UPDATE FROM THE FDA

CENTER FOR TOBACCO PRODUCTS

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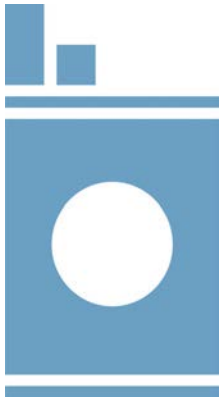
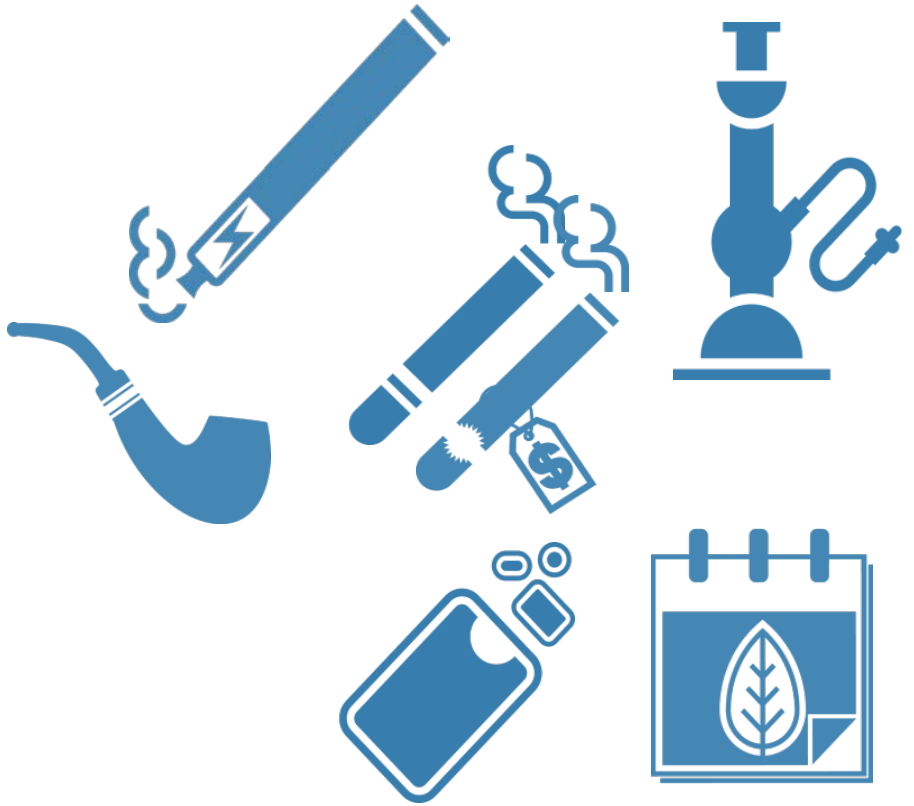
THE TOBACCO CONTROL ACT

- Since 2009, CTP had authority to regulate tobacco products intended for human consumption to reduce harm across the population
  - Reducing the number of people who start to use tobacco products
  - Encouraging more people to stop using these products
  - Reducing the adverse health impact for those who continue to use these products
- Initially regulated the manufacture, marketing, and distribution of cigarettes, cigarette tobacco, roll-your-own, and smokeless



NEW REGULATION

- FDA finalized a rule effective August 8, 2016 to regulate all tobacco products, including components or parts (but excluding accessories), 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 the FDA's authority
  - Future tobacco products



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
- Reporting of ingredients
- Reporting of harmful and potentially harmful constituents
- Adverse event reporting
- Health warnings
- Advertising and promotion restrictions
- User fees

THE TOBACCO CONTROL ACT'S AUTHORITIES

In general, CTP's regulatory authorities do **not** extend to:

- Setting tax rates for tobacco products
- Regulating therapeutic products, such as those marketed to treat tobacco dependence (regulated by other parts of FDA)
- Setting clean indoor air policies
- Regulating tobacco growing
- Requiring the reduction of nicotine yields to zero
- Providing cessation services
- Banning all cigarettes, smokeless tobacco products, little cigars, other cigars, pipe tobacco, or roll-your-own tobacco products
- Changing the minimum age to purchase tobacco products

POPULATION HEALTH STANDARD

- FDA/CTP regulates tobacco based on a population health model
  - Tobacco cannot be regulated using FDA's traditional "safe and effective" standard
- Regulatory actions are based on the risks and benefits to the population as a whole, including both users and nonusers of the product

TOBACCO REGULATORY SCIENCE

REGULATORY SCIENCE

- Scientific discipline with independent goals and measures not found in either the basic or applied sciences
- Ensures that scientifically valid techniques, tools, and models are available to evaluate products
- Informs regulatory actions that promote optimal public health outcomes

TOBACCO REGULATORY SCIENCE

- Informs FDA's regulatory authority
- Recognizes that tobacco products cannot be regulated using FDA's traditional "safe and effective" standard
- Enables FDA to best assess the "net" population-level health impacts

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Norman B. (2012). The Food and Drug Administration gets new tools to spur regulatory science. Health Affairs (Millwood), 31, 1919–1922.

SCIENCE-BASED REVIEW OF TOBACCO PRODUCTS

PRE-MARKET REVIEW OF NEW TOBACCO PRODUCT – RECENT PMTA DECISION

- FDA recently authorized the marketing of new tobacco products for Phillip Morris Products S.A's IQOS "Tobacco Heating System"
  - Electronic device that heats tobacco-filled sticks wrapped in paper to generate a nicotine-containing aerosol. Referred to as "heat-not-burn" or "heated" tobacco products but meet the definition of a cigarette in the FD&C Act.
  - Authorized products include the IQOS device, Marlboro Heatsticks, Marlboro Smooth Menthol Heatsticks and Marlboro Fresh Menthol Heatsticks

- The authorization of these products is appropriate for the protection of the public health because, among several key considerations, the products produce fewer or lower levels of some toxins than combustible cigarettes
  - Stringent marketing restrictions on the products to prevent youth access, use and exposure
  - Postmarket requirements include monitoring market dynamics such as potential youth uptake

ISSUING FOUNDATIONAL RULES AND GUIDANCES

- FDA is working to advance rulemaking on a number of foundational rules and guidances, including:
  - Substantial Equivalence (SE) rule *(proposed rule issued April 2, 2019)*
  - PMTA for ENDS Final Guidance *(final guidance issued June 11, 2019)*
  - Premarket Tobacco Product Application (PMTA) rule *(proposed rule issued Sept. 25, 2019; comment period open till Nov. 25)*
  - Modified Risk Tobacco Product Application (MRTP) rule
  - Tobacco Product Manufacturing Practice (TPMP) rule
- FDA has helped make the review process more efficient, predictable and transparent while upholding our public health mission
- FDA has also continued to provide information to manufacturers through online information, meetings, and webinars
  - Recent Public Meeting: ***Deemed Tobacco Product Applications, Oct. 28-29, 2019***

LITIGATION OVER 2017 COMPLIANCE POLICY

- As a result of litigation over the 2017 Compliance Policy, a court ordered that applications for marketing orders for deemed tobacco products on the market as of Aug. 8, 2016 must be filed within ten months of the order (no later than May 12, 2020)
  - Products for which applications have not been filed within this period shall be subject to FDA enforcement action
  - Products for which applications have been timely filed may remain on the market for up to a year (no later than May 12, 2021) while FDA reviews the application
  - If FDA has not made a final decision within a year, those products must come off the market or be subject to enforcement
- The order does not restrict FDA's authority to enforce premarket review requirements before the close of either the ten month application submission period or the FDA application review period

SCIENCE IS CENTRAL TO CTP REGULATORY ACTIVITIES

Data drives decisions that help CTP achieve its mission of reducing the morbidity & mortality associated with tobacco use

RESEARCH INTERESTS THAT ALIGN WITH NCTR

- Toxicity – Understanding how tobacco products and changes to tobacco product characteristics affect their potential to cause morbidity and mortality, including animal and cell culture models as well as novel alternative toxicology approaches that test the toxicity of tobacco smoke, aerosols, or specific constituents in tobacco
- Areas of interest include
  - Toxicological assays (in vivo and in vitro) to compare toxicity across different types of tobacco products within the same class including electronic nicotine delivery systems (ENDS), cigars, waterpipes and smokeless tobacco;
  - How product design characteristics (and changes in those characteristics) impact constituent exposure and toxicity from tobacco products;
  - Biomarkers to assess exposure, as well as biomarkers to assess harm or toxicity of non-cigarette tobacco products, including ENDS; and
  - Toxicological impact of nicotine, flavors, and other constituents across different routes of exposure.

COMPLETED CTP COLLABORATIONS WITH NCTR

- **Priority Setting of Harmful and Potentially Harmful Constituents (HPHCs) in Tobacco Smoke Products with Bioinformatics** E07509.01 (NCTR: Tong W, CTP: Orr M)
- Completed FY12-FY14
- Study Aims
  - Develop and apply the bioinformatics methods to identify relationships between the smoke constituents and the major health endpoints (cancer, cardiovascular, non-neoplastic respiratory, developmental, reproductive, and addiction) based on the scientific literature.
- Benefit to FDA and CTP
  - Support priority setting for tobacco smoke constituents and decision making on which constituents to evaluate further in standard scientific studies.
  - Findings showed that 47% of the tobacco smoke constituents have limited scientific data.

COMPLETED CTP COLLABORATIONS WITH NCTR

- **Extrapolation of in vitro acrolein dose-response derived in air-liquid-interface airway epithelial models to in vivo lung toxicity** E07603.01 (NCTR: Cao X, CTP: Healy S)
- Completed FY17-FY18
- Study Aims
  - Develop methodologies comprising an in vitro testing platform and computational modeling extrapolation strategies for conducting in vitro-to inform based assessment of human health risk associated with acrolein exposure.
- Benefit to FDA and CTP
  - Combined an in vitro human testing platform with a chemical-specific computational extrapolation strategy in an attempt to establish an in vitro-to-in vivo extrapolation.
  - Helped to develop an in vitro methodology to inform regulatory review of equivalent or modified health risk claims of tobacco products without animal testing.

COMPLETED CTP COLLABORATIONS WITH NCTR

- **14-Day Nose-Only Inhalation Toxicity Study of NNK in Rats** E07534.01 (NCTR: Hu S, CTP: Yeager R)
- Completed FY14-FY15
- Study Aims
  - Evaluate the subacute toxicity profile of NNK in Sprague Dawley rats following nose-only inhalation exposure for 1 hour per day, 7 days per week for 14 consecutive days.
- Benefit to FDA and CTP
  - Provided the dose-range of NNK in the subsequent studies where toxicity of NNK following 90-day repeated-dose inhalation administration was conducted.

ACTIVE CTP COLLABORATIONS WITH NCTR

Evaluating the Toxicity and Inflammation Produced by Cigarette Smoke Using Human In Vitro Airway Models E07549.01 (NCTR: Cao X, CTP: Healy S)

- Started/Ongoing FY14-FY20
- Study Aims
  - Measure and evaluate the toxic effects of cigarette smoke using human airway air-liquid interface (ALI) models and assays.
  - Identify the most informative intracellular molecular endpoints for measuring cigarette smoke toxicity in human airway ALI models.
- Benefit to FDA and CTP
  - Using the airway ALI model potentially will generate data that have better predictability of in vivo responses than other in vitro or rodent-based systems, and thus is anticipated to inform tobacco product risk evaluation.

ACTIVE CTP COLLABORATIONS WITH NCTR

Aerosol Inhalation Exposure Chamber Development by Simulation

E07709.01 (NCTR: Min S, CTP: Yee S)

- Started/Ongoing FY19-FY22
- Study Aims
  - Develop a simulation of the tiered inhalation exposure system to deliver equivalent aerosol flow rates to all exposure ports.
  - Optimize the inhalation exposure chamber to ensure consistent, uniform dosing during in vivo inhalation exposure studies.
- Benefit to FDA and CTP
  - If these simulations are successful in accurately modeling inhomogeneous flow rates, this may potentially decrease the method development phase of new studies reducing timelines and cost.
  - These simulations could inform the optimization of the inhalation exposure chamber and provide more exact dosing to animals in future inhalation studies.

ACTIVE CTP COLLABORATIONS WITH NCTR

- **Pharmacokinetic Analysis of Nicotine in Sprague Dawley Rats**
  - E07607.01, NCTR: Tang Y, CTP: Yee S
  - Started/Ongoing : FY16-FY20
- **Early Phase PK Analysis of Nicotine in Sprague Dawley Rats**
  - E07716.01, NCTR: Tang Y, CTP: Yee S
  - Started/Ongoing : FY19-FY22
- **Development of a Multi-Pathway Physiologically Based Pharmacokinetic (PBPK) Model for Nicotine in Humans**
  - E07682.01, NCTR: Fisher J, CTP: Bryant Y
  - Started/Ongoing : FY18-FY21

EXAMPLES OF POTENTIAL AREAS FOR FURTHER CTP COLLABORATIONS WITH NCTR

Inhalation Toxicity Studies

- The evaluation of toxicity with repeated nicotine inhalation exposure from tobacco.
- Determining if inhaled nicotine concentrations, representative of a NOAEL and LOAEL with acute nicotine inhalation exposure, do or do not lead to significant adverse outcomes under subacute exposure conditions.

EXAMPLES OF POTENTIAL AREAS FOR FURTHER CTP COLLABORATIONS WITH NCTR

In Vitro Toxicity of Electronic Nicotine Delivery Systems (ENDS) on Cells at the Air-Liquid Interface (ALI)

- Determining cytotoxic and genotoxic potential of aerosols generated from ENDS products using an ALI exposure system.
- Determining cytotoxic and genotoxic potential of aerosolized ingredients unique to ENDS products using an ALI exposure system.
- Simulation of human inhalation exposure with ALI cultures, and epithelial tissue model to study mode of action, and recapitulate key events involved in tobacco related diseases (e.g., COPD, inflammation)

EXAMPLES OF POTENTIAL AREAS FOR FURTHER CTP COLLABORATIONS WITH NCTR

Flavors in Tobacco Products

Chemicals in Flavorings (ENDS Products)

- Toxicity may result from chemicals formed when flavors are heated or burned
- Studies or information regarding:
  - What toxic chemicals might be formed from heating or burning these flavors or chemicals. What toxic chemicals might be formed from aerosolizing these flavors or chemicals.
  - Potential toxicity or adverse health effects from these chemicals when heated and aerosolized

THANK YOU

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Thank You