCE

- Legal Research
- Policy Development, Implementation, Defense
- Publications
- Trainings
- Direct Representation
- Lobby

12/17/2021
David Ashley is currently a Research Professor in the School of Public Health at Georgia State University. He received his PhD in Physical Chemistry in 1982 from Emory University. He spent 27 years, from 1983-2010 at the Centers for Disease Control and Prevention, National Center for Environmental Health. During this time, he carried out research on the impact of toxic chemicals in the environment on health, developed methods and systems to respond to chemical and biological terrorism, and built a tobacco product and biomarker laboratory. He has performed extensive research related to the impact of cigarette design and contents on the emissions from tobacco products, how people use tobacco products, and resulting biomarkers of exposure. From 2010 until 2017, he was the inaugural Director of the Office of Science at the Center for Tobacco Products (CTP) of the U.S. Food and Drug Administration. In that role, he was instrumental in carrying out the regulatory authorities of the 2009 law which gave FDA authority to regulate tobacco products. He has published over 180 peer-reviewed articles and book chapters related to biophysics, environmental chemicals, biomarkers of exposure and the constituents of tobacco and tobacco smoke. He retired in May 2016 at the Public Health Service rank of Assistant Surgeon General. He has presented extensively at scientific meetings on the chemistry of tobacco and tobacco smoke and biomarkers of exposure. He serves on the World Health Organization (WHO) Study Group for Tobacco Product Regulation and was the Chair of the WHO Tobacco Laboratory Network from 2006 until 2010.
Micah Berman is an associate professor of public health and law at The Ohio State University. He has written extensively about local, state, and federal tobacco regulation, and his is a co-author of The New Public Health Law: A Transdisciplinary Approach to Practice and Advocacy (Oxford University Press, 2018). Prior to joining Ohio State, he founded and directed two policy centers that provided support to state and local tobacco control programs. He has also served as a senior advisor to the FDA’s Center for Tobacco Products and as a trial attorney with the U.S. Department of Justice. He received his J.D. with distinction from Stanford Law School.

Andrew Seidenberg is a 2nd year cancer prevention fellow in the Behavior Research Program within the Division of Cancer Control and Population Sciences. He earned his Ph.D. in public health with an emphasis in Health Behavior from the Gillings School of Global Public Health at the University of North Carolina at Chapel Hill. Andrew also earned his MPH in Environmental Health Sciences at the Yale School of Public Health.
Patricia J. Zettler, JD is an associate professor at The Ohio State University Moritz College of Law and a member of Ohio State’s Drug Enforcement and Policy Center and its Comprehensive Cancer Center. Her research and teaching focus on FDA law and policy, torts, and legislation and regulation. Her scholarship has appeared in leading legal and health sciences journals such as the Indiana Law Journal, the Boston College Law Review, New England Journal of Medicine, JAMA, JAMA Oncology, and Science, and has covered various topics including stem cell interventions, gene therapy, opioids, cannabis products, tobacco and nicotine products, and COVID-19 countermeasures. She is serving or has recently served on the National Academies of Sciences, Engineering, and Medicine’s Committee on Reviewing the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), the International Society of Cell & Gene Therapy’s Committee on the Ethics of Cell and Gene Therapy, and the Black Lives Matter Advisory Committee for the Food and Drug Law Institute, among other things. Before entering academics, Zettler served as an associate chief counsel in the Office of the Chief Counsel at FDA. She received her undergraduate and law degrees from Stanford University, both with distinction.
I am an epidemiologist and assistant professor in the Division of Medical Oncology at The Ohio State University. As a member of the Cancer Control Program at the OSUCCC – James, I am interested in tobacco regulatory science, particularly regulations related to marketing and product characteristics. Most of my work is focused on the role of advertising in tobacco use behaviors among youth, as well as identifying key characteristics of tobacco products that drive their addiction potential. I am also interested in tobacco regulations to promote health equity, especially for Appalachian populations.

Dr. Brittney Keller-Hamilton, PhD, MPH
AGENDA

- Background: Dr. Andrew Seidenberg
- Chemistry overview: Dr. David Ashley
- Consumer perceptions: Dr. Brittney Keller-Hamilton
- Federal Regulation: Patti Zettler
- Tribal, State, and Local Regulation: Micah Berman
- Questions

- Moderator: Natalie Hemmerich
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An Introduction to Synthetic Nicotine

Andrew B. Seidenberg, PhD, MPH
The opinions expressed are my own and this material should not be interpreted as representing the official viewpoint of the U.S. Department of Health and Human Services, the National Institutes of Health, or the National Cancer Institute.
Nicotine Sources

Tobacco

Other Nightshade Plants

Synthetic

*Very low levels of nicotine

“Tobacco-free nicotine”
Nicotine first synthesized in a lab in 1904
Tobacco companies have had interest in synthetic nicotine since the 1960s.
Two Forms (enantiomers) of Nicotine

>99% S-nicotine

Early methods for synthetic nicotine yielded 50% S-nicotine and 50% R-nicotine (racemic mixture)
S-nicotine vs. R-nicotine

- Animal models reveal differences between S- and R-nicotine:
  - Formation of oxidative metabolites
  - Degradation kinetics
  - R-nicotine does not induce weight loss in rats (S-nicotine does)
  - R-nicotine is a much less potent agonist (10-fold) for nicotine receptors

![Diagram of S-nicotine and R-nicotine](image)

Jordt SE, 2021. PMID: 34493630
“In addition, all synthetic sequences will produce nicotine as a racemic mixture. **It has been established that only [S-nicotine] shows significant pharmacologic activity. Therefore, synthetic nicotine would be only 50% as potent as natural nicotine...** As a result, it appears that synthetic nicotine would be significantly more expensive than nicotine from natural sources.”

January 30, 1978
Synthetic Nicotine

Historically, synthetic nicotine was:

- More expensive
- Less “potent”

Recently:

- Newer methods for producing and isolating synthetic S-nicotine
- Costs to produce synthetic nicotine have been greatly reduced
- Numerous companies selling synthetic nicotine
- Many products marketed with synthetic nicotine
“We have moved from pricing from a multiple that was 10 times greater than tobacco nicotine, to ... pricing level that is only three to four times the current cost of tobacco-derived nicotine.”

https://tobaccoreporter.com/2019/12/01/mirror-image/
Method for preparing artificial synthetic nicotine

Abstract

The invention discloses a preparation method of artificially synthesized nicotine, belonging to the technical field of chemical synthesis. The synthesis method of the racemate (+/-) - (R, S) -nicotine and the natural optical active body (-) - (S) -nicotine provided by the invention adopts nicotinic acid ester and succinic acid diester or N-alkyl succinimide as initial raw materials, and can overcome the defects of difficult large-scale production, high cost and the like in the existing artificial nicotine synthesis technology. Specifically, the initial raw materials adopted by the method for synthesizing the racemate (+/-) - (R, S) -nicotine and the natural optical active substance (-) - (S) -nicotine are easily obtained, the preparation process is simple, the cost is low, and the prepared nicotine does not contain any harmful other tobacco compounds and is suitable for industrial large-scale production.
Synthetic Nicotine

Liquid Nicotine Wholesalers is the authorized USA supplier for TFN® Nicotine and synthetic nicotine solutions in a wide range of concentrations. From Pure Synthetic Nicotine to 100mg Tobacco Free e-liquid nicotine that require dilution by the purchaser before inclusion into your DIY vape juice recipes, we offer only high-quality products at the most affordable prices.

TFN® 100mg Nicotine Liquid
$749.99

Select Options

12 Reviews

TFN® 250mg Nicotine Liquid
$1,899.99

Select Options

1 Review

TFN® 100mg Nicotine Salt
$774.99

Select Options

7 Reviews
TFN nicotine used in “over 60 e-liquid brands and other nicotine containing products in the US and worldwide…” (Sept, 2020)

Projected annual volume growth from 2020-2021: 1,800%

[Links]
www.tobaccoasia.com/features/a-real-up-and-comer-synthetic-nicotine/
NN Syntha - Synthetic Nicotine - Now Available

NN “Syntha” - Synthetic Nicotine:

“Syntha,” Nude Nicotine’s Synthetic Nicotine, has been prepared in the laboratory and does not come from tobacco. That’s correct – nicotine, that is TRULY TOBACCO FREE!

Our ‘Syntha” Synthetic Nicotine is constructed in the laboratory from pyrrolidine and pyridine backbone chemistries, then further purified by chromatography, followed by a final distillation step. The purity and quality of our Syntha is like no other and has the benefits of being available in multiple two formulations of R and S isomers (see below). Synthetic “Syntha” Nicotine purity is on-par with our “Pharma” grade, at or above 99.5%, 0.5% purer than USP.

Syntha is available in two master formulations:

1. **Racemic** – 50% R / 50% S-Isomer – Racemic Syntha is a mixture of both nicotine isomers, with a unique chemical signature due to the presence of the R-isomer in the blend. Tobacco nicotine does not have the R-isomer. The performance of this blend is considered industry-standard for synthetic nicotine as it is the most widely adopted.

2. **Isomerized** – 100% S-Isomer – Isomerized Syntha is a 100% S-isomer synthetic nicotine that performs identical to tobacco-nicotine. The racemic Syntha is subjected to additional steps of processing and refinement to produce a synthetic nicotine that is devoid of R-isomer. We feel that this is the highest-performing synthetic nicotine.

E-cigarettes

Made with synthetic nicotine
Nicotine Pouches

Made with synthetic nicotine
Nicotine toothpicks

Tobacco-free moist snuff (green leaves)

Heated tobacco-free product (tea leaves)

Made with synthetic nicotine
Why Synthetic Nicotine?

**OUR INNOVATION**

Introducing high purity (typically 99.9%), synthetic (S)-Nicotine (SyNic) for commercial use that is free of TSNA (tobacco-specific Nitrosamines), toxins, carcinogens, odour, and harsh taste.

Benefits of Chemnovatic's synthetic nicotine

- Not derived from tobacco. - Provides the same level of satisfaction as tobacco nicotine. - Tasteless and odorless. - Manufactured with the use of only certified ingredients of the highest pharmaceutical quality from reliable European suppliers. - Fewer restrictions on entering new markets. - Meets USP and EP grade requirements. - Undergoes strict quality procedures which are confirmed by ISO 9001:2015, HACCP and GHP/GMP standard.
Puff Bar Defies FDA Crackdown on Fruity E-Cigarettes by Ditching the Tobacco

E-cigarette brand resumes online sales of its disposable vaporizers, saying they now contain ‘tobacco-free nicotine’
“Among high school current e-cigarette users (2020), 26.1% reported that their usual brand was Puff Bar, followed by Vuse (10.8%), SMOK (9.6%), JUUL (5.7%), and Suorin (2.3%).”
Synthetic Nicotine (SN) Product Observations

*Not based on any systematic surveillance of synthetic nicotine products*

- SN typically added to products with no tobacco leaf
  - e.g., e-cigarettes, nicotine pouches
- SN typically not used by major tobacco companies
- Companies typically do not disclose type of SN (R/S or S)
  - Nicotine labels may be misleading to consumers
- One product (made with R/S nicotine) listed the amount of S-nicotine (half of the total nicotine) on its label
- Other products listed the amount of total nicotine (S-nicotine + R-nicotine)
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  - Nicotine labels may be misleading to consumers

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6 mg Synthetic Nicotine
Could have 6 mg of S-nicotine or 3 mg of S-nicotine (+ 3 mg of R-nicotine)

12 mg Synthetic Nicotine
Could have 12 mg of S-nicotine or 6 mg of S-nicotine (+ 6 mg of R-nicotine)
Thank You!

Andrew B. Seidenberg, PhD, MPH
Cancer Prevention Fellow
Behavioral Research Program, National Cancer Institute

andrew.seidenberg@nih.gov
Methods for Identifying Synthetic Nicotine
Nicotine enantiomers

(R) - Nicotine

(S) - Nicotine
Typical nicotine analysis

- nicotine appears as a single peak in the GC/MS total ion chromatograph of a commercial e-liquid

Enantiomer-specific nicotine analysis

- Nicotine enantiomers can be separated using normal-phase high performance liquid chromatography

FIGURE 1 Separation of standard solution of (S)-(-)-nicotine and (R)-(+)-nicotine

FIGURE 2 The separation of (S)-(-)-nicotine and (R)-(+)-nicotine in tobacco leaf, smokeless tobacco, and e-liquid

Chiral column nicotine analysis

- Nicotine enantiomers can also be separated using a chiral column and ultra-fast liquid chromatography

**Fig. 1.** Ultra-fast LC enantioseparation of nicotine (NIC) using NicoShell, 50 × 4.6 mm (i.d.), PIM4 at 4 mL/min. S: S-NIC; R: R-NIC; t₀: impurities at dead time. See Section 2 for other acronyms and calculations (kᵢ = 0.7, α = 1.64, Rₛ = 2.6).
Enantiomer-specific nicotine analysis

- Even if you can determine (S)- and (R)-forms, can you tell the difference between natural and synthetic nicotine?
- There are analytical preparation methods for purifying a mixture of (R)- and (S)-nicotine
- There are simple ways of mixing (R)- and (S)-nicotine together to get what appears to be a synthetic mixture
- Identifying the source of a product that can be manipulated after isolation can be challenging
Tobacco alkaloids

- Generally, nicotine isolated from tobacco contains low level impurities
  - Other alkaloids
  - Tobacco-specific nitrosamines

Gar chromatogram of nicotine and alkaloid impurities

**Figure 1.** Total ion chromatogram of tobacco alkaloids analysis. Peaks NIC, NNIC, ANAB, and ANAT stand for nicotine, nornicotine, anabasine, and anatabine, respectively. Sample preparation and analysis were performed according to Wu W, Ashley DL, Watson CH. Determination of nicotine and other minor alkaloids in international cigarettes by solid phase microextraction and gas chromatography/mass spectrometry, Anal Chem 74: 4878-4884, 2002.
Impurity Analysis Challenges

- Methods could be used to clean-up tobacco-derived nicotine to reduce impurity levels and make it appear to be synthetic.
- Manufacturers could also purposefully contaminate synthetic nicotine to make it appear to be tobacco-derived.
- Different tobacco sources may have different levels of impurities. These would need to be evaluated.
NMR analysis

- Has been used to authenticate natural or synthetic vanillin, linalool, benzaldehyde
- Use to detect addition of sugars to fruit juices and wines.
- Basic Principle: Natural and synthetic nicotine are formed from different starting materials
- Natural nicotine has a lower $^2\text{H}/^1\text{H}$ peak intensity ratio (SPIR) because glucose and ornithine are the original sources of those parts of the chemical structure
- Ratios for different samples of synthetic nicotine may vary due to different starting reactants

NMR analysis

- Measure $^2\text{H}/^1\text{H}$ peak intensity ratio (SPIR)
- SPIR of certain sites differs between natural and synthetic nicotine
- Similar approach to identification of sources of nuclear materials

Liu, B., Chen, Y., Ma, X. and Hu, K. Site-specific peak intensity ratio (SPIR) from 1D ($^2\text{H}/^1\text{H}$) NMR spectra for rapid distinction between natural and synthetic nicotine and detection of possible adulteration. Anal Bioanal Chem. 2019 Sep;411(24):6427-6434.
NMR analysis

NMR analysis


rac-Nicotine = synthetic nicotine
Mixture = mixture
p-Nicotine = natural nicotine
Summary

- Methods are available to differentiate (R)- and (S)-nicotine. However, manufacturers may be able to alter these ratios in natural nicotine to appear to be synthetic nicotine.
- Impurities may be useful to identify natural nicotine. However, chemical techniques may be used to clean-up materials and falsify the methods.
- $^2\text{H}/^1\text{H}$ isotope ratio method looks promising. However, it needs to be fully evaluated and validated.
Consumer Perceptions of Synthetic Nicotine Products

Brittney Keller-Hamilton, PhD, MPH
“Tobacco-free” descriptors on warning labels

WARNING: This product contains nicotine. Nicotine is an addictive chemical.

WARNING: This product contains tobacco free nicotine. Nicotine is an addictive chemical.
“Tobacco-free” descriptors on warning labels

WARNING: This product contains nicotine. Nicotine is an addictive chemical.
Objectives

Evaluate whether “tobacco-free” language on warning labels affects:

1. Attitudes toward the product (enjoyable, likable, appealing)
2. Curiosity to use the product
3. Perceiving product as a “tobacco product”
4. Perceived substitutability for cigarettes and traditional smokeless tobacco
5. Absolute and relative harm and addiction perceptions
Sample

Participants enrolled in ongoing Buckeye Teen Health Study (BTHS)
- N=1220 male youth, ages 11-16 at baseline (2015-2016)
- Urban and rural Appalachian Ohio

Eligibility for current study: Has not withdrawn from BTHS, at least 18-years-old, agree to take online survey

N=239
Methods

- July and August
- Brief online survey administered via Qualtrics
- Participants randomly assigned to view: OR

WARNING: This product contains non-tobacco nicotine. Nicotine is an addictive chemical.
Methods

• Covariates
  • Age, race and ethnicity, parental education, region of Ohio
  • Peer & household tobacco use
  • Past 30-day tobacco use (cigarettes, e-cigarettes, cigars/cigarillos, smokeless tobacco, snus, nicotine pouches, hookah, and other)
  • Awareness and ever use of nicotine pouches

• Analysis
  • Confirm randomization balanced covariates
  • Chi-square tests/Fisher’s exact test, Wilcoxon rank sum tests
## Results

### Randomization

<table>
<thead>
<tr>
<th>Puff Bar label</th>
<th>“Tobacco free”</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Non-tobacco”</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Standard</td>
<td>60</td>
<td>59</td>
</tr>
</tbody>
</table>
## Results

### Sample Characteristics (N=239 young adult men)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>M (SD) or N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>20.2 (1.3)</td>
</tr>
<tr>
<td>White non-Hispanic (ref: all others)</td>
<td>194 (81.2)</td>
</tr>
<tr>
<td>Parental education $\geq$ Bachelor’s degree (ref: &lt;Bachelor’s degree)</td>
<td>174 (72.8)</td>
</tr>
<tr>
<td>Appalachian region of Ohio (ref: urban Ohio)</td>
<td>88 (36.8)</td>
</tr>
<tr>
<td>Lived with adult tobacco user at baseline (ref: did not)</td>
<td>52 (21.8)</td>
</tr>
<tr>
<td>Used any tobacco/nicotine in past 30 days (ref: never/former use)</td>
<td>52 (22.3)</td>
</tr>
<tr>
<td>“A few” or more friends use tobacco (ref: none)</td>
<td>199 (87.3)</td>
</tr>
<tr>
<td>Heard of nicotine pouches prior to survey (ref: no/don’t know)</td>
<td>105 (44.5)</td>
</tr>
<tr>
<td>Ever used nicotine pouches (ref: never)</td>
<td>21 (8.8)</td>
</tr>
<tr>
<td>Used nicotine pouches in past 30 days (ref: did not)</td>
<td>6 (2.6)</td>
</tr>
</tbody>
</table>
Results – Puff Bar

Perceptions of Puff Bar by Warning Label

- Attitude toward product (0-10)
- Curiosity about trying product (1-7)
- Substitutability for cigarettes (1-7)
- Substitutability for SLT (1-7)

Mean

- "Tobacco free" label
- Standard label

$p = 0.046$

Consider Puff Bar to be a Tobacco Product

- Yes
- No

"Tobacco free" label
Standard label
Harm and Addiction Perceptions of Puff Bar by Warning Label

- Absolute harm
- Harm relative to cigarettes
- Harm relative to SLT
- Absolute addictiveness
- Addictiveness relative to cigarettes
- Addictiveness relative to SLT

"Tobacco free" label  Standard label
Results – Fre Nicotine Pouches

Perceptions of Fre by Warning Label

<table>
<thead>
<tr>
<th>Mean</th>
<th>Attitude toward product (0-10)</th>
<th>Curiosity about trying product (1-7)</th>
<th>Substitutability for cigarettes (1-7)</th>
<th>Substitutability for SLT (1-7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&quot;Non-tobacco&quot; label</td>
<td>Standard label</td>
<td>&quot;Non-tobacco&quot; label</td>
<td>Standard label</td>
</tr>
</tbody>
</table>

Consider Fre to be a Tobacco Product

- Yes: "Non-tobacco" label (80%), Standard label (20%)
- No: "Non-tobacco" label (45%), Standard label (55%)

\( p = 0.005 \)
Harm and Addiction Perceptions of Fre Nicotine Pouches by Warning Label

- Absolute harm
- Harm relative to cigarettes
- Harm relative to SLT
- Absolute addictiveness
- Addictiveness relative to cigarettes
- Addictiveness relative to SLT

Warning labels:
- "Non-tobacco" label
- Standard label

Statistical significance: $p=0.006$
Discussion & Implications

Puff Bar’s “tobacco free” warning label → increased perceptions of substitutability for cigarettes and traditional SLT.

- Congruent with existing e-cigarette marketing strategies to implicitly or explicitly position e-cigarettes as cessation devices.¹-³
- However, did not ask directly about cessation.

Fre’s “non-tobacco” warning label → less likely to think of Fre as a tobacco product, reduced harm perceptions relative to traditional SLT.

- Reduced harm perceptions associated with increased risk of tobacco product initiation.⁴
- Preliminary data: Use of nicotine pouches is highest among SLT users.
- Interest in nicotine pouches is highest among SLT users, and most-stated reason for use is reduced harm perceptions.⁵

Conclusions

- “Tobacco-free” descriptors in warning labels affect product perceptions; effects might differ according to product.

- Current study limited by: Ohio sample; young adult male sample; small sample size/low response rate; one-time, brief exposure to “tobacco-free” warnings

- Remaining questions:
  - Do effects of “tobacco-free” descriptors differ for users & nonusers?
  - Is “tobacco-free” language in warning labels & advertisements noticed at the point of sale?
  - How do repeated exposures to “tobacco-free” language in warning labels & advertisements affect product perceptions and use behaviors?
Thank you!

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- Amy Ferketich, PhD

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Federal Regulatory Landscape for Synthetic Nicotine Products

Patricia J. Zettler, JD
Associate Professor, Moritz College of Law
Faculty Member, Drug Enforcement and Policy Center
Faculty Member, The James Comprehensive Cancer Center
The Ohio State University
This presentation is for informational and educational purposes only, and is not legal advice.
Are synthetic nicotine products “tobacco products” under the Federal Food, Drug, and Cosmetic Act?

Are synthetic nicotine products “drugs” (or drug-delivery devices) under the Federal Food, Drug, and Cosmetic Act?
“The term “tobacco product” means any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product . . .”

21 U.S.C. §321(rr)
CONCLUSION
We recently visited the Tobacco Plus Expo (TPE) in Las Vegas, with 350+ exhibitors and 5,000+ attendees. Many new brands of nicotine pouches and vapor products used the show to help launch new products, all of which use synthetic nicotine (i.e. not derived from tobacco), and therefore are not subject to FDA regulations (like a PMTA review to be authorized for legal sale). While many of the vapor companies at the January 2020 show no longer had a presence (following a PMTA filing deadline in September 2020), tobacco-free nicotine (TFN) products were very prominent. TFN may be a golden ticket: no FDA regulation, no tobacco taxes, no flavor restrictions, and no restrictions on direct to consumer e-commerce. Near-term, these launches appear to increase competition for Altria, BAT and Imperial in nicotine pouches and vapor, but their existence suggests TFN is commercially viable, and therefore likely an opportunity for big players.

• Why is synthetic nicotine important? Because the FDA only regulates tobacco and tobacco-derived products, TFN is not under the FDA’s authority, allowing these new products to launch legally without going through the lengthy PMTA authorization process.
Is synthetic nicotine a "golden ticket"?

The term “drug” means . . . (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals . . . 21 U.S.C. § 321(g)(1)

*Brown & Williamson and Sottera* do not apply

Synthetic nicotine products as drugs

- Companies’ representations may include both disease and structure/function claims
- Product design
- Circumstances surrounding distribution (consumer intent)

Where's the regulatory gap?

The product I manufacture contains no substance made or derived from tobacco, e.g. is zero-nicotine, or has synthetic nicotine or nicotine made from tomatoes. Is my product subject to FDA regulation?

The definition of "tobacco product" includes any product made or derived from tobacco, including any component, part, or accessory of a tobacco product. E-liquids that do not contain nicotine or other substances made or derived from tobacco may still be components or parts and, therefore, subject to FDA's tobacco control authorities.

However, it's possible that a disposable, closed system device that contains an e-liquid with truly zero nicotine (or synthetic nicotine) would not be regulated by the FDA as a tobacco product, if it is not intended or reasonably be expected to be used in such a fashion. FDA intends to make these determinations on a case-by-case basis, based on a totality of the circumstances.

Regulatory Options include . . .

FDA regulating the products as drugs

Congress amending the Federal Food, Drug, and Cosmetic Act
Thanks!
Questions?

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Denied FDA Authorization, Vaping Companies Start to Explore Loopholes

Some Vaping Companies Are Turning to Synthetic Nicotine to Outsmart the FDA
Chairman Krishnamoorthi Launches Investigation into the Production, Sale of Unregulated Synthetic Nicotine

Nov 8, 2021  |  Press Release

Requests Transcribed Interviews with Puff Bar Co-Chief Executive Officers

Washington, D.C. (November 8, 2021)—Today, Rep. Raja Krishnamoorthi, Chair of the Subcommittee on Economic and Consumer Policy, sent letters to two companies that manufacture or sell synthetic nicotine products, requesting information about the companies and their sale of these products, which are unregulated by the Food and Drug Administration (FDA). The Chairman sent a letter to Next Generation Labs LLC, which claims to be “the market leader” in the production and sale of synthetic nicotine. He also sent a letter to Puff Bar, the top children’s e-cigarette brand, which claims to have reformulated its products with synthetic nicotine after it was found to be in violation of Food and Drug Administration (FDA) law.
21  (b) TAXABLE NICOTINE.—Section 5702 is amended
22  by adding at the end the following new subsection:
23  “(q) TAXABLE NICOTINE.—
24  “(1) In general.—Except as otherwise pro-
25  vided in this subsection, the term ‘taxable nicotine’

\110321\110321.158.xml  (824876|1)
Mar 3, 2021 (3:00 p.m.)

\MISC\RECONCILIATION_RCP.XML

1974

1  means any nicotine which has been extracted, con-
2  centrated, or synthesized.
Tobacco Control Act

“The term ‘tobacco product’ means any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product).”

21 USC Sec. 321(rr)(1)
State/Local Definitions

• **Chicago** amended definition of “tobacco products” in its code:
  - “products containing nicotine derived from tobacco or any other source”

• **Wyoming**: “Electronic cigarette’ means any device that can be used to deliver aerosolized or vaporized nicotine or synthetic nicotine”
State/Local Definitions

• Implications for ALL tobacco-related laws:
  ➢ Licensing laws
  ➢ Smoke-free laws
  ➢ Taxes
  ➢ Minimum price
  ➢ Minimum sales age
  ➢ Etc.

f. “Tobacco product” means: (1) any product containing, made of, or derived from tobacco or nicotine that is intended for human consumption or is likely to be consumed, whether inhaled, absorbed, or ingested by any other means, including, but not limited to, a cigarette, a cigar, pipe tobacco, chewing tobacco, snuff, or snus; (2) any electronic smoking device and any substances that may be aerosolized or vaporized by such device, whether or not the substance contains nicotine; or (3) any component, part, or accessory of (1) or (2), whether or not any of these contain
Alabama, HB 273 (2021)

“Beginning on September 1, 2021, no e-liquid, e-liquid in combination with an electronic nicotine delivery system, or alternative nicotine product that, in the case of any such product, contains synthetic nicotine or nicotine derived from a source other than tobacco may be sold or otherwise distributed in this state without first obtaining approval from the United States Food and Drug Administration for sale as a [drug, device, or combination product].”
The Global Picture

• Some countries had laws/regulations broad enough to include SN (European Union)

• Some countries have recently amended laws to include SN (Russia, Kazakhstan, Paraguay)

• Other are in the process of amending laws in response to new products, tax evasion (Kenya, South Korea)
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