U.S. FOOD & DRUG ADMINISTRATION

June 22, 2022

The Honorable Raja Krishnamoorthi
Chairman
Subcommittee on Economic and Consumer Policy
Committee on Oversight and Reform
U.S. House of Representatives
Washington, D.C. 20515

Dear Chairman Krishnamoorthi:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the June 23, 2021, hearing before the Subcommittee on Economic and Consumer Policy, House Committee on Oversight and Reform, entitled "A Crisis Continues: Youth Vaping in America." This letter is a response for the record to questions posed by the committee.

Sincerely,

Kimberlee R. Trzeciak -S
Digitally signed by Kimberlee R. Trzeciak -S
Date: 2022.06.23 11:54:16 -04'00'

Kimberlee Trzeciak
Associate Commissioner for
Legislative Affairs

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

Questions for the Record
House Committee on Oversight and Reform
Subcommittee on Economic and Consumer Policy Hearing
June 23, 2021
"A Crisis Continues: Youth Vaping in America"

Questions from Chairman Raja Krishnamoorthi

1. **During the hearing, you stated that the Food and Drug Administration (FDA) is prioritizing review of five premarket tobacco product applications (PMTAs) of the companies with the highest market share. Please identify all companies being prioritized for review.**

FDA received thousands of submissions representing more than 6.5 million products by the court-ordered deadline of September 9, 2020. FDA dedicated a portion of its resources to prioritizing the review of products that account for the vast majority of the current market.

FDA continues to work expeditiously to complete review of all remaining pending applications, including applications from companies whose products have the highest market share. We are issuing decisions on a rolling basis. Please visit FDA's Tobacco Product Applications Metrics & Reporting webpage for the latest updates on our application reviews.[1]

FDA cannot comment on the status of pending applications from specific companies. We note that according to Euromonitor International, the five brands with the overall highest market share in 2020 were JUUL, Vuse, NJOY, myBlu, and LOGIC.

2. **During the hearing, you testified that you were not familiar with the Tobacco Products Scientific Advisory Committee (TPSAC). Since the hearing, I assume you have familiarized yourself with TPSAC, so will you now commit to referring JUUL's PMTA to TPSAC for review?**

The TPSAC advises the Secretary or designee in discharging responsibilities as they relate to the regulation of tobacco products (see Sec. 917(c) of the FD&C Act). The Committee reviews and evaluates safety, dependence, and health issues relating to tobacco products and provides appropriate advice, information and recommendations to the Secretary or designee.

TPSAC may provide recommendations to the Secretary regarding some regulations to be promulgated under the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), such as manufacturing practice requirements under Section 906, and may review applications for new tobacco products.[2] The Committee may consider and provide recommendations on any other matter as provided in the Tobacco Control Act.

[1] https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/tobacco-product-applications-metrics-reporting
[2] Section 910(b)(2)

The Committee has been a valuable asset to FDA, similar to other Advisory Committees. While Section 911(f) provides that FDA shall refer modified risk tobacco product applications (MRTPAs) to TPSAC for its recommendation on such applications, there is no such statutory requirement to refer a PMTA to TPSAC. The Committee has not been consulted on PMTAs before the Agency thus far.

FDA has not authorized any JUUL tobacco products for marketing at this time and cannot comment on a pending application.

3. What is FDA's formula for weighing the benefits against the harms of a PMTA— how many adult smokers would have to quit tobacco to justify the risk of addicting one non-using youth to nicotine through use of the product?

Under the statute, FDA's finding that permitting a product to be marketed would be appropriate for the protection of the public health (APPH) must be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account:

A. the increased or decreased likelihood that existing users of tobacco products will stop using such products; and

B. the increased or decreased likelihood that those who do not use tobacco products will start using such products.[3]

Under section 910(b)(1)(A) of the FD&C Act, FDA considers the health risks of a new tobacco product and whether the new tobacco product presents more or less risk than other tobacco products. In accordance with section 910(c)(5) of the FD&C Act, FDA will base its determination of whether the marketing of a product would be APPH on well-controlled investigations, where appropriate, and other valid scientific evidence that it finds sufficient to evaluate the product, which could include literature reviews and nonclinical studies.

FDA intends to consider the marketing of a new tobacco product to be APPH where a PMTA contains sufficient valid scientific evidence to demonstrate that the potential risks and benefits of the marketing of the new tobacco product would likely have a net positive effect on the health of the population as a whole, which includes youth, young adults, and other vulnerable populations.[4]

FDA evaluates the risks and potential benefits of permitting the marketing of a new tobacco product on a case-by-case basis depending on the available information pertaining to the specific tobacco product that is the subject of the application. FDA considers the relevant available evidence, as well as the strengths and limitations of the information, in the review of a PMTA to determine if permitting the marketing of the new product would be APPH.

---

[3] Section 910(c)(4)

[4] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems Guidance for Industry (June 2019) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/premarket-tobacco-product-applications-electronic-nicotine-delivery-systems-ends

ENDS product flavors are an important consideration in ascertaining the health risks of the products because of a flavor's potential impact on appeal to youth and young adults, consumer perceptions, and product toxicity. FDA considers consumer perceptions of product appeal and use intentions among current ENDS users, other tobacco product users and nonusers, based on labeling and actual use of flavors, as well as product design. FDA also considers information examining adult appeal of such flavors in their decisions to initiate use, cease use of more harmful products, or engage in dual use.

4. **Section 910(c)(4)(A) of the Food, Drug, and Cosmetic Act requires FDA to take into account "the increased or decreased likelihood that existing users of tobacco products will stop using such products." Confirm that, for purposes of FDA's PMTA analysis:**

    a. **"such products" means all tobacco products,**
    b. **a combustible cigarette smoker who began smoking fewer cigarettes did not "stop using such products,"**
    c. **a combustible cigarette smoker who now uses both cigarettes and e- cigarettes did not "stop using such products," and**
    d. **a combustible cigarette smoker who stopped smoking cigarettes and now exclusively uses e-cigarettes did not "stop using such products."**

As part of FDA's consideration under 910(c)(4) of the FD&C Act of the risks and benefits of permitting the marketing of the new tobacco product to the population as a whole, including users and nonusers of tobacco products, FDA reviews the health risks associated with changes in tobacco product use behavior (e.g., initiation of tobacco use with the new product, completely switching to the new product, dual use of the new product in conjunction with one or more other tobacco products, cessation of all tobacco use) that are likely to occur with the marketing of the new tobacco product. To inform our review of these health risks, we recommend an applicant compare the health risks of its product to both products within the same category and subcategory, as well as products in different categories as appropriate. As likely users of a new tobacco product will vary according to the type of product, and product use patterns vary across different populations, the appropriate comparison product(s) may vary. This comparative health risk data is an important part of the evaluation of the health effects of product switching.[5]

In conducting PMTA reviews, FDA considers all required statutory criteria, including the risks and benefits to the population as a whole. This includes users and nonusers of tobacco products, taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products. To help understand the impact a product may have on existing users, FDA considers, among other things, the likelihood of cessation of all tobacco use, poly/dual use of the new product in conjunction with one or more other tobacco products, and completely switching to the new product. For example, ongoing reviews of ENDS products, including e-cigarettes, have considered studies regarding whether permitting the marketing of the ENDS product under review could facilitate cessation by those who may have otherwise quit

[5] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems Guidance for Industry (June 2019) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/premarket-tobacco-product-applications-electronic-nicotine-delivery-systems-ends

using all tobacco products (i.e., current tobacco users will adopt the authorized ENDS product and then switch to an FDA-approved cessation medication, or current tobacco users who may otherwise quit using all tobacco products will instead use the authorized ENDS product). Additionally, FDA has considered whether permitting the marketing of the product could facilitate complete switching (e.g., smokers completely switching to the authorized ENDS product) or dual or poly use of tobacco products, including the authorized ENDS product.

5. **As FDA found in its July 20, 2020, warning letter, sales of Puff Bar products are illegal because they were not on the market as of the deeming date. Even after your warning letter, sales of these products continued. One reason is because multiple companies are selling Puff Bar products. In fact, two companies even submitted PMTAs for Puff Bar products: DS Technology Licensing and Al Khalifa Group LLC.**
    a. **As you consider their PMTA applications, will you commit to determining:**
        i. **the ownership structure of each organization,**
        ii. **the manufacturer of each product, and**
        iii. **the individuals involved with importing, distributing, and marketing the products?**

FDA cannot comment on specific pending applications nor any ongoing investigations. Generally, in a PMTA, the burden of showing that the marketing of a product is APPH is on the applicant. The PMTA must include all information that is required by section 910(b)(1) of the FD&C Act:

A) full reports of all information, published or known to, or which should reasonably be known to, the applicant, concerning investigations which have been made to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products;

B) a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product;

C) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of, such tobacco product;

D) an identifying reference to any tobacco product standard under section 907 which would be applicable to any aspect of such tobacco product, and either adequate information to show that such aspect of such tobacco product fully meets such tobacco product standard or adequate information to justify any deviation from such standard;

E) such samples of such tobacco product and of components thereof as the Secretary may reasonably require;

F) specimens of the labeling proposed to be used for such tobacco product; and

G) such other information relevant to the subject matter of the application as the Secretary may require.

FDA recommends that applicants provide a listing of all manufacturing, packaging and control sites for the product, including the facility names and addresses, the Facility Establishment Identifier number(s) (if available), and a contact name and telephone number at each facility.[6]

Note that in addition to the premarket application process, FDA may request information regarding ownership, importing, marketing and distribution of a tobacco product through our compliance and enforcement efforts. FDA has been concerned about individual disposable flavored ENDS cartridges such as Puff Bar since 2019. For example, FDA issued a letter to Eliquidstop, LLC, an importer of Puff Pods, individual disposable flavored ENDS cartridges resembling the Puff Bar brand, in June 2019 that requested information about the marketing and sale of their tobacco product, and in 2020, as part of a broader ongoing joint operation with Customs and Border Protection, we seized shipments of disposable flavored e-cigarette cartridges resembling Puff Bar brand from China.

b. Once you determine the people responsible for illegal sales of Puff Bar, will you commit to using all tools available to hold them accountable, including not only civil money penalties, but also the full extent of your authority to pursue criminal prosecutions?

FDA issued a warning letter to Cool Clouds Distribution Inc., d/b/a Puff Bar in July 2020. The warning letter cited violations of the law including selling or distributing unauthorized tobacco products that were first introduced or modified after Aug. 8, 2016—the effective date of the deeming rule that extended FDA's authority to all tobacco products—and marketing their products as modified risk tobacco products without an FDA order in effect that permits such marketing. FDA's investigation into Puff Bar is ongoing and we continue to assess our options under the law.

In addition to the warning letter, FDA worked with U.S. Customs and Border Protection officers to seize 42 separate shipments of ENDS products containing more than 33,000 units imported into the U.S. from China. The shipments included individual disposable flavored ENDS cartridges resembling the Puff Bar brand, including Puff XXL and Puff Flow.

6. During the hearing, you stated that menthol makes e-cigarettes more addictive. The same is true about similar cooling agents used in e-cigarettes such as WS-3, WS-5, and WS-23, correct?

Menthol enhances nicotine addiction through a combination of its flavor, sensory effects (which include its ability to produce a cooling sensation when inhaled), and its interaction with nicotine in the brain. While synthetic cooling agents, such as WS-3, WS-5, and WS-23, elicit cooling sensations similar to menthol when inhaled, they do not produce a minty taste and odor[7], and their effect on nicotine in the brain has not been evaluated. Therefore, given the limited information available, the extent to which synthetic cooling agents make e-cigarettes more addictive is currently unknown.

---

[6] https://www.fda.gov/media/127853/download

[7] Johnson, S., Tian, M., Sheldon, G., & Dowd, E. (2018). Trigeminal Receptor Study of High-Intensity Cooling Agents. J Agric Food Chem, 66(10), 2319-2323. doi:10.1021/acs.jafc.6b04838

7. **Studies indicate that new chemical compounds can form in e-liquid after mixing constituents and during storage and can have unexpected toxicological effects.[8] Do you agree that during FDA's consideration of PMTAs, FDA should base any safety and toxicity determinations on a review of the finished product that is the subject of a PMTA? Do you agree that it would be inappropriate and unreasonable for FDA to base safety and toxicity determinations on a review of just the individual ingredients, as opposed to a review of the finished products that are the subject of PMTAs?**

8. **Do you agree that it would be inappropriate and unreasonable for FDA to only review the safety or toxicity of individual ingredients, without analyzing how all ingredients act in concert when combined?**

The toxicity evaluation of a tobacco product that is the subject of a PMTA is not limited to tobacco product ingredients. Rather, the toxicity evaluation of a PMTA product is a comprehensive, multi-disciplinary approach that considers several factors, including:

- The product design (e.g., heating source), composition (e.g., ingredients, structural materials) and container closure system of the tobacco product and potential effects of these components on the formation of chemical constituents;
- Any leachables or extractables that may be present in the tobacco product under the expected conditions of product storage and shelf-life and/or use;
- HPHC and other toxicant content of the tobacco products, which for ENDS aerosol depends on several factors such as e-liquid composition, device design (e.g., device power, voltage, and operating temperatures), thermal degradation products generated during use, and transfer efficiency of ingredients or toxicants to aerosol;
- Toxicological profiles (e.g., genotoxicity, cytotoxicity, respiratory and cardiovascular toxicity) of the tobacco product, including considerations regarding additive or synergistic effects of individual tobacco product constituents;
- Reported biomarkers of exposure from product use;
- Exposure and risk assessments submitted by applicants; and
- Various product use scenarios (e.g., intense and non-intense product use, dual use).

From a clinical perspective, FDA evaluates the individual health effects of ENDS products by reviewing any adverse events reported after product use in clinical trials and/or the health effects reported in the literature. Some clinical studies may provide information that allows evaluation of individual constituents; however, a more complete assessment of the potential health effects of a product requires an evaluation of effects of the product after actual use. An assessment of the potential safety concerns of a product would be influenced not only by the ingredients included in the e-liquid but also the device used in conjunction with the e-liquid and the mode of use.

---

[8] *See* Zimmerman et al., *Formation of Flavorant-Propylene Glycol Adducts with Novel Toxicological Properties in Chemically Unstable E-Cigarette Liquids* (Aug. 19, 2019) (online at https://pubmed.ncbi.nlm.nih.gov/30335174/); Jordt et al., *Chemical Adducts of Reactive Flavor Aldehydes Formed in E-Cigarette Liquids Are Cytotoxic and Inhibit Mitochondrial Function in Respiratory Epithelial Cells* (Dec. 15, 2020) (online at https://pubmed.ncbi.nlm.nih.gov/33320255/)

9. Do you commit to finalizing the ban on menthol combustible cigarettes as soon as possible?

On April 29, 2021, FDA announced it is committing to issue tobacco product standards to significantly reduce disease and death from using combusted tobacco products, the leading cause of preventable death in the United States. FDA is working toward issuing proposed product standards by April 2022 to prohibit menthol as a characterizing flavor in cigarettes and prohibit all flavors (including menthol) in cigars. These actions are among the highest tobacco regulatory priorities for this Administration. We are committed to addressing this important public health and health equity issue using the tools of product regulation granted to FDA under the Tobacco Control Act.

FDA must follow the Administrative Procedure Act and other applicable laws to issue and finalize the rules, which includes publication of the proposed rules in the Federal Register with an opportunity for feedback and comments from the public on our proposals. When the comment period closes, we will review and carefully consider all the comments. FDA cannot prejudge the outcome of the rulemaking. Once all the comments have been reviewed and considered, FDA would then decide whether to issue final product standards, including the effective date for such standards.

For further updates on these product standards, please visit FDA's web page.[9]

Questions from Rep. Mark DeSaulnier

JUUL products are used by 41% of youth vapers, which makes JUUL the most popular brand among youth vapers.

1. Do you agree that a nicotine product used by 41% of youth vapers is hurting the public health?

FDA remains very concerned about the millions of U.S. youth who currently use e-cigarettes; there is much work that still needs to be done to curb youth use. FDA takes very seriously the problem of youth use of e-cigarettes, including those made by JUUL.

We are committed to a comprehensive approach, including compliance and enforcement, public education, and premarket review of new tobacco products, to combat youth use of tobacco products.

FDA has implemented a robust compliance and enforcement program aimed at stopping youth initiation or use of tobacco products. FDA previously issued final guidance explaining our intent to prioritize enforcement against all ENDS products for which the manufacturer has failed to take adequate measures to prevent minors' access, as well as all ENDS products that are targeted

[9] https://www.fda.gov/news-events/press-announcements/fda-proposes-rules-prohibiting-menthol-cigarettes-and-flavored-cigars-prevent-youth-initiation

to minors or likely to promote use of ENDS by minors. Per the guidance, FDA is prioritizing the enforcement of the tobacco premarket review requirements for certain unauthorized flavored e-cigarette products that appeal to youth, including those with fruit, candy, and mint flavors. Specifically, we stated our intent at that time to prioritize enforcement for cartridge-based flavored ENDS products (except for tobacco- or menthol-flavored products), like JUUL. FDA has also opened an investigation of JUUL and has inspected its headquarters and contract manufacturing facilities. FDA issued a warning letter to JUUL in September 2019 regarding the marketing of unauthorized Modified Risk Tobacco Products (MRTPs). At the same time, FDA also sent JUUL a request for documents regarding, among other things, its advertising and marketing practices.

In September 2018, FDA launched "The Real Cost" E-Cigarette Campaign to prevent youth e-cigarette use, and this campaign continues to be a top education priority for FDA. The campaign targets nearly 10.7 million youth aged 12-17 who have ever used e-cigarettes or are open to trying them, and highlights information about the potential risks of e-cigarette use. Since the launch, the campaign has shown positive results for effective reach and engagement. This campaign has reached up to 85 percent of all teenagers nationwide and has generated over 15 billion views from teen exposure to paid media messages and high online engagement. Across social media platforms, FDA has engaged teen audiences with more than 3.9 million likes, over 355,000 shares, and over 90,000 comments. Additionally, on the campaign's social media channels approximately 10 percent of the total comments from teens are asking for help and resources to quit vaping. In an ongoing collaboration with the National Cancer Institute (NCI), FDA and NCI developed vaping cessation content for teens on the *Teen.SmokeFree.gov* website. Since the web content launched in July 2019, there have been over 2 million page views with visitors spending an average of 4 minutes per page to learn how to quit vaping, manage nicotine withdrawal and acquire tips for managing stress and anxiety.

Ensuring new tobacco products undergo a robust premarket evaluation by FDA is also a critical part of our mission to protect the public health, and that of youth in particular. While no tobacco product is safe, the review process under the PMTA pathway ensures that the marketing of the product is APPH, taking into account the risks and benefits to the population as a whole. Under a federal court order, manufacturers of deemed new tobacco products, including e-cigarettes, that were on the market as of August 8, 2016, were required to submit premarket applications to FDA by September 9, 2020. FDA received thousands of submissions representing more than 6.5 million products by the deadline. It is public information that FDA received PMTAs for JUUL products. At this time, FDA has not authorized any JUUL tobacco products for marketing.

Section 910(c)(2)(A) of the Food, Drug and Cosmetic Act (FD&C Act) requires that FDA deny a PMTA where it finds "there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health." This includes, on a product-by-product basis, consideration of the risks and benefits to the population as a whole, including users and non-users of the tobacco product, and taking into account 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.

Prevention of initiation and assessment of a new product's likely impact on addiction, especially among youth, is important in determining whether permitting the marketing of a new tobacco product would be APPH. Issues related to the manufacturing and marketing of ENDS products, including e-cigarettes, from the use of flavors and nicotine salts to the levels of nicotine in the finished product, and the manner in which the product is marketed and sold, are all factors FDA considers as part of our review of marketing applications for these products.

FDA has made significant progress in reviewing premarket applications over the last year. As of September 2021, we have completed acceptance review for all applications submitted by the September 9, 2020 court-ordered deadline. As of October 8, 2021, we have completed filing review for about 98 percent of applications submitted via the PMTA pathway by the September 9, 2020, deadline. On August 26, 2021, FDA announced that the Agency had issued Marketing Denial Orders (MDO) for about 55,000 flavored ENDS products because the applications lacked sufficient evidence that they have a benefit to adult smokers sufficient to overcome the public health threat posed by the well-documented, alarming levels of youth use of such products. We continue to take action on a rolling basis. As of October 20, FDA has issued a total of 343 MDOs for over 1.2 million flavored ENDS products. FDA will continue to review other premarket tobacco applications for non-tobacco flavored ENDS to determine whether there is sufficient product-specific scientific evidence of a benefit to adult smokers to overcome the risk posed to youth.

For further updates on marketing orders, please visit FDA's web page.[10]

In 1954, an article published in the British Medical Journal confirmed the link between smoking and lung cancer. Despite some progress at the federal, state, and local levels on tobacco regulation in the following decades, it was not until 2009 that federal law granted FDA regulatory authority over tobacco products. While the tobacco industry misled the American public into believing that tobacco products were safe, the U.S. Surgeon General found that 20 million Americans died from smoking between 1964 and 2014. Given all the deaths caused by tobacco products despite the knowledge that they were harmful, there was clearly a missed opportunity to enact regulations earlier and reduce the public health burden of tobacco. We cannot let that happen again with e-cigarettes.

2. Do you agree that allowing youth-preferred products to remain on the market could constitute a similar missed opportunity?

Protecting our nation's youth from the dangers of tobacco products is among the Agency's most important responsibilities, and we are taking concerted steps to make sure tobacco products are not being marketed or sold to kids.

It is important to remember that to be legally marketed, new tobacco products must generally receive premarket authorization from the Agency. The products undergo FDA scientific review and need to meet the applicable statutory standard for marketing. For ENDS products going through the PMTA pathway, the Agency would have to find that the marketing of the product is APPH in order for the product to receive marketing authorization. Prevention of initiation,

[10] https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/tobacco-products-marketing-orders

particularly among youth, is an important part of determining whether permitting the marketing of a new tobacco product would be APPH. As of October 20, FDA has issued a total of 343 MDOs for over 1.2 million ENDS products, all of which are flavored ENDS products.

September 9, 2021, marked one year since the court-ordered deadline for the submission of premarket applications for new deemed tobacco products on the market as of August 8, 2016. As of November 8, 2021, FDA has completed filing review for about 99 percent of applications submitted via the PMTA pathway by the September 9, 2020, deadline. Many of the accepted applications ultimately received a Refuse-To-File (RTF) letter at the filing stage of the review process because the applications did not include required information. On August 26, 2021, FDA announced the issuance of MDOs for about 55,000 flavored ENDS products because the applications lacked sufficient evidence that they have a benefit to adult smokers sufficient to overcome the public health threat posed by the well-documented, alarming levels of youth use of such products. We continue to take action on a rolling basis. As of October 20, 2021, FDA has issued a total of 343 MDOs for over 1.2 million ENDS products, all of which are flavored ENDS products.

In light of the public health threat posed by the well-documented, alarming levels of youth use of flavored ENDS, the Agency reviewed each flavored ENDS application to determine whether it provided sufficient product-specific scientific evidence to demonstrate enough of a benefit to adult smokers to overcome the risk posed to youth.

The Agency will continue to review other PMTAs for non-tobacco flavored ENDS to determine whether there is sufficient product-specific scientific evidence of a benefit to adult smokers to overcome the risk posed to youth.

FDA continues to review PMTAs that were submitted by the September 9, 2020, deadline. FDA is committed to its responsibility to protect public health, follow the law, and carefully review the science presented in each application when determining if a product meets the standard for marketing.

3. If yes, how does this not subject future generations to further health risks and premature death?

As noted above, FDA remains committed to combatting youth use of all tobacco products and we remain focused on our regulatory oversight of e-cigarettes and other ENDS. Ensuring that new tobacco products undergo a robust premarket evaluation by FDA is a critical part of our mission to protect the public health, particularly youth, and to reduce tobacco-related disease and death.

Additionally, while FDA's review of premarket applications is ongoing, we remain vigilant in overseeing the market and continue to prioritize the use of our enforcement resources to curb the unlawful marketing of tobacco products. FDA prioritizes enforcement against products where the manufacturer fails to take adequate measures to prevent youth access or any product that is targeted to underaged persons or likely to promote use of ENDS by underage persons. FDA will

also continue to closely monitor the rates of all e-cigarettes' use among youth and, if needed, will take additional steps to address youth use of those products.

Questions from Rep. Byron Donalds

1. **FDA has jurisdiction over and regulates products containing nicotine derived from tobacco. A nascent category using synthetic nicotine in its products instead of nicotine from tobacco is emerging in the U.S. This potential "loophole" regarding the source of the nicotine could allow these products to potentially circumvent regulation. The concern is that this new product category, just like the vapor category 10 years ago, could lead to unregulated and underage use very quickly if the FDA does not assert jurisdiction over these products quickly.**

   a. **Does the FDA have concerns that there are products being sold in the United States containing synthetic nicotine and that synthetic nicotine is not currently regulated by the FDA's Center for Tobacco Products?**

   b. **Is the FDA aware that these products are largely being made in China with no oversight by the FDA in terms of ingredients or manufacturing processes?**

   c. **Is FDA working with Customs and Border Patrol [sic] to at least have importers of these products attest to where the synthetic nicotine is manufactured? If not, can you commit to doing that?**

   d. **We need to avoid manufacturers and importers claiming "synthetic nicotine" loophole when really, they are importing tobacco derived nicotine products. How will the FDA know if the nicotine in imported products is synthetic rather than from tobacco, which would make the products subject to FDA jurisdiction?**

   e. **Does the FDA have a plan to assert regulatory jurisdiction over synthetic nicotine products? What is that plan?**

The Federal Food, Drug, and Cosmetic (FD&C) Act defines tobacco products as products "made or derived from tobacco," including any component, part or accessory of a tobacco product. FDA is testing ENDS products claiming to contain only synthetic nicotine. If we find that such a product actually contains any tobacco-derived nicotine FDA would have jurisdiction under its tobacco authorities and could pursue enforcement if the product is in violation of those authorities.

However, if we find that a disposable ENDS product, for example, contains only synthetic nicotine, enforcement becomes more complicated. FDA is concerned that the number of companies purporting to market products containing exclusively synthetic nicotine appears to be rapidly increasing.

If Congress intends for recreational synthetic nicotine products to be regulated comparably to recreational tobacco-derived nicotine products, Congress may wish to amend the FD&C Act so that the definition of a tobacco product includes products containing nicotine from any source. If Congress wishes to make this change, the Agency stands ready to provide technical assistance.

We are exploring how to best address the growing number of companies purporting to market products containing synthetic nicotine. The Agency is reviewing all of our options to determine whether these products can be regulated under our existing authorities.

We take this issue very seriously, and we are engaging in discussions within FDA, and with HHS to find an appropriate, effective, and sustainable solution.

For further updates, please visit FDA's synthetic nicotine web page.[11]

2. The FDA has made multiple public statements, even has a public website, dedicated to distinguishing between the harms associated with nicotine, which is addictive, and smoke, which is the most harmful way to consume nicotine. The regulators and scientists know that the harm from tobacco products largely comes from cigarettes – and the smoke inhaled after it is lit on fire. But this is not well known by the American public or even their doctors.

A Rutgers study,[12] published last year in the *Journal of General Internal Medicine,* found that 80% of physicians mistakenly believe that nicotine itself leads to smoking related diseases. If physicians have misperceptions around the harms of nicotine vs. smoke, then how can we expect adult cigarette consumers to know the benefits of switching from smoking to any non-combustible nicotine products.

Patients, smokers specifically, deserve better information. They deserve to know what the FDA knows. That not all nicotine consumption is created equal.

Misperceptions surrounding nicotine must be addressed if we are to reduce tobacco harm in America.

a. With better education from the FDA on the continuum of risk surrounding nicotine and on awareness about FDA's reduced risk authorizations, physicians would better serve their patients. What are your plans for educating physicians about FDA's modified risk product approvals and more broadly about the misperceptions around nicotine v. tobacco smoke?

b. How will the Agency educate adult smokers about harm reduction and encourage them to move away from cigarettes to FDA-authorized non-combustible products?

[11] https://www.fda.gov/tobacco-products/ctp-newsroom/requirements-products-made-non-tobacco-nicotine-take-effect-april-14?utm_source=CTPTwitter&utm_medium=social&utm_campaign=ctp-regulation&linkId=160775931
[12] https://www.rutgers.edu/news/rutgers-led-national-survey-uncovers-doctors-misconceptions-about-nicotine-risks

c. How can smokers know what products have received PMTAs, or modified risk claims, would be worth trying as an alternative to cigarettes? It seems like you could use electronic data to reach them in a targeted way just like you are using electronic data to reach at risk youth with the Real Cost campaign. Will you commit to running an information campaign specifically for them?

FDA conducts robust outreach to the public, to smokers and nonsmokers, and to other targeted groups like physicians.

Tobacco products that FDA has authorized as MRTPs have been determined through FDA's careful review of scientific evidence to pose reduced risk of harm from a tobacco-related disease or reduced exposure to a substance in a tobacco product or its smoke for those who use them. FDA believes that it is important to appropriately communicate information to tobacco product users and healthcare providers about the authorization of any tobacco product that meets the rigorous public health standards defined by the Tobacco Control Act under the PMTA or the MRTPA pathways, while minimizing exposure of such information to youth or other unintended audiences.

FDA leverages a variety of communication channels to share information about newly authorized tobacco products or modified risk orders, including press releases, emails to listservs, social media posts (Facebook, Twitter, and LinkedIn) and updates to FDA's website. In response to stakeholders' requests for updates on MRTP applications under review, FDA developed a specific MRTP Update Email list dedicated solely to notifying subscribers about publicly available information on MRTP applications. The list has roughly 12,000 subscribers.

FDA also leverages its Strategic Outreach team and Stakeholder Relations Office (SRO) to personally reach out and communicate key FDA announcements, such as PMTA or MRTPA authorizations to state, local, and professional organizations. These outreach efforts include regular and robust teleconferences and email communication with various public health and professional health/medical organizations at the national, state, and local level, including many who have direct lines of communication with physicians. For example, several physician- and healthcare provider-affiliated organizations that FDA reaches out to include:

- American Medical Association
- American Academy of Family Physicians
- American Academy of Physician Assistants
- American College of Chest Physicians
- American College of Physicians
- American College of Preventive Medicine
- American Academy of Pediatrics
- Association of American Indian Physicians
- National Medical Association
- National Association of School Nurses
- American Nurses Association
- Association of Public Health Nurses
- Association of State and Territorial Health Officials

As of June 2021, FDA has authorized two sets of MRTP applications. Both authorizations were widely communicated using various communication channels, including press releases:

- In October 2019, the first-ever MRTP authorizations were announced via a press release and related FDA web updates, together which received more than 13,000 unique pageviews. Roughly 137 million people were reached via online and social media mentions, and the authorizations were covered extensively by top-tier outlets, including The Associated Press, Reuters, CNBC, NPR, *Bloomberg*, and *The Hill*.
- In July 2020, a set of four products received "exposure modification" orders, another type of MRTP authorization, which were announced via a press release and related FDA web updates, together which received more than 28,000 unique page views. Roughly 15 million people were reached via online and social media mentions, and the authorization was covered extensively by top-tier and health media outlets, including Reuters, *Bloomberg*, and MedPage Today.

In addition, FDA is currently developing additional educational materials for adult smokers and public health stakeholders that specifically address misperceptions about nicotine. The Agency is also conducting research to better understand public perceptions of nicotine. The findings will better enable the Agency to provide, in future messaging, accurate and understandable information about nicotine delivered via various types of tobacco products, including combustible, smokeless, and ENDS products. FDA intends to present such information in a way that strives to correct any public misperceptions about nicotine while minimizing the risk of reinforcing misunderstandings or introducing new confusion. Secondary objectives of this research include identifying specific populations that could benefit from understanding that the level of risk from inhaling nicotine depends on the type of nicotine products being used.

Finally, FDA has developed plain-language materials that aim to help addicted adult smokers better understand the risks associated with different types of tobacco products and how a particular MRTP may be used to achieve the expected reduction in harm and/or exposure. Examples of these materials include:

- How are Non-Combusted Cigarettes, Sometimes Called Heat-Not-Burn Products, Different from E-Cigarettes and Cigarettes?[13]
- FDA Authorizes Modified Risk Tobacco Products[14]

3. It is well known that cigarettes and other tobacco products are sold underground almost everywhere in the world – evading taxes and regulations and profiting criminal networks. These products are often made in unregulated facilities and consumers buy them without being age verified and have no way to verify the ingredients.

---

[13] *https://web.archive.org/web/20201220045254/https:/www.fda.gov/tobacco-products/products-ingredients-components/how-are-non-combusted-cigarettes-sometimes-called-heat-not-burn-products-different-e-cigarettes-and*

[14] *https://www.fda.gov/tobacco-products/advertising-and-promotion/fda-authorizes-modified-risk-tobacco-products*

In the Unites States, a joint task force of five federal agencies – HHS, DOJ, DHS, State, and Treasury – published a report under the Obama Administration,[15] titled *"The Global Illicit Trade in Tobacco: A Threat To National Security."* The report explains that *"for decades, cigarette smuggling has been a sizeable and dependable revenue stream for organized crime. Estimates for the annual state and local U.S. tax loss caused by the illicit trade in tobacco products range from $2.95 to $6.92 billion."* This means about 8-10% of cigarettes consumed in the U.S. today are "illicit" – sold outside of the stream of legal, regulated, tax-paid commerce. When the Senate was passing the 2009 bill giving the FDA regulatory authority over tobacco products, Senator Durbin explained why regulation, not product bans, was preferable to avoid a spike in the illicit market:

> ***"People often say to me: Well, why don't we just ban this product? If I thought that would end smoking in America, I might consider it. But we know better. With 43 million Americans currently addicted, they are not going to quit cold turkey tomorrow. A black market would emerge, and then the next thing you know the underground economy would be sustaining tobacco. That would not be the result we are looking for." Senator Dick Durbin, Extension of Morning Business, 111 ` Cong., 155 CONG. REC. 56405, S6406 (2009)[16]***

The FDA has publicly announced its intention to ban whole categories of legal products – specifically menthol cigarettes, which make up 1/3 of the U.S. cigarette market today. Similarly, if the FDA were to no longer allow the sale of legally manufactured, regulated flavored vapor products or flavored cigars, adult consumers who have been buying these products for years will be left without a lawful market location to purchase their products. The illicit market will undoubtedly grow to meet consumer demand and criminal networks will benefit. State and federal tax collections will be reduced, and consumers will turn to underground sources for their tobacco products. The products won't be made in regulated facilities, illicit imports from countries like China will probably skyrocket, and the sellers sure are not going to check I.D.s to make sure the purchaser is 21 or older.

a. **Prohibition did not work for alcohol. Many currently argue that prohibition is not working for marijuana. Why does the agency believe that prohibition will work now for flavored vapor or for menthol cigarettes?**

b. **If you move forward with prohibitionary policies such as no flavored tobacco products, what percentage illicit product market expansion do you estimate will immediately occur?**

c. **What is the human cost associated with those illicit markets – products breathed into lungs – I'm thinking specifically of the cost paid in the EVALI illness breakout. What other harms does Congress need to anticipate?**

---

[15] https://2009-2017.state.gov/documents/organization/250513.pdf
[16] https://www.congress.gov/111/crec/2009/06/10/CREC-2009-06-10-pt1-PgS6406.pdf

d. Wouldn't it make more sense for the FDA to achieve the intended health benefit of lowering adult smoking rates by spending time and effort getting more reduced harm nicotine products to market and educating smokers about the benefits of switching their nicotine source?

e. During the hearing, Acting Commissioner Woodcock explained her belief that menthol smokers find it harder to quit than non-menthol smokers, but she also explained that the average menthol smoker today smokes fewer total cigarettes than the non-menthol smoker. If menthol cigarettes are banned, isn't it logical that they will turn to non-nicotine cigarettes to meet their needs and that they will therefore begin smoking more cigarettes on average? This does not seem wise.

f. Are you aware that every state has laws on the books making the production, sale, and distribution of illegal tobacco products a crime? I know that FDA and its enforcement staff will not be in my congressional district on the streets enforcing the law when a carton of menthol cigarettes or a U-Haul truck of flavored vape pods is found during a routine traffic stop, but state and local law enforcement will find themselves in these situation [sic]. They can't just look away and ignore the violation of state law. Do you agree that with an increase in illicit market products caused by prohibitionary product bans, state and local law enforcement will need more training and more resources to deal with these incidents properly?

In 2009, the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) banned cigarettes with characterizing flavors, except menthol and tobacco. In April 2021, FDA announced its commitment to pursue a tobacco product standard to prohibit menthol cigarettes and a tobacco product standard to prohibit all characterizing flavors, including menthol, in cigars. FDA plans to issue these proposed product standards by the end of April 2022.

Please note that FDA has not made any announcement regarding prohibiting menthol in ENDS products, including e-cigarettes. Rather, FDA will review and make marketing decisions on ENDS products on a case-by-case basis via the premarket tobacco application process. FDA remains concerned about the presence of flavors in non-combusted products such as e-cigarettes due to their popularity with youth. However, the focus of the proposed product standards is on the products that make the greatest contribution to tobacco-caused disease and death. Given the inherent toxicity of combusted tobacco products, decreasing their appeal will maximize the potential public health benefits of these regulatory actions. With these actions, FDA will help significantly reduce youth initiation, increase the chances of smoking cessation among current smokers, and address health disparities experienced by communities of color, low-income populations, and LGBTQ+ individuals, all of whom are far more likely to use these tobacco products.

FDA's work towards issuing a proposed product standard to prohibit menthol as a characterizing flavor in cigarettes and all characterizing flavors, including menthol, in cigars is based on clear science and evidence establishing the addictiveness and harm of these products.

The Agency has been considering, exploring, and gaining a better understanding about menthol and its effects over the last several years through investing in research, reviewing the literature, and seeking public comment.

Although menthol itself does not increase the toxicity of cigarettes, the presence of menthol in cigarettes leads to more youth initiation, progression to regular smoking, and difficulty quitting. Research has shown links between menthol in cigarettes and the following outcomes:

- *Youth initiation:* Menthol in cigarettes masks the harshness and irritation of tobacco smoke and reduces initial aversive responses to smoking, particularly for young people.
- *Progression to regular smoking:* Menthol increases product appeal and facilitates repeated experimentation and progression to regular smoking, particularly among youth and young adults. Once a user is addicted, menthol makes it harder for existing smokers to quit.
- *Increased addiction/nicotine dependence:* Menthol in cigarettes enhances nicotine addiction through a combination of its flavor and sensory effects, and interaction with nicotine in the brain.
- *Difficulty of quitting:* Menthol in cigarettes contributes to reduced cessation success among smokers; this effect is especially prevalent among Black menthol smokers.

FDA will consider risks posed by a menthol rule, including potential unintended consequences such as illicit trade as we engage in the rulemaking process. FDA cannot prejudge the outcome of the process. First, FDA will publish a product standard as a proposed rule. The public will then have an opportunity to submit comments on the proposed rule. FDA encourages all interested stakeholders to participate in this process. After the comment period closes, we will review and carefully consider all the comments, including any comments that specifically address the issue of potential illicit trade were the Agency to promulgate a final rule. Once all the comments have been reviewed and considered, FDA would then decide whether to finalize the rule, any changes that might be necessary to the proposed rule, and effective dates.

It is important to note that if implemented, FDA's enforcement of any ban on menthol cigarettes and all flavored cigars will only address manufacturers, distributors, wholesalers, importers and retailers. FDA cannot and will not enforce against individual consumer possession or use of menthol cigarettes or any tobacco product. We take very seriously the concerns that have been raised about enforcement against individuals. Moving forward, FDA remains committed to engaging with stakeholders to ensure full understanding of this issue.

FDA remains committed to regulating all tobacco products, including potentially less harmful products like non-combustibles. Any future product standard would contribute to FDA's comprehensive approach to tobacco control, which also encompasses compliance and enforcement, public education, and premarket review of new tobacco products to combat youth use of tobacco products and protect Americans from tobacco-related death and disease.

For further updates on these product standards, please visit FDA's web page.[17]

4. In reaction to the increasing youth vaping numbers, Congress acted quickly to determine what the biggest sourcing problem was – we knew underage individuals couldn't legally buy the products so one of three things had to be happening:

1) Friends who were 18 and up might be purchasing and then passing the products along

2) Fake IDs could be used to purchase by the 17 or under individual at retail; or

3) Products could be coming via mail to underage individuals who enter parents or friend's ages / verification data to complete the order.

Looking at these possibilities found the following:

The Population Assessment of Tobacco and Health (PATH) Study,[18] a joint project of the National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA), data told us that "social sourcing" accounted for almost 75% of products that were getting into the hands of minors. These sources included giving someone old enough money to buy for them, buying them from someone else that already had them, asking someone for them, or being offered them without payment. This data drove Congress to act quickly to dry up these social sources – if friends ages 18, 19, and 20 could no longer buy for minors 17 and under, we believed great progress could quickly be made. The latest available data says we were right. According to the National Youth Tobacco Survey released in October 2020, not only do traditional tobacco products continue to be at historic lows – low single digits, but the data show the vapor use rate among high school students dropped by 1/3 – 8 million less high school vapers in just 3 months after 21 was made law of the land.

Do you acknowledge that FDA had long concluded that age 21 was a good policy idea for combating youth usage? Do you acknowledge that the current data shows that its passage did just that?

In 2020, many factors—ranging from federal legislation raising the minimum age for the sale of tobacco products to 21, to FDA's policy of prioritized enforcement of certain illegally marketed e-cigarettes, to the global COVID-19 pandemic—may have affected tobacco product use rates.

FDA remains committed to taking action using the full scope of our regulatory authority to prevent youth initiation of all tobacco products, ensuring comprehensive regulatory review of all new tobacco products, performing regular monitoring of consumer use, and market analysis to

---

[17] *https://www.fda.gov/news-events/press-announcements/fda-proposes-rules-prohibiting-menthol-cigarettes-and-flavored-cigars-prevent-youth-initiation*

[18] *Wave3 data (2015-16)*

stay aware of current tobacco product information and trends, and providing numerous resources to tobacco product users who wish to quit.

a. My understanding that, in compliance cases involving minors, the FDA compliance check data improved *significantly* between data published in FY2019, 2020, and 2021. Is this correct?

While FDA provides the results of tobacco retailer compliance check inspections for public access, the program and resulting data are not designed for the purpose of reporting on the overall compliance of tobacco product retailers. The states and jurisdictions each have unique situations that are reflected in their retail inspection contracts. Many factors and variables go into determining which tobacco retailers are inspected in a given time period. For example, a tobacco retailer with a recent history of violations is prioritized for reinspection. Additionally, tobacco retailer inspections were halted entirely from March through September 2020 due to the COVID-19 pandemic and resumed as public health considerations allowed. Even though inspections resumed in October 2020, they remain at a reduced level and have not yet completely returned to the pre-pandemic level of inspectional activity. It is therefore even more difficult to use FDA retail inspection data to assess relative violation rates over the timeframe indicated.

b. Additionally, are all state compliance rates recorded by SAMHSA[19] currently at or below the violation percentages required receive federal matching funds under the Synar Amendment – with the guidance[20] now being updated to age 21?

The Synar program is administered by the Substance Abuse and Mental Health Services Administration (SAMHSA). SAMHSA's Synar program and FDA's retail inspection program are separate, unique programs, though there may be states that utilize some of their FDA inspection data toward fulfilling their Synar reporting requirements. FDA and SAMHSA developed a document[21] that provides information about both programs and can be found on both agencies' websites. SAMHSA would be the appropriate source to provide Synar Program and related Substance Abuse Prevention and Treatment Block Grant funding information.

c. On the issue of mail access, Congress didn't have as much information to work with. But, we knew we had made traditional products non-mailable by the U.S. Postal Service a decade earlier with the passage of the PACT Act, so it made sense to extend this same non-mailability to nicotine vapor products. Starting this year, all vapor products will need to be purchased in person at a brick and mortar location with a valid I.D. Do you agree that this is good policy and that this is also likely to decrease the availability of youth access via the mail system if it was occurring?

FDA's work to protect youth from tobacco products is comprehensive and includes compliance and enforcement, premarket review, public education, and regulatory science research. It is also part of a broader federal effort that includes multiple agencies such as the Federal Trade

[19] https://www.samhsa.gov/synar
[20] https://www.samhsa.gov/sites/default/files/synar-guidance-tobacco-21.pdf
[21] https://www.fda.gov/tobacco-products/retail-sales-tobacco-products/fdas-tobacco-retail-compliance-inspection-contracts-and-samhsas-synar-program

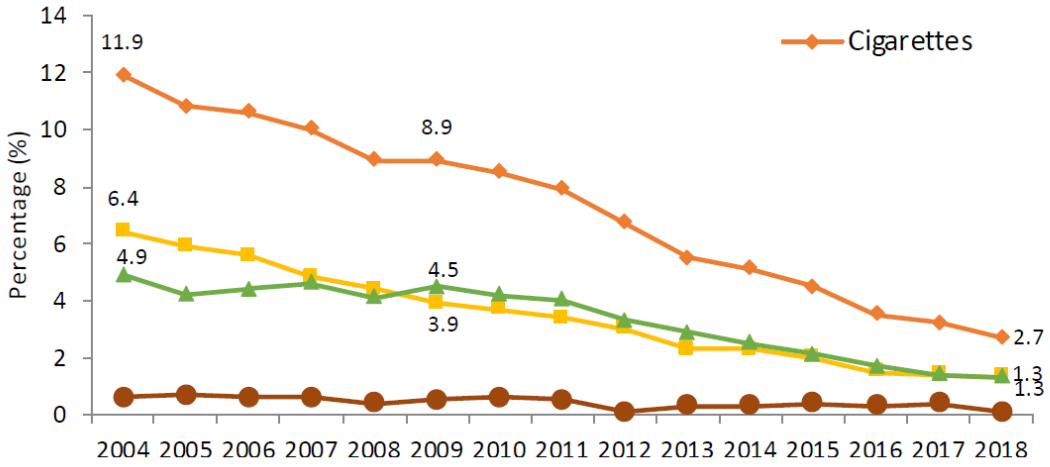
Commission, U.S. Customs and Border Protection, and the U.S. Postal Service. The Prevent All Cigarette Trafficking (PACT) Act and its recent expansion in scope to include ENDS products is part of that effort. Working in concert, all of these efforts aim to reduce youth access to and use of tobacco products.

5. **In recent news we've read a lot about a UC Davis Study published in Preventative Medicine[22] that gave us great news about daily smoking rates in the group of adults that fall between the age that used to be legal to smoke – 18 – and the age that is now legal to smoke – 21. According to the UC Davis News release:[23]**

> **"The great news is that the prevalence of 'daily' smoking among 18-20-year-olds went from 2.2% in 2016 to nearly zero in 2019," said Stewart, professor with UC Davis Department of Public Health Sciences, Division of Biostatistics.**

Similarly, all-time record LOWS were recorded in the under 18 group in the last set of national data from the National Youth Tobacco Survey – an average of less than 2%.

Past 30-day Cigarette Smoking Overall, Menthol, Nonmenthol (12 to 17 year-olds)



a. I want to congratulate the FDA and the Center for Tobacco Products specifically for the terrific progress that has been made on the rates of young adult as well as youth smoking. This success is what we are now attempting to achieve in the area of vaping.

---

[22] https://reader.elsevier.com/reader/sd/pii/S0091743521001377?token=D0BAD37CBA67CDA787336739CECD8469D71D17A2CB3D0B98BA78585DE972A86B1754A7CA2B370E1B7A53C29865D6710C&originRegion=us-east-1&originCreation=20210621224553

[23] https://health.ucdavis.edu/health-news/newsroom/is-raising-the-sales-age-of-tobacco-reducing-youth-smoking/2021/04#:%7E:text=%E2%80%9CThe%20great%20news%20is%20that,Health%20Sciences%2C%20Division%20of%20Biostatistics

When it comes to the under 18 group, in the 1990s the problem seemed insurmountable – about 1/3 of high schoolers were smoking regularly in 1995. Now, the number is the lowest on record – an average of less than 2% nationwide.

I would ask the FDA to comment publicly on that success and to explain how the same principles can be used in the current vaping situation at a much quicker rate – now that we have the benefits of Age 21, technology that can target youth vapers with the "Real Cost" campaign, and improvements to age verification technology being made at retail.

Data on youth use of tobacco products from the 2020 NYTS showed that in 2020 youth use of any tobacco product—which may include cigarettes or e-cigarettes—declined by 1.73 million youth compared to 2019. After disturbing increases in youth e-cigarette use in 2018 and 2019, we were encouraged by the overall significant decline reported in 2020. While the 2020 NYTS showed that youth use of any tobacco product—which may include cigarettes or e-cigarettes—declined by 1.73 million fewer youth using any tobacco product in 2020, 3.6 million youth still currently use e-cigarettes.

Since the passage of the Tobacco Control Act in 2009, FDA has taken a comprehensive, multi-pronged approach to protect youth from tobacco products. The Agency's efforts included compliance and enforcement activities, premarket review, and public education, among other activities.

This comprehensive approach to regulating tobacco products expanded in scope to all tobacco products, including ENDS, but excluding accessories of such newly regulated products, when the agency issued the Final "Deeming Rule" in 2016. The Agency is committed to preventing kids from using tobacco products, including ENDS, and has taken a number of actions to help address the epidemic of youth use of ENDS.

Since the beginning of FY2020, as part of the Youth Tobacco Prevention Plan, the Agency has taken actions to stop youth use of, and access to, ENDS products. For example, FDA conducted over 74,000 retail inspections to crack down on the sale of tobacco products, including ENDS products, to underage persons at both brick-and-mortar and online retailers, and issued more than 7,300 warning letters and civil money penalties to retailers for illegally selling tobacco products, including ENDS products to underage persons. FDA also issued over 250 warning letters to online and brick-and-mortar establishments, including 7-Eleven and Shell locations, for selling unauthorized flavored, cartridge-based e-cigarette products. Prior to temporarily halting inspection activities due to the COVID-19 pandemic, and then including the time period from October 2020 – May 2021 when inspections resumed, FDA conducted inspections of over 170 tobacco manufacturing establishments and over 550 vape shops and conducted investigations involving thousands of websites. Additionally, FDA conducts surveillance of websites, social media, and publications that promote and sell regulated tobacco products, including ENDS in the U.S. market, and also conducts investigations of events where free samples of tobacco are distributed and events by the tobacco industry to ensure compliance with the Tobacco Control Act.

The September 9, 2020, premarket submission deadline for certain deemed new tobacco products marked a major milestone for tobacco product regulation and for public health. Through its implementation of the Tobacco Control Act's premarket review requirements for deemed new tobacco products, including for new ENDS, new hookah products, and new pipe tobacco products, FDA is taking steps to transform the marketplace toward one where new tobacco products available for sale will have undergone careful, science-based review and oversight.

From its launch in February 2014 to November 2016, "The Real Cost" campaign, FDA's first public education cigarette prevention effort, prevented up to 587,000 youth ages 11 to 19 from initiating smoking. Over time those prevention efforts will save more than $53 billion in smoking-related costs for youth, their families, and society at large—a cost savings of $180 for every dollar of the nearly $250 million invested.

Leveraging the success of "The Real Cost," FDA began prioritizing prevention efforts to address youth use of e-cigarette products in 2017. Targeting over 10 million teens who have used e-cigarettes or are susceptible to such use, FDA launched "The Real Cost" Youth E-Cigarette Prevention Campaign[24]—a full-scale mass media effort in 2018, urging teens to "know the real cost of vaping" by highlighting the potential addiction and health risks. The campaign has successfully reached and engaged teens, generating over 5 billion views, more than 3.5 million likes, 350,000 shares, and 88,000 comments. More importantly, the latest wave of outcome evaluation results assessing the impact of "The Real Cost" are promising, indicating that 75% of youth are aware and receptive to our ads. Over time, increased exposure to the campaign is expected to increase population-level shifts in youth beliefs about e-cigarettes.

For further NYTS information, please visit FDA's web page.[25]

6. Can a new tobacco product be legally marketed to consumers as harm-reducing or reduced exposure without FDA's authorization?

No. MRTPs are legally defined as tobacco products that are sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products. Before an MRTP can be introduced or delivered for introduction into interstate commerce, an order from FDA under section 911(g) of the FD&C Act must be in effect.

7. Does the FDA consider there to be important differences in how a modified exposure MRTP such as IQOS may be marketed, compared to a product that has not completed the MRTP review process?

Yes. By law, an MRTP means any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco

---

[24] *More information is available at: https://www.fda.gov/tobacco-products/real-cost-campaign.*
[25] *https://www.fda.gov/tobacco-products/youth-and-tobacco/results-annual-national-youth-tobacco-survey*

products.[26] "Sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products" means a tobacco product:

1) where the label, labeling, or advertising of which represents either implicitly or explicitly that:
    a. the tobacco product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products;
    b. the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or
    c. the tobacco product or its smoke does not contain or is free of a substance;
2) that uses the descriptors "light," "mild," "low," or similar descriptors in its label, labeling, or advertising; or
3) for which the tobacco product manufacturer has taken any action directed to consumers through the media or otherwise, other than by means of the tobacco product's label, labeling, or advertising, after June 22, 2009, respecting the product that would be reasonably expected to result in consumers believing that the tobacco product or its smoke may present a lower risk of disease or is less harmful than one or more commercially marketed tobacco products, or presents a reduced exposure to, or does not contain or is free of, a substance or substances.[27]

Before an MRTP can be introduced or delivered for introduction into interstate commerce, an order from FDA under section 911(g) of the FD&C Act must be in effect with respect to the tobacco product.

Under section 301(pp) of the FD&C Act (21 U.S.C. 331(pp)), introduction or delivery for introduction into interstate commerce of a tobacco product in violation of section 911 is a prohibited act. In addition, under section 902(8) of the FD&C Act (21 U.S.C. 387b(8)), a tobacco product is deemed adulterated if it is in violation of section 911 of the FD&C Act, and the introduction or delivery for introduction into interstate commerce of any adulterated tobacco product is also a prohibited act. Section 301(a) of the FD&C Act (21 U.S.C. 331(a)). Violations of the FD&C Act are subject to regulatory and enforcement action by FDA, including, but not limited to, seizure and injunction. In addition, note that if the MRTP is a new tobacco product within the meaning of section 910(a)(1), any applicable premarket review requirements under section 910 of the FD&C Act must also be satisfied.[28]

8. With regard to MRTP reviewed products, does the FDA have an on-going monitoring role or other tools to protect against youth marketing or access? Does this differ from how the FDA monitors or protects against youth marketing or access to products that have not participated in the PMTA or MRTP process?

[26] *Section 911(b)(1)*
[27] *Section 911(b)(2)*
[28] *Section 910(a)(2)(A)*

An MRTP is a tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products. Companies must submit an MRTP application and receive an order from FDA before marketing a product as modified risk. To obtain a risk modification order under section 911(g)(1) of the FD&C Act, an applicant must demonstrate that the tobacco product, as actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. FDA may issue an exposure modification order under section 911(g)(2) when risk reduction has not yet been demonstrated but is reasonably likely based on demonstrated reductions in exposure (e.g., a finding that a reduction in morbidity or mortality among individual users is reasonably likely in subsequent studies; a finding that issuance of an order is expected to benefit the health of the population as a whole). However, obtaining either a risk modification order or exposure modification order alone is not a guarantee that the MRTPs will continue to meet the standards for being marketed as MRTPs. This applies particularly if, despite these measures, there is a significant increase in youth initiation or initiation by non-users. FDA will continue to monitor the marketing of MRTPs and their impact on the population.

Applicants who receive risk modification orders must conduct postmarket surveillance and studies and submit the results of such surveillance and studies to FDA annually.[29] Similarly, applicants who receive an exposure modification order must agree to conduct postmarket surveillance and studies in accordance with a protocol approved by FDA and must submit the results of postmarket surveillance and studies annually.[30] The objective of conducting postmarket studies is to gather and assess information about the product after introduction into the marketplace, including but not limited to: data on real world use of the MRTP in a general population of tobacco users; tobacco-related adverse events; longer-term assessment of exposure and health outcomes, including intermediate clinical outcomes and mortality; and ongoing assessment of consumer perception and tobacco use behavior (e.g., initiation, cessation, frequency of use). Firms that have received MRTP orders have specific requirements outlined in those orders that FDA monitors and assesses. Examples of marketing restrictions and requirements include:

- Reporting serious and unexpected adverse experiences
- Requiring that for any digital sales, firms must establish, maintain, and monitor use of independent age and identity verification service(s) to prevent the sale of products to individuals who are under the federal minimum legal age to purchase tobacco products
- Age restrictions on shared digital properties (e.g., product branded social media accounts or content promoting products on behalf of a firm through another entity's social media accounts)

Note that a new tobacco product within the meaning of section 910(a)(1) must also comply with any applicable premarket review requirements under section 910 of the FD&C Act. New products may not be legally marketed in the United States without a marketing authorization

[29] *Section 911(i)(1).*
[30] *Section 911(g)(2)(C)(ii),(iii).*

from FDA. A "new tobacco product" is any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007, or the modification of a tobacco product where the modified product was commercially marketed in the U.S. after February 15, 2007. There are three pathways to market for new tobacco products: PMTA, Substantial Equivalence (SE), and Request Exemption from Demonstrating Substantial Equivalence (EX).

Tobacco manufacturers are required to establish and maintain records and make reports to FDA for their PMTA market authorizations so that the Agency can determine whether there are grounds for withdrawing or temporarily suspending their PMTA orders.[31]

Postmarket surveillance and studies requirements are outlined within the modified risk order:

- The applicant submits a postmarket surveillance protocol to FDA
- FDA reviews the applicant's proposed protocol and determines whether to approve the protocol
- FDA monitors and reviews data submitted as part of postmarket surveillance.

The FD&C Act limits authorized modified risk order claims to a term specified in the modified risk order. The applicant can renew a modified risk order claim. The applicant can also choose to edit the claim based on new information found during the postmarket surveillance and studies, and seek renewal of the MRTPA, referencing the previous application and noting any changes.

FDA published a draft guidance on MRTP applications, available at https://www.fda.gov/media/83300/download, which, when finalized, will represent the Agency's current thinking.

After authorizing the marketing of a tobacco product, FDA monitors the actual marketing of the product, including whether the company fails to comply with any regulatory requirements or if credible evidence emerges of significant use by individuals who did not previously use a tobacco product, including youth. FDA will take action as appropriate, including withdrawing marketing authorization and initiating compliance or enforcement actions if needed.

The Agency's compliance and enforcement efforts go well beyond monitoring compliance with marketing orders. FDA has a comprehensive tobacco compliance and enforcement program, which includes, among other things: inspecting brick-and-mortar tobacco retail establishments; inspecting tobacco manufacturing establishments, including vape shops that perform manufacturing activities; monitoring and surveillance of websites, publications, and social media sites that sell, distribute, promote, or advertise regulated tobacco products; and reviewing and investigating reports submitted to the Potential Tobacco Product Violation Reporting (PTVR) system by stakeholders and other members of the public.

[31] *Section 910(f)*

9. Can you describe the relative rigor of the MRTP review and authorization process, especially as compared to the process for permitting the sale of a non-MRTP product?

10. Can you clarify the distinction between a PMTA and a MRTP application, including any differences in the health-related analyses engaged by the FDA? Is it fair to characterize the scientific analysis required by the MRTP review process as more extensive and rigorous?

11. Does the MRTP authorization process set a higher bar for demonstration of exposure reduction than the PMTA process?

MRTPs are tobacco products that are sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products. Before an MRTP can be introduced or delivered for introduction into interstate commerce, an order from FDA under section 911(g) of the FD&C Act ("risk modification order" or "exposure modification order") must be in effect with respect to the tobacco product.[32] If the MRTP is a new tobacco product within the meaning of section 910(a)(1), any applicable premarket review requirements under 910 of the FD&C Act must also be satisfied.[33] Therefore, the MRTP and PMTA processes are separate, but may apply to the same product.

In general, FDA shall issue an order under section 911(g)(1) of the FD&C Act (risk modification order) only if it determines the applicant has demonstrated that the product, as it is actually used by consumers, will:

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.[34]

With respect to tobacco products for which risk modification orders are issued, FDA has the authority to require that the product comply with requirements relating to advertising and promotion of the tobacco product.[35]

FDA may issue an order under section 911(g)(2) of the FD&C Act (exposure modification order) if it determines that the applicant has demonstrated that:

- Such an order would be appropriate to promote the public health;
- Any aspect of the label, labeling, and advertising for the product that would cause the product to be a modified risk tobacco product is limited to an explicit or implicit representation that the tobacco product or its smoke does not contain or is free of a

[32] *Section 911(a) of the FD&C Act*
[33] *Section 910(a)(2)(A) of the FD&C Act*
[34] *Section 911(g)(1) of the FD&C Act*
[35] *Section 911(h)(5) of the FD&C Act*

substance or contains a reduced level of a substance, or presents a reduced exposure to a substance in tobacco smoke;

- Scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards for obtaining an order under section 911(g)(1); and
- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.[36]

Furthermore, for FDA to issue an exposure modification order, FDA must also find that the applicant has demonstrated that:

- The magnitude of overall reductions in exposure to the substance or substances which are the subject of the application is substantial, such substance or substances are harmful, and the product as actually used exposes consumers to the specified reduced level of the substance or substances;
- The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users;
- Testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product is or has been demonstrated to be less harmful, or presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products; and
- Issuance of the exposure modification order is expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.[37]

Pursuant to section 911(d), an MRTPA must include:

1. a description of the proposed product and any proposed advertising and labeling;
2. the conditions for using the product;
3. the formulation of the product;
4. sample product labels and labeling;
5. all documents (including underlying scientific information) relating to research findings conducted, supported, or possessed by the tobacco product manufacturer relating to the effect of the product on tobacco-related diseases and health-related conditions, including information both favorable and unfavorable to the ability of the product to reduce risk or exposure and relating to human health;

---

[36] *Section 911(g)(2)(A) of the FD&C Act*
[37] *Section 911(g)(2)(B) of the FD&C Act*

6. data and information on how consumers actually use the tobacco product; and such other information as the Secretary may require.

In making the above determinations under section 911(g)(1) and 911(g)(2), FDA must consider under section 911(g)(4):

- the relative health risks to individuals of the tobacco product that is the subject of the application;
- the increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to the tobacco product that is the subject of the application;
- the increased or decreased likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application;
- the risks and benefits to persons from the use of the tobacco product that is the subject of the application as compared to the use of products for smoking cessation approved as medical products to treat nicotine dependence; and
- comments, data, and information submitted by interested persons.

A PMTA is an application submitted under Section 910 of the FD&C Act for a new product seeking an FDA marketing order. Section 910(c)(2)(A) of the FD&C Act requires that FDA deny a PMTA where it finds "there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health." In making this determination, FDA considers the risks and benefits to the population as a whole, including users and non-users of the tobacco product, and taking into account 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.

As part of its evaluation of a PMTA, FDA will consider whether to authorize the marketing of a new tobacco product under the APPH standard, and will consider doing so only where marketing is expected to have at least some net benefit to public health based upon the risks and benefits to the population as a whole, which includes youth, young adults, and other vulnerable populations.[38]

Pursuant to section 910(b)(1), a PMTA must include:

1. full reports of all information, published or known to, or which should reasonably be known to, the applicant, concerning investigations which have been made to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products;
2. a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product;

[38] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/premarket-tobacco-product-applications-electronic-nicotine-delivery-systems-ends

3. a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of, such tobacco product;
4. an identifying reference to any tobacco product standard under section 907 which would be applicable to any aspect of such tobacco product, and either adequate information to show that such aspect of such tobacco product fully meets such tobacco product standard or adequate information to justify any deviation from such standard;
5. such samples of such tobacco product and of components thereof as the Secretary may reasonably require;
6. specimens of the labeling proposed to be used for such tobacco product; and
7. such other information relevant to the subject matter of the application as the Secretary may require.

The MRTPA and PMTA review processes follow similar steps:

- *Pre-application meeting phase*: a forum to discuss and provide feedback to the applicant prior to application submission (not required)
- *Acceptance:* FDA ensures the product falls under the Center for Tobacco Products' jurisdiction and confirms the regulatory requirements of an application are included in submission
- *Filing:* FDA ensures the application contains requirements of section 911(d) for MRTPs and section 910(b)(1) for PMTAs
- *Substantive Review:* The substantive reviews for both PMTAs and MRTPAs are generally multidisciplinary and will generally include evaluation of product engineering, toxicology, behavioral and clinical pharmacology, microbiology, individual health impact and population health impact.
- *Postmarket Reporting*: Under section 911(i) (for risk modification orders) and 911(g)(2)(C) (for exposure modification orders), MRTP applicants who have received a modified risk order must conduct postmarket surveillance and studies to determine the impact of the order on consumer perception, behavior, and health, to allow FDA to review the accuracy of the determinations upon which the order was based. The results of such postmarket surveillance and studies must be submitted annually to FDA. Under section 910(f), PMTA applicants who have received a marketing granted order must establish and maintain records and provide reports to FDA, as FDA may by regulation or in the marketing order prescribe if FDA has determined that such records and reports are necessary for FDA to determine whether there may be grounds for withdrawing or temporarily suspending the order.

Both the MRTPA and PMTA review processes consider exposure reduction in the overall assessment of individual health risks. For example, information regarding how consumers will actually use the tobacco product informs FDA's review because it helps demonstrate the health risks of the new tobacco product by showing the levels and frequency of exposure to harmful or potentially harmful constituents (HPHC) and other toxic substances contained in and delivered

from the tobacco product. In addition, information regarding the health risks of the tobacco product is a basic piece of information that FDA needs to determine the risks and potential benefits to the population as a whole associated with changes in tobacco use behavior. Therefore, an overall assessment of individual health risks including but not limited to exposure to a substance, in combination with other parts of FDA's assessment of PMTA or MRTPA, inform FDA's determination if the respective standards have been met.