CTP'S EVALUATION OF PREMARKET AND MODIFIED RISK TOBACCO PRODUCT APPLICATIONS

Presented by
Benjamin Apelberg, PhD, MHS
Director, Division of Population Health Science
Office of Science, CTP, FDA

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AGENDA

- Statutory framework for PMTAs
- Application of the framework: Swedish Match North America (SMNA) PMTAs
- Statutory framework for MRTPAs
- Application of the framework: SMNA MRTPAs

BACKGROUND: PREMARKET TOBACCO APPLICATION (PMTA)

- Before a new tobacco product can be legally marketed (per Section 910(a)(2) of the FD&C Act), a premarket tobacco application must be submitted, reviewed by FDA, and determined to be appropriate for the protection of public health.[1]
  - Unless the product is found to be substantially equivalent (SE) to a predicate tobacco product, or the product is found to be exempt from SE.

1. For products on the market as of the effective date of the deeming rule, the rule requires that PMTAs be submitted within two years after the effective date. Unless FDA has issued an order denying or refusing to accept the submission, products for which a PMTA was submitted by this date will be subject to a continued compliance period for 12 additional months. FDA recently announced its intention to defer for three months the enforcement of compliance deadlines set for May 10, 2017, or later, for newly regulated products.

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

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

PUBLIC HEALTH CONSIDERATIONS

FDA must take into account: (A) the likelihood that users of tobacco products will stop using such tobacco products; and (B) the likelihood that those who do not use tobacco products will start using such products.

BACKGROUND: PMTA STATUTORY REQUIREMENTS

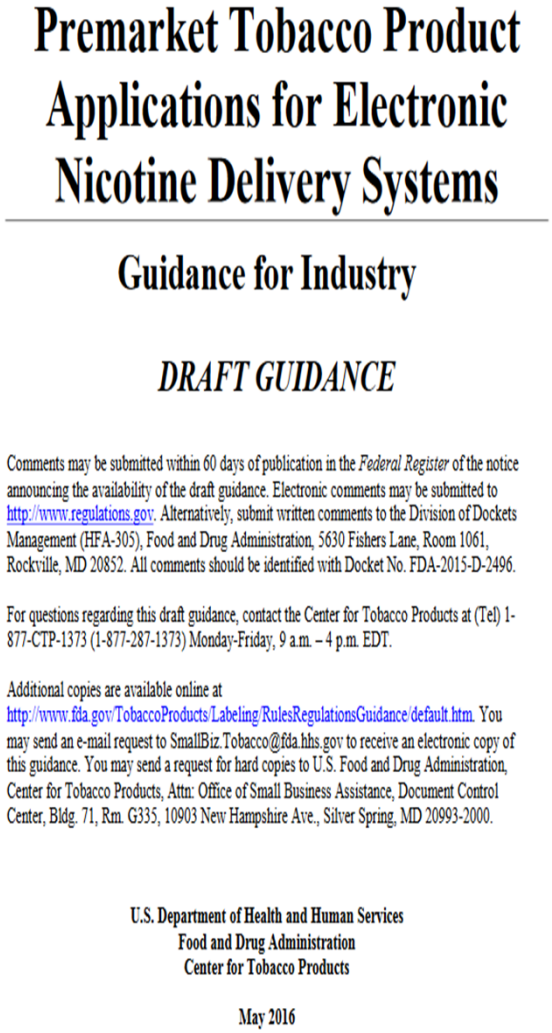
- Per section 910(b)(1), a PMTA must contain:
  - Full reports of all information, published or known to, or which should reasonably be known to, the applicant, concerning investigations that have been made to show the health risks of the tobacco product *and whether the tobacco product presents less risk than other tobacco products*
  - A full statement of the components, ingredients, additives, properties, and the principle or principles of operation, of 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

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
- 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
- An environmental assessment must be included in a PMTA unless the action qualifies for a categorical exclusion (21 CFR 25.35)

PMTA DRAFT GUIDANCES

- The PMTA draft guidances "Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems" and "Applications for Premarket Review of New Tobacco Products" includes recommendations on 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
- When finalized, these guidances will represent FDA's current thinking on PMTAs for regulated products



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

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SWEDISH MATCH NORTH AMERICA PMTAs

SWEDISH MATCH NORTH AMERICA PMTAS

- On March 11, 2015, Swedish Match North America (SMNA) submitted eight General brand snus premarket tobacco product applications (PMTAs) to FDA seeking authorization under Section 910(b) of the Federal Food, Drug and Cosmetic Act (FD&C Act).

- One snus product was a loose product and the others were portioned snus products.

PRODUCT EVALUATION

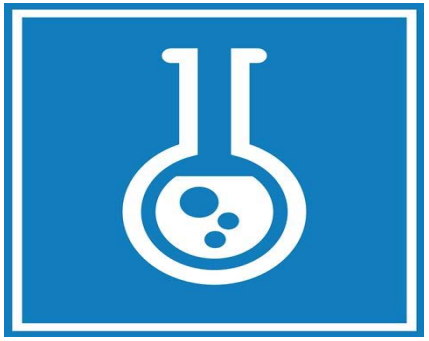
- The chemistry evaluation took into consideration product formulation, chemistry design (nicotine, moisture, pH), tobacco blend, ingredients other than tobacco, manufacturing steps and controls, performance criteria and stability.
- Design parameters are assessed to understand the comprehensive design of the products as each parameter contributes to the overall constituent yields, such as:
  - Tobacco cut size
  - Tobacco moisture (tobacco leaf, blend, and final)
  - Portion mass, length, width, thickness
  - Pouch paper porosity/permeability and wicking
- Product stability (including moisture, pH, water activity, bacterial counts and validation parameters), heat treatment, additives, fermentation, storage and microbial concerns were evaluated.

TESTING AND INSPECTION

- FDA conducted sample testing involving the following evaluations:
  - Chemistry
  - Engineering
  - Microbiology
- Inspections of facilities involved on-site clinical and manufacturing locations

HPHC EVALUATION

- The SMNA ST products have significantly lower levels of NNN and NNK compared to over 97% the ST products currently on US market.
- Levels of other HPHCs (including As, Cd, acetaldehyde, crotonaldehyde, formaldehyde, and BaP) are similar to or lower than levels in ST products currently on the US market.
- Certain HPHCs (such as acetaldehyde, cadmium, acrolein, and nickel) have been identified as constituents of more toxic concern in the smoke of combusted products as compared to smokeless products.



TOXICOLOGICAL EVALUATION

- The products in the SMNA PMTAs may decrease the individual risk among current ST users due to their favorable toxicological profile without posing increased risk to the general population.
- Assuming that the only users of these products are persons who would have used other ST (smokeless tobacco) products currently on the US market, individuals using these products with lower NNN levels could decrease their lifetime excess cancer risk due to NNN by 38-92%.

INDIVIDUAL HEALTH RISKS

- SMNA provided a review of the literature stating individual snus user health risks are lower, or at least no greater, than those associated with cigarette smoking.
- When used exclusively instead of combusted tobacco products, these products offer lower risk of developing respiratory diseases (i.e., chronic obstructive pulmonary disease (COPD), emphysema, chronic bronchitis) and cancers (such as oral, esophageal, and lung) than smokers.

INDIVIDUAL HEALTH RISKS (CONTINUED)

- Use of these products is not associated with significant “second-hand” exposure, which decreases disease risks for the general population.
- When used exclusively instead of other smokeless tobacco products or cigarettes on the US market, these products offer potential for reductions in oral cancer risk.
- Use of Swedish snus products is not risk-free and its use is associated with increased risk of various adverse health outcomes, including adverse pregnancy outcomes, certain types of cancer, and fatal cardiovascular events.

POPULATION HEALTH IMPACT

- Data indicate there is limited switching behaviors from exclusive smoking to exclusive smokeless tobacco use.
- It is more likely that uptake of the proposed products occurs among current smokeless tobacco users.
- It is anticipated that with the marketing of the proposed products, as described in the PMTAs, there is a low likelihood of nonuser uptake of these products, decreased or delayed cessation, or other significant shifts in user demographics.

SMNA PMTA DECISIONS

PMTA DECISIONS

- Given the reasons described, **authorization of these products was issued to SMNA** so that current ST users who choose to continue using tobacco products will have additional options for less toxic ST products, thereby potentially decreasing the negative health impact from tobacco product use.

STATUTORY FRAMEWORK FOR MODIFIED RISK TOBACCO PRODUCTS

MODIFIED RISK TOBACCO PRODUCTS (MRTPS) DEFINED

- Tobacco products sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products
  - Label, labeling or advertising represents that:
    - The product is less harmful or presents a lower risk of tobacco-related disease
    - The product or its smoke contains a reduced level of, presents a reduced exposure to, or does not contain/is free of a substance

THE STANDARD FOR MODIFIED RISK

The FD&C Act requires FDA to determine if a proposed MRTP, as it is actually used by consumers, will:

(1) significantly reduce harm and the risk of tobacco-related disease to individuals and

(2) benefit the health of the population as a whole

SPECIAL RULE FOR CERTAIN PRODUCTS

- The FD&C Act allows FDA to issue an order if :
  - appropriate to promote the public health;
  - the label, labeling, and advertising is limited to a claim that
    - the product does not contain or is free of a substance or
    - contains a reduced level or presents a reduced exposure
  - scientific evidence is not available without conducting long-term epidemiological studies; and
  - scientific evidence that is available demonstrates that a reduction in morbidity or mortality is reasonably likely.

THE FOUR-STEP MRTP EVALUATION

These questions are relevant to the evaluation of whether the applicant has met the applicable 911 standard:

1. Is there adequate scientific substantiation of the proposed modified risk information?
2. Will the MRTP significantly reduce the harm and risk of tobacco-related disease to individual tobacco users?
3. How do consumer's perception, understanding, and comprehension of the modified risk information impact potential benefits and harms?
4. What are the potential benefits and harms to the health of the population as a whole?

MRTP CONTEXT

- An MRTP order is for a specific product, not for a class of products.
- Evaluations are in the context of a specific product and specific modified risk claim.
- Form and wording of the claim have a critical impact on the final decision.

HOW WAS THIS FRAMEWORK APPLIED TO THE SWEDISH MATCH MRTPA?

OVERVIEW OF SWEDISH MATCH NORTH AMERICA (SMNA) APPLICATIONS

- Modified Risk Tobacco Product (MRTP) applications were received by FDA on June 10th 2014 for the following tobacco products:
  - General Loose
  - General Dry Mint Portion Original Mini
  - General Portion Original Large
  - General Classic Blend Portion White Large – 15 ct*
  - General Classic Blend Portion White Large – 12 ct
  - General Mint Portion White Large
  - General Nordic Mint Portion White Large – 15 ct*
  - General Nordic Mint Portion White Large – 12 ct
  - General Portion White Large
  - General Wintergreen Portion White Large

** Subsequently withdrawn by the applicant.*

SMNA MRTPA INFORMATION

- The SMNA MRTPAs contained information from various types of scientific studies:
  - Product analyses (chemistry, engineering, microbiology)
  - Toxicological assessments
  - Pharmacokinetic studies
  - Clinical trials (for impact on cessation)
  - Epidemiological studies (health and behavior)
  - Consumer perception and comprehension studies
  - Statistical modeling
  - Plans for postmarket surveillance and studies

SMNA MRTPA REQUEST

- **Warnings to be removed:**
  - *WARNING: This product can cause gum disease and tooth loss*
  - *WARNING: This product can cause mouth cancer*

- **Revision to the warning:**
  - *<u>From:</u> WARNING: This product is a not a safe alternative to cigarettes*
  - *<u>To:</u> WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes*

- **SMNA did not request to change the required warning:**
  - *WARNING: Smokeless tobacco is addictive*

SMNA MRTPA BASIS OF PROPOSAL

- Similar products and users in Norway and Sweden:
  - Conform to the same standards
  - Pose the same level of exposures of harmful constituents to users
  - Users of these products will experience the same health outcomes
- Have relatively low levels of harmful constituents, particularly TSNAs
- In Sweden, smoking rates among men and rates of tobacco-related disease and death are lower
- Lower smoking rates are due to a “grassroots” movement among Swedes

FDA EVALUATION OF THE SMNA MRTPAS

- FDA completed the following activities during the application review process:
  - Reviewed applications as an interdisciplinary team with expertise in chemistry, engineering, microbiology, toxicology, environmental science, pharmacology, medicine, epidemiology, social science, and statistics.
  - Requested clarification on specific topics/questions from the applicant.
  - Reviewed public comments received on redacted applications.
  - Convened the TPSAC and integrated findings from the committee.
  - Evaluated all relevant evidence to determine whether the statutory requirements were met.

FDA FINDING ON GUM DISEASE AND TOOTH LOSS

- The warning "*WARNING: This product can cause gum disease and tooth loss*" is currently required for all smokeless tobacco products.
  - Smokeless tobacco products have been required to bear a warning related to gum disease and tooth loss since 1986.
- Omission of this warning represents an implied modified risk claim that the eight General Snus products, unlike other smokeless tobacco products, cannot cause gum disease or tooth loss.
- Epidemiological evidence indicates that use of these products increases the risks of certain outcomes classified as gum disease or tooth loss, or precursors to gum disease and tooth loss.

FDA FINDING ON GUM DISEASE AND TOOTH LOSS

- There is little biologically plausible reason to expect that outcomes related to gum and teeth of users would differ between these products and other smokeless tobacco products.
- The evidence supports the statement that smokeless tobacco products in general and these products in particular can cause gum disease and tooth loss.
- The evidence does not substantiate the proposed implied modified risk claim.

FDA FINDING ON MOUTH CANCER

- The warning "*WARNING: This product can cause mouth cancer*" is currently required for all smokeless tobacco products.
  - Smokeless tobacco products have been required to bear a warning related to mouth cancer since 1986.
- Omission of this warning represents an implied modified risk claim that the eight General Snus products, unlike other smokeless tobacco products, cannot cause mouth cancer.
- Although epidemiological studies observed a lack of a consistent association, the most recently published study presented in the applications reported a large and statistically significant association.
  - Inconsistency across studies may be due to the lack of precision in the estimates of risk, the variability in the definition of oral cancer, and other study limitations.

FDA FINDING ON MOUTH CANCER

- The products contain significantly lower levels of carcinogens than other smokeless tobacco products on the market; however, they still expose users to elevated levels of harmful carcinogens.
- NNN, in particular, is a potent oral carcinogen and no biologically plausible rationale was provided for why the levels of NNN found in these products do not pose an increased risk of oral cancer.
- Available scientific evidence supports the statement that smokeless tobacco products in general and these products in particular can cause mouth cancer.
- The evidence does not substantiate the proposed implied modified risk claim.

FDA FINDING ON RISK RELATIVE TO CIGARETTES

- The eight General Snus products can expose users to levels of constituents at levels lower than smoking.
- Evidence supports that exclusive use of the eight General Snus products as compared to smoking cigarettes may significantly reduce harm and the risk of certain tobacco-related disease to individual tobacco users.
  - There are clear, substantial differences in the risk of certain diseases, such as lung cancer and respiratory disease.
  - The reduction in health risks to an individual is dependent on patterns of use of the snus products, i.e., whether individual users switch completely to the use of the eight General Snus products.
- The evidence partially substantiates the proposed modified risk claim.

ADDITIONAL SELECT FDA FINDINGS – IMPACTS ON BEHAVIOR

- The information on the behavior of the Swedish and Norwegian populations with respect to snus type products has limited applicability to the U.S. population.
  - Snus products are currently available in the U.S., with limited uptake.
  - Snus holds cultural and traditional significance among Swedish users.
  - SMNA describes a historical shift away from smoking to snus use that occurred in Sweden, but does not provide evidence or information to suggest that a similar process could or would occur in the U.S.
  - Labeling and marketing of snus in Sweden has not referred to the product as reduced risk.

ADDITIONAL SELECT FDA FINDINGS – CONSUMER PERCEPTION STUDY

- The Consumer Perception Study conducted by SMNA does not provide sufficient insight as to what consumers understand about the risks of using the eight General Snus products after viewing the modified risk information, especially in the context of a warning.
  - The applicant did not provide evidence regarding how the removal of warnings would impact consumer behavior or comprehension.
  - For the revised warning statement, the applicant did not assess the impact of the context – within a warning or as a stand-alone promotional statement, or in the context of an advertisement – of the modified risk information.
  - The stimuli (images of the product package with the label) included in the study did not present the actual proposed revised warning statement verbatim.

ADDITIONAL SELECT FDA FINDINGS – POPULATION MODEL

- Although the applicant modeled a number of different scenarios of the impact to users and non-users, some resulted in population health benefits and some resulted in population health harms, and the applicant provided inadequate evidence as to which scenarios were more or less likely.

SMNA MRTPA DECISIONS

SMNA MRTPA DECISION

- With respect to the request to remove the gum disease and tooth loss warning, FDA concluded that SMNA did not demonstrate that, as actually used by consumers, the product would significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole.

This request was denied.

SMNA MRTPA DECISION

- With respect to the requests to remove the mouth cancer warning and revise the “not a safe alternative” warning, in their present form, the applications do not contain sufficient evidence to satisfy the modified risk standard.
- However, the applications could be amended in several ways
  - changing the proposed claims
  - supplementing the evidence, and
  - conducting new studies

  which could provide sufficient evidence to support issuance of modified risk orders relating to mouth cancer and health risks compared to cigarettes for these tobacco products.

MODIFIED RISK TOBACCO PRODUCT MARKETING DECISIONS

- While the FDA isn't authorizing these specific products as MRTPs at this time, the lessons learned through these first applications provide key insights for a potential path forward through an amended application and for others considering submitting an application.

- The FDA is committed to authorizing modified risk tobacco products for any company which submits adequate data demonstrating that the standard has been met.

QUESTIONS?