PREMARKET TOBACCO PRODUCT APPLICATION CONTENT OVERVIEW

Presented by:

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October 28, 2019

CENTER FOR TOBACCO PRODUCTS

OVERVIEW: 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
- 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
- Other information relevant to the subject matter of the application (e.g., Environmental Assessment)

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

OVERVIEW: PMTA PROPOSED RULE

The PMTA proposed rule is open for public comment on FDA's current thinking about the content and format of a PMTA. If finalized, the rule will:

- Provide the general procedures for review from application receipt to order issuance including communications by FDA
- Require manufacturers to maintain records establishing that their tobacco products are legally marketed
- Help ensure that applications contain sufficient information for FDA to determine whether to issue a marketing order

PUBLISHED DOCUMENT

Start Printed Page 50566

AGENCY:

Food and Drug Administration, HHS.

ACTION:

Proposed rule.

SUMMARY:

The Food and Drug Administration (FDA) is issuing a proposed rule that would set forth requirements for premarket tobacco product applications (PMTAs) and would require manufacturers to maintain records establishing that their tobacco products are legally marketed. The proposed rule would help to ensure that PMTAs contain sufficient information for FDA to determine whether a marketing order should be issued for a new tobacco product, including detailed information regarding the physical aspects of a tobacco product, as well as full reports of information to demonstrate the scope of, and details regarding, investigations that may show the potential health risks of the product. The proposed rule would codify the general procedures FDA would follow when evaluating PMTAs, including application acceptance, application filing, and inspections, and would also create postmarket reporting requirements for applicants that receive marketing orders. The proposed rule would allow for the submission of PMTAs in alternative formats in certain instances to reduce the burden of submitting a PMTA for modifications to a product that previously received a PMTA marketing order or resubmitting a PMTA to address deficiencies specified in a no marketing order. The proposed rule would also require tobacco product manufacturers to keep records regarding the legal marketing of certain tobacco products without a PMTA, such as documents showing that a tobacco product is not required to undergo premarket review or has received premarket authorization.

DATES:

Submit either electronic or written comments on the proposed rule by November

DOCUMENT DETAILS

Printed version:
PDF

Publication Date:
09/25/2019

Agencies:
Food and Drug Administration

Dates:
Submit either electronic or written comments on the proposed rule by November 25, 2019.

Comments Close:
11/25/2019

Document Type:
Proposed Rule

Document Citation:
84 FR 50566

Page:
50566-50658 (93 pages)

CFR:
21 CFR 1100
21 CFR 1107
21 CFR 1114

Agency/Docket Number:
Docket No. FDA-2019-N-2854

RIN:
0910-AH44

Document Number:
2019-20315

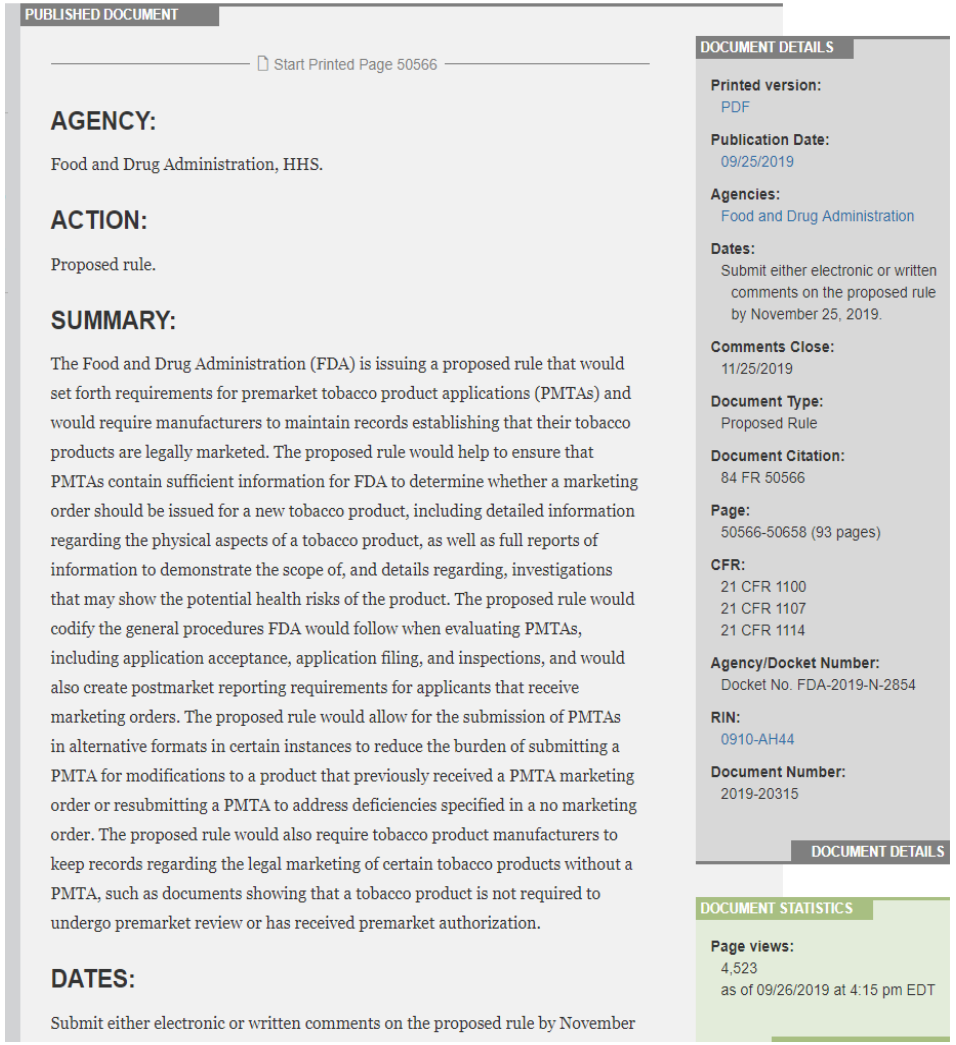
DOCUMENT DETAILS

DOCUMENT STATISTICS

Page views:
4,523
as of 09/26/2019 at 4:15 pm EDT

OVERVIEW: PMTA PROPOSED RULE (CONT.)

- Describe the 180-day review period (review clock) and describe when FDA may pause or extend the review clock
- Explain when FDA may refuse to file applications that do not contain substantive information
- Explain two alternative application formats that allow applicants to cross-reference content from a PMTA that FDA has already reviewed
- Describe how applicants may use scientific literature or bridge the results of an existing study
- Identify postmarket reporting requirements for tobacco products that receive orders



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COMMENTS REQUESTED

FDA is inviting comments on a number of topics in this proposed rule, such as:

- Submission of specific design parameters as part of the final rule, (e.g., for filtered sheet wrapped cigars, unfiltered sheet wrapped cigars, leaf-wrapped cigars, cigar wrappers, waterpipes, ENDS etc)
- Information on how co-packaging products impacts consumer use and behavior
- Proposed definitions for the terms ‘commercially marketed’ and ‘test marketing,’ including what evidence would be sufficient to demonstrate that a product was commercially marketed (other than in test markets) as of February 15, 2007
- Specific information required and requested related to marketing plans
- In regards to the length of time it takes a tobacco product user to consume a single unit of the product, it defines the appropriate metrics for determining what should constitute a single unit for various product types, whether FDA should require an average time for all users to consume a single unit, the median time to consume a single unit, and the range of time it takes users to consume a single unit of the product.

WHEN WILL THE RULE BE FINALIZED

- Per the rulemaking process, once the comment period for the proposed rule closes (currently set to 60 days, but may be extended), FDA will review and analyze the comments, and then determine the appropriate next steps.

- The final rule may be different from the proposed rule

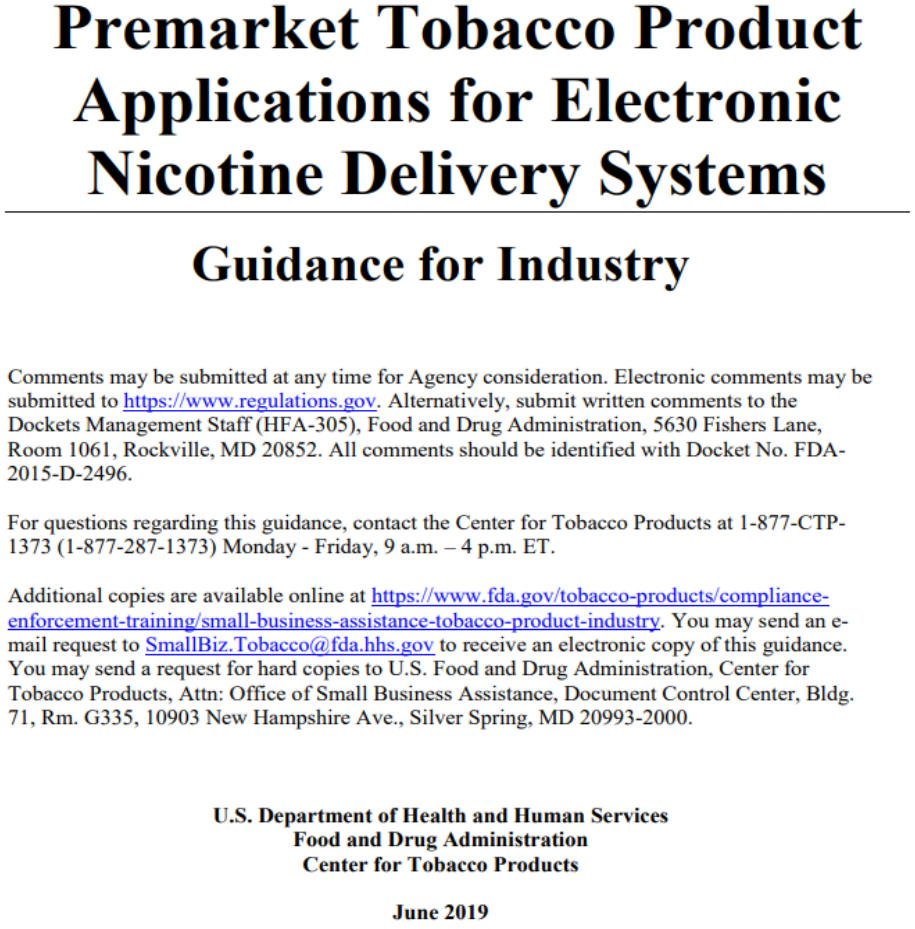
- Comments can be submitted electronically to *https://www.regulations.gov* or mailed to:

  Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852

OVERVIEW OF PMTA ENDS GUIDANCE

- The PMTA for ENDS Guidance was published to clarify and assist in the review of ENDS tobacco products

- The ENDS PMTA Review Guidance includes:
  - Public health considerations for ENDS Products
  - Recommendations for scientific content to be included in PMTAs for e-liquid, e-cigarettes and products that package e-liquids and e-cigarettes together
  - Postmarket requirements



Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems

Guidance for Industry

Comments may be submitted at any time for Agency consideration. Electronic comments may be submitted to https://www.regulations.gov. Alternatively, submit written comments to the Dockets Management Staff (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 guidance, contact the Center for Tobacco Products at 1-877-CTP-1373 (1-877-287-1373) Monday - Friday, 9 a.m. – 4 p.m. ET.

Additional copies are available online at https://www.fda.gov/tobacco-products/compliance-enforcement-training/small-business-assistance-tobacco-product-industry. 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

June 2019

PROPOSED RULE VS GUIDANCE

- The PMTA rule is a proposed rule. It is an official document that announces and explains the agency's **plan** to address content, format, and review of a PMTA. It provides the public an opportunity to submit comments. The proposed rule and the public comments received on it informs a final rule.

- The PMTA for ENDS Guidance was published to further clarify and assist in the review of ENDS tobacco products. A final guidance is **not binding** on FDA or the public; however, it represents FDA's current thinking on a topic.

OVERVIEW OF PMTA NPRM: SCIENTIFIC STUDIES AND ANALYSES TO SUPPORT A PMTA

PROPOSED RULE 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 (e.g. including HPHCs)
  - Chemistry design (e.g. nicotine, moisture, pH)
  - Tobacco blend
  - Ingredients other than tobacco
  - Manufacturing steps and controls
  - Performance criteria
  - Stability
  - Ranges of exposure
  - Aerosol content

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

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

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

- Product design
  - Battery use and foreseeable misuse leading to overhearing, fire, and explosion during operation, charging, storage, and transportation
  - 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

PROPOSED RULE SCIENTIFIC STUDIES AND ANALYSES: TOXICOLOGICAL RISK / NONCLINICAL STUDIES

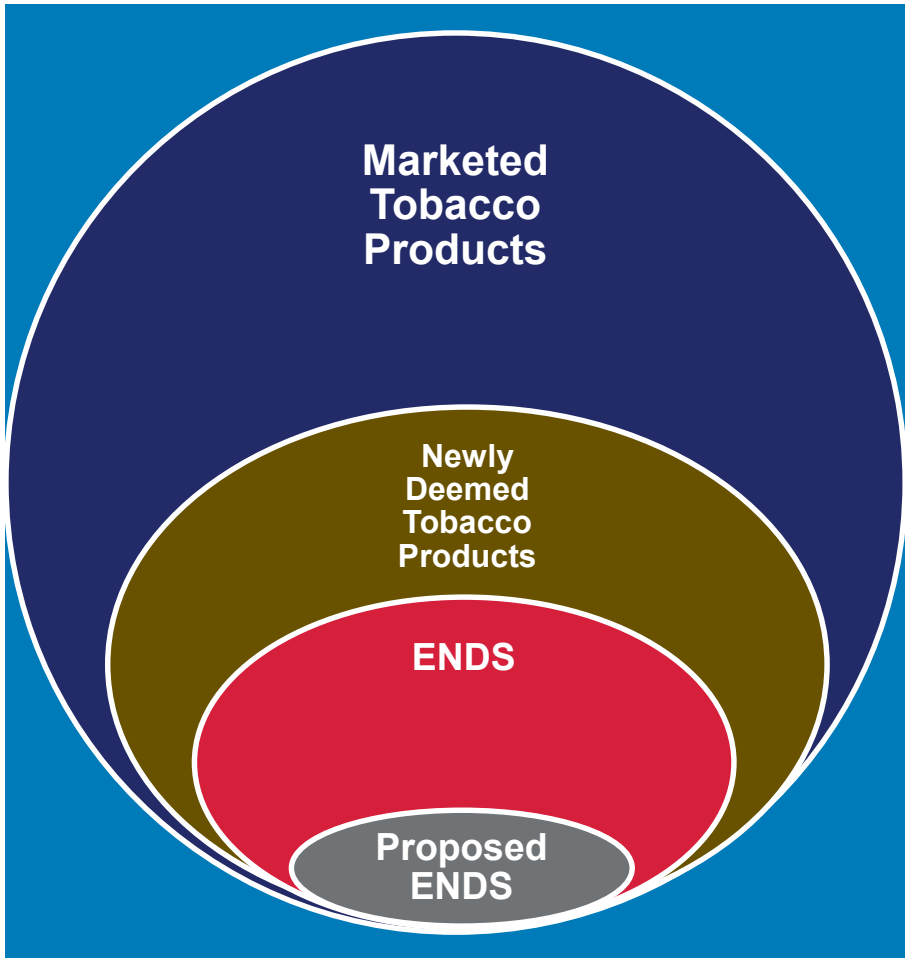
- Identifies potential human health risks, including carcinogenic and non-carcinogenic health effects, and addiction.
- Focuses on exposures to users
- Describes packaging that may mitigate risks of accidental exposure to e-liquids, includes child-resistant packaging and exposure-limiting packaging
- Evaluation includes ingredients, leachables and extractables, constituents that are created with 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.

PROPOSED RULE TOBACCO PRODUCT: COMPARATORS

The Proposed Rules states 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 PRODUCTS AVAILABLE FOR COMPARISON

PROPOSED RULE 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

The proposed rule states that.. “each clinical investigation included in the PMTA should have been reviewed and approved by an Institutional Review Board (IRB) operating to safeguard the rights, safety, and well-being of all trial subjects, with special attention being paid to vulnerable subjects” such as pregnant women, prisoners, children, economically and/or educationally disadvantaged, and cognitive impaired persons.

PROPOSED RULE 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

PROPOSED RULE: 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

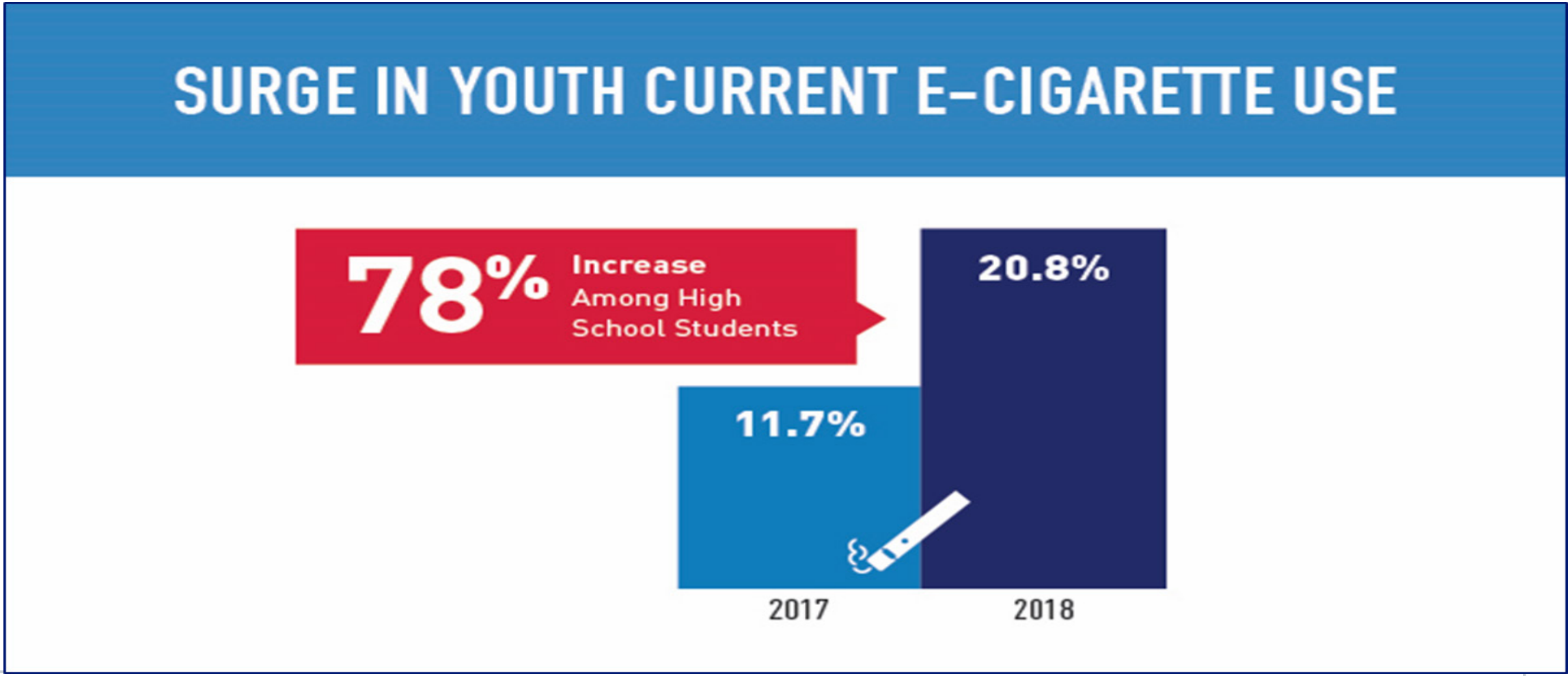
PROPOSED RULE: CONSUMER PERCEPTION (CONT.)

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 subjects

PROPOSED RULE: YOUTH USE OF PROPOSED TOBACCO PRODUCT

National Youth Tobacco Survey 2018



PROPOSED RULE: 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

- Determination of a product's abuse potential/abuse liability can be accomplished through multiple lines of evidence.

PROPOSED RULE: 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.

PROPOSED RULE: 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

PROPOSED RULE: 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

PROPOSED RULE: HUMAN HEALTH RISK

- Consider including studies and other scientific evidence that identify biomarkers of exposure, biomarkers of harm, and health outcome measurements or endpoints
- Provide data to support the impact of the new product user and nonuser health
- 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

PROPOSED RULE 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

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

- 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

PROPOSED RULE: BRIDGING

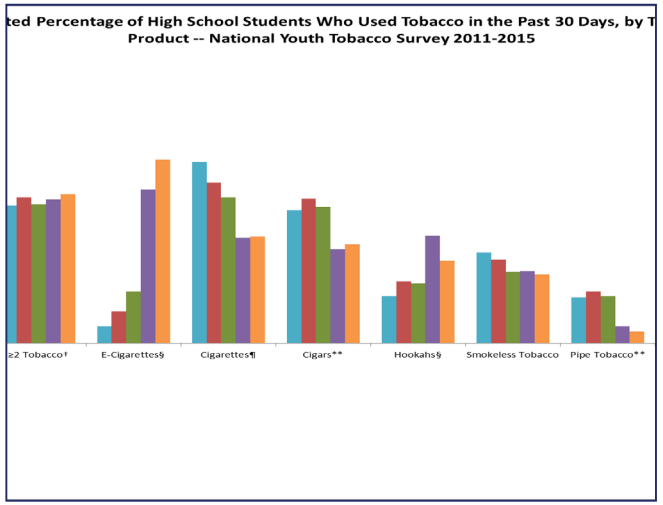
- Uses existing clinical, nonclinical, or product information for an original product and applies this information to the new product
- A commonly-used tool that can verify product characteristics through comparability
- Can be useful if the applicant explains why submitted data is applicable to each individual product (e.g., different flavors, nicotine concentration and PG/VG)

PROPOSED RULE: 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



PROPOSED RULE 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?

PROPOSED RULE: WHAT IS APPROPRIATE FOR PROTECTION OF PUBLIC HEALTH?

- It is the applicant's responsibility to provide scientific evidence and justification to support that product is appropriate for the protection of public health

- A product that is found APPH today may not be APPH in the future – depending on other available products and the current marketing environment and regulations

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

Examples of incomplete information identified during PMTA scientific review:

- 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 REVIEW CHALLENGES

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

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

EXAMPLES OF INFORMATIVE STUDIES AND OTHER SUPPORTIVE INFORMATION FROM THE IQOS SUBMISSION

IQOS – WHAT IS IT?

- IQOS is a noncombusted cigarette product
- Includes Heatstick, Holder, and Charger
- Tobacco is heated, not burned or combusted

TYPES OF DATA SUBMITTED TO SUPPORT THE APPLICATIONS

- Engineering:
  - Complete description of product design and parameters
  - Description of manufacturing steps and quality control measures
  - Process controls and quality assurance measures to ensure products meet the manufacturing specifications set by the applicant and that products will be manufactured in a consistent manner with minimal variability
  - Performance testing to verify product design
  - Specifications and independent test results for the battery

TYPES OF DATA SUBMITTED TO SUPPORT THE APPLICATIONS (cont.)

- Chemistry
  - A complete list of uniquely identified components, ingredients, and additives with applicable specifications and a description of the intended function for each
  - A description of the manufacturing steps and quality control measures
  - Evidence of product stability (this also included microbiological testing)
  - Testing data for certain harmful and potentially harmful chemicals (HPHCs)
    - Formaldehyde
    - Acrolein
    - Carbon Monoxide
    - NNN
    - NNK

Note: Applicants should provide data that will assist FDA in determining their product is APPH. The specific types of information may vary depending on the product.

TYPES OF DATA SUBMITTED TO SUPPORT THE APPLICATIONS (cont.)

- Toxicological Risk Assessment
  - Measures of HPHCs in IQOS aerosols and 3R4F cigarette smoke
  - Comparison measures of HPHCs and tar in U.S. marketed cigarettes
  - Measure of nicotine in the Heatsticks and the aerosol
  - Non-targeted differential screening assay of Heatstick aerosols
  - In Vitro Studies
    - Neutral Red Uptake Assays
    - Ames test
    - Mouse Lymphoma Assay
  - In Vivo Studies

TYPES OF DATA SUBMITTED TO SUPPORT THE APPLICATIONS (cont.)

- Behavioral & Clinical Pharmacological Assessment
  - Four pharmacokinetic/pharmacodynamic (PK/PD) studies
  - Four exposure [REX] studies (two for 5 days, two for 90 days)
  - One Actual Use study

Note: Information to consider may include nicotine exposure relative to other tobacco products, abuse liability, attractiveness/likeability of the product, likelihood of switching and/or use of multiple products

TYPES OF DATA SUBMITTED TO SUPPORT THE APPLICATIONS (cont.)

- Individual Health Impact
  - The four exposure studies included measures of Biomarkers of Exposure (BOE)
  - Measured BOEs were selected by the applicant to correspond with 14 HPHCs + nicotine and nicotine alkaloids;
    - Assessed after a 5-day confinement period and a 90-day ambulatory period
    - Compared results in U.S. and other countries where product is currently marketed
  - Measure of Biomarkers of Potential Harm
    - Selected on basis of key mechanisms of three smoking-associated diseases: cardiovascular disease, chronic obstructive pulmonary disease, and lung cancer
    - Applicant provided significant literature on the selected BOPH and the relationship with the diseases of interest

TYPES OF DATA SUBMITTED TO SUPPORT THE APPLICATIONS (cont.)

- Individual Health Impact (cont.)
  - Adverse Experiences associated with acute exposure in the clinical studies
  - Actual Use Study to evaluate uptake and use in current U.S. adult cigarette smokers
  - Consumer reports/complaints from countries where the product is marketed
  - Literature review of case studies or other reports
  - Long-term (6 month) continuation of one clinical study; this provided long-term BOE and BOPH data as well as information on uptake, continued use, and dual use

Note: Applicants may not need all of these studies for a given product; consider what information FDA needs to determine the product is APPH and how it can best be provided.

TYPES OF DATA SUBMITTED TO SUPPORT THE APPLICATIONS (cont.)

- Individual Health Impact (cont.)
  - Human Factors
    - Actual Use Study to assess product misuse
    - Evaluation of the events, device malfunctions, and potential for serious issues
  - Consumer Comprehension
    - Study evaluating ability of prospective consumers to understand and comply with product instructions

Note: The type of human factors and comprehension testing may vary depending on product type and potential for misuse. It may also be important to demonstrate the product is unlikely to expose high-risk groups such as children.

TYPES OF DATA SUBMITTED TO SUPPORT THE APPLICATIONS (cont.)

- Population Health Impact
  - Likelihood of product use by current cigarette smokers
    - Perception study with different brochures, package labeling, and warning statements; the study included smokers, former smokers, never smokers, and young adult never smokers
    - Actual Use Study conducted in the U.S. that evaluated product initiation and use patterns (including dual use and switching) over 6 weeks
    - "Whole Offer Testing" (WOT) – evaluated product initiation and use patterns (including switching) in five different countries where the product is currently marketed
  - Poly-use of the product with cigarettes or other tobacco products
    - Applicant provided data from two different post-marketing surveys in a country where the product is currently marketed
    - Additional data was presented from the Actual Use Study and the clinical studies
  - Likelihood of IQOS use leading to cigarette smoking cessation
    - Actual Use and WOT evaluated likelihood of CC smokers switching to the product
    - Post-market survey

TYPES OF DATA SUBMITTED TO SUPPORT THE APPLICATIONS (cont.)

- Population Health Impact (cont.)
  - Uptake of the product by former/never smokers or youth
    - Perception study provided some information regarding intent to try or the product in former smokers, never smokers, and young adults
    - Cross-sectional studies conducted to monitor prevalence of this and similar products by adult non-smokers
    - These were non-U.S. data from countries where the product is currently marketed
    - Face-to-face survey data was presented from a different country – which included participants as young as 15 years old
    - Of note: the applicant provided no U.S. data specifically for youth

Note: FDA must consider the likelihood those not using a tobacco product will start using the proposed new product. Although youth studies are not required, consider how the information you provide can be used to support this aspect of FDA review.

TYPES OF DATA SUBMITTED TO SUPPORT THE APPLICATIONS (cont.)

- Marketing Plans (provided in the applications)
  - Provided a general approach to marketing strategy with sample labeling
  - Clarified for FDA their strategy for limiting youth exposure and (hopefully) uptake of the products

- Postmarketing Reporting (included in the Marketing Authorization)
  - Will provide FDA with periodic reports of product sales and distribution by location, market type (e.g., retail, company-owned store, tobacco shop, online), and product type
  - Will provide prior notification to FDA for marketing plans and materials
  - Will provide analyses of delivery of advertising impressions by age break-outs
  - Adverse health effects reports
  - Other consumer complaints (e.g., product quality)

PMTA PROPOSED RULE: SUMMARY OF SUPPORTIVE INFORMATION FOR APPLICATIONS

- Include all the information in your original submission
- Amendments are challenging.
  - Each amendment must be evaluated as to whether it is ‘major’ or ‘minor’
  - Major amendments may prolong your product review and delay the decision
- Provide FDA a “Clear Picture”
  - Use consistent terminology, e.g., product naming, study name
  - Organize the data and provide an accurate table of contents all codes or definitions needed
  - If ‘bridging’ data – clearly explain the rationale
  - Clearly describe your approach, e.g., study methods, approach to statistical analysis, literature search methods and terms