DRAFT with Proposed Edits: January 31, 2012

SUMMARY: TPSAC REPORT ON DISSOLVABLE TOBACCO PRODUCTS

Introduction and Statement of Charge

This document provides a summary of the report of the Tobacco Products Scientific Advisory Committee (TPSAC) on dissolvable tobacco products (DTP). Under Section 907(f) of the Family Smoking Prevention and Tobacco Control Act, the TPSAC was charged with developing a report on "…the nature and impact of the use of dissolvable tobacco products on the public health, including such use among children." (see Table 1) As detailed below, the TPSAC reviewed and discussed a wide array of

materials, submissions, and presentations relevant to its charge. Those materials, along with the transcripts of the open portions of the TPSAC meetings, constitute the evidence evaluated by TPSAC in responding to its charge. This summary, together with the materials considered by TPSAC and the transcripts of its meetings, constitute its report.

Table 1. Charges to the Tobacco Products Scientific Advisory Committee (TPSAC) under the Family Smoking Prevention and Tobacco Control Act

Section 907(a)(3)(B) Tobacco Product Standards
TPSAC is to consider: "(I) the risks and benefits to the population as a whole, including users and nonusers of tobacco products, of the proposed

standard;
(II) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and
(III) the increased or decreased likelihood that those who do not use tobacco products will start using such products."

Section 907(f) Dissolvable Tobacco Products

TPSAC is required to review and provide recommendations to the FDA regarding the "the nature and impact of the use of dissolvable tobacco products on the public health, including such use among children."

Committee Approach

The committee completed the task of developing this report over the course of three meetings, July 21-22, 2011, January 18-20, 2012, and March 1-2, 2012. The initial meeting was largely for the

purpose of information-gathering, as were the initial two days of the second. The TPSAC spent most of January 20, 2012 in open discussion of the full set of materials that it had received. In this discussion, the committee members: 1) evaluated the relevant papers from the peer-reviewed literature for key findings; 2) considered the findings of the scan of the industry documents and the main points of the tobacco industry presentations; 3) reviewed themes from the open public hearing and submissions to FDA; and 4) considered the presentations on the experience and perceptions of youth with regard to DTPs. Following this meeting a summary was prepared and reviewed by the TPSAC on March 1 and revised based on these discussions before approval on March 1, 2012.

TPSAC addressed the charge as stated and did not consider the broader issue of harm reduction and how dissolvable tobacco products might figure into harm reduction strategies. For this report, TPSAC considered dissolvable tobacco products to be those so-labeled by industry without offering a specific definition.

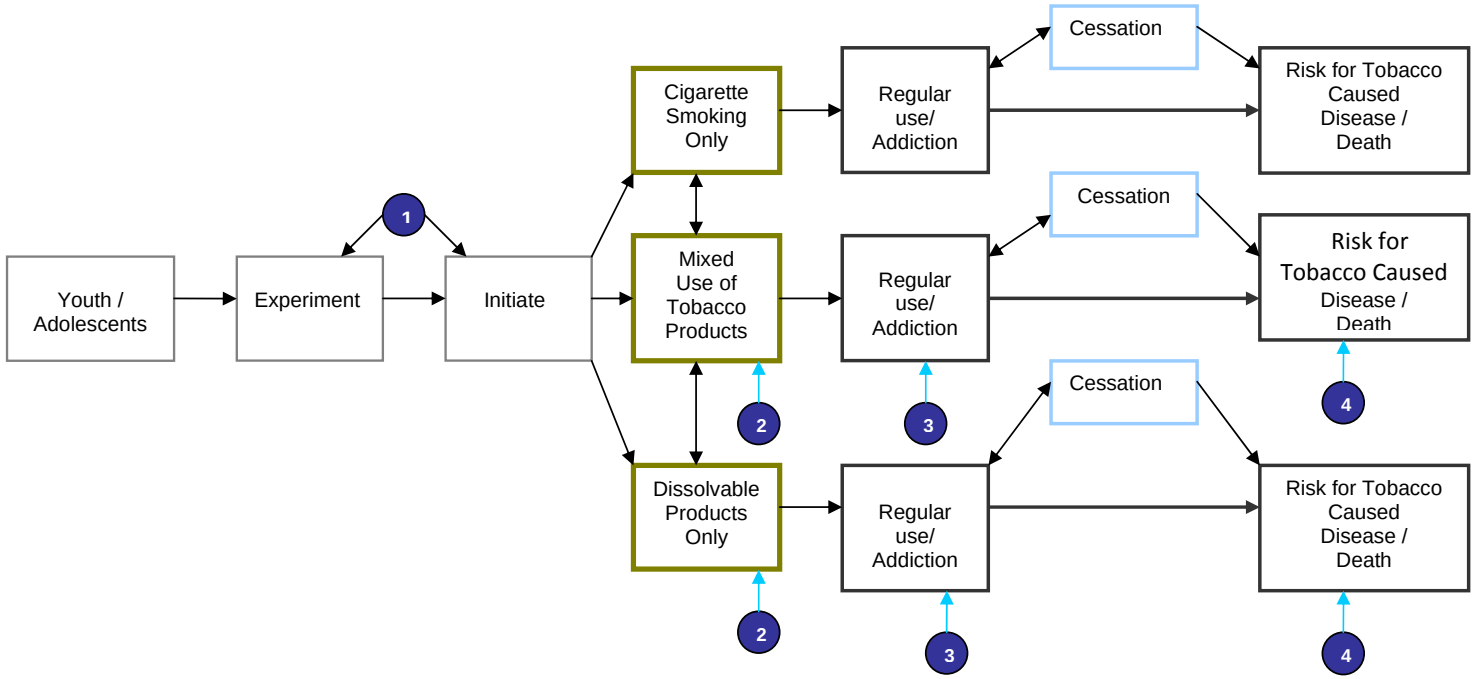
Committee Framework

To guide its integration of the evidence, the TPSAC developed a conceptual framework describing the potential roles of DTPs in smoking experimentation and initiation, addiction and regular tobacco use, and risks and benefits to health (Figure 1). *The TPSAC acknowledges that the framework necessarily oversimplifies the potential complexities of tobacco use,*

particularly if the array of nicotine-containing products continues to expand. For simplicity the framework represents only three potential patterns of tobacco-product use: cigarettes alone, DTPs alone, and mixed patterns involving multiple products, including DTPs. The numbers on the figure indicate those points at which the availability of DTPs could have impact. In this framework, the availability of DTPs might affect the likelihood of experimentation and initiation of tobacco product use (#1 in the figure) and also affect progression to regular use and addiction (#2); the model also reflects the possibility that DTPs would influence the maintenance of tobacco use and nicotine addiction and the likelihood of cessation (#3). Further, the framework acknowledges that risk for morbidity and premature mortality

caused by use of tobacco products could be affected by use of DTPs (#4) either increased or decreased. A potential benefit of availability of DTPs would be a reduction in risk of tobacco caused morbidity and premature mortality. In addressing its charge, TPSAC searched for evidence relevant to determining if the availability of DTPs might have any consequences at these points in the framework and to estimating the potential magnitude of any effects.

Figure 1. Conceptual Framework: From Experimentation to Disease



Hypothesized mechanisms by which dissolvable tobacco products could have impact on public health. The pathways include 1) effects on experimentation and initiation of cigarette smoking as a consequence of access to an oral, nicotine-containing product; 2) experimental use leading to an established pattern of mixed use of tobacco products (e.g., dissolvable products, other smokeless products, and/or cigarettes); 3) decreased or increased likelihood of smoking cessation, given a nicotine-delivering product that can be used where smoking is not permitted; and 4) differing risk profile for tobacco-caused diseases and premature mortality from, or partial to complete replacement of cigarette use by DTPs

Key Findings from the Evidence Review [*Lauterbach*: *When using the evidence, it should be specifically stated what brand-styles were considered. For example, did cited evidence apply to Camel DTP or to all contemporary brand-styles of DTP?]*

As described, the TPSAC reviewed a variety of sources of evidence on DTPs marketed up to this date. On the whole the evidence was limited and did not provide any information relevant to evaluating some individual DTPs. The transcripts of the TPSAC discussions document the synthesis and summarization of the evidence by the TPSAC. A brief, tabular summary of the main findings of TPSAC's review of the evidence follows, organized by the type of evidence:

Peer-Reviewed Literature *[Simons-Morton: Maybe a sentence about current prevalence of use.][*

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- Constituents: *[Lauterbach: This paragraph is at best misleading and the statement on nicotine yields is wrong. All DTP TPSAC considered met the GothiaTek standard. This needs to be stated explicitly. Nicotine contents of the products were different by design, but there were no data to support the contention that there was more than normal manufacturing variation within a design. Nicotine yield of STONEWALL was more than mainstream yield for any cigarette, including Health Canada intensive smoking. TSNA yields of DTP lower ___ lower than mainstream smoke yields from cigarettes]* There is variation across products in

contents of nicotine and tobacco-specific nitrosamines (TSNAs). Available data for some products show delivery to users of lower amounts of nicotine and TSNAs than are delivered by cigarettes. Heavy metals are present, also in variable amounts. *[Lauterbach: TPSAC needs to clarify which studies came from ISO 17025-accredited laboratories and which studies were conducted on samples obtained under validated sampling plans such as CORESTA Recommended Method #71]*.

- Abuse liability: The limited data available indicate that abuse liability is lower for current DTPs than for conventional cigarettes and for most conventional smokeless tobacco products (STs) *[Peters: First mention;:*

write it out][Lauterbach: The term "SMTs" needs to be defined at first use in the report] now available in the United States. *[Lauterbach: Which literature citations were used to support this?]*

- Cessation: Evidence considered by the TPSAC suggests that use of DTPs may reduce cigarette consumption, but does not completely substitute for smoking in most regular cigarette smokers.
- Health risk: Based on understanding of the delivery of toxins to cigarette smokers, exclusive use of DTPs should be less hazardous than regular smoking of cigarettes now marketed in the United States *[Lauterbach: This statement is not accurate. There is no evidence to support any increase in*

health risks for current DTP that are not present from use of NRT such as nicotine lozenges.]. The TSNA content of DTPs is lower than that of most currently marketed ST products but the public health implications of this difference are not presently known. There are no epidemiological data available on the absolute health risks of these products as they're currently used in the population.

- Consumer perception: Little data are available. One study *[Lauterbach: if this study is not reported in the peer-reviewed literature, it should be deleted. I could find one article, Romito et al., 2011, which covers Camel DTP]* showed that Ariva was perceived as being a non-tobacco product. This perception may extend to other DTPs.

- Consumer response: In general, consumers have not responded positively to current products.
- Childhood poisoning: Studies in the literature indicate that to date there have been few accidental ingestions with serious consequences.

Industry Presentations and Documents *[Lauterbach: Does this only apply to documents that were in public domain?]*

- Product range: There are a variety of products with different contents of nicotine, TSNAs and other constituents, such as benzo-a-pyrene and heavy metals.

- *[Heck: The HPHC data for current DTPs shows them to be within the Gothiatek standards for snus – in some instances substantially lower [e.g. TSNAs].*
- Cigarette use: Among those who both smoke cigarettes and use DTPs, users of DTPs smoke fewer cigarettes than nonusers.
- Marketing: DTPs are presently marketed as accessory products for smokers or other tobacco users to deal with craving in circumstances where social perceptions or bans make smoking difficult or impossible.
- Cessation: Presently, and consistent with current regulatory standards, DTPs are not being positioned by the industry as effective for cessation of cigarette smoking *[Peters: Wasn't*

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there one advertising exception to this that the tobacco reps on the committee brought up?].

- Youth: Presentations by industry indicate that DTPs are not directed at youth.

Open Public Hearing and Public Submissions

- Product perception: Based on the reports of individuals, TPSAC found evidence that DTPs were neither well liked nor being widely used by themselves for smoking cessation. Some commenters suggested that people may have a perception of the risks of DTPs that is exaggerated. Data presented from youth surveys suggested that DTPs may not be recognized as tobacco products.

- Government actions: Concern was expressed by some that DTPs might be banned *[Peters: Was the concern about DTPs or e-cigarettes being banned? I thought it was the latter but maybe it was both]*. Additionally, some recommended that government agencies should more pro-actively educate the public on the risks associated with specific products and not just the risks of tobacco in general.

Review of Swedish Experience with Snus *[Heck: True, Sweden's unique society does impose constraints on extrapolation elsewhere without some qualifications. However, I feel that the "Swedish experience" is more worthy re DTPs than the draft's "limited generalizability" statement conveys. May I suggest this*

additional bullet here. The recent Rodu 2011 review discusses the Swedish and the emerging US experiences with cessation, youth, dual use, smoking gateway concerns, etc. for snus. Given the HPHC similarity, I think the snus literature can offer considerable value until the DTP literature matures. Ref: Rodu, Harm Reduction Journal 2011, 8:19 http://www.harmreductionjournal.com/content/8/1/19] [Lauterbach: This review is not fully accurate. US government required warnings on DTP tell consumers that DTP use is just as hazardous as cigarette use. We know that is not true. Please go to transcript of meeting that gives Dr. Rutqvist's answer to question asking him to compare US health warning and Swedish health warning for same product.]

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- Context: The context of the Swedish experience with snus has unique characteristics (historic use of snus, marketing, government engagement, voluntary product standard and exclusive use pattern) that limits generalizability for DTPs in the United States.
- Health benefits: Presentations to TPSAC and peer reviewed literature document a lowering of rates of lung cancer as snus use increased and cigarette smoking decreased in Sweden. Epidemiological studies showed lower relative risks for major smoking caused diseases among snus users compared with regular cigarette smokers. Data from the Swedish experience indicate that for health benefits of snus

use to be obtained, complete substitution of snus for cigarettes was needed.

- New users: At present, 50% of snus users are new tobacco users.
- Use by sex: More males tend to be exclusive snus users, reflecting historical Swedish tradition, while most female tobacco users continue to smoke cigarettes. *[Heck: To me, the main take-away was that so relatively few Swedish females use snus (under 5%) vs. males (20-25%), while they still smoke at levels similar to other developed countries & consequently have similarly high health risks (in contrast to men). I haven't been able to reconstruct the basis in the record for what seems to be expressed here – i.e., that dual*

use is markedly higher among the (relatively few) female snus users. Perhaps I overlooked it. Is that the intended meaning? If so, is this a key point? The heavily-referenced RJRT presentation by Dr. Curtin last July indicated that dual users seem more likely to quit smoking than exclusive smokers (about 10 studies). Although that was an industry presentation, the published papers are mainly on snus, so perhaps it should be mentioned here if dual use by women (or anyone) in Sweden is a key point to the Committee.]

- Labeling: Labeling in Sweden differs from that in the United States.

Information on Youth

- Youth use of DTPs: To date, there is little use of DTPs by youth, even though several products have been on the market for about 10 years. The Indiana experience during test marketing of one DTP suggested that some youth would try DTPs, particularly those already smoking cigarettes. Data from a survey in Virginia suggested that youth not perceiving DTPs as a tobacco product would be more likely to try them. *[Lauterbach: It needs to be stated explicitly that Indiana experience refers to Camel DTP only. Furthermore, are Indiana officials credible? See their inaccurate statements on health risks of DTP at http://www.in.gov/isdh/tpc/files/Dissolvable_tobacco_products_7_18_11.pdf .]*

- Packaging: Appeal to youth is likely to depend on packaging. *[Lauterbach: Youth presentation was biased by semi-hidden image of TicTac package in the "ballot" they gave to other students.]*

Responses to Charge Issues *[Lauterbach: A continuing critique of DTP is that the products taste like candy. Those who have tasted the products know that most products are far from candy-like and taste characteristics are inferior to those of oral NRT.]*

The risks and benefits to the population as a whole, including users and non-users of tobacco products;

This element of the charge addresses the risks and benefits of DTPs. As noted, the TPSAC considerations of this question are based in counterfactual comparisons of a scenario of the United States, absent DTPs, to scenarios with current types of DTPs available. In constructing comparison scenarios, the TPSAC was constrained *[Lauterbach: "was constrained" should be replaced by "chose to be constrained" as TPSAC not given evidence that there was a longer history of dissolvables than just products new on market over past few years.]*

by the limited "real world" experience to date—10 years with products from *Star Scientific Inc.* (Ariva and Stonewall) and test

marketing of new products in several locations in the United States by several companies.

TPSAC considered the burden of tobacco-related morbidity and premature mortality to be the appropriate indicator in addressing this element of its charge. That burden reflects the number of users of tobacco products, their patterns of use, and the risks of the products that they use, as set out in Figure 1. Additionally, TPSAC considered how DTPs might affect the risk for individuals.

With regard to benefit, TPSAC concludes that exclusive use of DTPs by an individual would greatly reduce risk for smoking caused disease compared with regular use of cigarettes. The

TPSAC framework indicates several ways that DTPs could reduce the population disease burden caused by tobacco use: 1) decreasing the number of smokers, if availability of DTPs increases successful cessation or decreases the likelihood of initiation and use of smoked products, and 2) decreasing the risk of tobacco caused disease, if availability of DTPs sufficiently reduces cigarette smoking.

The TPSAC framework indicates several ways that DTPs could increase the population disease burden caused by tobacco use: increasing the number of smokers, if availability of DTPs decreases successful cessation or increases the likelihood of initiation and use of smoked products.

[Lauterbach: This paragraph assumes that tobacco use of all kinds will result in premature mortality and serious morbidity. This is not supported by the facts. For example, what is morbidity/premature mortality for use of US-style chewing tobacco except for dental caries?] The TPSAC noted the great uncertainty concerning how availability of DTPs would impact the burden of tobacco-caused morbidity and premature mortality in the population. To date, experience is limited and observational evidence on how DTPs might affect use of tobacco products is lacking. After 10 years of availability, the products made by Star *Scientific, Inc.* have had extremely limited market penetration and no apparent overall impact on disease burden. Furthermore,

TPSAC concluded that the context set by all aspects of industry marketing and regulation will be critical in determining the impact of DTPs. *[Lauterbach: This statement is incorrect. I do not concur with it. Was there a vote taken in closed session?]* The committee was concerned that availability of DTPs with lower risks to health than cigarettes might affect the public perception of all tobacco products, leading to increased use because of reduced concern about health risks of tobacco products generally.

Given the substantial uncertainties and the potential for either risks or benefits, TPSAC could not reach a conclusion as to the potential point of balance between potential risks and benefits of DTPs on public health.

The increased or decreased likelihood that existing users of tobacco products will stop using such products;

TPSAC concluded that DTPs are presently being positioned as a tobacco product that provides nicotine in circumstances where smoked products and specifically cigarettes cannot be used. Smokefree regulations and changing social norms have narrowed the range of venues where smoking is allowed and acceptable. Marketing strategies examined by TPSAC gave emphasis to use of DTPs in circumstances under which nicotine intake by smoking is not possible. Additionally, findings of several peer-reviewed papers, industry studies, and anecdotal reports from the public

hearing speakers suggest that cigarette smokers do not find the current DTPs to be sufficient by themselves, as an alternative to cigarette smoking. Beyond some anecdotal reports, TPSAC found no information on whether DTPs would increase the likelihood of cessation of cigarette use.

In considering scenarios for addressing this element of its charge, TPSAC offers the reminder that context will be critical in determining use patterns for DTPs. Will current marketing and product development approaches be continued, giving emphasis to use of DTPs when smoking is not possible or perceived unfavorably? Will DTPs be marketed as a complete substitution for combustible tobacco products? Will adopters use the product

as a cessation tool or to maintain their addiction to nicotine? Will the nicotine yield in forthcoming products be different from that of current products *[Lauterbach: Is a 2-mg or 4-mg DTP any more harmful than a 2-mg or 4-mg piece of nicotine-containing gum or nicotine-containing lozenge?]* ?

TPSAC concluded that the availability of DTPs could either increase the likelihood of cessation of smoking, if they proved to facilitate cessation, or decrease the likelihood of stopping if they served to maintain use of tobacco products and nicotine addiction by offering a product that can be used in circumstances where smoking is generally not possible. As noted, TPSAC could not reach any overall judgment as to whether the net consequence of

DTPs would be an increase or decrease in the number of people who successfully quit smoking. This uncertainty provides a strong rationale for close surveillance of cessation and any impact of DTPs *[Lauterbach: Why is TPSAC avoiding the obvious? If all cigarette smokers switched to DTP, we would have far less lung cancer, COPD, and emphysema.].*

The increased or decreased likelihood that those who do not use tobacco products will start using such products.

For this component of the charge, the TPSAC concluded that the available evidence, while limited, leads to a qualitative judgment that availability of DTPs could increase the number of users of

tobacco products. This judgment was based on experience with other SMTs, data presented from the State of Indiana showing that some adolescents were already using DTPs, the survey data on youth perceptions of the products from the State of Virginia, and the potential for youth to be drawn to a novel product *[Lauterbach: As noted in my earlier comments, there was substantial anti-DTP bias in both the IN and VA studies.]* . The TPSAC could find no basis for the contrary finding—that availability of DTPs would decrease tobacco product initiation. With the very limited information available, however, the TPSAC could not estimate the magnitude of any potential increment in numbers of new tobacco-product users because of sales of DTPs. Based on its finding, the TPSAC offers strong recommendations as

to the need for informative surveillance related to DTPs and youth including marketing approaches.

Recommendations for Further Information Gathering, Surveillance, and Research *[Lauterbach: The recommendations on information gathering, surveillance, and research are excessive. If TPSAC is concerned about chemical composition of DTP, then the recommendation should be that DTP should meet the GothiaTek® standards for impurities in Swedish snus. There are no need for development of short-term bioassays as such studies have already be done on several types of STP and the results show that contemporary STP have little if any activity in common bioassays used to assess cytotoxicity and genotoxicity. Also, it is likely that*

human studies using biomarkers of dose and biomarkers of harm will not yield significant new information.] [Lauterbach: How come there is not a recommendation on packaging in terms of resistance to opening/use of product by infants and young children?]

To guide regulatory activities and to facilitate accumulation of data on various DTPs a standard product definition is needed.

Testing of Current and Future Products

- Further characterization of within-product variation in content of nicotine, TSNAs, and other health-relevant components as set out in the FDA list of harmful and

potentially harmful constituents. PH should also be measured.

- Characterization of variation in product composition at point-of-sale across the country.
- Characterization of change in product composition with time since manufacture, and the influences of heat and moisture exposure on composition.
- For each product, doses of key components delivered to users should be assessed with an appropriate suite of biomarkers.
- For each product, detailed information is needed on abuse liability and topography in actual use.

Surveillance

TPSAC notes that the following recommendations in regard to DTPs apply to other novel tobacco products.

- Existing surveillance systems should be reviewed and selected based on their suitability and sensitivity to track patterns of DTP use and the various mixed use patterns, particularly among key sentinel populations, e.g., youth, and vulnerable population subgroups.
- Appropriate survey questions will need to be developed for tracking DTP use and a mechanism developed for their rapid integration into ongoing surveys.

- The impact of availability of DTPs on use of other tobacco products, particularly cigarettes, needs to be monitored closely.
- Research/surveillance will be needed to assess perceptions of DTPs and how availability and marketing (including packaging and product development) of DTPs affects perceptions of them and other tobacco products.
- Appropriate survey questions will need to be developed for tracking perceptions and a mechanism developed for their rapid integration into ongoing surveys.
- Information is needed on if and how underage users obtain DTPs.

Research

For DTPs as for other tobacco products there is a need for research methodology and applied research that will be informative with regard to individual risks and public health consequences. Additionally population models are needed for assessing the consequences of DTP availability.