Synthetic Nicotine: Frequently Asked Questions

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SUMMARY

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Synthetic Nicotine: Frequently Asked Questions

Some electronic-cigarette brands have begun using synthetic nicotine solutions, or nicotine derived from non-tobacco sources, in their nicotine delivery systems. The manufacturer of one the most popular brands of these products has asserted that the Food and Drug Administration (FDA), which has the authority to regulate the manufacture, marketing, sale, and distribution of tobacco products, cannot regulate these synthetic nicotine products under the current regulatory system.

Synthetic nicotine products are available in a variety of flavors, which may make them appealing to youths and young adults. Recent data suggest that synthetic nicotine products have become increasingly popular among youths, overtaking other electronic-cigarette brands in popularity. The short- and long-term physiological effects of synthetic nicotine solution products as compared with tobacco-derived nicotine products is currently unclear.

Because some synthetic nicotine products may not currently meet the definition of a "tobacco product," it is unclear whether FDA has the authority to regulate them and, if so, under what regulatory scheme. Given this uncertainty and the potential health impacts associated with e-cigarettes, Congress may consider taking steps to clarify how synthetic nicotine is regulated.

This report provides answers to frequently asked questions regarding synthetic nicotine and synthetic nicotine products.

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Introduction

About 2 million young people reported using electronic cigarettes (e-cigarettes) in 2021. In specific, *Morbidity and Mortality Weekly Report* (MMWR) stated that 11.3% of high school students (approximately 1.7 million individuals) and 2.8% of middle-school students (approximately 320,000 individuals) reported using e-cigarettes in 2021.[1] Approximately 85% of these individuals reported using flavored e-cigarettes, and among the high-school students, 26.1% reported that their usual brand of e-cigarette was an e-cigarette which uses synthetic nicotine.[2] Recent studies have suggested that such products have overtaken other e-cigarette brands in popularity.[3]

E-cigarettes operate by creating an aerosol out of a solution containing nicotine, flavorings, and other additives.[4] This solution, sometimes called "e-liquid," may be supplied with the device. Depending on the type of e-cigarette, after the user has depleted the solution, the device can be disposed of.[5] Some of these products utilize solutions containing nicotine derived from tobacco (i.e., tobacco-derived nicotine, or TDN), while other products purport to contain tobacco-free solutions (i.e., tobacco-free nicotine, or TFN).[6] Some manufacturers of synthetic nicotine products assert that the nicotine in solution is not derived from tobacco but is instead manufactured through a "patented manufacturing process."[7] Other manufacturers of e-cigarettes have begun using similar tobacco-free solutions in their products. These synthetic nicotine products are available in a variety of flavors, some of which may be appealing to youths and young adults.[8] Some of these products are also available in different forms, such as lozenges and mints.

The Federal Food, Drug and Cosmetic Act (FFDCA) gives the Food and Drug Administration (FDA) the authority to regulate the manufacture, marketing, sale, and distribution of tobacco products.[9] A *tobacco product* is defined as "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

[1] Centers for Disease Control and Prevention (CDC), "Use Among Middle and High School Students-National Youth Tobacco Survey, United States, 2021," *Morbidity and Mortality Weekly Report*, vol. 70, no. 39 (October 1, 2021), pp. 1387-1389, https://www.cdc.gov/mmwr/volumes/70/wr/mm7039a4.htm.

[2] Ibid.

[3] See Hongying Dai and Jianqiang Hao, "Online popularity of JUUL and Puff Bars in the USA: 2019–2020," *Tobacco Control*, vol. 13 (October 2020), https://tobaccocontrol.bmj.com/content/early/2020/10/13/tobaccocontrol-2020-055727.info.

[4] CDC, "About Electronic Cigarettes (E-Cigarettes)," https://www.cdc.gov/tobacco/basic_information/e-cigarettes/about-e-cigarettes.html.

[5] In other e-cigarette products, the solution is provided in a refillable cartridge.

[6] Most e-cigarette devices contain nicotine derived from tobacco. See United States Department of Health and Human Services (HHS), "E-Cigarette Use Among Youth and Young Adults," "Introduction, Conclusions, and Historical Background Relative to E-Cigarettes," in *E-Cigarette Use Among Youth and Young Adults* (2016), p. 17, https://e-cigarettes.surgeongeneral.gov/documents/2016_SGR_Full_Report_non-508.pdf.

[7] Ibid.

[8] Puff Bar, "About Us," https://puffbar.com/pages/about-puff-bar.

[9] For an overview of FDA regulation of tobacco products, see CRS Report R45867, *FDA Regulation of Tobacco Products*. For a discussion on the legal framework for federal regulation of tobacco, see CRS In Focus IF11321, *Federal Regulation of Tobacco: Legal Framework and Issues for the 116th Congress*.

accessory of a tobacco product)."[10] Some manufacturers of synthetic nicotine products claim that their products cannot be regulated by the FDA as a tobacco product because they are not derived from tobacco and thus do not meet the definition of "tobacco product" in statute.[11] Even so, public health organizations have expressed concern that e-cigarettes containing synthetic nicotine are potentially enticing to youths and young adults and may eventually lead to increased smoking.[12] Additionally, these organizations assert that synthetic nicotine products may still be regulated by FDA.[13]

This report provides answers to frequently asked questions regarding synthetic nicotine and synthetic nicotine products. Specifically, this report

- examines how synthetic nicotine solutions differ from tobacco-derived nicotine (TDN) products;
- discusses some of the unique characteristics of synthetic nicotine solutions and products;
- outlines the existing regulatory framework for synthetic nicotine; and
- notes issues that may be of potential interest to Congress.

Because the use of synthetic nicotine is relatively new, this report will be updated periodically to reflect relevant developments.

What is the difference between synthetic nicotine and nicotine derived from tobacco?

E-cigarettes come in a variety of forms produced by many different manufacturers. E-cigarette products contain a cartridge that stores the e-liquid, which is typically composed of a mixture of water, propylene glycol, vegetable glycerin, and nicotine.[14] In some cases, the e-liquid may contain additional ingredients such as flavoring, cannabis,[15] or other biologically active compounds.[16] The e-liquid is heated by the e-cigarette, which then creates an inhalable aerosol that delivers the nicotine to the user.[17] The nicotine found in the solutions of some of these

[10] FFDCA §201(rr); 21 U.S.C. §321(rr).

[11] Next Generation Labs, "FDA Finally Addresses Synthetic Nicotine; Confirming Next Generation Labs' Position that Synthetic Nicotine Is Not A Tobacco Product," January 20, 2017, https://www.globenewswire.com/fr/news-release/2017/01/20/909720/0/en/FDA-Finally-Addresses-Synthetic-Nicotine-Confirming-Next-Generation-Labs-Position-that-Synthetic-Nicotine-Is-Not-A-Tobacco-Product.html.

[12] Letter from Tobacco Free Kids to Janet Woodcock, Acting Commissioner of FDA, September 2, 2021, https://www.tobaccofreekids.org/assets/content/what_we_do/federal_issues/fda/regulatory/2021_09_02_Letter-to-FDA-Synthetic-Nicotine.pdf.

[13] See. "What is the current regulatory status of synthetic nicotine?"

[14] For a more detailed discussion on electronic nicotine delivery systems (ENDS), please see CRS Report R46928, *Regulation of Electronic Nicotine Delivery Systems (ENDS): Background and Select Policy Issues in the 117th Congress*.

[15] Although tetrahydrocannabinol, the primary psychoactive compound found in marijuana is an illicit substance at the federal level, some states have implemented their own laws pertaining to the recreational and medical use of the substance. See Ibid.

[16] CDC, "E-Cigarette, or Vaping, Products Visual Dictionary," https://www.cdc.gov/tobacco/basic_information/e-cigarettes/pdfs/ecigarette-or-vaping-products-visual-dictionary-508.pdf.

[17] Ibid.

products are derived from tobacco (i.e., tobacco-derived nicotine, or TDN), while other products purport to contain tobacco-free e-liquids (i.e., tobacco-free nicotine, or TFN).[18]

Although nicotine is typically extracted from tobacco plants, it can also be extracted from other sources or synthesized in a laboratory.[19] The technology to produce synthetic nicotine was initially cost prohibitive; however, recent advancements made the mass production of synthetic nicotine more affordable.[20] The cost of producing synthetic nicotine is estimated to be approximately three to four times the cost of manufacturing tobacco-derived nicotine.[21]

Although nicotine derived from tobacco and synthesized nicotine share the same molecule, consumers may notice different effects from ingesting one compared with the other. This variation largely stems from the fact that different forms of nicotine interact differently with an individual's cells.[22] Generally, a nicotine molecule exerts its effect by binding to a specific receptor on the surface of specific human cells, into which it fits like a key into a lock. However, not all nicotine molecules are the same. A collection of nicotine molecules contains *stereoisomers*, or molecules that are composed of the same elements bonded to one another in the same sequence but arranged in different orientations in space. These different orientations form non-superimposable mirror images of one another, called *enantiomers*.[23] An easier way to model this concept is to conceive the two mirror images as two hands, one left and the other right.[24] The *chirality*, or "handedness," of the nicotine enantiomer may be represented by either a left ("S") or right ("R") denotation, and may affect how the nicotine binds with the receptor on the surface of certain human cells, and thus may affect the user experiences.

Nicotine Enantiomers

(Tobacco-Derived Nicotine; Tobacco-Free Nicotine)

Enantiomers are two nicotine molecules made of the same atoms which have the opposite three-dimensional shapes. These two molecules are mirror images of each other. *This difference in shape may lead to a difference in biological effect.*

Nicotine extracted from a tobacco plant is almost entirely in the "S" configuration (S-Nicotine), although a small amount of nicotine may be present in the "R" configuration (R-Nicotine).[25] Synthetic nicotine solutions, however, may be available in various mixtures, some of which may contain a greater percentage of R-Nicotine.[26] The different nicotine enantiomers may have a

[18] Most e-cigarette devices contain nicotine derived from tobacco. See United States Department of Health and Human Services (HHS), "E-Cigarette Use Among Youth and Young Adults," "Introduction, Conclusions, and Historical Background Relative to E-Cigarettes," in *E-Cigarette Use Among Youth and Young Adults* (2016), p. 17, https://e-cigarettes.surgeongeneral.gov/documents/2016_SGR_Full_Report_non-508.pdf.

[19] Neal L. Benowitz, Janne Hukkanken, and Peyton Jacob III, "Nicotine Chemistry, Metabolism, Kinetics and Biomarkers," *Handbook of Experimental Pharmacology*, vol. 192 (October 13, 2010), p. 30, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2953858/pdf/nihms235126.pdf.

[20] HHS, "Introduction, Conclusions, and Historical Background Relative to E-Cigarettes," in *E-Cigarette Use Among Youth and Young Adults* (2016), p. 17, https://e-cigarettes.surgeongeneral.gov/documents/2016_SGR_Full_Report_non-508.pdf.

[21] Stefanie Rossel, "Synthetic Nicotine is Gaining Acceptance," *Tobacco Reporter*, December 1, 2019, https://tobaccoreporter.com/2019/12/01/mirror-image/.

[22] See "Are synthetic nicotine products less addictive than products containing tobacco-derived nicotine?"

[23] R.F. Tester and J. Karkalas, "Properties of Enantiomers – Optical Isomerism," in *Encyclopedia of Food Sciences and Nutrition (Second Edition)*, 2nd ed. (2003).

[24] Ibid.

[25] Garrett Hellinghausen, Jauh T. Lee, Choyce A. Weatherly, et al, "Evaluation of Nicotine in Tobacco-free-nicotine Commercial Products," *Drug Testing and Analysis*, vol. 9 (January 25, 2017).

[26] Sven-Eric Jordt, "Synthetic nicotine has arrived," *Tobacco Control*, September 7, 2021,

different physiological impact on an individual because R-nicotine appears to interact differently with an individual's cell receptors.[27] As a consequence, individuals who use products containing synthetic nicotine may have a different experience than those who use products containing TDN products.

Some synthetic nicotine solutions may contain a higher percentage of R-Nicotine, which is an enantiomer whose physiological effects on users are less researched than those of S-Nicotine.[28] Certain studies have indicated that R-Nicotine may bind less selectively to particular receptors in specific human cells and therefore may produce different, or less of a physiological effect on a user.[29]

Several findings support this distinction. For example, although higher doses of S-Nicotine appear to induce a lower body weight in animal models, R-Nicotine does not appear to affect weight.[30] Some data seem to indicate that R-Nicotine may cause less damage to human cells than its counterpart.[31]

Are synthetic nicotine products less addictive than products containing tobacco-derived nicotine?

Some manufacturer-funded research has suggested that synthetic nicotine products that contain higher ratios of R-Nicotine to S-Nicotine may be less addictive than TDN, although data are limited.[32] This consideration, alongside of some of the previously mentioned health effects of R-Nicotine, leads some researchers to suggest that R-Nicotine may have potential for being a therapeutic agent in the treatment of both neurodegenerative disease and smoking cessation.[33] Further research may determine whether synthetic nicotine products are more, or less addictive than their tobacco-derived nicotine product counterparts.

Have any concerns been documented regarding the use of synthetic nicotine products?

Some researchers have noted that the term 'nicotine' on a product label may not clarify which enantiomers of nicotine are available in which quantity. For example, some products may only list

https://tobaccocontrol.bmj.com/content/tobaccocontrol/early/2021/09/07/tobaccocontrol-2021-056626.full.pdf.

[27] Jaap van Brakel, "Substances," *Philosophy of Chemistry*, ed. Andrea I. Woody, Robin Findlay, Henry and Paul Needham, vol. 6 (2011), p. 3, https://tobaccocontrol.bmj.com/content/tobaccocontrol/early/2021/09/07/tobaccocontrol-2021-056626.full.pdftine.

[28] See, for example, Next Generation Labs, "The Synthetic Nicotine Marketplace: Next Generation Nicotine Delivery USA, 2021," 2021, p. 9, https://www.nextgenerationlabs.com/wp-content/uploads/2021/06/THE-SYNTHETIC-NICOTINE-MARKETPLACE-NGL.pdf.

[29] Dariusz Pogocki, Tomasz Ruman, Magdalena Danilczuk, et al., "Application of nicotine enantiomers, derivatives, and analogues in therapy neurodegenerative disorders," *European Journal of Pharmacology*, vol. 563 (February 27, 2007), p. 29.

[30] Ibid., p. 29.

[31] Ibid., p. 29.

[32] Stefanie Rossel, "Synthetic Nicotine is Gaining Acceptance," *Tobacco Reporter*, December 1, 2019, https://tobaccoreporter.com/2019/12/01/mirror-image/.

[33] Dariusz Pogocki, Tomasz Ruman, Magdalena Danilczuk, et al., "Application of nicotine enantiomers, derivatives, and analogues in therapy neurodegenerative disorders," *European Journal of Pharmacology*, vol. 563 (February 27, 2007), p. 30.

the amount of a particular type of nicotine, and neglect to mention the other.[34] Synthetic nicotine solutions produced by different manufacturers may have differing ratios of R- and S-Nicotine.[35] Some synthetic nicotine solutions may list only the amount of S-Nicotine on their product labels, while other solutions from the same manufacturer may contain varying amounts of R- and S-Nicotine.[36] When labels fail to accurately account for the amount of R-Nicotine present in a solution, an individual using that solution may be exposed to a higher dose of nicotine than they expected.[37] The physiological impact on chronic users of synthetic nicotine compared with individuals who prefer TDN is unclear. For example, research has not conclusively established whether it is safer to use a product containing synthetic nicotine or TDN. Limited data suggest that products labelled "tobacco-free" may increase an individual's use of that product and may reduce the perception of harm associated with smoking.[38]

A number of questions about synthetic nicotine remain unanswered because of insufficient data. For example, it is unclear whether users accustomed to inhaling TDN products and are consequently accustomed to a more potent dose of nicotine, are more likely to use more of a TFN product to compensate. Although it is unclear whether TFN product users engage in compensatory behavior, data suggest that individuals accustomed to higher doses of nicotine who switch to a lower nicotine-yielding product may subsequently consume larger amounts of that product.[39] It is also unclear whether individuals using TFN solutions who do engage in compensatory behavior experience poorer health outcomes than individuals who use TDN solutions. Moreover, it is unclear if exposure to the other substances in synthetic nicotine solutions can cause long-term health problems for users. For example, many synthetic nicotine products are flavored. Previous studies have indicated that certain flavors may contain a substance called diacetyl, which has been associated with the development of "popcorn lung," an irreversible respiratory disease.[40]

What is the current regulatory status of synthetic nicotine?

The Family Smoking Prevention and Tobacco Control Act of 2009 (P.L. 111-31, TCA) established Federal Food, Drug, Cosmetic Act Chapter IX, under which FDA is authorized to regulate tobacco products.[41] Pursuant to the TCA, FDA established the Center for Tobacco Products (CTP) in 2009. A *tobacco product* is defined in statute as "any product made or derived

[34] Sven-Eric Jordt, "Synthetic nicotine has arrived," *Tobacco Control*, September 7, 2021, https://tobaccocontrol.bmj.com/content/tobaccocontrol/early/2021/09/07/tobaccocontrol-2021-056626.full.pdf, p.3.

[35] Garrett Hellinghausen, Jauh T. Lee, Choyce A. Weatherly, et al, "Evaluation of Nicotine in Tobacco-free-nicotine commercial products," *Drug Testing and Analysis*, vol. 9 (January 25, 2017), p. 946.

[36] Ibid., p. 947.

[37] For tobacco products manufactured for commercial distribution, manufacturers must register for that product, submitting information for review which includes labeling, and listing of all ingredients and nicotine amount for each tobacco product. FDA, *Guidance for Industry: Registration and Product Listing for Owners and Operators of Domestic Tobacco Product Establishments*, December, 2017, https://www.fda.gov/media/78165/download.

[38] Julia Chen-Sankey, Ollie Ganz, Andrew Seidenberg, et al., "Effect of a 'tobacco-free nicotine' claim on intentions and perceptions of Puff Bar e-cigarette use among non-tobacco-using young adults," *Tobacco Control*, October 25, 2021.

[39] See Gerhard Scherer, "Smoking behaviour and compensation: a review of the literature," *Psychopharmacology*, vol. 145, March 22, 1999, https://link.springer.com/content/pdf/10.1007/s002130051027.pdf.

[40] Konstantinos E. Farsalinos, Kurt A. Kistler, Gene Gillman, et al., "Evaluation of Electronic Cigarette Liquids and Aerosol for the Presence of Selected Inhalation Toxins," *Nicotine & Tobacco Research*, vol. 9, January 25, 2017, p. 944.

[41] For more information, see CRS Report R45867, *FDA Regulation of Tobacco Products*.

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)."[42] Because it is not always clear whether a product derived from tobacco should be regulated as a drug, device, combination product, or a tobacco product, FDA has promulgated regulations to help those manufacturers intending to market products that are made or derived from tobacco, based on the products' "intended uses."[43] Specifically, in 2016, FDA promulgated regulations (known as "the deeming rule") that extended the agency's authority over all tobacco products that were not already explicitly subject to the FFDCA, including electronic nicotine delivery systems (ENDS), cigars, pipe tobacco, hookah tobacco, nicotine gels, dissolvable tobacco, and other tobacco products.[44] Following the 2016 deeming rule, all newly deemed tobacco products became subject to premarket review requirements.[45]

In April 2020, FDA released final guidance outlining its enforcement priorities for ENDS and other deemed products currently on the market without premarket authorization. The guidance clarified that all new tobacco products may not legally be marketed without premarket authorization.[46] FDA then detailed how it would prioritize enforcement of the premarket review requirements for certain ENDS product and that, among others products, FDA would prioritize enforcement against flavored, cartridge-based ENDS products.[47] Subsequently, in July 2020, FDA issued warning letters to several companies for failing to comply with premarket notification requirements, asking them to remove their flavored ENDS products from the market.[48] Soon after, one of these companies began selling a new line of disposable products that used a non-cartridge based system containing synthetic nicotine in its e-liquid in place of TDN. These products were and are currently available in a variety of sizes and flavors, including fruit and candy flavors, which FDA has previously stated are associated with first-time and continued ENDs use among individuals, particularly youths.[49]

On the subject of synthetic nicotine, FDA has stated 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

[42] FFDCA §201(rr); 21 U.S.C. §321(rr).

[43] To determine a product's intended use, the FDA may look to "any ... relevant source," such as (but not limited to) "product labeling, promotional claims, and advertising." FDA, "Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products: Amendments to Regulations Regarding 'Intended Uses,'" 82 *Federal Register* 2193, January 9, 2017.

[44] 21 C.F.R. Part 1100.

[45] For a more detailed discussion on electronic nicotine delivery systems (ENDS), see CRS Report R46928, *Regulation of Electronic Nicotine Delivery Systems (ENDS): Background and Select Policy Issues in the 117th Congress*.

[46] FDA, *Guidance for Industry: Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization*, April 2020, https://www.fda.gov/media/133880/download., p. 10.

[47] Ibid p. 10.

[48] FDA, "FDA Notifies Companies, Including Puff Bar, to Remove Flavored Disposable E-Cigarettes and Youth-Appealing E-Liquids from Market for Not Having Required Authorization" (July 20, 2020), https://www.fda.gov/news-events/press-announcements/fda-notifies-companies-including-puff-bar-remove-flavored-disposable-e-cigarettes-and-youth.

[49] Ibid. See also FDA, "FDA finalizes enforcement policy on unauthorized flavored cartridge-based e-cigarettes that appeal to children, including fruit and mint" (January 2, 2020), https://www.fda.gov/news-events/press-announcements/fda-finalizes-enforcement-policy-unauthorized-flavored-cartridge-based-e-cigarettes-appeal-children.

> 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.[50]

Manufacturers of synthetic nicotine have stated that synthetic nicotine products cannot be regulated as tobacco products because they are not derived from tobacco.[51] Public health organizations, however, have sent letters to FDA claiming that these synthetic nicotine products are attempting to "evade regulation" as a tobacco product.[52] This coalition of public health organizations has stated that FDA has clear jurisdiction over synthetic nicotine products through its Center for Drug Evaluation and Research (CDER), and that synthetic nicotine falls within the FFDCA's definition of "drug."[53] Some legal scholars have supported this claim, stating that the determinative factor for whether these synthetic nicotine products can be considered a drug is through an analysis of their intended use.[54] These scholars cite, as an example, that the FDA has previously stated that

> the mere presence of a pharmacologically active ingredient could make a product a drug even in the absence of explicit drug claims. In these cases, the intended use would be implied because of the known or recognized drug effects of the ingredient.[55]

As of the date of this report, FDA has not attempted to further regulate the synthetic nicotine market. In the interim, at least one state has begun investigating synthetic nicotine products, citing concerns that the flavor options of these products may make them more appealing to youths.[56]

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[50] FDA, "Commonly Asked Questions: About the Center for Tobacco Products," https://www.fda.gov/tobacco-products/about-center-tobacco-products-ctp/commonly-asked-questions-about-center-tobacco-products#14.

[51] See, for example, Next Generation Labs, LLC., "FDA Finally Addresses Synthetic Nicotine; Confirming Next Generation Labs' Position that Synthetic Nicotine Is Not A Tobacco Product" (January 20, 2017), https://www.globenewswire.com/fr/news-release/2017/01/20/909720/0/en/FDA-Finally-Addresses-Synthetic-Nicotine-Confirming-Next-Generation-Labs-Position-that-Synthetic-Nicotine-Is-Not-A-Tobacco-Product.html.

[52] Letter to Janet Woodcock, Former Acting FDA Commissioner, March 18, 2021, https://www.tobaccofreekids.org/assets/content/what_we_do/federal_issues/fda/regulatory/2021_09_02_Letter-to-FDA-Synthetic-Nicotine.pdf, p. 4.

[53] The FFDCA defines a drug (in part) as, "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals." FFDCA §201(g)(1); 21 U.S.C. §321(g)(1). FDA's regulation of drugs also extends to biologics and certain devices. For more information, see CRS In Focus IF11083, *Medical Product Regulation: Drugs, Biologics, and Devices*.

[54] FDA can determine the intended use of a product through a variety of means, including the product label; non-speech evidence, such as product formulation; product claims; or any relevant source of evidence. For example, in cosmetic products, the inclusion of a drug product in the formulation of a cosmetic may cause it to be regulated as both a cosmetic and a drug. See FDA, "Regulations Regarding "Intended Uses," 86 *Federal Register* 41383, September 1, 2021.

[55] Patricia J. Zettler, Natalie Hemmerich, and Micah L. Berman, "Closing the Regulatory Gap for Synthetic Nicotine Products," *Boston College Law Review*, vol. 59, no. 6 (2018), pp. 10-11, https://www.tobaccofreekids.org/assets/content/what_we_do/federal_issues/fda/regulatory/2021_09_02_Letter-to-FDA-Synthetic-Nicotine.pdf. See also, Dariusz Pogocki, Tomasz Ruman, Magdalena Danilczuk, et al., "Application of nicotine enantiomers, derivatives, and analogues in therapy neurodegenerative disorders," *European Journal of Pharmacology*, vol. 563 (February 27, 2007), p. 30.

[56] "North Carolina Attorney General launches probe into e-cigarette maker Puff Bar," *Reuters*, November 17, 2021, https://www.reuters.com/legal/litigation/north-carolina-attorney-general-launches-probe-into-e-cigarette-maker-puff-bar-2021-11-16/.

Considerations for Congress

In response to the popularity of synthetic nicotine products alongside their unknown health effects, and in consideration of FDA's current review of marketing applications for ENDS, Congress may consider whether additional congressional oversight is necessary at this time to address the regulatory status for synthetic nicotine products. Should Congress determine that additional oversight is warranted, it may consider the following options.

- **Expand the statutory definition of *tobacco product* to include nicotine from all sources.** As stated above, the definition of *tobacco product* does not necessarily consider the source of the nicotine and instead focuses on tobacco and tobacco accessories.[57] Congress may consider amending the FFDCA to expand the definition of *tobacco product* to explicitly include products containing nicotine from any source, including synthetic nicotine. Some states have already begun adopting such an expanded definition.[58]
- **Direct federal agencies to conduct studies documenting the health effects that synthetic nicotine products may have compared with TDN products.** Some synthetic nicotine solutions may contain varying ratios of nicotine enantiomers whose physiological effects on the human body are not well understood. Congress may consider directing the Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), or FDA's CTP or CDER to conduct studies on synthetic nicotine products to determine the degree to which they may be more or less harmful than, or roughly equivalent to, products that use nicotine derived from tobacco. Additionally, Congress may consider directing these same federal agencies to conduct studies that review the impact that synthetic nicotine products may have on public health. Currently, a manufacturer who wishes to legally market a new tobacco product may only receive market authorization from the FDA after the manufacturer has demonstrated that the product is "appropriate for the protection of public health."[59] This determination is made by analyzing, in part whether the product will result in "the increased or decreased likelihood that existing users of tobacco products will stop using such products; and the increased or decreased likelihood that those who do not use tobacco products will start using such products."[60]

  Currently, it is unclear whether synthetic nicotine products are impacting either of these two likelihoods. It is unclear whether an individual who has never previously used a product that delivers nicotine would be *more* likely to use a synthetic product. It is equally unclear whether that individual would experience comparable, greater, or less negative health effects from prolonged use of a synthetic nicotine product as compared to a TDN product. Additional studies may help public health experts determine the impact that synthetic nicotine may have on public health.
- **Direct the FDA to assert jurisdiction over synthetic nicotine products through CDER.** Several organizations have stated that FDA may be able to

[57] FFDCA §201(rr); 21 U.S.C. §321(rr).

[58] See, for example, "Tobacco product," a product containing, made or derived from tobacco or nicotine," M.G.L.A. 270, §6.

[59] FFDCA §910(c)(4); 21 U.S.C. §387j(c)(4).

[60] Ibid. For more information, see CRS Report R45867, *FDA Regulation of Tobacco Products*.

- regulate synthetic nicotine products under CDER and not CTP by establishing that synthetic nicotine products meet the FFDCA definition of *drug*.[61] Congress may consider directing FDA to determine whether synthetic nicotine products meet this definition and, if so, whether any existing regulatory schemes are applicable to synthetic nicotine products or if new regulatory schemes are warranted.

Conclusion

Synthetic nicotine products represent a novel mechanism through which consumers can ingest nicotine. Although the full physiological impact of these products is unknown, they are today marketed with flavors that likely appeal to youths and young adults. Because some of these products may not meet the definition of a "tobacco product," it is unclear whether FDA has the authority to regulate these products and if so, under what regulatory scheme. Given this uncertainty and the potential health impacts associated with e-cigarettes, Congress may consider steps to clarify how synthetic nicotine is regulated.

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[61] Letter to Janet Woodcock, Former Acting FDA Commissioner, March 18, 2021, https://www.tobaccofreekids.org/assets/content/what_we_do/federal_issues/fda/regulatory/2021_09_02_Letter-to-FDA-Synthetic-Nicotine.pdf, p. 4.