Premarket Tobacco Applications Session One: A Review of FDA's ENDS Guidance and the IQOS Marketing Order

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Moderated by **Scott Ballin**, Tobacco and Health Policy Consultant

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THE ENDS GUIDANCE, IQOS MARKETING AUTHORIZATION, AND THE FUTURE OF PREMARKET TOBACCO APPLICATIONS: THE FDA PERSPECTIVE

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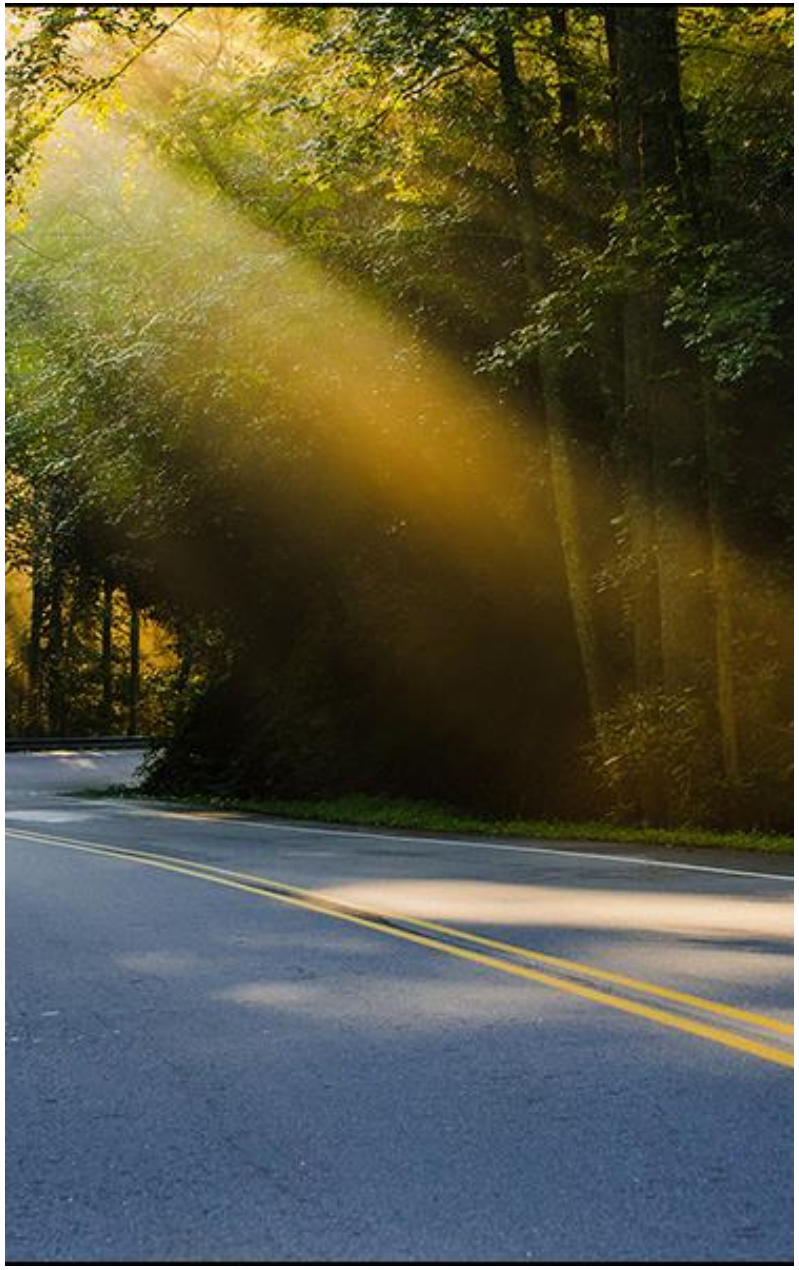
- ENDS PMTA Guidance
- IQOS Marketing Authorization
- The Future of Premarket Tobacco Applications



REGULATORY BACKGROUND

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

The statute provides that FDA must determine the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account:

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

GENERAL PMTA REQUIREMENTS

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

- Full reports of all information concerning health risks of the tobacco product
- A full statement of the components, ingredients, additives, properties, and principles of operation of the product
- A full description of the methods used, and the facilities and controls for the manufacturing, processing, packing, and installation of the tobacco product
- An identifying reference to any applicable tobacco product standard with information to show the product meets the standard or adequate justification for any deviation from the standard
- Specimens of proposed labeling
- Samples of the tobacco product and any components
- Any other relevant information

PMTAs for Electronic Nicotine Delivery Systems (ENDS)

- Final Guidance published June 2019

- The Guidance explains:
  - Products for which the guidance applies
  - When a PMTA is required
  - General procedures for review of an ENDS PMTA
  - What information the FD&C Act requires to be submitted in a PMTA
  - What information FDA recommends be submitted in a PMTA (to demonstrate the marketing of the new tobacco product would be appropriate for the protection of the public health)

INFORMATION TO SUPPORT AN ENDS PMTA

I. Product Analysis and Manufacturing

- Complete description of the product and all ingredients/components/additives
- Demonstration the product can and will be manufacture consistently
- Assessment of product design hazards and how these will be reduced, mitigated, or eliminated
- Evidence of product stability
- Consideration of specific constituents or chemical in the e-liquids and/or aerosols

II. Nonclinical Information

- Toxicological data from the literature
- Analysis of constituents under intense and non-intense use conditions
- In vitro and in vivo toxicology studies
- Computational modeling of the toxicants in the product

INFORMATION TO SUPPORT AN ENDS PMTA (cont.)

III. Human Health Impact Information

- Information relative to tobacco users who:
  - switch from their current product(s) to the new product
  - adopt the new product and subsequently switch back or initiate use of a higher risk product
  - begin use of the new product rather than ceasing tobacco use
  - use the new product instead of an FDA-approved therapeutic product
  - use the new product in conjunction with other tobacco products
- May also evaluate nonusers (e.g., youth, never users, former users) who initiate or relapse to the new product
- Evaluation of health effects/adverse experiences in new product users or nonusers exposed to the new product

INFORMATION TO SUPPORT AN ENDS PMTA (cont.)

III. Human Health Impact Information (continued)

- Consumer perceptions and intentions
- Review of published literature related to the new product (or similar products)
- Clinical studies conducted by the applicant (e.g., RCTs, observational studies, perception studies, actual use studies)
- Evaluation of user topography
- Other adverse experience reports (e.g., consumer complaints, published literature/case reports)

IV. Other Information

- Human Factors
- Abuse Liability
- Biomarkers of harm and/or exposure

INFORMATION TO SUPPORT AN ENDS PMTA (cont.)

V. Special considerations with respect to ENDS
- Flavors
- Design Features (e.g., battery, atomizers, coil, software)

VI. A summary of the marketing plan including:
- Information on potential consumer demographics
- Information on marketing in other countries
- Information on top selling brands as a comparison

IQOS MARKETING AUTHORIZATION

IQOS PRODUCT DESCRIPTION

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

SUMMARY OF DATA SUPPORTING THE IQOS APPLICATIONS

- Engineering
  - Complete description of product design, manufacturing process, quality control measures
  - Performance testing information on all parts of the device
- Chemistry
  - Complete list of ingredients, compounds, and additives; evidence of product stability
  - Testing data for harmful and potentially harmful chemicals (HPHCs)
    - Note: HPHCs selected for testing will vary by product type
- Toxicological Assessment
  - Comparative HPHC data for products and marketed cigarettes
  - In vivo and in vitro studies
- Behavioral and Clinical Pharmacology Assessment
  - Evaluated nicotine delivery, product attractiveness, abuse liability, and likelihood of switching

SUMMARY OF DATA SUPPORTING THE IQOS APPLICATIONS

- Individual Health Impact
  - Measured biomarkers of exposure in 5-day confined and 90-day ambulatory studies
  - Measured biomarkers of potential harm for three smoking-associated diseases
  - Evaluated adverse experiences in the studies as well as consumer reports in other countries
  - Comprehensive literature review
  - Assess human factors and consumer comprehension of product instructions
- Population Health Impact
  - Perception study and Actual Use study to evaluate likelihood of product use by current cigarette smokers and whether product use would lead to ‘dual use’ or cigarette smoking cessation
  - Post-market surveys in other countries where product is marketed - included information on youth initiation, cigarette cessation, dual use

THE FUTURE OF PMTAs

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- CTP anticipates a large number of applications
- We are planning for the processing and review of the applications
- We are working to educate all stakeholders on the PMTA submission process
  - Public Meeting Oct 28-29 (on-site attendance is full; may register for webcast)
  - PMTA Proposed Rule published Sept 25, 2019
  - ENDS PMTA Final Guidance published June, 2019
  - We encourage applicants to communicate with FDA prior to submission
    - For example, a meeting request to discuss specific issues, challenges, and questions
    - A Final Guidance on requesting meetings related to tobacco products was published July 2016

PMTA SUBMISSION SUGGESTIONS

- Follow the PMTA Proposed Rule and refer to the ENDS Guidance for information specifically related to e-cigarettes
  - Include all the required information in your initial 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” - the submission should clearly relate the data/information to the product(s) under review
  - Use consistent terminology, e.g., product naming, study name
  - Organize the data and provide an accurate table of contents and all necessary codes & definitions
  - If ‘bridging’ data – clearly explain your rationale
  - Clearly describe your approach, e.g., study methods, approach to statistical analysis, literature search methods and terms

IMPORTANT POINTS: TOBACCO PRODUCT MARKETING AUTHORIZATION

- No tobacco product is safe. Tobacco Product authorization does NOT use a safety/efficacy standard

- FDA does not ‘approve’ tobacco products; we authorize marketing of the products. There may be time limits, reporting or marketing requirements, and other conditions placed on the marketing authorization.

- Although there is not a regulatory definition, FDA considers a product ‘Appropriate for Protection of the Public Health’ (APPH) if we determine marketing of the product has the potential to result in decreasing morbidity and/or mortality. A product found APPH today may not be APPH in the future – depending on other available products, the current marketing environment, and regulations. The APPH ‘standard’ allows change over time.

Questions?

How the PMTA Process Can Provide Scientific Clarity

Jim Solyst, Swedish Match

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PMTA Process is Challenging

- Time consuming and resource intensive; conducted in a relatively short timeframe
- Great uncertainty
- Very limited track record on decisions
- From a company perspective the view should be “it is the cost of doing business.”

However, maybe the PMTA process is not so bad after all

- Things have changed in the past year that put the PMTA process in a different perspective.
- Change the Winston Churchill quote “Democracy is the worst form of government, except for all the others” to the “PMTA process is the worst form of nicotine product approval, except for the others.”
- The Federal regulatory process can be difficult to navigate and unsatisfying, but it is well documented. You know how it works.
- For example, with the PMTA process companies have the opportunity to submit scientific evidence that will be reviewed by scientists.

Compare the PMTA Process to that of State/Local Authorities and Retailers

- Local and state authorities may allow for companies to make a case and provide evidence, but their process is not nearly as rigorous as the federal regulatory process.
- And retail establishments have no obligation to follow any process.

Going Forward

- A key question is how can the rigorous, science-based PMTA process protect against actions taken by local and state authorities and retailers.
- I understand the political pressure facing state and local authorities; and retailers addressing the concerns of vocal consumers, and I don't doubt their sincerity in acting, but….
- Ideally, they will make decisions on information provided by a credible source charged with protecting the public health, and to me that source is FDA.
- For example, if a product is awarded a PMTA then it should not be banned by state and local authorities or retailers.

How will that work?

- Will FDA reach out to state and local authorities and retailers? Probably not.
- The best approach might be for stakeholders, particularly industry, to ensure that state and local authorities and retail decision makers are aware of PMTA decisions and how they relate to proposed actions.

Thoughts on the General Snus MRTP Decision

- A MRTP is a PMTA but with a marketing claim that must be tested through rigorous consumer perception studies.
- The initial General snus marketing claim –remove existing warning labels and add “substantially less risky”– was driven by science.
- The December 2016 “partial decision” was disappointing but did lead to a cooperative process with CTP.
- The postmarket surveillance process should provide very useful information.

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