December 31, 2020

The Honorable Frank Pallone, Jr.
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Chairman Pallone:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the September 25, 2019, hearing before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, entitled "Sounding the Alarm: The Public Health Threats of E-Cigarettes." This letter is a response for the record to questions posed by the committee.

If you have further questions, please let us know.

Sincerely,

/s

Andrew Tantillo
Acting Associate Commissioner for
Legislative Affairs

cc: Hon. Greg Walden, Ranking Member, Committee on Energy and Commerce
Hon. Diana DeGette, Chair, Subcommittee on Oversight and Investigations
Hon. Brett Guthrie, Ranking Member, Subcommittee on Oversight and Investigations

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The Honorable Frank Pallone (D-NJ)

1. **In your testimony before the Subcommittee, you stated that despite the Administration's announcement that FDA intends to finalize a compliance policy that would prioritize enforcement of the pre-authorization requirements for non-tobacco-flavored e-cigarettes, including mint- and menthol-flavored products, this does not mean that [quote] "flavored e-cigarettes can never be marketed." What kind of evidence will have to be provided for the manufacturers in their PMTA submissions to convince FDA that flavored products should be legally marketed?**

Ensuring new tobacco products undergo a robust premarket evaluation by FDA is a critical part of our mission to protect the public health, particularly among youth, and to reduce tobacco-related disease and death. While the authorization of new tobacco products doesn't mean they are safe, the review process under the PMTA pathway requires FDA to determine that permitting the marketing of the product is appropriate for the protection of the public health, taking into account the risks and benefits to the population as a whole. This includes consideration of the increased or decreased likelihood that users of tobacco products will stop using such products and the increased or decreased likelihood that nonusers will start using tobacco products. For example, FDA will consider whether marketing of a tobacco product would increase the likelihood of youth use of the product, and the potential for the product to move adult smokers away from use of combustible cigarettes. As part of a marketing granted order for a new tobacco product, FDA may also put in place post-marketing requirements if needed to enable it to determine whether there is or may be grounds for withdrawing or temporarily suspending an order, which could include, among other things, requirements for monitoring market dynamics such as potential youth uptake. FDA must also withdraw a PMTA marketing order if FDA determines that the continued marketing of a product is no longer appropriate for the protection of the public health (e.g., if there is an uptake of the product by youth).

Issues related to the manufacturing and marketing of electronic nicotine delivery systems (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 will consider as part of our review of marketing applications for these products.

With respect to PMTA submissions for flavored ENDS products, FDA will assess, among other things, potential health risks to determine if permitting the marketing of a new tobacco product would meet the statutory standard of "appropriate for the protection of the public health" for marketing. As explained in FDA's June 2019 guidance regarding PMTAs for ENDS products,[1] because of the potential impact of flavors on product toxicity and appeal to youth and young adults, scientific reviews of flavors (e.g., toxicological analyses of flavor additives, chemistry analyses, clinical studies, literature reviews), should be included in a PMTA for an e-liquid. There may be significant differences in the health risk of flavors depending on their route of exposure as well as the formation of additional chemicals due to heating or burning of the flavored e-liquid.

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

FDA considers the appeal and use of ENDS product flavors important in ascertaining the health risks of these products. In this regard, FDA recommends that PMTA applicants describe research on flavor development including, but not limited to, market segmentation analysis or sensory testing. Applicants should describe consumer perceptions among current ENDS users and other tobacco product users for appeal and use intentions, based on labeling and actual use of flavors, as well as product design. It is also important that PMTAs for flavored products examine the impact of the flavoring on consumer perception, especially given the attractiveness of flavors to youth and young adults. Additionally, to provide a better understanding of the appeal of flavors to adults, FDA recommends that PMTA applicants provide information examining adult appeal of such flavors in their decisions to initiate use, cease use of more harmful products, or engage in dual use.

2. **Despite FDA's 2016 deeming rule making it illegal to sell e-cigarettes to individuals under age 18, some underage young people have turned to the internet to purchase e-cigarettes online. One study found as many as 97 percent of online purchase attempts by those under the age of 18 were successful.[2]**

    a. **What are the challenges of regulating internet sales of e-cigarettes to youth?**

    FDA conducts routine surveillance of sales, distribution, marketing, labeling, and advertising activities related to regulated tobacco products on the internet, including in social media; in publications; at promotional events; and through other compliance and enforcement activities. Through its activities including online surveillance, FDA has observed that online tobacco retailers utilize a variety of age verification methods, with varying levels of sophistication. FDA has taken action against hundreds of websites and other online media sites for violations such as sales of tobacco products to minors. The enormous volume and everchanging nature of these websites, however, can present challenges to enforcement.

    b. **What more, if anything, should FDA be doing to ensure that sellers are not able to get e-cigarettes into the hands of underage young people through the internet?**

    FDA remains committed to tackling the troubling epidemic of e-cigarette use among kids. Preventing youth access to and use of ENDS remains one of FDA's top priorities. Our plan includes compliance and enforcement activities and high-profile, impactful public education efforts designed to reach nearly 10.7 million youth at risk of starting or continuing to use e-cigarettes.

    On December 20, 2019, the President signed legislation to amend the Federal Food, Drug, and Cosmetic Act, raising the Federal minimum age of sale of tobacco products from 18 to 21 years. It is now illegal for a retailer to sell tobacco products—including cigarettes, cigars and e-cigarettes—to anyone under 21.

[2] Nikitin, D., et al., "Is the E-Liquid Industry Regulating Itself? A Look at E-Liquid Internet Vendors in the United States," Nicotine & Tobacco Research (Mar. 19, 2016).

FDA has taken swift action aimed at the manufacturers of youth-appealing ENDS products and continues to take action to stop sales to minors. FDA has also taken a number of actions to remove tobacco products that lack FDA premarket authorization, including ENDS, from the market. These include:

- issuing warning letters to companies for illegally marketing backpacks and sweatshirts designed with stealth pockets to hold and conceal ENDS products that resemble smartwatches, or devices appearing as children's toys;
- issuing warning letters to companies marketing e-liquids that imitate packaging for food products such as candy, or feature cartoon characters like SpongeBob SquarePants;
- conducting investigations of more than 115 companies that may be illegally marketing more than 150 unauthorized tobacco products, including ENDS, to youth; and
- issuing seven warning letters to companies for illegally marketing over 170 unauthorized tobacco products, prior to the 2020 compliance policy, that includes a warning letter issued in October 2019 to a company for illegally marketing nearly 100 unauthorized ENDS products.

In March 2020, in line with the Agency's actions to protect the health and well-being of staff during the COVID-19 outbreak, FDA issued a partial stop work order to the entities the Agency contracts with at the state level for activities such as compliance checks and vape shop inspections. The Agency continues to evaluate the effect of COVID-19 on its programmatic activities and will continue to communicate any changes as they occur. Guided by health and safety considerations, FDA will continue taking appropriate actions, as outlined by its priorities, on a rolling basis. Certain enforcement efforts, such as monitoring the online marketing and sale of regulated tobacco products and issuing import alerts for unauthorized tobacco products, remain uninterrupted by COVID-19.

3. Section 904(a)(4) of Food, Drug, and Cosmetic Act requires tobacco manufacturers, importers or agents to submit to FDA documents that relate to "health, toxicological, behavioral, or physiologic effects of current or future tobacco products, their constituents (including smoke constituents), ingredients, components, and additives."

a. What of this information has FDA required or requested from e-cigarette manufacturers under this provision?

FDA has required ENDS manufacturers to preserve all documents relating to health, toxicological, behavioral, or physiologic effects of finished tobacco products ("health documents"). This should include, for example, cell-based, tissue-based, animal, or human studies, computational toxicology models, information on addiction, intentions to use, and other behavioral effects such as abuse liability. FDA is taking an incremental approach to enforcing this provision with respect to the timeframe that documents were developed and the date that documents must be submitted. The compliance deadline for submitting certain documents (i.e., health documents developed between June 23, 2009

and December 31, 2009), was February 8, 2017, or in the case of small-scale tobacco product manufacturers, November 8, 2017. FDA generally does not intend to enforce the requirement with respect to health documents developed after December 31, 2009, at this time. However, tobacco manufacturers and importers are still to preserve all health documents developed after December 31, 2009 for future submission to FDA.

In addition to the authority in Section 904(a)(4), FDA may request health-related and other information under Section 904(b) at any time. Based on the growing concerns about the popularity of their products among youth, in April and May 2018, FDA requested that Juul Labs, Inc. and several other e-cigarette manufacturers submit additional research documents in accordance with section 904(b) of the FD&C Act. With the goal of understanding youth use of the products and what aspects could be driving their youth appeal, these requests[3] sought information including marketing practices and research on marketing, adverse experiences and product complaints, effects of product design, and public health impact.

b. In light of the outbreak of vaping lung illnesses and increasing evidence of a youth epidemic of e-cigarette use, has FDA considered revising its compliance guidelines for Section 904 of the FDCA to start requiring e-cigarette manufacturers to submit more information, particularly health studies, related to their products as such studies are developed? If not, why?

Premarket applications for all currently marketed e-cigarettes were required to be submitted to FDA by September 9, 2020. FDA expects to receive extensive information including health studies in Premarket Tobacco Product Applications (PMTAs) submitted under Section 910(b) for e-cigarettes. FDA has published a guidance for industry on Premarket Tobacco Product Applications for ENDS,[4] which includes detailed recommendations on the scientific studies and data to be submitted by industry in PMTAs for e-cigarettes. In addition, FDA intends to continue requiring that manufacturers submit other documents under the provisions of 904(a)(4) and 904(b) as appropriate.

The Honorable Diana DeGette (D-CO)

1. In 2018, a report by the National Academies of Sciences, Engineering, and Medicine found that there is "conclusive evidence that in addition to nicotine, most e-cigarette products contain and emit numerous potentially toxic substances." In that same report, the National Academies also reported that the long-term health effects of e-cigarettes are not yet clear.

[3] These letters are posted at: *https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/ctp-letters-industry*

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

a. Do you anticipate that long-term public health studies will be available for FDA as a part of its application review process, either from the manufacturers, federally funded studies, or elsewhere?

E-cigarettes are presently too new a technology for there to be long-term studies in existence that follow morbidity and mortality over a long period of time (e.g., decades). There are a number of national public health surveys that may yield so-called surrogate data on long-term health effects of ENDS: The Population Assessment of Tobacco and Health (PATH) study, the National Health Interview Survey (NHIS) and the Tobacco Use Supplement to the Current Population Survey (TUS-CPS) have been linked to mortality data from the National Death Index (NDI).

The PATH Study is an on-going national, longitudinal, cohort study of users of tobacco products and those at risk for tobacco use ages 12 and older and how use affects the health of people in the United States. Research topics in the PATH study include evaluating patterns of tobacco use such as switching products and using multiple products, as well as seeking to understand perceptions, knowledge, attitudes and use of tobacco products. CTP is also funding biospecimen analyses via a research contract and is working with the Division of Laboratory Science within CDC's National Center for Environmental Health and other laboratories to support analyses of biomarkers of tobacco exposure and potential harm. CTP is exploring additional short and long-term measures for PATH that capture potential health effects of e-cigarette and other tobacco use.

It may take several to many years to make definitive statements about e-cigarette use and long-term disease risk. In the meantime, we are looking at how often current e-cigarette users report certain illnesses and at differences in chemical exposures and other health measures taken at the time of the survey compared with other types of tobacco product users and non-users. Since long-term studies presently are limited, applicants may submit studies, published reports, or data on relevant biomarkers of harm or exposure such as cotinine, NNAL, and N-Nitrosonornicotine which may have a longer history of research and data.

We will also learn about any studies from manufacturers as we review premarket applications. It is likely that applicants will conduct certain investigations themselves and submit their own research findings as a part of their PMTA.

b. How will FDA weigh potential long-term public health impacts in the possible absence of such studies?

FDA uses long-term studies to examine trends of concern and develop strategies to mitigate those concerns. Without these studies we will rely on reviewing current and available evidence (such as shorter-term biomarker studies, and nonclinical studies) that may be extrapolated to long term health impacts. While long-term studies are most useful for identifying chronic effects associated with use of a product, such studies are not

routinely expected to be submitted as part of a premarket application. In general, FDA does not expect that applicants will need to conduct long-term studies to support an application; in some cases, it may be possible to support a marketing order for an ENDS product without conducting new nonclinical or clinical studies. Some applicants may be able to use published literature reviews to help support a PMTA, reference Tobacco Master Files (TPMFs) submitted by other manufacturers, or bridge to other studies. "Bridging" allows a PMTA applicant to refer to other research studies if there is applicable data or findings from those studies previously conducted by themselves or another party. For example, if there is an established body of evidence regarding the health impact (individual or population) of the product or a similar product that can be adequately bridged to the product in question, such as data from the published literature or government-sponsored databases, these data may be sufficient to demonstrate that the marketing of a product would be appropriate for the protection of the public health and support a PMTA.

Additionally, postmarket surveillance and reporting may help to ensure anticipated health impacts based on premarket information continued to be applicable.

Information about the use of bridging studies in PMTAs is publicly available in the PMTA ENDS guidance,[5] CTP websites,[6] and CTP presentations available online.[7]

The Honorable Brett Guthrie (R-KY)

1. Once a provider or state collects a sample, where are the samples that are collected sent for testing?

Initially, most samples were submitted to FDA's Forensic Chemistry Center (August-October 2019). In late October 2019, sample triaging based on testing requirements began, with CDC's laboratory focused on aerosol testing, and FDA's Irvine, San Juan, and Detroit Medical Products Laboratories performing liquid testing. As of February 3, 2020, CDC and FDA are no longer accepting clinical or product samples related to EVALI cases.

Please refer to CDC's response to this question for additional details.

a. How many samples have been received for testing to date?

As of October 9, 2020, FDA laboratories had received a total of over 1,600 product samples from 31 states and the U.S. Virgin Islands. Of these, 1,238 samples were specifically connected to an EVALI patient.

Please refer to CDC's response to this question for additional details.

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

[6] "Marketing ENDS as New Tobacco Products: A Guide for Manufacturers." *https://www.fda.gov/tobacco-products/manufacturing/marketing-ends-new-tobacco-products-guide-manufacturers*

[7] *https://www.fda.gov/media/117507/download*

b. How many of those samples have been tested and what are they being tested for?

FDA analyzed e-liquids for the presence of a broad range of chemicals to provide insight into the nature of the chemical exposure(s) contributing to the EVALI outbreak. As of October 9, 2020, testing had been completed on 1,015 of 1,238 product samples specifically connected to an EVALI patient. The remaining samples include devices and empty packaging with no product available for testing.

Laboratory analyses have included testing the samples for nicotine, substances such as tetrahydrocannabinol (THC) or other cannabinoids, and other chemicals and ingredients such as cutting agents/diluents, additives, pesticides, opioids, and toxins.

c. Has the CDC or FDA requested samples from commercial e-cigarette manufacturers to compare to those collected in the investigation?

FDA has tested devices and e-liquids from some commercial e-cigarette manufacturers, however most products involved in the investigation are illicit products and not commercialized e-cigarettes.

Please refer to CDC's response to this question for additional details.

d. How do the samples compare? Are you finding that the samples are the same, or are commercial samples being modified after purchase?

Results of testing of products associated with illnesses and deaths have shifted the focus from e-cigarettes and associated nicotine containing fluids, to vaping cartridges containing fluids comprised of tetrahydrocannabinol (THC) and associated diluents.

Please refer to CDC's response to this question for additional details.

e. Can you determine from the samples provided how many are counterfeit products?

This issue is not related to counterfeit products but to the availability and use by consumers of products containing unknown materials of unknown origin. National and state data from patient reports and product sample testing suggest THC-containing e-cigarette, or vaping, products, particularly from informal sources like friends, or family, or in-person or online dealers, are linked to most EVALI cases and play a major role in the outbreak.

Please refer to CDC's response to this question for additional details.

f. What additional information or samples would you need to determine whether the samples involved in the investigation are counterfeit?

Investigations of counterfeit products require authentic samples for comparison. In these cases, this would involve authentic samples of any associated marketing materials and packaging, devices, cartridges and liquid contents. As previously discussed, the current issue is not related to counterfeit products but to the availability and use by consumers of products containing unknown materials of unknown origin.

2. In addition to analyzing the vaping liquid, do CDC and FDA investigators also receive and examine the vaping or e-cigarette device itself?

As part of the investigation, FDA received various products and substances to analyze, including products containing varied levels of liquid as well as packaging and other documentation. However, relatively few vaping devices were received.

Please refer to CDC's response to this question for additional details.

a. Have investigators found modified e-cigarette or vaping devices in any of the outbreak cases? If so, how many cases?

The devices have not been the focus of this investigation. Preliminary data suggested that the liquids contained in the devices were the most likely cause of the illnesses. In November 2019, CDC published a study report noting that products containing THC, particularly those obtained off the street or from other informal sources (e.g., friends, family members, illicit dealers), were linked to most of the EVALI cases and played an important role in the EVALI outbreak.[8]

Please refer to CDC's response to this question for additional details.

b. Are most of the devices closed system products or open system products?

As mentioned previously, FDA received various products and substances to analyze. While a variety of products are involved in the investigation, the cause is strongly linked to the liquid and not the device used. To date, this type of information (open or cartridge-based systems) is not reflected in the samples packages or data received by the ORA Laboratories and is not being tracked or generated.

Please refer to CDC's response to this question for additional details.

c. Are you at least receiving the devices? Why not also collect and examine the devices themselves to look for commonalities?

As stated previously, the cause is strongly linked to the liquid and not the device used and relatively few vaping devices have been received.

[8] *https://www.cdc.gov/mmwr/volumes/68/wr/mm6843e1.htm?s_cid=mm6843e1_e&deliveryName=USCDC_921-DM11790*

3. How many different chemicals is FDA testing for? What criteria did FDA use to select the chemicals for screening?

Laboratory analyses have included testing the samples for nicotine, substances such as tetrahydrocannabinol (THC) or other cannabinoids, and other chemicals and ingredients such as cutting agents/diluents, additives, pesticides, opioids, and toxins.

a. How is FDA conducting the testing? Are the samples being tested as if it they are coming out of a vaping device?

FDA testing has focused on liquid product testing rather than testing the aerosol that is formed when the liquid is vaped. CDC conducted aerosol emissions of case-associated e-cigarette, or vaping, products in order to replicate patients' exposure to aerosols produced by these products and to identify constituents associated with health risk.

4. What does scientific research show about the effects of nicotine on the adolescent brain? What is the effect of nicotine delivered by e-cigarettes as compared to combustible cigarettes?

Studies of the effects of nicotine exposure in the adolescent brain find that it is uniquely vulnerable to nicotine compared to the adult brain. Repeated exposure to nicotine during adolescence induces long-lasting structural and functional changes in brain regions involved in addiction, attention, learning, and memory. These changes in the brain can persist after nicotine exposure has ended and prime the adolescent brain for addiction to nicotine and other drugs, such as cocaine and methamphetamine. Studies further suggest that nicotine-induced changes in the adolescent brain can lead to long-lasting effects on cognitive function, such as cognitive deficits following nicotine abstinence, and may contribute to the risk for mood and anxiety disorders.

Nicotine is the primary addictive substance in tobacco products, including e-cigarettes and combustible cigarettes. The rate and extent of nicotine delivery significantly impacts product abuse liability. Higher nicotine content and faster rates of nicotine delivery increase products' abuse liability due to the rapid absorption of nicotine into the brain. The e-cigarette product category includes a range of product types and features. Some e-cigarettes can achieve similar or greater rates of nicotine delivery as cigarettes.

Nicotine delivery by e-cigarettes is influenced by nicotine yield (the amount of nicotine heated and released) in e-cigarette aerosol. Nicotine yield is impacted by e-liquid nicotine concentration and several product characteristics, including battery power/wattage. Nicotine exposure (the amount of nicotine absorbed by the body) from e-cigarettes is influenced by e-liquid composition (e.g., propylene glycol to vegetable glycerin ratio, pH, presence of nicotine salts) and user behavior (e.g., puff volume/duration, number of puffs per use session, length of use session). Emerging evidence on nicotine salt formulations suggests that these e-liquids may result in greater nicotine exposure and faster nicotine absorption than freebase nicotine e-liquids with the same nicotine concentration. Notably, e-cigarette use behavior is not self-limiting due to a large

e-liquid volume capacity (i.e., one tank/pod may deliver as much nicotine as one pack of cigarettes) and the ability to use the product for a longer duration than a cigarette. As a result, nicotine exposure from an e-cigarette can vary in rate and magnitude to a greater degree compared to a cigarette.

5. What is the FDA's plan for increasing enforcement of non-FDA regulated products, such as THC vaping e-liquids, or CBD oils?

FDA has been actively monitoring the CBD market and seeking to remove violative products that pose a risk to consumers. For example, we have seen many CBD products being marketed with claims of therapeutic benefit, or other drug claims, without having gone through the drug approval process. Some of these products are marketed for serious diseases and conditions like cancer, Alzheimer's disease, and opioid use disorder. Selling products with unsubstantiated therapeutic claims can put consumers at risk by influencing them not to use proven, approved therapies to treat serious and even fatal diseases. These products are unapproved drugs, and their sale and distribution are illegal. FDA has sent warning letters to companies marketing such unlawful products, and we will continue to monitor the marketplace and take action, as needed, when we encounter violations that deceive consumers and put them at risk.

We also have serious concerns about CBD products that put the public at risk in other ways. For example, we are acutely aware of the risks posed by product contaminants (e.g., heavy metals, toxic minerals, or other potentially harmful substances). We also have significant concerns about products marketed with false claims or statements (e.g., omitted ingredients, incorrect statements about the amount of CBD), products marketed for use by vulnerable populations (e.g., children or infants), and products that otherwise put the public health at risk.

The Joint Explanatory Statement that accompanied the Further Consolidated Appropriations Act, 2020 (P.L. 116-94) directed FDA to provide a report regarding the Agency's progress toward obtaining and analyzing data to help determine a policy of enforcement discretion and the process in which CBD meeting the definition of hemp will be evaluated for use in FDA-regulated products within 60 days of enactment. We provided this report, and an additional report with a sampling study of the current CBD marketplace, to Congress.

It is possible that some individual products containing CBD fall outside of FDA's jurisdiction. Specifically, a product containing CBD falls outside FDA's jurisdiction if it is not intended for use as a human or animal drug; is not a human or animal food; and is not a cosmetic, medical device, biological product, tobacco product, or combination product. FDA does not have authority to exercise regulatory oversight over such products, even to address potentially serious matters of public health and safety.

FDA continues to review information received following the 2019 public hearing and has more information on these products on FDA's website: *https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-were-working-find-out-about-products-containing-cannabis-or-cannabis*

Further, FDA enforces the FD&C Act. The FD&C Act gives FDA jurisdiction over foods (including dietary supplements), drugs, cosmetics, and tobacco products among other products. In some situations, the use of cannabis and its derivatives (including THC and CBD) is a violation of the FD&C Act, regardless of whether it is also a violation of the Federal Controlled Substances Act (CSA). Whether a product containing cannabis is subject to FDA regulation – and, if so, whether it violates the FD&C Act – is determined by a fact-specific inquiry. FDA inspects manufacturing facilities, conducts investigations and responds to consumer complaints in all states including those where local laws have lifted restrictions on cannabis. These actions by state and local governments have increased situations where FDA may encounter products containing cannabis while performing routine activities, and prompt questions as to the regulatory status of these products under the FD&C Act.

6. **According to your testimony, FDA has issued more than 1,400 civil money penalties to retailers for sales of ENDS and their components to youth. How much money has been fined in Civil Monetary Penalties generated to date?**

If FDA finds subsequent violations at a retail establishment after the issuance of a warning letter, it generally seeks a Civil Money Penalty (CMP) in accordance with the penalty schedule published in the Tobacco Control Act (TCA) and adjusted for inflation. A CMP is an administrative enforcement action and retailers are entitled to a hearing in front of a U.S. Health and Human Services Departmental Appeals Board (DAB) Administrative Law Judge (ALJ) to contest some or all the allegations, and the amount of the penalty.

Since FDA began issuing CMPs in 2011, the Agency has collected more than $17 million as a result of CMPs issued to tobacco retailers for repeated violations (largely due to the sale of tobacco products to minors) since the retail compliance check inspection program began.

   a. **How much is outstanding and how much has been collected?**

      As noted above, since FDA began issuing CMPs in 2011, the Agency has collected more than $17 million. Please note that FDA does not disclose the status of CMP cases until they are closed, including the amount sought. This protects the integrity of the process.

   b. **What has been done with that money?**

      All CMP payments are deposited in the U.S. Treasury as miscellaneous receipts, not allocated to FDA or FDA's Center for Tobacco Products (CTP).

7. **Did the FDA use research from the United Kingdom when deciding to postpone the PMTA deadline and if so, what evaluations or studies did the FDA conduct in the difference between UK regulations from the FDA regulations before using the UK research as a basis for policy decision-making? Explain the difference in the United Kingdom's regulation of e-cigarettes versus the FDA's.**

In July 2017, FDA announced a new comprehensive plan for tobacco and nicotine regulation that would serve as a multi-year roadmap to significantly reduce tobacco-related disease and death.

Prior to this announcement, nationally representative data suggested that youth use of e-cigarettes had declined.[9] The comprehensive plan was announced in part to afford the Agency time to explore clear and meaningful measures to make combustible tobacco products less toxic, less appealing, and less addictive. In accordance with this plan, in August 2017, FDA extended timelines to submit tobacco product review applications for newly-regulated products that were on the market as of August 8, 2016.[10] This extension of time was intended to enable FDA to strike a balance between regulation and encouraging development of innovative tobacco products that may be less harmful than cigarettes. FDA did not rely on research from the United Kingdom (UK), including work produced by Public Health England, when it set out this extension.

FDA notes that we monitor relevant global e-cigarettes studies. of the rules governing e-cigarettes in the UK differ from those in the U.S. The UK Medicines and Healthcare products Regulatory Agency (MHRA) is the competent authority for the notification scheme for e-cigarettes and refill containers in the UK and is responsible for implementing many of the provisions under Article 20 of the Tobacco Products Directive 2014/14/EU (TPD). Example provisions include:

- Restricting the maximum volume of nicotine-containing e-liquid for sale in one refill container to 10ml;
- Requiring nicotine-containing products or their packaging to be child-resistant;
- Banning certain ingredients such as colorings, caffeine and taurine;
- Including new labelling requirements and warnings; and
- Requiring all e-cigarettes and e-liquids be notified to MHRA before they can be sold.[11]

In the U.S., FDA has had authority over all tobacco products, including ENDS, since the final deeming rule went into effect in 2016. As a result of the final deeming rule, manufacturers, importers and retailers of newly-regulated tobacco products are subject to applicable provisions related to tobacco products in the FD&C Act and FDA regulations. This brings them in line with other tobacco products FDA has regulated under the TCA in 2009. For example, requirements include:

- Registering manufacturing establishments and providing product listings to FDA;
- Reporting ingredients, and harmful and potentially harmful constituents;
- Premarket review and authorization of new tobacco products by FDA;
- Placing health warnings on product packages and advertisements; and
- Not selling modified risk tobacco products (including those described as “light,” “low,” or “mild”) unless authorized by FDA.

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[9] Jamal A, Gentzke A, Hu SS, et al. Tobacco Use Among Middle and High School Students — United States, 2011–2016. MMWR Morb Mortal Wkly Rep 2017;66:597–603. DOI: *https://www.cdc.gov/mmwr/volumes/66/wr/mm6623a1.htm*.

[10] FDA notes that as a result of a court order, premarket submissions became due to FDA on September 9, 2020, for all new deemed tobacco products currently on the market.

[11] *https://www.gov.uk/guidance/e-cigarettes-regulations-for-consumer-products*

FDA's premarket review process is unique to the U.S. In the UK, in contrast, manufacturers of new e-cigarette products only must submit notification to MHRA six months before they intend to put their product on the UK market, and can begin marketing their product as soon as their notification is published on the MHRA website.

a. Has the FDA evaluated research results of e-cigarette use presented in support of, and research results following the implementation of the UK and EU e-cigarette regulations to study the effectiveness of the UK and EU regulations?

FDA regularly looks to regulatory and scientific counterparts, both domestically and internationally, to inform our regulatory actions to the extent feasible and appropriate given distinctions in respective authorities, tobacco product marketplaces, and populations. This includes the treatment of ENDS under the EU Tobacco Products Directive (TPD). In 2018, the US National Academy of Sciences released a CTP-commissioned report on the Public Health Consequences of ENDS.[12] This report built upon 2014 and 2015 reports commissioned by Public Health England on the cumulative evidence of potential public health benefits and harms related to ENDS in the UK.

Policy impact analysis is among CTP's research priorities. CTP's Office of Science (OS) conducts targeted evaluations of domestic and international policies of interest that are relevant to our regulatory authorities. We have funded and are currently funding evaluations of policies to inform future regulatory actions (e.g., impact of sales restrictions on flavored tobacco products).

Specific examples of areas in which OS is monitoring the EU and UK ENDS experience to inform tobacco regulatory science include but are not limited to, TPD restrictions on e-liquid volume and constituents; tobacco product labeling; post market and adverse event reporting; and child-resistant packaging.

Please note, however, that while global experience may inform FDA regulatory authority, FDA regulations must reflect U.S. consumer use and unique U.S. marketing. E-cigarette use in the UK differs from that in the U.S., as the UK has not experienced the same youth use epidemic. Public Health England found that, while youth experimentation with e-cigarettes has steadily increased in recent years, regular use remains low. In 2018, 1.7 percent of 11-18 year old youth in Great Britain reported at least weekly use. Adult e-cigarette prevalence has remained stable since 2015. In 2017-2018, an estimated 5.4 percent to 6.2 percent of all adults in Great Britain used e-cigarettes.[13]

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[12]National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems; Eaton DL, Kwan LY, Stratton K, editors. Public Health Consequences of E-Cigarettes. Washington (DC): National Academies Press (US); 2018 Jan 23. Available from: *https://www.ncbi.nlm.nih.gov/books/NBK507171/* doi: 10.17226/24952

[13] Vaping in England: evidence update summary February 2019. *https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/821179/Vaping_in_England_an_evidence_update_February_2019.pdf*

8. Will the FDA plan to add questions to the National Youth Tobacco Survey asking which substances youth are smoking in e-cigarettes other than nicotine?

The 2020 National Youth Tobacco Survey (NYTS) included a question asking whether youth have ever used marijuana or cannabis (including concentrates, waxes, or hash oils) in an e-cigarette. Questions for the 2021 NYTS are not finalized; should there be changes to this newly added question about marijuana or cannabis use, we will inform the Committee.

The Population Assessment of Tobacco and Health (PATH) Study is a national longitudinal study of tobacco use and how it affects the health of people in the United States. PATH annually collects a comprehensive set of measures concerning ENDS use among youth and adults, and over time improvements have and are being made to the survey design to disentangle use of ENDS for vaping nicotine as well as other substances.

The Honorable Michael C. Burgess (R-TX)

1. We know that teen use of e-cigarettes has rapidly and steadily increased in recent years. What has the FDA been doing to study this steep increase in youth vaping?

On September 9, 2020, FDA, in partnership with the Centers for Disease Control and Prevention (CDC), released new data from the 2020 National Youth Tobacco Survey (NYTS), which show 1.8 million fewer U.S. youth are currently using e-cigarettes compared to 2019. After two years of disturbing increases in youth e-cigarette use, we are encouraged by the overall significant decline reported in 2020. This is good news; however, FDA remains very concerned about the 3.6 million U.S. youth who currently use e-cigarettes and we acknowledge there is work that still needs to be done to curb youth use. Youth use of e-cigarettes remains a public health crisis that is affecting children, families, schools and communities, and we will do everything possible to stop it.

FDA has taken a multi-pronged approach to study youth vaping. We are analyzing data from well-established studies such as the NYTS and Population Assessment on Tobacco and Health (PATH) Study to understand e-cigarette (or ENDS, electronic nicotine delivery systems) use by youth. In addition, FDA is collaborating with NIH to fund tobacco regulatory science grants; with nearly 20 active grants focusing on behaviors associated with youth use of ENDS.

FDA has also conducted research using a method known as social media listening, which monitors social media platforms to help identify emerging products used by youth as well as trending topics. Retail sales data are also used to provide near real-time information on tobacco product sales and to assess overall tobacco marketplace trends in the U.S.

Lastly, FDA participates in a cross-agency tobacco-focused work group along with CDC and NIH that meets routinely to enhance our understanding of the troubling epidemic of e-cigarette use among kids.

2. What conversations has the FDA had with e-cigarette manufacturers about curbing teen vape use?

In late 2017, FDA started to see a marked increase in complaints about ENDS products. FDA initiated an investigation of these complaints, the majority of which pertained to minors' access to and use of these products. This new information indicated an alarming increase in the use of ENDS products by middle and high school students. As part of FDA's response to the increasing use of ENDS products by youth, FDA contacted manufacturers directly to hold them accountable, and to solicit their input in combating youth use of these products. Some examples of FDA interactions with e-cigarette manufacturers about curbing teen vape use include:

- In April and May of 2018, FDA sought information from manufacturers of certain ENDS products commonly used by minors requiring them to submit documents to inform the Agency's understanding of the reported high rates of youth use and the particular youth appeal of these products.
- On September 12, 2018, FDA issued letters to manufacturers of five of the top-selling ENDS brands (JUUL, Vuse, MarkTen XL, blu e-cigs, and Logic), requesting each company to submit a plan describing how it would address minors' access to and use of its products. At the time, these products made up most products illegally sold to minors as part of an FDA enforcement blitz. In response to the September 12th letters to industry, manufacturers described safeguards that they could implement to help to restrict minors' access to ENDS products sold at brick and mortar retailers and online.
- FDA leadership met numerous times with e-cigarette manufacturer with a call to action for the five largest to specifically address the issue of youth use.
- CTP Director, Mitch Zeller, continues to meet with manufacturers as well as various trade associations for both large and small vaping companies and vape shops. Agency representatives also speak frequently at trade associations and host industry listening sessions where the issue of curbing teen e-cigarette use is directly addressed.

3. I believe a critical part of this conversation should be the health concerns associated with counterfeit products. What has the FDA done in recent years to deal with counterfeit products?

U.S. Customs and Border Protection (CBP) allows brand owners to record their registered trademarks and copyrights with the Intellectual Property Rights (IPR) Branch within the Regulations and Rulings Directorate of CBP's Office of Trade. CBP then uses this registration information to help detect counterfeit goods at ports of entry, including at international mail facilities (IMFs) and express courier locations.

In addition to using our regulatory authorities to combat counterfeit e-cigarettes, where appropriate, the Office of Criminal Investigations (OCI) may investigate and refer criminal violations to the Department of Justice for prosecution. Prosecutorial thresholds and criteria vary depending upon the particular U.S. Attorney's Office receiving the referral. OCI also works with closely other Federal, state and international law enforcement agencies to combat the manufacture and sale of any counterfeit FDA-regulated product.

4. Is the FDA prepared to monitor and combat a potential surge in counterfeit or black market products following the flavor ban?

FDA has regulatory tools and enforcement authorities to address ENDS and other tobacco products that are marketed without authorization, that are counterfeit, and/or that are otherwise involved in illicit trade. FDA uses its resources to inspect, detect, and prevent products that violate the FD&C Act, including counterfeit or other illicit products, from entering the U.S. market. FDA has a comprehensive tobacco compliance and enforcement program, which is overseen by CTP and in some areas utilizes FDA's Office of Regulatory Affairs (ORA) staff. Enforcement activities include tobacco retail compliance check inspections, inspections of domestic manufacturers and imported tobacco products, and surveillance and review of tobacco promotions, advertising, and labeling. FDA also has eight import alerts in place to ensure that products presented for entry into the U.S. meet the requirements set forth by the FD&C Act. FDA's import alerts are intended to prevent products that are in violation of certain provisions of the Act from entering the country.

FDA could utilize its advisory, administrative, and judicial enforcement tools against illicit trade in tobacco products. For example, adulterated or misbranded products might be seized at any time. Entities involved in initiating and taking a seizure action include CTP, ORA, FDA's Office of Chief Counsel, the U.S. Attorney's Office, and the U.S. Marshal's Service. FDA also might seek to enjoin any company or person from engaging in a prohibited act. If a firm had a history of violations and had promised correction in the past, but had not made the corrections, an injunction might be pursued. In considering an injunction, FDA evaluates the seriousness of the offense, the actual or potential impact of the offense on the public, whether other possible actions could be as effective or more effective, the need for prompt judicial action, and whether FDA will be able to demonstrate the likelihood of the continuance of the violation in the absence of a court order. Finally, FDA might refer a criminal enforcement action to the U.S. Department of Justice through FDA's OCI.

FDA also receives reports about potential violative tobacco products. FDA evaluates all reports submitted to determine if the activity is a violation of the FD&C Act or related regulations. Before deciding what follow-up action, if any, is necessary, the Agency will check to see if the product named in the complaint is regulated by FDA. If the product is regulated by a different Federal or state agency, or different part of FDA, we will forward the complaint to the applicable entity for review. FDA does not rely solely on what was submitted to take enforcement action. After reviewing a complaint, FDA's investigation may include:

- performing an inspection of a tobacco product manufacturer, distributor, or importer;
- conducting a compliance check inspection of a tobacco retailer; or
- initiating monitoring and surveillance of a tobacco product manufacturer's or retailer's website.

FDA may determine that there is no evidence of a violation or may find evidence of the reported violation or of other potential violations that requires additional surveillance, monitoring, and/or inspections.

Lastly, OCI conducts criminal investigations of illegal activities involving FDA-regulated products and referring them to the Department of Justice for prosecution. OCI utilizes FDA's Forensic Chemistry Center, which provides forensic laboratory support by performing many different tests on products that are the subject of investigations. CTP refers potential criminal activity, which would include potential counterfeit or other illicit tobacco products, to OCI to investigate.

From FY 2019 to mid-year of FY 2020, OCI's investigations involving counterfeit, adulterated and misbranded tobacco products have resulted in 13 arrests, 5 convictions, and over $700,000 in court ordered fines and restitution. In FY 2020 alone, OCI's Tobacco Enforcement Program has initiated over 15 criminal investigations. These cases are based upon a combination of referrals from CTP, complaints from the general public and Center-initiated inspections, as well as information provided by sources within regulated industry. In a recent OCI-led investigation, a defendant was charged in Federal court for trafficking in a counterfeit electronic nicotine delivery system. Thus far, the investigation has led to the seizure of thousands of illicit nicotine delivery devices.

5. Under the new proposed rule requiring manufacturers to submit premarket tobacco product applications, how will the FDA weigh factors such as the product components, ingredients, additives, constituents, toxicological profile and health impact in determining whether a manufacturer has demonstrated appropriate protection of public health?

The Premarket Tobacco Product Applications and Recordkeeping Requirements proposed rule, if finalized, would explain what information applicants would need to include in their applications in order for FDA to find that the marketing of a new tobacco product is appropriate for the protection of public health. The proposed rule does not provide a calculus as to how the Agency will weigh various factors in determining whether the marketing of the new tobacco product would be appropriate for the protection of public health; how all the many factors are weighed to make this determination will vary depending on the tobacco product being evaluated. The proposed rule's preamble does provide some examples of how an applicant could help show that permitting the marketing of its new tobacco product would meet the statutory standard of appropriate for the protection of the public health.

In accordance with section 910(c)(5) of the FD&C Act, FDA will base its determination of whether permitting the marketing of a product would be appropriate for the protection of public health 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. In addition to the proposed rule, in June 2019, FDA published a guidance[14] to provide recommendations on some appropriate means of addressing the premarket authorization requirements for deemed ENDS products. CTP will consider the totality of the evidence, as well as the strengths and limitations of each information source and study in the review of a PMTA to determine whether the marketing of the proposed new product is appropriate for the protection of public health.

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

6. **Will the health impact analysis include things such as adult versus teen use and preferences, flavors, marketing of products, and potential for e-cigarette users to return to traditional cigarettes?**

Yes, FDA's premarket review of new tobacco products includes an evaluation of a number of health impacts. FDA's finding that permitting a new tobacco product to be marketed through the PMTA pathway would be appropriate for the protection of the public health 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 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, including youth, will start using such products.

For example, FDA's consideration of the likelihood that nonusers, including youth, will start using an e-cigarette product could involve consideration of youth flavor preferences, how the product will be marketed, and the extent to which youth will be exposed to the marketing. Youth appeal and use behaviors are an important aspect for applicants to include in a premarket tobacco product application.

The Honorable Markwayne Mullin (R-OK)

1. **During last week's Senate Ag Appropriations mark up, the Committee added report language that "commended" the Administration's actions to confront underage nicotine vaping, but also described the Committees "deep concern about a separate public health crisis involving vapor products ... likely caused by low quality or adulterated vaping products that contain THC."**

   The newly added bill language requires FDA to determine how product design requirements could help prevent consumers from modifying or adding any substances to these products not intended by the manufacturer.

   Is this the real root of the lung illness outbreak issue?

FDA, CDC, and state health authorities have made progress in identifying substances of concern in the e-cigarette, or vaping, product use-associated lung injury (EVALI) outbreak. National emergency department data and active case reporting from state health departments around the country show a sharp rise in symptoms or cases of EVALI in June 2019, a peak in September 2019, and a gradual, but persistent decline since then.

National and state data from patient reports and product sample testing suggest THC-containing vaping products, particularly from informal sources like friends, or family, or in-person or online dealers, are linked to most EVALI cases and played a major role in the outbreak.

Vitamin E acetate is strongly linked to the EVALI outbreak. Vitamin E acetate has been found in product samples tested by FDA and state laboratories and in patient lung fluid samples tested by CDC from geographically diverse states. Vitamin E acetate has not been found in the lung fluid of people that do not have EVALI. However, there is not sufficient evidence to rule out the contribution of other chemicals of concern, including chemicals in either THC or non-THC products, in some of the reported EVALI cases.

On February 18, 2020, in accordance with the "Further Consolidated Appropriations Act, 2020," FDA published a Request for Information (RFI) in the *Federal Register* to solicit information regarding EVALI. The Agency specifically sought information related to the use of vaping products that are associated with EVALI, including comment on product design and ways to prevent the public from modifying or adding substances to these products that are not intended by the manufacturer. FDA is reviewing the information submitted to the RFI.

2. Vapor products started being sold in the U.S. around 2007 – and began to be regulated by the FDA in 2016. We are more than a decade into vapor use in American – but these cases are just now appearing. Legal vapor sellers have had to register with the FDA, list product ingredient with the FDA, and open their facilities up to FDA inspections.

Is there a recent change in what is being put into products before being sold on the black market that is responsible for these newly and rapidly occurring illnesses?

As mentioned above, national and state data from patient reports and product sample testing suggest THC-containing vaping products, particularly from informal sources like friends, or family, or in-person or online dealers, are linked to most EVALI cases and played a major role in the outbreak.

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With respect to distribution, FDA is investigating the supply chains related to the products these patients used.