DRAFT GUIDANCE: PREMARKET TOBACCO PRODUCT APPLICATIONS FOR ELECTRONIC NICOTINE DELIVERY SYSTEMS

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OVERVIEW

- BACKGROUND
- PMTA SUBMISSION
- PUBLIC HEALTH CONSIDERATIONS
- PMTA REQUIREMENTS
- ENDS PMTA CONTENT
- SCIENTIFIC STUDIES AND ANALYSES
- ADDITIONAL INFORMATION FOR E-LIQUIDS AND E-CIGARETTES
- POSTMARKET REQUIREMENTS
- REQUESTING MEETINGS WITH FDA

BACKGROUND: ENDS DRAFT GUIDANCE

- FDA issued this draft guidance for comment purposes only and when finalized, the guidance will make recommendations on:
  - How to meet the statutory requirements for Premarket Tobacco Product Application (PMTA) content under section 910(b)(1) and
  - Present information in a way that helps FDA make its decision regarding whether to issue a marketing order under 910(c)(1)(A)(i) of the FD&C Act for ENDS products

- Guidance documents do not create binding requirements, once finalized this draft guidance will represent FDA's current thinking on submitting PMTAs for ENDS products

DRAFT GUIDANCE: BACKGROUND - DEEMING AND ENDS PRODUCTS

- FDA issued this Draft Guidance on PMTAs for Electronic Nicotine Delivery System (ENDS) Products together with the Deeming Final Rule.

- The Deeming Final Rule brought all products meeting the statutory definition of "tobacco product," except accessories of newly deemed tobacco products, under FDA's tobacco product authorities (Chapter IX of the FD&C Act)

    - This includes all ENDS products, including products such as e-cigarettes, e-cigars, e-hookah, vape pens, personal vaporizers, and electronic pipes

DRAFT GUIDANCE: BACKGROUND - ENDS PRODUCTS

- ENDS products include both the e-liquid and aerosolizing apparatus whether sold as a unit or sold separately

- ENDS products also include components and parts, such as e-liquids, atomizers, tank systems, flavors, and programmable software

DRAFT GUIDANCE: BACKGROUND - ENDS PRODUCTS (CONT.)

- Liquids that do not contain nicotine or material derived from tobacco, but are intended or reasonably expected to be used with or for the consumption of tobacco (e.g., mixed with liquid nicotine) may be considered ENDS components or parts and therefore subject to regulation

- FDA is limiting enforcement at this time to finished tobacco products, which are products that are sealed in final packaging intended for consumer use

DRAFT GUIDANCE: BACKGROUND - PREMARKET REVIEW

- FDA anticipates that most ENDS products are new tobacco products (those not marketed in the United States on February 15, 2007), which must go through premarket review before they may be introduced or delivered for introduction into interstate commerce

- For new tobacco products, Section 910 requires that companies submit a PMTA and receive a marketing order under section 910(c)(1)(A)(i), unless the product is found substantially equivalent (SE) to a predicate tobacco product, or the product is found to be exempt from substantial equivalence, an abbreviated report was submitted and the applicant waited 90 days to market

- Due to the limited availability of eligible predicate products that would allow ENDS products to use the SE pathway, FDA expects to receive PMTAs for these products

DRAFT GUIDANCE: BACKGROUND - PMTA PATHWAY

- Applicants submitting a PMTA must provide information regarding investigations into health risks, product characterization, manufacturing information, product samples, labeling samples, and other information that FDA requires in section (910(b)(1))

- To issue a marketing order under section 910(c)(1)(A)(i), FDA must find that:
  - Marketing of the product would be appropriate for the protection of the public health,
  - The product complies with product standards issued under section 907,
  - The product complies with manufacturing standards issued under section 906(e), and
  - The labeling is not false or misleading

TOPIC ONE:

DRAFT GUIDANCE: PMTA SUBMISSION

DRAFT GUIDANCE: WHEN MUST A PMTA BE SUBMITTED?

- When an ENDS product is a new tobacco product, it must have a PMTA marketing order prior to being introduced or delivered for introduction into interstate commerce unless it either has received a marketing order through the SE pathway or, has received an order granting an SE exemption, submitted an abbreviated report and waited 90 days to market the product

- Enforcement is limited to finished ENDS products at this time

- Retail establishments that mix or prepare combinations of e-liquids for sale to consumers are creating new tobacco products and must obtain marketing orders

- We recommend that companies visit FDA's website or request a pre-submission meeting with FDA to discuss PMTA development and submission

DRAFT GUIDANCE: HOW SHOULD A PMTA BE SUBMITTED?

- Applicants should submit a PMTA electronically through the electronic submissions gateway (ESG)

- Applicants should submit a second, marked-for-redaction version to prepare for the potential referral to the Tobacco Products Scientific Advisory Committee

- Applicants may withdraw an application at any time before FDA issues or denies a marketing order

DRAFT GUIDANCE: HOW WILL FDA REVIEW A PMTA?

- FDA intends to issue a marketing order or no marketing order within 180 days of receiving a PMTA that meets the requirements of section 910(b)(1) (i.e., a complete application)

- A PMTA must include all information required by section 910(b)(1) when submitted; FDA may refuse to file the incomplete application

- FDA may request additional information under 910(b)(1)(G) that is necessary to complete the review of a PMTA

- FDA may also want to inspect manufacturing, clinical, and nonclinical research sites to aid its PMTA review

TOPIC TWO:

DRAFT GUIDANCE - PUBLIC HEALTH CONSIDERATIONS

DRAFT GUIDANCE: PUBLIC HEALTH CONSIDERATIONS

- FDA must deny a PMTA where it finds "there is a lack of a showing that permitting such tobacco product to be marketed would be ***appropriate for the protection of the public health***" (section 910(c)(2)(A))

- To make this finding, FDA must consider under section 910(c)(4):

  - The ***risks and benefits to the population as a whole***, including users and nonusers, and

  - The increased or decreased likelihood that ***existing users of tobacco products will stop*** using such products and ***those who do not use tobacco products will start*** using such products

DRAFT GUIDANCE: PUBLIC HEALTH CONSIDERATIONS (CONT.)

- FDA's public health determination must be based on well-controlled investigations, unless FDA determines that other valid scientific evidence is sufficient to evaluate the new tobacco product

- When clinical data on the specific product are lacking, other clinical and nonclinical (not involving human subjects) data may be used, where appropriate

- The new tobacco product can be compared to a range of tobacco products, on the market legally or as the result of an announced compliance policy, to completely assess the potential impact of the new product on public health

DRAFT GUIDANCE: PUBLIC HEALTH CONSIDERATIONS (CONT.)

- Nicotine exposure warnings: The FDA draft guidance states for applicants to include nicotine exposure warnings in specimens of labeling

- Child-resistant (CR) packaging: Given the health hazards associated with exposure to e-liquids, the FDA draft guidance includes a recommendation to include information on CR packaging

- While the draft guidance addresses these topics in context of a PMTA, we also note that FDA published an advanced notice of proposed rulemaking seeking comments and information about possible required nicotine exposure warnings and CR packaging on July 1, 2015

TOPIC THREE:

DRAFT GUIDANCE - PMTA REQUIREMENTS

DRAFT GUIDANCE: PMTA REQUIREMENTS

A PMTA must contain per section 910(b)(1):

- 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, and properties, and of the principle or principles of operation, of such tobacco product

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

DRAFT GUIDANCE: PMTA 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

- Specimens of the labeling proposed to be used for such tobacco product

- The samples of such tobacco product and of components thereof as the Secretary may reasonably require

- The other information relevant to the subject matter of the application as the Secretary may require

TOPIC FOUR:

DRAFT GUIDANCE - ENDS PMTA CONTENT

DRAFT GUIDANCE: CONTENTS OF A PMTA FOR ENDS PRODUCTS

Section VI of the draft guidance states that an ENDS PMTA should include the following:

- Cover letter
- Table of contents
- Descriptive information
- Product samples
- Labeling
- Environmental assessment
- Summary of all research findings
- Scientific studies and analyses

DRAFT GUIDANCE: CONTENTS OF AN ENDS PMTA - COVER LETTER

Section VI-A of the draft guidance states that the ENDS PMTA cover letter should include:

- The name and address of the applicant's company
- The applicant's authorized U.S. agent or representative's name, title, address, phone number, email address, and fax number
- Information identifying the new product including unique identification information
- Information about prior submissions for the new product
- Dates and purpose of any prior meeting with FDA regarding the new tobacco product
- A brief statement regarding how the PMTA satisfies the content requirements of section 910(b)(1) of the FD&C Act
- A list identifying all enclosures and labeling being submitted with the PMTA

DRAFT GUIDANCE: CONTENTS OF AN ENDS PMTA - TABLE OF CONTENTS

Section VI-B of the draft guidance states that the ENDS PMTA table of contents be comprehensive and contain:

- Contents that specifies the section and page number for each heading
- Hyperlinks to relevant pages
- A comprehensive index
- Amendments

DRAFT GUIDANCE: CONTENTS OF AN ENDS PMTA – DESCRIPTIVE INFORMATION

Section VI –C of the draft guidance states than an applicant should provide the following information to describe the new tobacco product:

- A unique identification of the new tobacco product
- A complete description of the new tobacco product
- An identifying reference to any tobacco product standard under section 907 of the FD&C Act
- An overview of the product's formulation and design
- The name and description of any characterizing flavor the product contains
- The nicotine strength
- The conditions for using the product or instructions for use
- If applicable, any restrictions on the sales and distribution of the new tobacco product to support that the marketing of the product is appropriate for the protection of public health

CONTENTS OF AN ENDS PMTA: DESCRIPTIVE INFORMATION

The draft guidance states that unique identification of an ENDS tobacco product includes:

Open E-liquids	Closed E-cigarette (or Closed Aerosolizing Apparatus)	
• Product Name • Category: ENDS • Subcategory: Open E-Liquid • Package type • Package quantity (mL) • Characterizing flavor • Nicotine content (%) • PG/VG ratio • Additional properties (if applicable)	• Product Name • Category: ENDS • Subcategory: Closed E-cigarette • Package type • Characterizing flavor • E-liquid capacity (mL) • Nicotine Content (%) • PG/VG ratio	• Coil resistance (Ohms) • Wattage (W) • Battery capacity (mAh) • Additional properties (if applicable)

DRAFT GUIDANCE: CONTENTS OF AN ENDS PMTA - PRODUCT SAMPLES

Section 910(b)(1)(E) of the FD&C Act requires that a PMTA contain such samples of the new tobacco product as the Secretary may reasonably require. The draft guidance states in Section VI-D that:

- Applicants should be ready to send a sample soon after they submit a PMTA
- Samples are sent to the Southeast Regional Laboratory (SRL) no later than seven calendar days after the date on the letter acknowledging receipt of the PMTA
- Applicants should send at least one sample of the new finished tobacco product to SRL (the FDA may request additional samples for testing and analysis)

The FDA acknowledgment letter will include information about where to send samples.

DRAFT GUIDANCE: CONTENTS OF AN ENDS PMTA - LABELING

Tobacco product labeling is required by section 910(b)(1)(F)

The draft guidance states in section VI-E that:

- Proposed labeling for all products panels should reflect the actual size and color for use with the new tobacco product

- Labeling should include any warning statements appropriate for the product category and should comply with all other applicable labeling requirements under the FD&C Act

- Product labeling should include text or graphic elements to identify the product and to minimize risks associated with use of the product

DRAFT GUIDANCE:
CONTENTS OF AN ENDS PMTA - ENVIRONMENTAL ASSESSMENT

- An environmental assessment must be included in an ENDS PMTA unless the action qualifies for a categorical exclusion (21 CFR 25.15)
  - Currently PMTA related categorical exclusions include:
    - Issuance of an order under section 910(c) that a new tobacco product may **not** be introduced or delivered for introduction into interstate commerce (21 CFR 25.35(b))
    - Rescission or temporary suspension of an order authorizing the marketing of a new tobacco product under section 910 of the FD&C Act (21 CFR 25.35(c))

- The environmental assessment should be prepared in accordance with 21 CFR 25.40

DRAFT GUIDANCE:
CONTENTS OF AN ENDS PMTA - SUMMARY OF ALL RESEARCH FINDINGS

Section VI-G of the draft guidance states to include a section summarizing all research findings. The discussion should include information such as:

- A summary of favorable/unfavorable nonclinical and clinical studies relevant to the PMTA
- The relative health risks of the new tobacco product for both users and nonusers compared to other tobacco products on the market and the health risk compared to never using tobacco products
- Emission levels of aerosols under the range of operating conditions and use patterns
- The likelihood of current nonusers of tobacco products initiating or reinitiating tobacco use by using the new tobacco product
- The likelihood that consumers will adopt the new tobacco product and then switch to other tobacco products that may present higher levels of risk

DRAFT GUIDANCE:
CONTENTS OF AN ENDS PMTA - SUMMARY OF ALL RESEARCH FINDINGS (CONT.)

Section VI-G of the draft guidance states to include a section summarizing all research findings. The discussion should include information such as:

- The likelihood of consumer dual use
- The likelihood of consumers switching to the product instead of ceasing tobacco product use or using an FDA-approved cessation product
- An assessment of abuse liability
- An assessment of user topography
- A discussion demonstrating how the data and information in the PMTA establish that the new tobacco product is appropriate for the protection of public health
- An assessment of the effect that the new tobacco product may have on the health of the population as a whole

TOPIC FIVE:

DRAFT GUIDANCE - SCIENTIFIC STUDIES AND ANALYSES

DRAFT GUIDANCE:
SCIENTIFIC STUDIES AND ANALYSES - PRODUCT ANALYSIS AND MANUFACTURING

Section VI-H of the draft guidance discusses the product analysis and manufacturing section which should contain detailed technical information and analyses.

- For components, ingredients and additives, include:
  - A complete list of uniquely-identified components, ingredients and additives by quantity in the new product, including applicable specifications and a description of the intended function for each
  - Full statements of properties and of the principle of operation
  - A complete list of uniquely identified constituents as appropriate for the product, and other toxic chemicals contained within the product or delivered by the product

DRAFT GUIDANCE:

SCIENTIFIC STUDIES AND ANALYSES - PRODUCT ANALYSIS AND MANUFACTURING (CONT.)

Section VI-H of the draft guidance states that the applicant should include information describing the new tobacco product properties such as:

- A description of the product dimensions and the overall construction of the product
- A description of all design features of the product
- A quantitative description of the manufacturer performance specifications
- A description of the product container closure system
- A description of how the product's properties differ from comparator products
- Storage and stability information for the new tobacco product
- Assessment of product design hazards that could be expected to result in illness or injury from normal use and misuse

DRAFT GUIDANCE:

SCIENTIFIC STUDIES AND ANALYSES - PRODUCT ANALYSIS AND MANUFACTURING (CONT.)

Section VI-H1 of the draft guidance states that an applicant should include the following information about the principles of operation:

- A narrative description of how a consumer will use the new tobacco product
- A description of how the consumer operates the product
- How the manufacturer reasonably believes a consumer could change the product characteristics, adjust the performance, or add or subtract ingredients

In addition, the draft guidance states that an applicant should include the following information about manufacturing:

- A list of all manufacturing, packaging, and control sites for the product
- A narrative description, list and summary of all standard operating procedures, including forms and records

DRAFT GUIDANCE:
ADDITIONAL INFORMATION FOR E-LIQUID PRODUCTS IN A PMTA

Section VII of the draft guidance states that an applicant should include the following information for e-liquids:

- Information to characterize the constituents in the e-liquid
- Characteristics of the e-liquid that may impact the constituents in the aerosol
- E-liquid design parameters that would be affected by and that would affect aerosolizing apparatus performance
- Toxicological review of flavor additives
- Research on flavor development
- Perceptions among current ENDS users and other tobacco users regarding appeal and use intentions based on labeling, flavors and design
- The impact of flavoring on consumer perceptions and the appeal of flavors to youth and adults

DRAFT GUIDANCE: ADDITIONAL INFORMATION FOR E-CIGARETTES IN A PMTA

Section VIII of the draft guidance states an applicant should include the following information for e-cigarettes:

- A precise description of the e-cigarette
- Detailed e-cigarette schematics
- A discussion of the electrical safety and identification of standards to which conformance has been demonstrated
- A description of built-in electrical safety features
- A description of battery characteristics, components for e-cigarette and software

For e-liquids packaged with an e-cigarette, the draft guidance states in section IX to include a discussion of items for both the e-liquid and the e-cigarette.

DRAFT GUIDANCE:

SCIENTIFIC STUDIES AND ANALYSES - NONCLINICAL AND HUMAN SUBJECT STUDIES

The draft guidance in section VI-H2 states to include the following information related to studies evaluating health risk:

- Full reports of all information (published, known to, or should be reasonably known to the applicant) conducted in and outside the U.S.
- A bibliography and full articles for each published study
- An explanation of the scope of the literature review conducted to identify the published studies
- A summary of the results and methods including: the study objective, the study design, how the statistics were analyzed, and a description of the findings and conclusion

DRAFT GUIDANCE:

SCIENTIFIC STUDIES AND ANALYSES - NONCLINICAL AND HUMAN SUBJECT STUDIES (CONT.)

Section VI-H2 of the draft guidance further states that applicants should include to the extent available or reasonably obtainable when submitting studies evaluating health risks additional documents such as:

- Documentation of all actions taken to ensure reliability of the study and the protection of human subjects for clinical studies
- A list of study sites
- All versions of the study protocol and any amendments
- A list of contractors who participated in the study, their roles and the dates of participation
- All versions of the questionnaires, case report forms including raw data, and informed consent forms used in the clinical study
- A signed report of the findings (final study report)

DRAFT GUIDANCE:

SCIENTIFIC STUDIES AND ANALYSES - NONCLINICAL AND HUMAN SUBJECT STUDIES (CONT.)

Section VI-H2a of the draft guidance states for applicants to include the following information to assess the nonclinical health risks of a new tobacco product:

- A full assessment of the toxicological profile of each of the ingredients, mixture of ingredients and aerosols produced by the new tobacco product
- A thorough literature review
- A justification for the potential daily exposure levels of users to an aerosol from an ENDS product
- A list of characteristics in the product that affect the toxicants in the aerosol and evidence that product parameters are stable with testing
- Computational modeling using surrogate chemical structures can be used in absence of toxicological data for a particular toxicant
- A summary discussing how the new product would be appropriate for the protection of public health relative to a similar comparator

DRAFT GUIDANCE:

SCIENTIFIC STUDIES AND ANALYSES - NONCLINICAL AND HUMAN SUBJECT STUDIES (CONT.)

Section VI-H2b of the draft guidance states for applicants to include the following information to assess the human health impact of a new tobacco product:

- Evaluations of acute and chronic health effects using biomarkers and health outcome measurements and endpoints
- An evaluation of perceptions of product risks (absolute, in comparison to other tobacco products, and in comparison to quitting all tobacco use)
- Evaluations of the likelihood of initiation and cessation by both users and nonusers of tobacco products
- Evaluation of product use patterns
- Marketing plan
- Sales data (if the tobacco product is or has been on the market)

DRAFT GUIDANCE:

SCIENTIFIC STUDIES AND ANALYSES - NONCLINICAL AND HUMAN SUBJECT STUDIES (CONT.)

The draft guidance in section VI-H2b states to include the following information to assess the human health impact of a new tobacco product:

- Provide studies demonstrating that users and nonusers understand the product's labeling and instructions for use, and use the product according to its labeled instructions
- Describe the product's intended and potential unintended use by the consumer
- Evaluate the risk associated with use and demonstrate how potential risks may be mitigated for users and nonusers
- Evaluate abuse liability reports and data

Applicants should ensure to the extent possible that studies be conducted in a way that the study findings are generalizable to the population of U.S. users and nonusers of the new tobacco product.

DRAFT GUIDANCE:
ALTERNATIVE TO U.S.-CONDUCTED RANDOMIZED CONTROLLED CLINICAL TRIALS

- Alternatives to U.S.-conducted randomized controlled clinical trials may be appropriate when potential bias associated with alternative controls can be addressed
- Literature reviews or reports may be acceptable to support a PMTA, but are considered less robust
- Conducting independent analyses of published studies can support a PMTA; however, critical study details should be included for FDA to review
- Providing master files gives FDA access to tobacco product information that can be used to support the PMTA
- Bridging data and studies can reduce the need for large amounts of additional data

TOPIC SEVEN:

DRAFT GUIDANCE - POSTMARKET REQUIREMENTS

DRAFT GUIDANCE: POSTMARKET REQUIREMENTS

- Restrictions on the sale and distribution of a tobacco product could be required by marketing orders if the tobacco product does not meet future regulatory requirements

- FDA may require the maintenance of post-market records and reports as a condition of a marketing order

TOPIC EIGHT:
REQUESTING MEETINGS WITH FDA

REQUESTING MEETINGS WITH FDA

If the applicant requires further guidance from FDA regarding the planned submission, the applicant may request a formal meeting with FDA. FDA usually considers granting no more than one or two meetings per applicant.

FDA applicants should have developed a complete approach before submitting a formal meeting request. The meeting request should focus on a discussion of:

- The application completeness
- Any significant challenges identified
- The approach to the application

Pre-submission meetings are not intended as a substitute for an application review.

ADDITIONAL INFORMATION

If you would like to submit a PMTA, you can consider submitting a meeting request prior to submission. Guidelines for submitting a meeting request can be found here:

http://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM305282.pdf

For further information, visit our website:

http://www.fda.gov/TobaccoProducts/Labeling/TobaccoProductReviewEvaluation/ucm304506.htm

Questions? Send an email to :

AskCTP@fda.hhs.gov

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