PREMARKET TOBACCO PRODUCT APPLICATION CONTENT OVERVIEW

Presented By:
Iilun Murphy, MD
Director
Division of Individual Health Science
Office of Science, CTP, FDA

Disclaimer: This is not a formal dissemination of information by FDA and does not represent Agency position or policy.

BACKGROUND: PREMARKET TOBACCO APPLICATION (PMTA)

- Before a new tobacco product can be legally marketed (Section 910(a)(2) of the FD&C Act), a premarket tobacco application (PMTA) must be submitted, reviewed by FDA, and determined to be appropriate for the protection of public health - unless the product is grandfathered, found to be substantially equivalent (SE) to a predicate tobacco product, or the product is found to be exempt from SE.




PUBLIC HEALTH CONSIDERATIONS

Section 910(c)(4) requires that FDA assess the **risks and benefits to the population as a whole**, including users and nonusers

PMTA STATUTORY REQUIREMENTS - CONTENT

Per section 910(b)(1), a PMTA must contain:

- Full reports of all information, published or known to, or which should reasonably be known to, the applicant, concerning investigations that have been made to show the health risks of the tobacco product *and whether the tobacco product presents less risk than other tobacco products*

- A full statement of the components, ingredients, additives, properties, and the principle or principles of operation, of the tobacco product

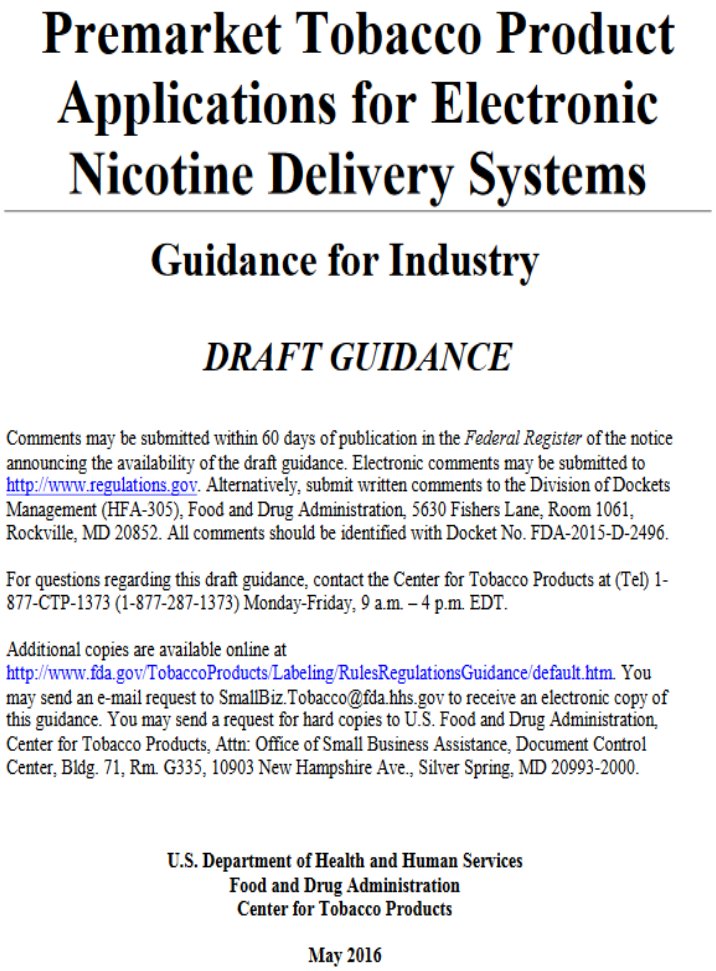
- A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, packing and installation of the tobacco product

BACKGROUND: PMTA STATUTORY REQUIREMENTS (CONT.)

- An identifying reference to any tobacco product standard under section 907 that would be applicable to any aspect of the tobacco product, and either adequate information to show that the aspect of the tobacco product fully meets the tobacco product standard or adequate information to justify any deviation from the standard
- Labeling proposed to be used for the tobacco product
- Samples of tobacco product and of components
- Other information relevant to the subject matter of the application (e.g., Environmental Assessment)

PMTA DRAFT GUIDANCES

- Guidances:
  - "Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems"
  - "Applications for Premarket Review of New Tobacco Products"
  - Recommendations for how to:
    - Meet the statutory requirements for PMTA content under section 910(b)(1)
    - Present information in a way that helps FDA make its decision on whether to issue a marketing order under 910(c)(1)(A)(i) of the FD&C Act
- Not FDA-implemented policy, available for public comment



Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems

Guidance for Industry

DRAFT GUIDANCE

Comments may be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Electronic comments may be submitted to http://www.regulations.gov. Alternatively, submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with Docket No. FDA-2015-D-2496.

For questions regarding this draft guidance, contact the Center for Tobacco Products at (Tel) 1-877-CTP-1373 (1-877-287-1373) Monday-Friday, 9 a.m. – 4 p.m. EDT.

Additional copies are available online at http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/default.htm. You may send an e-mail request to SmallBiz.Tobacco@fda.hhs.gov to receive an electronic copy of this guidance. You may send a request for hard copies to U.S. Food and Drug Administration, Center for Tobacco Products, Attn: Office of Small Business Assistance, Document Control Center, Bldg. 71, Rm. G335, 10903 New Hampshire Ave., Silver Spring, MD 20993-2000.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Tobacco Products

May 2016

OVERVIEW OF SCIENTIFIC STUDIES AND ANALYSES TO SUPPORT A PMTA

SCIENTIFIC STUDIES AND ANALYSES: PRODUCT SCIENCE (CHEMISTRY)

- Section 910(b)(1) of the FD&C Act states that a PMTA will include “a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product”

- The chemistry evaluation considers:
  - Product formulation (including HPHCs)
  - Chemistry design (nicotine, moisture, pH)
  - Tobacco blend
  - Ingredients other than tobacco
  - Manufacturing steps and controls
  - Performance criteria
  - Stability

- Supportive information such as test protocols, quantitative acceptance criteria, data sets, and summary of results assist review

SCIENTIFIC STUDIES AND ANALYSES: PRODUCT SCIENCE (ENGINEERING/MICROBIOLOGY)

Engineering/microbiology analyses address topics including, but not limited to:

- Product design
  - Product dimensions and overall construction (diagrams helpful)
  - Target specification, range limits, and test data
  - Container closure system description
  - Storage and stability
- Principles of operation
  - Heating source, product use, product adjustment
- Manufacturing and packaging
  - Production steps and facilities
  - Supplier information
  - Controls and release testing

PRODUCT SAMPLES

- Applicants may submit at least one sample of the new finished product
- FDA scientists will recommend the number of samples to be submitted to FDA for testing and analysis
- Applicant will receive a letter requesting a specific number of samples and instructions for submission

SCIENTIFIC STUDIES AND ANALYSES: TOXICOLOGICAL RISK / NONCLINICAL STUDIES

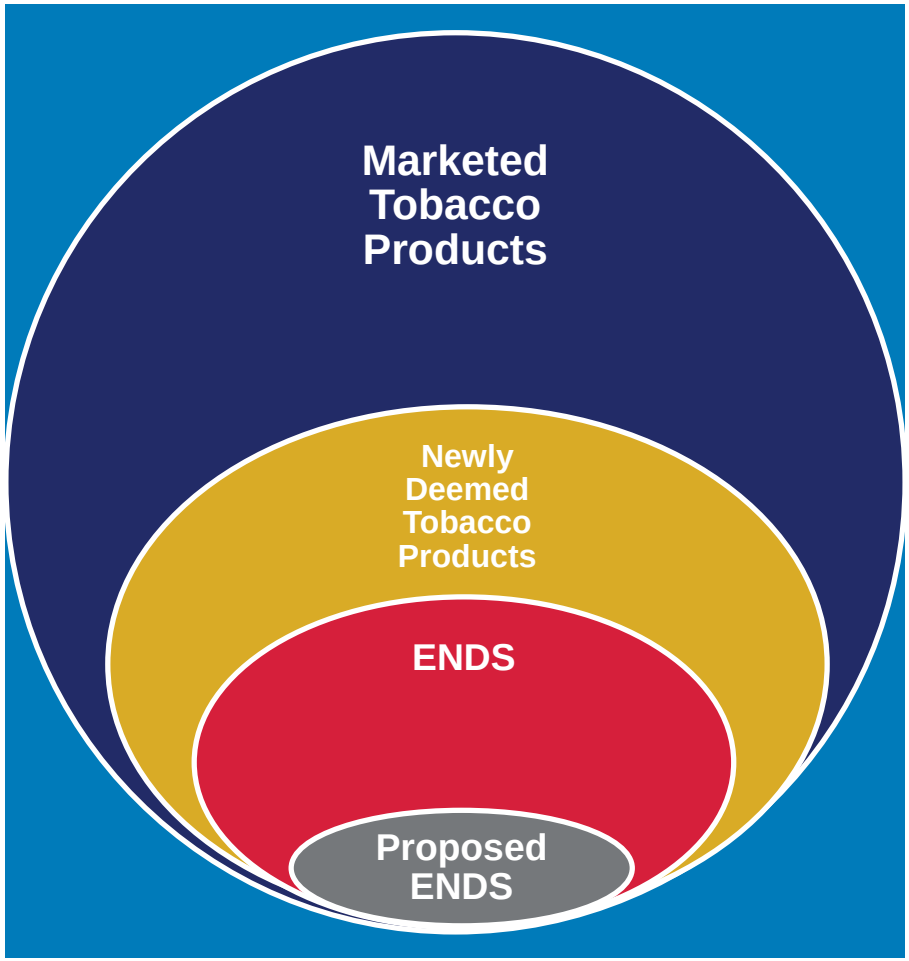
- Identifies potential human health risks, including carcinogenic and non-carcinogenic health effects, and addiction.
- Focuses on exposures to users. Evaluation provides context for data obtained from clinical and epidemiological studies.
- Evaluation includes ingredients, leachables and extractables, constituents that are created the use of the tobacco product, and an analysis of the tobacco mixture to which a user will be exposed.
- Evaluation is useful to include, if available:
  - Rationale for how submitted toxicology studies address user exposures accounting for route of exposure and human exposure levels.
  - Toxicology data from the literature (i.e., all relevant publications)
  - Analysis of toxicants under both intense and non-intense use conditions
  - In vitro toxicology studies (e.g., genotoxicity studies, air-liquid interface studies)
  - Computational modeling of the toxicants in the product (to estimate the toxicity of the product)
  - In vivo toxicology studies if there are unique toxicology issues that cannot be addressed by alternative approaches.

TOBACCO PRODUCT COMPARATORS

Draft guidance out for public comment proposes that the PMTA:

- Compare the new tobacco product to a representative sample of tobacco products on the market (i.e., either grandfathered or with marketing authorization)

- Include justification for why using evidence or data from other products is appropriate



EXAMPLES OF TOBACCO PRODUCT COMPARISON

SCIENTIFIC STUDIES AND ANALYSES: HUMAN SUBJECT STUDIES

Consider including the following information to assess human health impact:

- Likelihood of initiation and cessation by both users and nonusers
  - Perceptions and appeal of product
  - Abuse liability/addictiveness
- Product use patterns (e.g. topography, frequency of use, use by demographics)
- Short and longer-term health effects
- Labeling comprehension
- Human factors impacting product use

SCIENTIFIC STUDIES AND ANALYSES: INITIATION AND CESSATION

- Useful if there are clear definitions and rationale to support meaningful interpretation of research findings
- May not be feasible to directly measure the rate of uptake of a new product in the population
- Multiple lines of evidence strengthen argument related to the likelihood of tobacco product initiation and cessation

EXAMPLES OF HUMAN STUDIES

CONSUMER PERCEPTION

- Consumer perceptions: Widely accepted as predictors to use behavior (may inform likelihood of initiation/cessation)
- Understanding health can be informed by understanding of perception/appeal → impact on behavior intentions, impact on actual behavior
- Product perceptions/intentions, including how consumers (especially youth) perceive, use, or intend to use the products is useful information to FDA
- Qualitative research provides “deep dive” into individuals’ thoughts, feelings, and behaviors; can help put other sources of data into context

CONSUMER PERCEPTION (CONT.)

Studies of consumer perceptions generally follow established methods:

- Best practices for questionnaire design to avoid bias (e.g., AAPOR "Best Practices for Research http://www.aapor.org/Standards-Ethics/Best-Practices.aspx, Designing and Conducting Health Surveys: A comprehensive Guide)
- Rationale and justification for sample sizes
- Use of validated items whenever possible or description of item development and testing
- Clearly defined and pre-specified aims
- Well-explained and justified methods and sample
- Protection of human subject

YOUTH USE OF PROPOSED TOBACCO PRODUCT

- Youth behavioral data **not** required at this time
- **However**, information allowing FDA to evaluate how the proposed new product may influence tobacco initiation and use among youth is useful to determine protection of public health
- Inferences regarding youth may be extrapolated from young adults, as well as derived from marketing data, scientific literature reviews, national surveys, and/or bridging information
- It is useful to clearly explain how such data can be extrapolated to youth for the specific products in the PMTA

ABUSE LIABILITY

- Abuse liability testing may offer data and information to support Section 910(c)(4) of the FD&C Act, including understanding:
  - "(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."

- Traditional abuse liability assessments: Designed to evaluate *likelihood* of abuse, can also assess *consequences* of abuse.
- Determination of a product's abuse potential/abuse liability can be accomplished through multiple lines of evidence.

ABUSE LIABILITY & TOPOGRAPHY

Common principles in pharmacology studies:

- Pharmacodynamic (PD) properties often collected concurrently with pharmacokinetics (PK): allows comparisons of nicotine's effects on PK and PD
- Switching studies: Participants could be directed to substitute an e-cigarette with similar nicotine delivery for usual brand cigarette
- Explanation of selection of prescribed puffing regimens
- Rationale for selection of comparator products (e.g.,e-liquid nicotine concentrations, flavors, etc.)
- Study limitations are identified
  - Literature is often used to provide sufficient rationale for "bridging" between products and studies
- Discussion of existing literature is often included in the study rationale and/or publication

LABELING

Section 910(c)(1)(A)(ii) of the FD&C Act requires FDA to deny a PMTA and issue an order that the product may not be introduced into interstate commerce where FDA finds that……the proposed labeling is false or misleading.

LABELING (CONT.)

General design concepts of label comprehension studies:

- Establish primary communication objectives
- Specify study design that meets objectives and calculate appropriate sample size
  - Open-label, uncontrolled trials
  - Preliminary research and pilot testing with different label prototypes may be required prior to conducting the larger study
  - Label development is typically an iterative process
- Enroll an appropriate population (demographics, vulnerable populations, literacy)
- Construct a questionnaire that targets objectives
  - Note: You may not be able to accomplish all your objectives in a single study, but more than one objective can be tested in a single study
- Set *a priori* target thresholds (i.e., correct answer to question); a target should be established for each communication objective
- Using test labeling **as close as possible** to your final labeling is the most useful

HUMAN FACTORS

- Human Factors: Process to design products that people can use correctly
  - Considers the use environment, user and user interface when designing a product to maximize the likelihood of correct use and minimize the potential for unintended risk of product use

- Risk management: Tool for determining and controlling hazards

HUMAN HEALTH RISK

- Consider including studies and other scientific evidence that identify biomarkers of exposure, biomarkers of harm, and health outcome measurements or endpoints
- Data to support the impact of the new product user and nonuser health may include health effects related to specific constituents
- Design studies so that findings are generalizable to U.S. users and nonusers of the new product
- If relying on published reports to support PMTA: Justify why data can be bridged to your product and are appropriate for determining the product's impact on the U.S. population

HUMAN SCIENTIFIC STUDIES AND RISK ANALYSES: BIOMARKERS

Biomarker: A defined characteristic measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions

-- Types include: molecular, histologic, radiographic, or physiologic characteristics

-- Can serve to measure human exposure to tobacco product constituents

-- May provide useful information on health risk without having to wait decades for disease to develop

HUMAN SCIENTIFIC STUDIES AND ANALYSES: CONSIDERATION FOR SCIENTIFIC STUDIES AND ANALYSES

- No specific studies are required for a PMTA; it may be possible to support a marketing order for an ENDS product without conducting new nonclinical or clinical studies given other data sources can support the PMTA
- Alternatives to U.S.-conducted randomized controlled clinical trials may be appropriate when potential bias associated with alternative controls can be addressed
- Study findings that are generalizable to the U.S. population are the most useful

BRIDGING

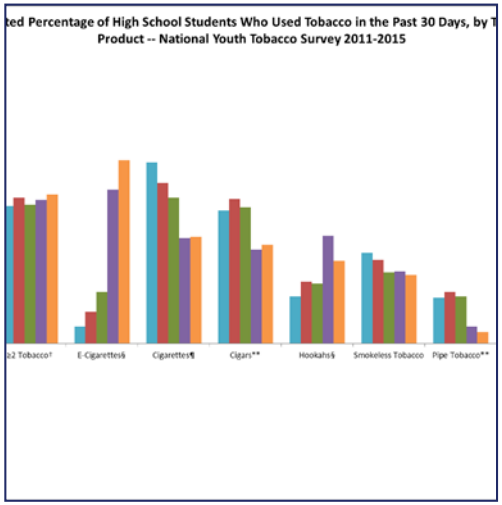
- Bridging information: Used to explain why data used are applicable to a new product
- Uses existing clinical, nonclinical, or product information for an original product and applies this information to the new product
- A commonly-used tool that can verify product characteristics through comparability
- It is useful if a clear rationale and justification to support bridging is provided

VARIOUS DATA SOURCES

Researchers have used a variety of data sources to provide information, supplement or complement other information in a PMTA

Includes, but is not limited to:

- Published, peer-reviewed literature
- Analyses of existing national datasets
- Original scientific investigations



SCIENTIFIC STUDIES AND ANALYSES: LITERATURE REVIEWS

- Literature reviews typically include:
  - Purpose of Review
    - Describe topic or question, and describe methods used to gather studies to inform the question
  - Evaluation of Methods
    - In individual studies, across studies of similar type or design
    - In some instances, systematic reviews, with “risk of bias” methods may be appropriate
  - Review of Results
    - What are similarities and differences among the studies?
    - What are strengths and limitations of methods and how does that inform result?
  - Bibliography

- Literature reviews may be acceptable to support a PMTA, but generally are considered less robust
- Conducting independent analysis of published studies can support a PMTA; it is useful if study details are included

PMTA REVIEW

WHAT IS APPROPRIATE FOR PROTECTION OF PUBLIC HEALTH?

- Section 910(c)(2)(a) of the FD&C Act states that FDA must determine whether permitting this product to be marketed would be appropriate for the protection of the public health

- Applicants submitting a PMTA must respond to the statutory requirements specified by section 910 of the FD&C Act

- All ingredients, components and constituents are evaluated based upon how they contribute, directly and indirectly, to the total health impact of a specific product

WHAT IS APPROPRIATE FOR PROTECTION OF PUBLIC HEALTH? (CONT.)

These are considerations that FDA has used in deciding whether a product is appropriate for the protection of public health:

- Are the levels of HPHCs and other constituents of toxic concern in the new tobacco product similar or lower than levels of similar TPs or other appropriate comparator tobacco products currently on the US market?
- Does the scientific evidence provided in the application support that the use of the TP has a lower risk of disease for the individual than the use of other similar or appropriate comparator TPs on the market?
- Will the marketing of the new TP affect the likelihood of nonuser uptake, cessation rates or other significant shifts in user demographics in a manner to decrease morbidity and mortality from tobacco product use?

Applicant's responsibility: Provide scientific evidence and justification to support that product is appropriate for the protection of public health

PMTA REVIEW CHALLENGES

Examples of issues during PMTA acceptance review:

- No Environmental Assessment provided
- Submission is sent in a format FDA can not process (e.g., password locked)
- Insufficient product identifying information (i.e., manufacturer; product name; brand/subbrand; category/subcategory; package type and package quantity; and characterizing flavor)

PMTA REVIEW CHALLENGES (CONT)

- FDA receives voluminous PMTAs
  - FDA reviewers spend considerable time locating information within the PMTA that is needed for their scientific review
  - Well-organized table of content and functional hyperlinks facilitate review

- Applicants have sent new study data and large amendments to FDA for review towards the end of FDA's Scientific Review Phase
  - Reviewing additional information has caused delays in FDA issuing a marketing/no marketing order

PMTA REVIEW CHALLENGES (CONT)

FDA reviewers have observed the following issues during the PMTA Review:

- Omission of protocols and methodology validation reports
- Missing data from nonclinical and clinical studies
- Studies submitted were conducted on a prototype of the device and not the device actually subject for marketing – and bridging data not provided to clearly link the information
- Distinguishing which version of the product is intended for market
- Deciphering tobacco product naming conventions

FDA has received PMTAs that include incomplete information on:

- Ingredients (HPHC data)
- Product stability testing
- Design parameters (i.e. test protocols, quantitative acceptance criteria, data sets)
- Manufacturing steps (i.e. process and equipment information, range limits for quality control)
- Manufacturing facilities
- Study design and reports
- Biomarkers (e.g., rationale for selection)

PMTA RESOURCES

CTP PMTA Website

https://www.fda.gov/TobaccoProducts/Labeling/TobaccoProductReviewEvaluation/PremarketTobaccoApplications/default.htm

PMTA Draft Guidance

http://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM273425.pdf

PMTA ENDS Draft Guidance

http://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM499352.pdf

PMTA ENDS Draft Guidance Webinar

http://fda.yorkcast.com/webcast/Play/69473e299d1f467bab97ced2f392c9611d

PMTA Informational Seminar

https://www.fda.gov/downloads/TobaccoProducts/Newsroom/UCM529302.pdf