SCIENTIFIC BASIS FOR SWEDISH MATCH NA PREMARKET TOBACCO PRODUCT AUTHORIZATION

Presented by:
Ii-Lun Chen, MD
Director
Division of Individual Health Science
Office of Science, CTP, FDA

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

BACKGROUND - STATUTORY REQUIREMENT SECTION 910

Appropriate for the Protection of Public Health

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 - 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.

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

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

Users

Nonusers

PUBLIC HEALTH CONSIDERATIONS (CONT.)

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

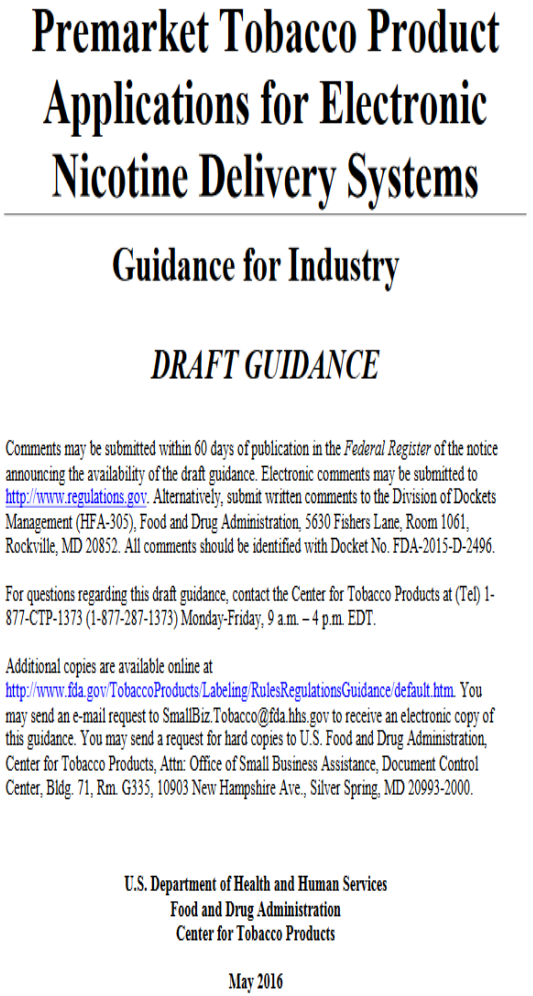
BACKGROUND: PMTA STATUTORY REQUIREMENTS (CONT.)

- 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

May 2016

SCIENTIFIC STUDIES AND ANALYSES: NONCLINICAL STUDIES

The Draft Guidances on PMTAs state the following information is helpful to assess the nonclinical health risks information of a new tobacco product:

- Details on what the product is and how the product is made
- A full assessment of the toxicological profile including a thorough literature review
  - Probative information on health risks and addictiveness by evaluating user exposure to tobacco related compounds
- A summary discussing how the new TP would be appropriate for the protection of public health relative to a similar comparator as well as to general tobacco market

SCIENTIFIC STUDIES AND ANALYSES: HUMAN SUBJECT STUDIES

The Draft Guidance on PMTAs available for comment states applicants consider including the following information to assess the human health impact of a new tobacco product such as:

- Evaluation of perceptions of product risk both absolute and in comparison to other TPs as well as to quitting all tobacco use
- Evaluations of the likelihood of initiation and cessation by both users and nonuser of TP
- Evaluation of product use patterns (e.g. topography, frequency of use, use by demographics)
- Abuse liability and addictiveness
- Evaluations of acute and chronic health effects using biomarkers and health outcome measurements and endpoints
- Marketing plan
- Sales data (foreign market experience or similar products in US market)

SCIENTIFIC STUDIES AND ANALYSES: HUMAN SUBJECT STUDIES

The Draft Guidance on PMTAs available for comment states that applicants consider providing information to assess the human health impact of a new tobacco product:

- 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 TP intended and potential unintended use by the consumer
- Evaluate the risk associated with use and demonstrate how potential risk maybe mitigated for users and nonusers

It is most helpful when study findings are generalizable to the population of U.S users and nonusers of the new TP.

CONSIDERATION FOR SCIENTIFIC STUDIES AND ANALYSES

The Draft Guidance on PMTAs available for comment states:

- 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
- Bridging data and studies can reduce the need for large amounts of additional data

SWEDISH MATCH NORTH AMERICA PMTAs

SWEDISH MATCH NORTH AMERICA PMTA SUBMISSION

- 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.

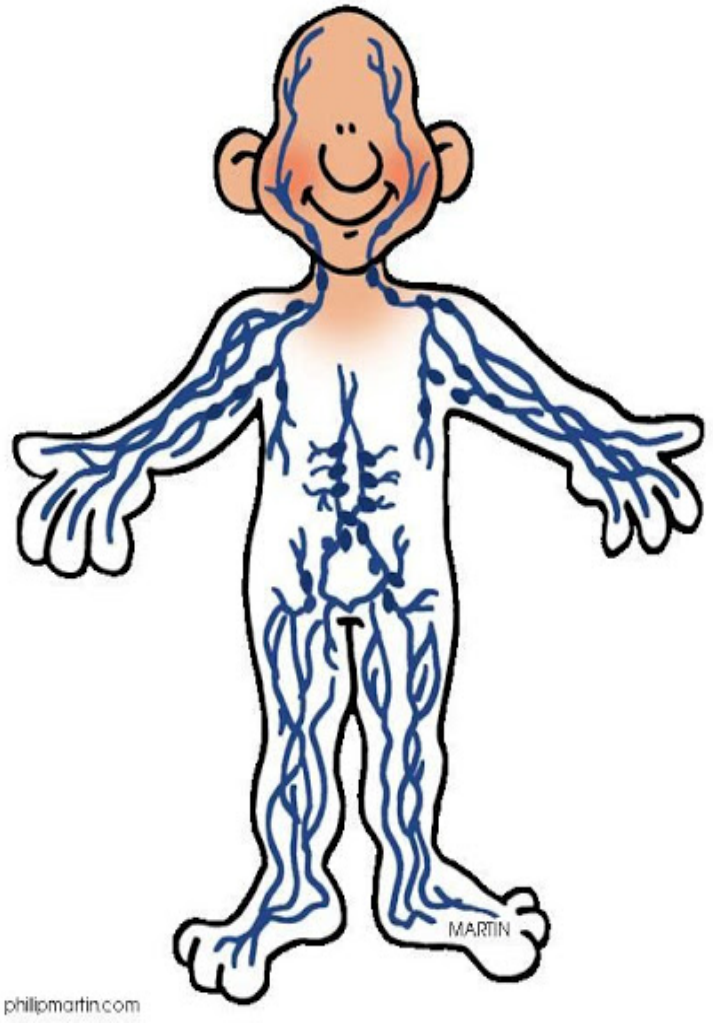
GOALS FOR REVIEWING THE SMNA SUBMISSION

- FDA utilizes the PMTA process to evaluate the morbidity and mortality associated with tobacco use.

- In evaluating how marketing authorization for these Swedish snus products impacts the current market, FDA considered the possibility that a PMTA order may increase use and initiation of snus due to its perceived favorable profile.

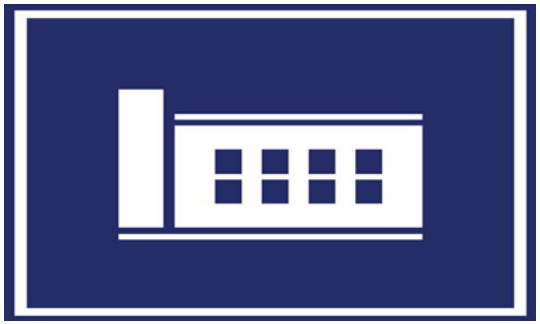
GOALS FOR REVIEWING THE SMNA SUBMISSION (CONT.)

Based on the products' characteristics and properties, the impact on health, impact on smoking cessation, impact on snus initiation and uptake, and impact on current ST users was considered in totality.



MANUFACTURING PROCESS

- These products are produced with a voluntary, proprietary manufacturing process that distinguishes Swedish snus from other types of ST, including snus-like products sold in the US market. The proprietary standard for Swedish snus products was developed to ensure product quality.
- The principal components of this standard include constituent standards, manufacturing standards, manufacturing process requirements, and consumer package labeling with a “best before” date. The constituent standards set maximum levels that must not be exceeded for selected constituents including certain carcinogens in the finished 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

TOXICOLOGICAL EVALUATION

- The SMNA ST products have significantly lower levels of NNN and NNK compared to over 97% the ST products currently on US market.

- 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.

HPHC EVALUATION

- Levels of other HPHCs (including As, Cd, acetaldehyde, crotonaldehyde, formaldehyde, and BaP) are similar to or lower than levels of 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.

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.
- The applications provided evidence that use of the proposed products is not likely to be associated with lung cancer, COPD, or chronic respiratory disease.
- Data are insufficient to support a lack of association between product use of these products and the other disease endpoints specified in the applications (e.g., stomach, pancreatic cancers, CVD, stroke, all-cause mortality).
- Use of these products is not associated with significant “second-hand” exposure, which decreases disease risks for the general population.

POPULATION IMPACT

- Data indicate there is limited switching behaviors from exclusive smoking to exclusive smokeless tobacco use.
- Findings from Tam et al. indicate that in the US, switching from ST use to smoking is more common than switching from smoking to ST use. Nevertheless, limited data suggest that the adoption of snus use in the US is low and, therefore, unlikely to lead to use of other tobacco products.

POPULATION IMPACT (CONT.)

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.

HEALTH IMPACT SUMMARY

- When used exclusively instead of cigarettes, these snus products offer lower risk of developing respiratory diseases (e.g., COPD, emphysema, chronic bronchitis) and certain cancers (e.g., lung).

- 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 excess cancer risk by 90% compared use of moist snuff (market share: 82%), by 67% compared to use of chewing tobacco (market share:15%), by 38% compared to use of US-style snus, and by 92% compared to use of dry snuff.

SUMMARY OF SCIENTIFIC RATIONALE: PMTA DECISION

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.

QUESTIONS