FOOD AND DRUG ADMINISTRATION
Center for Tobacco Products (CTP)

Tobacco Products Scientific Advisory Committee (TPSAC)
Center for Tobacco Products
9200 Corporate Boulevard
Rockville, MD 20850

April 16-18, 2014

These summary minutes for the April 16-18, 2014 meeting of the Tobacco Products Scientific Advisory Committee of the Food and Drug Administration were approved on __May 14, 2014______.

I certify that I attended the April 16-18, 2014 meeting of the Tobacco Products Scientific Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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/s/ Caryn Cohen, MS          /s/ Jonathan Samet, MD, MS
Designated Federal Official, TPSAC  Committee Chair, TPSAC
Meeting of the Tobacco Products Scientific Advisory Committee  
April 16-18, 2014

The Tobacco Products Scientific Advisory Committee (TPSAC) of the Food and Drug Administration, Center for Tobacco Products met on April 16-18, 2014 at the FDA Center for Tobacco Products (CTP), 9200 Corporate Boulevard, Rockville, Maryland, 20850. Prior to the meeting, committee members and invited guests were provided copies of the background material from the FDA and the submissions from the public. The meeting was called to order by Jonathan Samet, MD, MS (Committee Chair); the conflict of interest statement was read into the record by Caryn Cohen, MS (Designated Federal Official). There were approximately 75 persons in attendance. There were 9 speakers for the Open Public Hearing session: 2 on the first day, 2 on the second day and 5 on the third day.

Agenda: On April 16, 2014, the Committee considered scientific issues pertaining to dependence and addiction, including the development of addiction, measurement of dependence and addiction and concepts concerning the assessment of addiction in the review of product submissions. On April 17, 2014, the Committee received information on population modeling in the assessment of tobacco product applications, and discussed the ways modeling can inform decisions critical to population health. On April 18, 2014, the Committee discussed possible approaches for evaluating information on the risks and potential benefits of a proposed modified risk tobacco product (MRTP) to the health of individual tobacco users and to the population as a whole.

Attendance:

TPSAC Members Present (Voting):
Jonathan M. Samet, MD, MS (Committee Chair)
Warren K. Bickel, PhD
Thomas E. Eissenberg, PhD (Attended April 16 and 17)
Philip P. Huang, MD, MPH (Employee of a state or local government or of the Federal Government)
Suchitra Krishnan-Sarin, PhD
Richard J. O’Connor, PhD

Industry Representative Members Present (Non-voting):
Hampton H. Henton (Representative of the interests of tobacco growers)
James Swauger, PhD, DABT (Representative of the tobacco manufacturing industry)
David M. Johnson, PhD (Representative for the interest of small business tobacco manufacturing industry-participated by phone)

Ex Officio Members Present (Non-Voting):
Timothy McAfee, MD, MPH (CDC)
Elinore McCance-Katz, MD, PhD (SAMHSA)
Mirjana Djordjevic, PhD (NIH)

Special Government Employee Consultants Present (Non-Voting):
Dorothy Hatsukami, PhD (Attended April 16)
Jack Henningfield, PhD (Attended April 16)

FDA Participants (Non-Voting):
Mitch Zeller, JD (Attended April 16)
David Ashley, PhD
Conrad Choiniere, PhD (Attended April 17 and 18)
The agenda on April 16-18, 2014 was as follows:

April 16, 2014

Call to Order
Jonathan Samet, MD, MS
Chair, TPSAC

Conflict of Interest Statement
Caryn Cohen, MS
Designated Federal Official, FDA/CTP

Introduction of Committee Members
Jonathan Samet, MD, MS
Chair, TPSAC

Welcome and Introduction
Carolyn Dresler, MD, MPA
Associate Director for Medical and Health Sciences
Office of Science, FDA/CTP

Addiction and Dependence
Michael C. Fiore, MD, MPH, MBA
Professor
University of Wisconsin

Conceptual and Methodological Clarity in Abuse Liability Studies
John R Hughes, MD
Professor, Departments of Psychiatry, Psychology and Family Practice
University of Vermont

Clarifying questions from the Committee for the speakers

Measuring Nicotine Addiction
Joseph R. DiFranza, MD
Professor
University of Massachusetts Medical School

Tobacco Dependence and Addiction
Saul M. Shiffman, PhD
Professor, Department of Psychology
University of Pittsburgh

Clarifying questions from the Committee for the speakers

Presentation on product review factors related to dependence/addiction
Allison C. Hoffman, PhD
Chief, Addiction Branch
Office of Science, FDA/CTP

Clarifying questions from the Committee for the speaker

Open Public Hearing
Michael Hufford, PhD, e-Nicotine Technology
Wallace B. Pickworth, PhD, Battelle
Questions to the Committee

Adjourn

April 17, 2014

Call to Order
Jonathan Samet, MD, MS
Chair, TPSAC

Conflict of Interest Statement
Caryn Cohen, MS
Designated Federal Official, FDA/CTP

Introduction of Committee Members
Jonathan Samet, MD, MS
Chair, TPSAC

Welcome and Presentation:
Applying Simulation Models in Assessing
Health Effects of Tobacco Products
George Rochester, PhD
Chief, Statistics Branch
Office of Science, FDA/CTP

Tobacco Surveillance Data for Population Modeling: Getting
the Inputs Right
Cristine Delnevo, PhD, MPH
Professor
Rutgers School of Public Health

Data Harmonization
Matthew Sobek, PhD
Principal Research Scientist
University of Minnesota

Modeling Approaches:
Dynamic Population Health Modeling for
Multi-Product Tobacco Environment
Stephen J. Verzi, PhD
Sandia National Laboratories

SnapDragon: A Social-Network Behavioral
Dynamics Model of Tobacco Product Use
Patrick Finley, PhD
Sandia National Laboratories

Estimating the Potential Effect of Modified
Risk Tobacco Product Use (MRTP) on Population
Mortality: A Dynamic Population Modeler (DPM)
Annette Bachand, PhD
Associate Professor
Colorado School of Public Health

Clarifying questions from the Committee for
the speaker

Open Public Hearing
Ray Niaura, Legacy
Dr. Yezdi Pithawalla, Altria Client Services Inc.

Questions to the Committee
George Rochester, PhD
Chief, Statistics Branch
Office of Science, FDA/CTP

Committee Discussion

Committee Discussion (continued)

Adjourn
Questions to the committee April 16, 2014:

1) What are your views on the differences, if any, between dependence and addiction? Have these changed over time? If so, what are the factors that influenced this change?

2) How can current assessments of dependence/addiction be used for non-traditional products and/or nondaily users? How can current assessments be applied to individuals who use multiple products? Are new assessments necessary?

3) On the topic of dependence/addiction, what review factors should be included in the evaluation of product submissions?

Discussion:

The committee heard four presentations related to addiction and dependence, how these terms are defined in research and clinical practice, and how these definitions may have changed over time. While there were some disparate views about the appropriate usages and definitions, it was generally agreed that in treatment settings a diagnosis of either addiction or dependence would not reasonably be required to elicit treatment, given that any use of tobacco products presents sufficient risk to individual health. For research purposes, while dependence has traditionally been associated with a physical phenomenon, the terms are often interchangeable and precise definitions depend in large degree on the designations...
assessed by the measurement tools used (for example, the diagnostic manuals, practice guidelines, survey instruments, etc.).

**Questions to the committee April 17, 2014:**

1) Considering the examples of modeling approaches presented for assessing the effects of tobacco product on population health:
   - What are merits and limitations to these approaches for assessing these effects prior to allowing a product to market?
   - Are there other modeling approaches that may be appropriate for assessing these effects prior to allowing a product to market?

2) Discuss the quality of data sources for parameter inputs for modeling.
   - Specifically, do you have recommendations for the process of assessing the best sources of data used for inputs?
   - Do you have recommendations for addressing gaps in the information used to needed as model input parameters?
   - Are there particular inputs that you deem critical for modeling the effects of tobacco products on population health?
   - Discuss the need for common terminology in defining key parameters, for example, initiation, cessation, smoking status (former or current smoker).

3) Do you have recommendations regarding metrics that may be used to assess the effects of tobacco products on the population as a whole? For example:
   - Morbidity and mortality (all-cause, cause-specific mortality).
   - Quality-adjusted Life Years (QALYs), Disability-adjusted Life-years (DALYs).

**Discussion:**

*The second day of the meeting was focused on mathematical modeling. The committee heard six presentations including three that described specific models currently in development. The availability, reliability, validity and quantity of data available to provide useful parameters were key topics. Particularly in the case of new products, there may be a scarcity of data. Data collection tools will need to catch up to the marketplace (when the tools were developed many of the current products didn’t exist). Historically, as more has been learned about tobacco products and how they work physiologically, the tools change (questions change, variables are added, eliminated, combined and/or become more precise) – consequently longitudinal data may require refinement in order to be accurately used in modeling schema – data harmonization as a means of using longitudinal data to strengthen predictive modeling was discussed. Successful model development and maintenance requires extensive documentation, repeated testing and extensive expert review. Some committee members suggested the use of standard models to provide consistency and repeatability - the feasibility of this is questionable.*

**Questions to the committee April 18, 2014:**

1) For MRTPAs seeking to market a product under Section 911(g)(1) of the FD&C Act, i.e., risk modification order:
   - What concerns, if any, do you have about the use of certain types of studies, or data, to draw inferences about the potential impact of product use on health outcomes in individuals?
• What recommendations do you have for placing greater weight on certain types of data or studies, as they relate to the assessment of health outcomes in individuals?

Examples to consider:
• Epidemiological data in the tobacco product, but on populations outside of the US
• Epidemiological data for a class of tobacco products, but not on the individual tobacco product
• Clinical trials in adult smokers only, in the absence of long-term epidemiological data

2) For MRTPAs seeking to market a product under Section 911(g)(1) of the FD&C Act, i.e., exposure modification order:
• What concerns, if any, do you have about the use of certain types of studies, or data, to draw inferences about the potential impact of product use on exposures in individuals?
• What concerns, if any, do you have about the use of certain types of studies, or data, on exposures to individuals to infer potential health outcomes?
• What recommendations do you have for placing greater weight on certain types of data or studies, as they relate to the assessment of exposures to individuals?

Examples to consider:
• Epidemiological data on the impact from exposure(s) to certain constituents, but not on the use of a tobacco product
• Chemical analyses that demonstrate a substantial reduction in all harmful and potentially harmful constituents identified by FDA, in the absence of toxicological data on the product itself
• Toxicological analyses that indicate that a substance that has been removed from the product is harmful, in the absence of a well-characterized dose-response relationship for the substance

3) For all MRTPAs:
• What concerns, if any, do you have about the use of certain types of studies, or data, to draw inferences about the potential impact of the marketing of an MRTP on tobacco use behavior, such as product adoption, initiation, poly-tobacco use, or likelihood of cessation?
• What recommendations do you have for placing greater weight on certain types of data or studies, as they relate to the assessment of tobacco use behaviors?

Examples to consider:
• Perception studies on adult users that indicate that users have a high level of interest in trying the product, in the absence of information on non-users
• Actual use studies that demonstrate that the majority of established smokers use the product as directed and are likely to switch completely from smoking to the product after a certain period of use, in the absence of strong evidence that demonstrates comprehension of modified risk information

4) When making a determination to allow an MRTP to market, FDA will need to assess the impact on the population as a whole:
• What recommendations do you have for placing greater weight on certain types of data or studies, as they relate to the either the assessment of health outcomes or tobacco use behaviors, when considering the impact on the population as a whole?

Examples to consider:
• Conclusive data that risks of using the product are significantly lower than risk of smoking, but only suggestive data that young adults are not likely to initiate tobacco use with the product
Conclusive data that risks that marketing of the product as an MRTP will not have deleterious impacts on the likelihoods of initiation or cessation, but suggestive data that the reduction in exposures to smokers that switch to the product may reduce the risks of tobacco-related disease.

5) An evaluation of an MRTPA will require reliance on indirect evidence on various impacts on exposure, health, and tobacco use behavior. In addition, the data in an MRTPA may not provide direct evidence of the long-term impacts of an MRTP.

- What recommendations do you have for strategies that industry or FDA could undertake to address any areas of concern after an MRTP has been allowed to market to the US population?

Discussion:

The third day of the meeting was devoted to the discussion of possible approaches for evaluating modified risk tobacco product applications (MRTPAs), including the potential risks and benefits to the health of individual tobacco users and to the population as a whole. This will likely be a complex process, wherein FDA reviewers and the TPSAC will be presented with extensive and possibly expansive claims along with supporting evidence, which will require complete a thorough evaluation. Ideally, an MRTP would help current tobacco users either quit or switch to a new less dangerous product. Simultaneously, the MRTP would, ideally, be of little or no appeal to new users and would not serve to prolong the use of tobacco products by people who would otherwise have quit. Additionally, the risk of “normalizing” the use of products that simulate cigarette use could lead to, albeit unintentionally, more acceptance of smoking. For some members of the TPSAC a product that holds any appeal to youth, or would potentially encourage youth to start using it, would be unacceptable.

Committee members encouraged CTP to work with other FDA centers who may have faced similar issues (i.e., use of common terminology, designing models to address complex issues, and strategies for weighing the risk and benefits of new products), thereby gaining knowledge and insight from their experiences. Working with other agencies faced with similar issues may also yield useful insight.

Meeting adjourned at approximately 2:00 p.m.

Please see the verbatim transcript for details of the discussion.