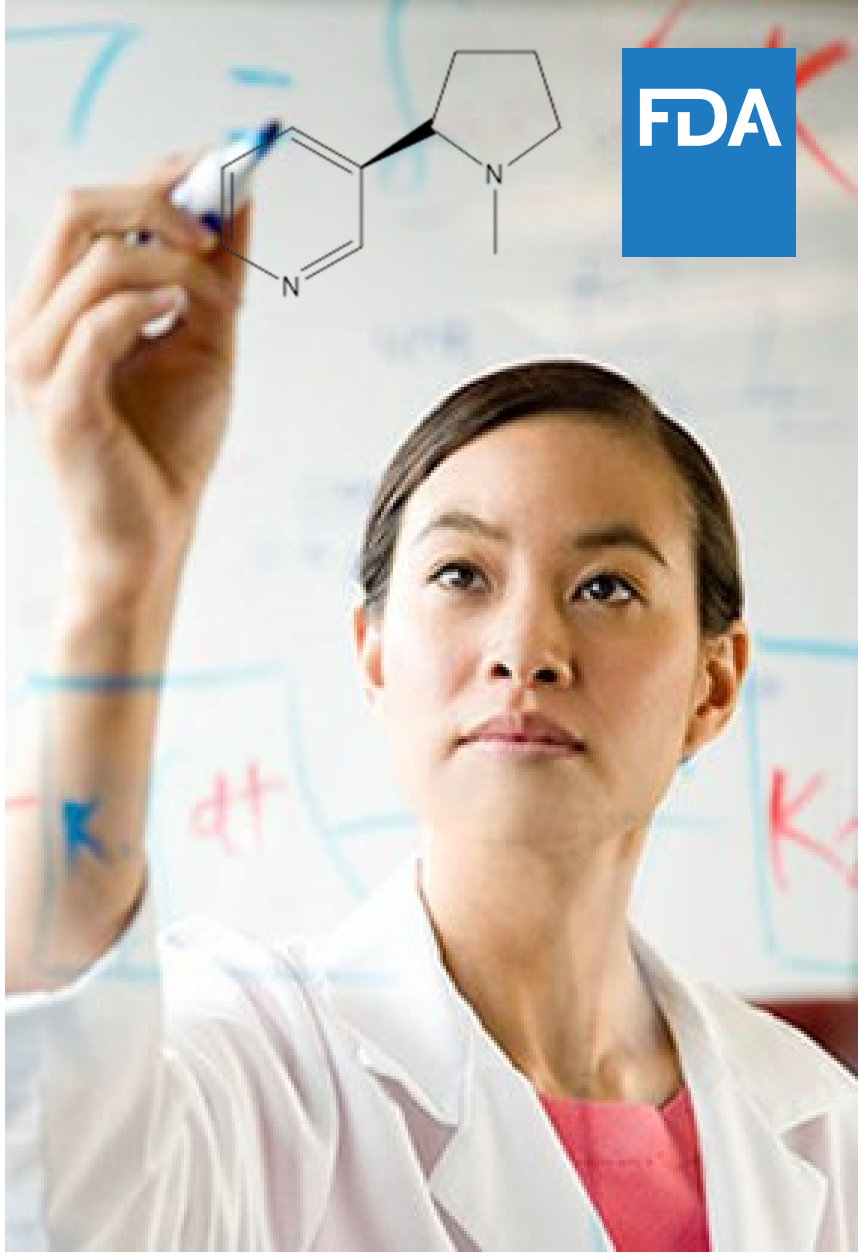
TOBACCO AND NICOTINE: HISTORY, REGULATION, AND LESSONS LEARNED

Presented by
Priscilla Callahan-Lyon, MD
Senior Science Advisor
Office of Center Director, CTP, FDA



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Sept 16, 2021

CENTER FOR TOBACCO PRODUCTS

AGENDA

- Brief History of Tobacco in the United States
- U.S. Consumer Protection and the Tobacco Control Act
- E-cigarettes – Nicotine addiction, Other Concerns
- FDA Evaluation of New Tobacco Products
- Reporting Tobacco Product Adverse Events to FDA

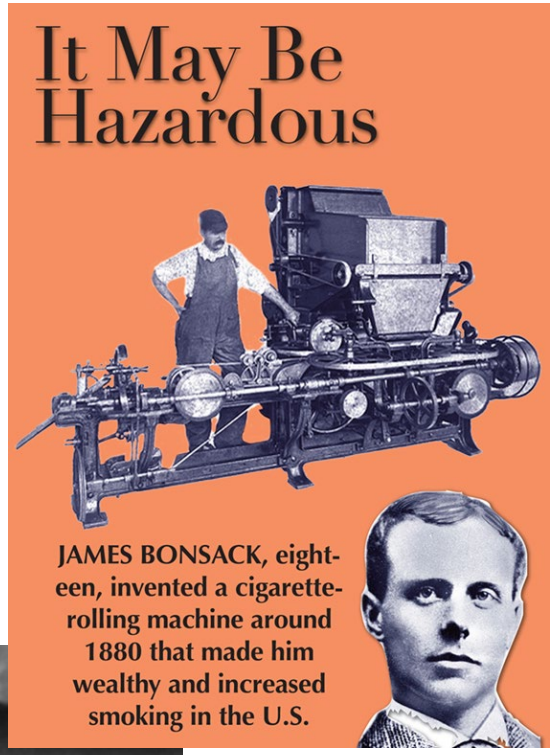
HISTORY OF TOBACCO IN THE UNITED STATES

BRIEF HISTORY OF TOBACCO IN THE U.S.

- Columbus noted residents using tobacco in 1492 and brought it to Europe.
- Tobacco was used as currency in colonial America.
- Growing tobacco is labor intensive and enslaved people were commonly used.
- Tobacco is in same plant family as potato, pepper, nightshade, tomatoes, and eggplant.
- In U.S., chewing tobacco – made by mixing molasses with tobacco leaves – was primary method of use until late 1800s. Cigarettes became more popular in the U.S. after the Civil War.

BRIEF HISTORY OF TOBACCO IN THE U.S. (CONT.)

- The first U.S. tobacco company was Lorillard – established in 1760.
- Cigarette rolling machine was invented in 1881 and “safety” matches ~ 1900 – this helped make smoking a major domestic industry.
- During World War I, Army surgeons praised cigarettes for helping the wounded relax and easing their pain.
- Even in World War II, military rations included cigarettes.

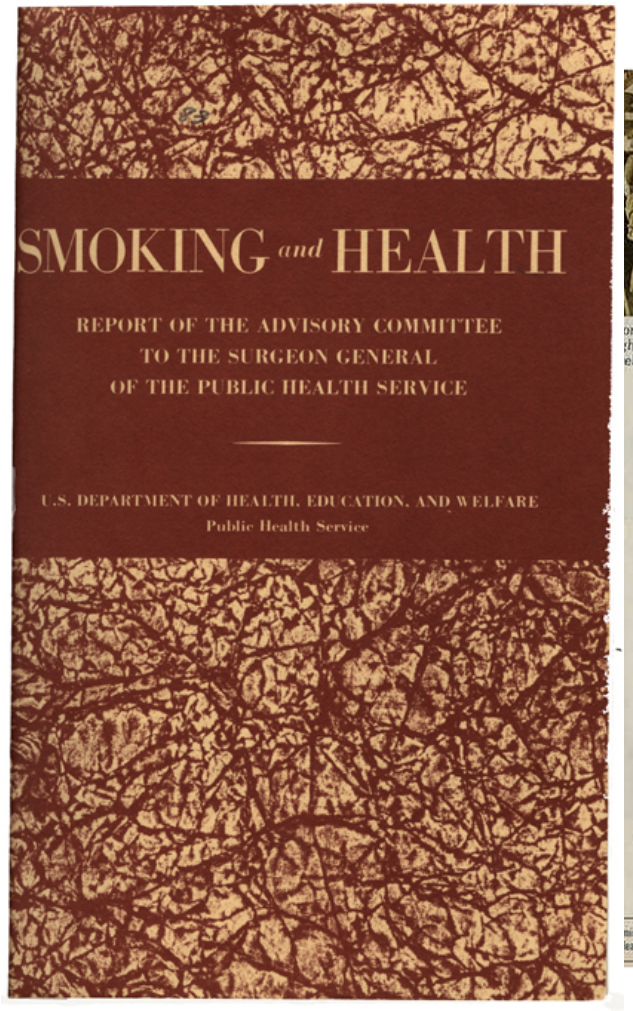


BRIEF HISTORY OF TOBACCO IN THE U.S. (CONT.)

- Smoking was first linked to lung cancer and other diseases in the late 1940s and early 1950s. In 1952 Reader's Digest published "Cancer by the Carton."
- The tobacco industry responded by forming the "Tobacco Industry Research Council" to counter growing health concerns. Marketing of filtered and 'low-tar' cigarettes resulted in a rebounding of dropping sales.
- In 1956, a Surgeon General's scientific study group determined that there was a causal relationship between excessive cigarette smoking and lung cancer.

BRIEF HISTORY OF TOBACCO IN THE U.S. (CONT.)

- In England, the 1962 Royal College of Physicians report emphasized smoking's causative role in lung cancer.
- The first Surgeon General's report on Smoking and Health – issued in 1964 – stated unequivocally that "cigarette smoking is causally related to lung cancer in men."
- First warnings on cigarette packs appeared in 1966.
- 1968 – Virginia Slims brand introduced – targeting women.



BRIEF HISTORY OF TOBACCO IN THE U.S. (CONT.)

- All broadcast advertising was banned in 1971.
- In 1975, the Army and Navy stopped including cigarettes in rations for service members. Smoking was restricted in all federal government facilities in 1979 and was banned in the White House in 1993.
- 1987 – debut of Joe Camel (kid-friendly cartoon character).

BRIEF HISTORY OF TOBACCO IN THE U.S. (CONT.)

- Additional “Influencer” advertisements

BRIEF HISTORY OF TOBACCO IN THE U.S. (CONT.)

- In 1994, Mississippi became the first state to sue the tobacco industry to recover Medicaid costs for tobacco-related illnesses, settling its suit in 1997. A total of 46 states eventually filed similar suits. Three other states settled individually with the tobacco industry—Florida (1997), Texas (1998), and Minnesota (1998).
- On November 23, 1998, the tobacco industry approved to a 46-state Master Settlement Agreement, the largest settlement in history, totaling nearly $206 billion to be paid through the year 2025.
- 2006 – Final ruling finding tobacco industry guilty of lying for 50 years and deceiving American public on health issues and marketing to children.

WHAT THE INDUSTRY KNEW ABOUT NICOTINE – AND WHEN

"Nicotine is addictive. We are, then, in the business of selling nicotine – an addictive drug."

- Brown and Williamson (1963)

"The cigarette should be conceived not as a product but as a package. The product is nicotine…Think of the cigarette pack as a storage container for a day's supply of nicotine…Think of a cigarette as a dispenser for a dose unit of nicotine. Think of a puff of smoke as the vehicle of nicotine."

- Phillip Morris (1972)

"In a sense, the tobacco industry may be thought of as being a specialized, highly ritualized, and stylized segment of the pharmaceutical industry. Tobacco products uniquely contain and deliver nicotine, a potent drug with a variety of physiological effects."

- R. J. Reynolds (1972)

WHAT THE INDUSTRY KNEW ABOUT NICOTINE (CONT.)

The "confirmed smoker"

"His choice of product and pattern of usage are primarily determined by his individual nicotine dosage requirements and secondarily by a variety of other considerations…Our industry is then based upon design, manufacture and sale of attractive dosage forms of nicotine."

- R. J. Reynolds (1972)

The "pre-smoker" or "non-smoker"

"…the things which keep a confirmed smoker habituated and 'satisfied'…are unknown and/or largely unexplained to the non-smoker…only after experiencing smoking for some period of time do the physiological 'satisfactions' and habituation become apparent and needed…we must somehow convince him with wholly irrational reasons that he should try smoking, in the hope that he will for himself then discover the real 'satisfactions' obtainable."

- R. J. Reynolds (1972)

WHAT THE INDUSTRY KNEW ABOUT NICOTINE (CONT.)

"BAT should learn to look at itself as a drug company rather than as a tobacco company."

- British American Tobacco (1980)

"The entire matter of addiction is the most potent weapon a prosecuting attorney can have in a lung cancer/cigarette case. We can't defend continued smoking as 'free choice' if the person was 'addicted'."

- The Tobacco Institute (1980)

U.S. CONSUMER PROTECTION AND THE TOBACCO CONTROL ACT

BRIEF HISTORY OF U.S. CONSUMER PROTECTION

- FDA founded by the Pure Food and Drugs Act (1906)
- Culmination of about 100 bills over a quarter-century that aimed to rein in long-standing, serious abuses in the consumer product marketplace
- Act was partially in response to public outrage at the unhygienic conditions in the Chicago stockyards as described in “The Jungle”
- Consumer Bill of Rights established (1962) and expanded (1985):
  - Right to Safety
  - Right to Information
  - Right to Choose
  - Right to be Heard
  - Right to Satisfaction of Basic Needs
  - Right to Redress
  - Right to Consumer Education
  - Right to Health Environment

THE TOBACCO CONTROL ACT BECAME LAW JUNE 22, 2009

Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act or TCA)

- Authority to regulate the manufacture, distribution and marketing of tobacco products
  - Restricts Tobacco Marketing and Sales to Youth
  - Requires Smokeless Tobacco Product Warning Labels
  - Ensures “Modified Risk” Claims are Supported by Scientific Evidence
  - Requires Disclosure of Ingredients in Tobacco Products
  - Preserves State, Local and Tribal Authority
- Authority to help protect the public and create a healthier future for all Americans
  - Requires tobacco company owners and operators to register annually
  - Allows FDA to implement standards for tobacco products to protect public health (regulate nicotine and ingredient levels)
  - Bans cigarettes with characterizing flavors except menthol and tobacco
  - Funds FDA regulation of tobacco products through a user fee on the manufacturers of certain products sold in the US, based on their market share

FINAL DEEMING REGULATION

- TCA provided for FDA regulation of the manufacturing, marketing, and distribution of cigarettes, cigarette tobacco, roll-your-own, and smokeless tobacco
- On August 8, 2016, a final rule went into effect that "deemed" all products meeting the statutory definition of *tobacco product*, including components or parts (but excluding accessories), to be subject to FDA's tobacco product authorities, including:
  - ENDS (e-cigarettes, e-cigars, vape pens, etc.)
  - All cigars
  - Pipe tobacco
  - Nicotine gels
  - Waterpipe (hookah)
  - Dissolvables not already under FDA's authority
  - Future tobacco products

IMPORTANT DETAILS ABOUT TOBACCO PRODUCT REGULATION

- CTP regulates products “made or derived from tobacco” – this includes components, parts and accessories if they are intended or expected to alter or affect the tobacco product performance or be used with or for the human consumption of a tobacco product.

- The statute excludes CTP jurisdiction over products that are a drug, device, or combination product.

- CTP jurisdiction is not based on the way a product is delivered; tobacco does not need to be inhaled or vaped to be regulated by CTP.

HOW FDA IS USING ITS REGULATORY AUTHORITY

- Restricting product changes to protect public health
- Prohibiting modified risk claims that state/imply reduced exposure or risk without scientific evidence, FDA review, and an order
- Restricting marketing and distribution to protect public health
- Ensuring industry compliance with FDA regulation through education, inspections, and enforcement
- Educating the public about FDA's regulatory actions
- Working to prevent youth initiation and encourage cessation of tobacco by all ages via public education campaigns designed to create behavior change
- Expanding the science base for regulatory action and evaluation

EXPANDING OUR SCIENCE BASE

To expand the scientific foundation for FDA tobacco product regulation

- We fund research that is then administered by the National Institutes of Health Tobacco Regulatory Science Program
  - Investigator initiated awards
  - Supplements to existing grants or cooperative agreements
  - Tobacco Centers of Regulatory Science (TCORS) performs research in areas of importance to FDA
  - Population Assessment of Tobacco and Health (PATH) Study (tobacco longitudinal cohort study)
- We support national surveys (e.g., National Youth Tobacco Survey)
- We support and conduct laboratory analyses (FDA, CDC, National Center for Toxicological Research)

E-CIGARETTES: NICOTINE ADDICTION, AND OTHER CONCERNS

E-CIGARETTES: THE BASICS

- Electronic Nicotine Delivery Systems (ENDS) are a heterogeneous group of products that include e-cigarettes, e-cigars, and e-hookah
- The devices heat an “e-liquid” that usually contains nicotine into an aerosol inhaled by the user. (also known as ‘vaping’)
  - E-liquids include varying compositions of flavorings, propylene glycol, vegetable glycerin and other ingredients
- Come in a variety of shapes and designs (open tank vs closed system)
- Some devices closely resemble a USB flash drive and have emissions that are hard to see
  - These characteristics may make the products more attractive to youth
  - Kids may be trying these products and liking them without knowing they contain nicotine

NICOTINE AND THE ADOLESCENT BRAIN: NOT A GOOD COMBINATION

FDA

Nicotine negatively affects the developing brain

- Nicotine can rewire the brain to crave more nicotine, particularly because adolescent brains are still developing[1]
- Nicotine exposure during adolescence may have long-lasting effects such as increased impulsivity and mood disorders[2, 3]
- Nicotine exposure during adolescence may have long-term effects on parts of the brain responsible for addiction, learning, and memory[4-10]
- Nicotine exposure during adolescence affects brain functions important for reward processing, which makes it easier for youth to become addicted to nicotine[11, 12]
- Youth who exclusively use e-cigarettes are more likely to start smoking conventional cigarettes[13]

1 - USDHHS 2010; 2 - USDHHS 2016; 3 - England et al. 2017; 4 - Ehlinger et al. 2016; 5 - McDonald et al. 2007; 6 - Smith et al. 2015
7 - Xu et al. 2003; 8 - Bergstrom et al. 2010; 9 - Adermark et al. 2015; 10 - Lee et al. 2015; 11 - Trauth et al. 2001; 12 - Placzek et al. 2016
13 - Chaffee et al. 2018

OTHER E-CIGARETTE-RELATED CONCERNS

- From 2015 – 2017 battery-related injuries from ENDS led to ~1000 ER visits/year
  - FDA received 41 reports to the Safety Reporting Portal in 2018, 25 in 2019, 10 in 2020

- FDA continues to receive reports of seizures associated with ENDS use
  - There have been 310 reports of seizures/neurological symptoms in ENDS users between Dec 19, 2010, and Dec 31, 2020 (some may be duplicates)
  - No clear etiology for the symptoms has been identified

- In July 2019, FDA and CDC became aware of youth developing respiratory symptoms, some severe. All were using 'vaping' devices, many using multiple products
  - By Feb 2020, CDC had received reports of 2807 hospitalized patients with e-cigarette, or vaping, associated lung injury (EVALI) with 68 deaths; still seeing case reports occasionally
  - The lung injury was linked to Vitamin E acetate – an illicit additive/cutting agent added to vaped cannabis products

CANNABIS AND TOBACCO OVERLAP

- Aerosolized delivery; i.e., vaping - increasingly popular for cannabis and nicotine products
- Populations Assessment of Tobacco and Health (PATH) study data:
  - Prevalence of any Wave 1 (2013-2014) cigarette use, e-cigarette use, and dual use was significantly higher for youth who reported Wave 1 cannabis use
  - 39% of adults (≥18) surveyed in Wave 4 (2016-2018) report ever vaping (n=13,191)
    - Of these; 28% ever vaped with marijuana
- National Youth Tobacco Survey 2020 data:
  - 19.5% of middle and high school students reported ever using marijuana in an e-cigarette
    - In 2017 this was 11.1%
  - 68% of those who report currently using e-cigarettes reported ever using marijuana in e-cigarettes
- Monitoring the Future 2020 data:
  - Daily marijuana rate is highest since 1991 (6.9% for 12th graders)
  - The overall annual marijuana use did not increase in 2020 despite an increase in vaped cannabis

FDA EVALUATION OF NEW TOBACCO PRODUCTS – INCLUDING E-CIGARETTES

FDA EVALUATION OF NEW TOBACCO PRODUCTS

- New Tobacco Product – means any tobacco product that was not commercially marketed in the U.S. as of Feb 15, 2007 (all ENDS are new tobacco products)
- This includes products which were marketed on that date but were modified after that date
  - Modification includes a change in “design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery, or form of nicotine, or any other additive or ingredient” of a tobacco product.
  - Modifying a marketed product = creating a new tobacco product
- There are three pathways to market for tobacco products
  - Substantial Equivalence (SE)
    - Found by FDA to have the same characteristics as a predicate product or, if different, to not raise different questions of public health. Predicate product = marketed prior to 2/15/2007 or previously found SE
  - Exemption from Substantial Equivalence – relatively uncommon
  - Premarket Tobacco Application (PMTA) – will be discussed on future slides

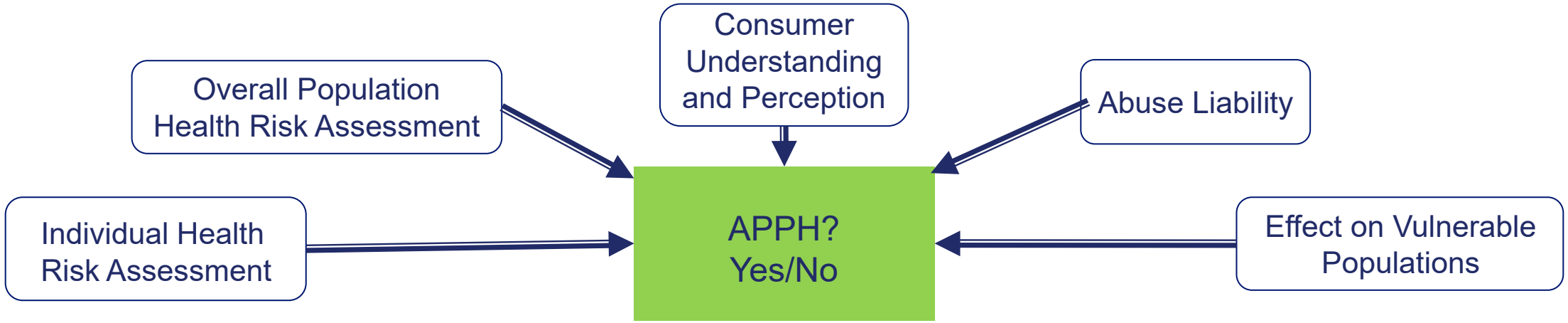
FDA REVIEW OF PMTAs

- Public Health Considerations: Section 910(c)(4) requires that FDA assess whether the marketing of a tobacco product....is **appropriate for the protection of the public health***....with respect to the **risks and benefits to the population as a whole**, including users and nonusers...
- PMTA review is multidisciplinary. The scientific review team may include:
  - Product Science: Chemistry, Engineering, Microbiology
  - Nonclinical Science: Environmental, Toxicology
  - Individual Health Science: Medical, Behavioral & Clinical Pharmacology
  - Population Health Science: Epidemiology, Social Science, Statistics
  - Staff from other offices (Compliance and Enforcement, Health Communication and Education)

*APPH

PMTA REVIEW: LINES OF EVIDENCE

- As reflected in the proposed rule on Premarket Tobacco Product Applications and Recordkeeping Requirements, many different lines of evidence can be used to support the determination whether marketing of the new product submitted under the PMTA pathway is appropriate of the protection of the public health
- Lines of evidence can include, but are not limited to, nonclinical studies, original scientific investigations, analyses of existing national datasets, or published peer-reviewed literature



EVALUATION OF ENDS PRODUCTS

- The PMTA for ENDS Guidance published in June 2019
- This Guidance provides FDA's thinking on the types of information needed to support a PMTA for an ENDS, or electronic nicotine delivery system, product(s)
- The Guidance includes:
  - Public health considerations for ENDS products
  - Recommendations for scientific content to be included in PMTAs for e-liquids, ENDS devices, and products that package these together
  - Postmarketing information

NOTE: This is a guidance. FDA publishes guidances to assist industry and others. Guidances are not binding on FDA or the public; rather they represent FDA's current thinking on a topic.

REPORTING TOBACCO PRODUCT ADVERSE EVENTS TO FDA

REPORTING TOBACCO-RELATED ADVERSE EXPERIENCES

- FDA wants to know about unexpected health or safety problems that may have been caused by use of or exposure to a particular tobacco product.
- Report using Adverse Safety Reporting Portal: **www.safetyreporting.hhs.gov**
- Report unexpected health or safety problems such as:
  - Overheating, fires, explosions, or burns
  - Seizures or other serious nervous system issues
  - Unusual or unexpected health concern
  - Toxic or allergic reactions
  - An unusual problem in a long-time user
  - Foreign material in the product
  - Problems with packaging, labeling or product parts

POTENTIAL TOBACCO PRODUCT VIOLATIONS REPORTING

- Report potential tobacco-related violations using FDA Form 3779
- Any member of the public can submit a report (reports are not collected from children < 13 years)
- Information to include:
  - When you saw the potential violation
  - Where you saw the potential violation
  - What you saw
- All reports will remain private to the extent allowed by law
- Information from the public is helpful in identifying problems with marketed products and possible violations of the laws we enforce

QUESTIONS

THE TOBACCO CONTROL ACT'S AUTHORITIES

The Tobacco Control Act amended the Food, Drug, and Cosmetic Act to provide FDA authority for:

- Premarket review of new and modified risk tobacco products
- Post-market surveillance
- Product standards
- Testing and reporting of ingredients
- Reporting of harmful and potentially harmful constituents
- Adverse event reporting
- New warning labels
- Advertising and promotion restrictions
- User fees – entirely funded through industry-paid user fees based on market share (not applications)