8.1: POSTMARKET ASSESSMENT PLAN

TABLE OF CONTENTS

8.1. POSTMARKET ASSESSMENT PLAN

8.1.1. Background and Objectives

FDCA §911(i) requires an MRTP applicant to "conduct postmarket surveillance and studies for [the candidate product] to determine the impact of the order issuance on consumer perception, behavior, and health." As stated in the Food and Drug Administration's (FDA's) Modified Risk Tobacco Product Application (MRTPA) Draft Guidance (2012), "postmarket surveillance is a very important tool for monitoring the effects of the MRTP [modified risk tobacco product] on individual and population health" that can allow for identification and collection of "unanticipated and undesired events related to the tobacco product once it is introduced to the market."

ALCS proposes, on behalf of U.S. Smokeless Tobacco Company (USSTC), a Postmarket Surveillance Program consisting of multiple and diverse approaches to collect both quantitative and qualitative data over time, once the candidate product is introduced into the market with the proposed modified risk claim.

USSTC designed its Postmarket Surveillance Program to be consistent with the requirements outlined in the MRTPA Draft Guidance. This program will evaluate the effect of the MRTPA authorization and the subsequent marketing of the candidate product[1] on consumer perception, behavior, and health over time. This program will enable the identification and collection of unanticipated and undesired events related to the use of the candidate product, once authorization is granted and marketing of the candidate product with the claim begins.

Section 4.1 details the proposed advertising and labeling of the candidate product.

8.1.2. General Scope of the Candidate Product Postmarket Surveillance Program

The Postmarket Surveillance Program will include both passive and active surveillance activities, a series of postmarket studies, and population modeling. Within 30 days after receiving notice to conduct such surveillance, we plan to submit fully developed plans, study protocols, and study-related documentation, including the final survey instrument(s), recruitment strategy, and data analysis plans.

8.1.2.1. Postmarket Surveillance Activities

The postmarket surveillance will consist of a combination of passive and active surveillance activities, which include collection of unverified adverse events (AEs) reported by callers,

[1] The candidate product is a grandfathered product (FDA Grandfather Status # GF1200194) (Appendix 2.3-1), commercially marketed in the U.S. as of February 15, 2007. As such, it is not a new tobacco product as defined by FDCA Section 910(a) (1) and does not require premarket review and authorization. Copenhagen® Fine Cut and variants thereof have been on the market since 1822. Since 2007, USSTC made minor modifications to Copenhagen® Snuff Fine Cut, which are the subject of a separate pending Substantial Equivalence review. The candidate product subject to the MRTPA is the product for which FDA granted grandfathered status on November 1, 2012.

literature monitoring, review and secondary data analysis of national surveys (e.g., Population Assessment of Tobacco and Health (PATH) Study, National Survey on Drug Use and Health (NSDUH)), and other available sources of information.

We will use ALCS' established AE collection system to capture and classify reports of AEs associated with use of the candidate product in the context of passive safety surveillance. All AEs for the candidate product reported through the ALCS AE collection system will be included in an annual report.

In addition to passive surveillance through the ALCS AE collection system, we plan to collect and analyze AEs published in the literature and those that are reported to the FDA Adverse Events Reporting System and to the Health and Human Services Safety Portal. We also plan to register the candidate product with the National Poison Data System from the American Association of Poison Control Centers to track and report any AEs from these sources. We will develop a safety database as the central repository for all health- and safety-related data and reports captured from all data sources.

8.1.2.2. Postmarket Studies Overview

Based on recommendations in the MRTPA Draft Guidance, we plan to conduct a series of observational, cross-sectional surveys to evaluate the impact of the order issuance on consumer perceptions and behavior, among adults of legal age to purchase tobacco products under real world conditions, taking into consideration all the factors that influence an adult consumer's purchase decision for the candidate product. We plan to complement these observational, cross-sectional surveys with an ongoing, cross-sectional survey designed to measure tobacco use prevalence and trends over time.

Collectively, postmarketing studies will be designed to provide information on use of the candidate product and to assess trends over time, with regard to:

- overall tobacco product use prevalence (including the candidate product as feasible, recognizing the challenge of estimating prevalence for products with low marketplace penetration);
- use patterns of the candidate product in context with other tobacco product use;
- initiation and cessation-related behaviors; and
- perceptions of the candidate product (including reasons for use of the candidate product and perceived health risks).

The Postmarket Surveillance Program may also include observational postmarketing behavioral cohort studies of the candidate product. These studies would recruit consumers of the candidate product and follow them over a period of time to assess:

- tobacco product use patterns;
- switching behaviors between tobacco products;
- dual tobacco use or poly-tobacco use patterns and rates;
- transitions to more or less harmful tobacco products;

- quitting of cigarettes and other tobacco products; and
- perceptions of risk.

8.1.2.3. Population Modeling

Section 7.4.2 details the development, testing, and validation of the ALCS Cohort Model. This section focuses on how the ALCS Cohort Model will be used within the Postmarket Surveillance Program.

The ALCS Cohort Model will be used as a tool to quantify the impact of marketing the candidate product and subsequent use of the product on the population as a whole. The ALCS Cohort Model estimates the effect of marketing an MRTP with the reduced risk claim, using a hypothetical population, by calculating the difference in estimated all-cause mortality (or survivors) between a base-case scenario and a master-case scenario. In the context of this MRTPA, the *base case* is defined as the status quo (i.e., the current marketing authorization for the candidate product). The master case would be one where the candidate product exists with the proposed modified risk claim, taking into consideration a composite of all the various scenarios. The ALCS Cohort Model allows us to examine a variety of informed "what-if" scenarios and to predict all-cause mortality over time by comparing the number of survivors in base cases versus master cases.

Over time, data from the postmarket studies, once collected, can be used to refine the modeling assumptions. This will allow the ALCS Cohort Model to monitor and make better projections of the effect of marketing the candidate product with the modified risk claim using data from real-life, in-market observations.

8.1.3. Postmarket Surveillance

8.1.3.1. Passive Adverse Events Reporting

The ALCS AE[2] collection system will capture and classify AEs associated with use of the candidate product that are reported to the ALCS Consumer Call Center. The ALCS Consumer Call Center has experience systematically collecting unsolicited consumer complaints and unverified AEs associated with the use of and exposure to tobacco products.

Calls to the ALCS Consumer Call Center can include cases with various issues, such as general questions about product use, complaints about product quality, and reports of potential AEs associated with the use of the candidate product. Each consumer call is received by a call handler who is trained to follow a series of predefined scripts, ensuring that every consumer complaint is collected in a defined and consistent manner in order to identify potential AEs. If the call includes a potential AE, the call handler administers the Adverse Event Survey (Appendix 7.4.3-1). The survey consists of questions to obtain detailed information about the nature of the reported AE, as well as the caller's pre-existing medical conditions, medications, and exposure to the candidate product.

[2] The ALCS Consumer Call Center currently uses the term alleged physical effect (APE) rather than AE. APE is defined by ALCS as any complaint that alleges symptoms, illness or injury.

Certified coders with a clinical background review, process and code all AEs received by the ALCS Consumer Call Center. A quality control specialist reviews each AE following the ALCS coding guidelines.

All reported AEs are assessed and coded as described in Section 7.4.3. The MRTPA Draft Guidance provides a list of criteria to assess whether or not an AE is a serious adverse event (SAE). We describe additional details regarding our characterization of SAEs in Section 7.4.3.

Since this is an established product, we do not anticipate conducting any additional clinical studies or consumer research on the candidate product, at this time. However, if we do conduct human studies, we will collect and report the AEs from such studies.

8.1.3.2. Assessing the Expectedness of the Event

We plan to determine "expectedness" for the candidate product by assessing the reported AE term against the cumulative safety data sources, such as consumer complaints, clinical studies, published literature, Poison Control Center data, and FDA safety portal monitoring.

An unexpected AE is one in which the nature, severity, or frequency is not consistent with the known or foreseeable risks associated with exposure to the candidate product. In assessing expectedness of an AE, we also consider the consistency of the event with the natural progression of any underlying diseases, disorders, or conditions that the person(s) may have.

8.1.3.3. Poison Control Center Surveillance

We plan to register the candidate product with the American Association of Poison Control Centers to monitor the types and frequencies of spontaneous AEs reported into the National Poison Data System database.

8.1.3.4. Comprehensive Literature Review

We will implement a comprehensive literature review, including any literature specific to the candidate product. The protocol (Section 7.5.1) defines the literature search, which includes the searched sources, inclusion and exclusion criteria, search time frame and the search terms used. The literature search will focus in the following categories:

1. the safety of the candidate product (e.g., studies, case reports);
2. the perceptions of the candidate product;
3. the candidate product use and use patterns; and
4. the candidate product misuse, abuse, and tampering.

Once the potential articles are identified, we will evaluate the abstracts based on inclusion and exclusion criteria. We will then assess the suitability of the full articles based on the quality of the publication, including the data; and determine if there are other relevant publications for review based on the article's reference list. We will summarize the findings from the literature review in the annual report.

8.1.3.5. Monitoring and Secondary Data Analysis of National Surveys

We plan to monitor and analyze national surveys such as, but not limited to the PATH Study, NSDUH, National Health Interview Survey (NHIS), Monitoring the Future, and National Youth Tobacco Survey, as relevant data become available. The purpose of this effort is to monitor prevalence of tobacco product use among representative samples of the U.S. population, including youth and young adults. Our monitoring will include the major tobacco categories, including smokeless tobacco products. Within the smokeless tobacco category, it may entail a more granular review by brands and forms as feasible, given the respective study design, available measures, and sample limitations. Depending on the survey, we will monitor other relevant factors, such as risk perceptions, attitudes related to tobacco harm reduction, susceptibility of use, and self-reported health-related measures. Monitoring national survey data will also allow us to assess changes in trends over time, including initiation and use among youth.

8.1.4. Postmarket Studies

8.1.4.1. Cross-sectional Studies

As indicated in this section, we plan to engage with and seek feedback from FDA on our postmarket studies prior to implementation. We intend to share our plans, study protocols, survey instruments, recruitment strategies, and data analysis plans.

We anticipate conducting an observational, cross-sectional study of adult consumers of the candidate product on an annual basis, commencing approximately 12 months after the introduction of the candidate product with the modified risk claim in the commercial marketplace.

The purpose of the observational, cross-sectional study will be to collect data on the real-world use and perceptions of the candidate product and other tobacco products. The study will focus on current and past users of the candidate product and be designed to provide data on:

- patterns of use of tobacco products;
- how consumers use the candidate product and how the candidate product use changes over time;
- initiation and cessation of tobacco products in context with the candidate product;
- risk perceptions of the candidate product and other tobacco products and changes in the risk perceptions over time; and
- reasons for candidate product use.

This study also will obtain information on whether nonusers or former tobacco users initiate with, or current tobacco users switch to, the candidate product.

We anticipate that the observational, cross-sectional study will be limited in its ability to use probability-based sampling to recruit sufficient numbers of participants because of relatively low candidate product market penetration. Therefore, we expect that the study will rely on

nonprobability sampling strategies to obtain data sufficient to examine the outcomes of interest.

We expect to complement this approach with an ongoing cross-sectional study designed to provide a national probability-based sample to estimate tobacco use prevalence, including use of the candidate product, as feasible.

8.1.4.2. Observational Cohort Study

Additionally, we may conduct an observational cohort study. This study would primarily focus on adult consumers of the candidate product and may also include adult consumers of cigarettes. This prospective cohort study would monitor the impact of the claim on tobacco product use patterns over time. The timing of any cohort study would depend on consumer uptake of the candidate product to yield a sufficient number of study participants to track over time.

8.1.5. General Description of Postmarket Studies

All observational, cross-sectional and cohort studies conducted within the Postmarket Assessment Plan involving the enrollment of participants and the active collection of data will comply with Good Epidemiological Practice (International Epidemiological Association, 2007), Council of American Survey Research Organization's Code of Standards and Ethics (Council of American Survey Research Organizations, 2016), and the International Chamber of Commerce/European Society for Opinion and Marketing Research's International Code on Market and Social Research (International Chamber of Commerce/ESOMAR, 2008).

The study protocols for observational, cross-sectional and cohort studies and the informed consent statements, as well as all participant-related materials, will be submitted for review to an institutional review board for approval before the study is initiated. For studies that recruit participants by online registration, an independent, third-party organization (e.g., Veratad Technologies, LLC, New Jersey) will be used to verify the age of potential respondents in real time based on the information provided during the respondent screening process (e.g., name, address, telephone number, e-mail address, and date of birth). The following sections address major domains of items that will be commonly applied in the survey instrument across the observational, cross-sectional and cohort studies (collectively, "postmarket studies").

Data generated by postmarket studies will be considered highly confidential by the study staff. The confidentiality of records that could identify participants will be protected, respecting the privacy and confidentiality rules in accordance with applicable legal or regulatory requirement(s).

8.1.5.1. Demographics and Socioeconomic Status

Our postmarket studies will collect a range of items to fully describe the demographic characteristics of the study population. Demographic characteristics, including age, sex, race, and ethnicity will also be collected in national surveys (e.g., PATH, NHIS, etc.).

Additionally, to gather insights about other populations of interest, the postmarket studies may also include items to identify military service, sexual orientation, pregnancy, and preexisting medical or mental health conditions.

Questions will be used to identify socioeconomic status within the U.S. population. The questions are related to, for example, annual household income, education, and employment status.

8.1.5.2. Tobacco Product-Use History

We have developed a product-use questionnaire to evaluate self-reported trial and use of a variety of tobacco products, including the following:

- the candidate product;
- conventional cigarettes;
- e-vapor;
- cigars;
- other smokeless tobacco; and
- pipe tobacco.

This product-use questionnaire is administered in a hierarchical manner. Participants will be asked if they have ever tried different tobacco products, and then, only participants who have tried the product, will be asked about their current and past use of it.

For current consumers of the candidate product and/or other tobacco products, participants are also asked about the quantity and frequency of use. Participants who are past consumers of a given tobacco product will be asked questions about the quitting of that product.

8.1.5.3. Intention to Quit

Research suggests that intentions to quit tobacco products can predict quit attempts. For example, according to a systematic review of the scientific literature, "[I]ntention to stop smoking was found to predict a quit attempt in all six studies to examine it" (Vangeli, Stapleton, Smit, Borland, & West, 2011, p. 2118). In our postmarket studies, current adult cigarette smokers will be asked their intention to quit smoking within the next 30 days (Etter & Sutton, 2002). In addition, we will assess intention to quit in the next 30 days for each tobacco product that respondents report currently using.

8.1.5.4. Quit Attempts

Research suggests that a recent quit attempt may predict a future attempt (Zhou et al., 2009). In accordance with the NHIS, our questionnaire will ask participants who report current use of one or more tobacco products if they have stopped use of these products for more than one day during the past 12 months because they were trying to quit all tobacco products. Furthermore, adult cigarette smokers and candidate product consumers will be asked if they have stopped use of these products for more than one day because they were trying to quit.

In addition to asking about past quit attempts, our questionnaire will ask participants about methods used to quit among those currently trying to or who had previously quit smoking (e.g., over-the-counter quit aids, FDA-approved cessation medication, cutting back, using another tobacco product, or some other way). The intent is to determine whether participants are using the candidate product as a method to quit smoking.

8.1.5.5. Tobacco Dependence

Our postmarket studies may include assessments of tobacco dependence that are sensitive to varying levels of dependence across product categories and individuals. For example, the PATH Study contains measures of tobacco dependence that have the ability to distinguish differences in dependence between cigarettes and reduced harm products (Liu, Wasserman, Kong, & Foulds, 2017; Strong et al., 2017).

8.1.5.6. Perception of Risk

The postmarket studies will examine risk perceptions associated with the candidate product in absolute terms and relative to using cigarettes, other tobacco products, nicotine replacement therapies, and quitting all tobacco. The studies may also assess risk perceptions related to specific disease outcomes. The data collected will be used to understand the overall perception of risk among current users of the candidate product and, as applicable to the final designs, tobacco consumers more broadly, and to understand how trends in risk perceptions change over time once the candidate product is marketed with the modified risk claim.

8.1.5.7. Reasons for Use

The survey items will assesses the candidate product users' reported reasons for now using the product, drawing upon items from the PATH Study (2017), as well as upon information presented in several recent studies among adult tobacco consumers. (Biener & Hargraves, 2015; Pepper, Emery, Ribisl, Rini, & Brewer, 2015; Richardson, Pearson, Xiao, Stalgaitis, & Vallone, 2014).

8.1.6. Conclusion

ALCS, on behalf of USSTC, has designed a multifaceted Postmarket Surveillance Program to assist the FDA in evaluating the population effects resulting from a risk reduction order for the candidate product. This program will also enable the identification and collection of unanticipated and undesired events related to the use of the candidate product.

8.1.7. Literature Cited

Biener, L., & Hargraves, J. L. (2015). A longitudinal study of electronic cigarette use among a population-based sample of adult smokers: association with smoking cessation and motivation to quit. *Nicotine Tob Res, 17*(2), 127-133. doi:10.1093/ntr/ntu200

Council of American Survey Research Organizations, CASRO. (2016). Code of Standards and Ethics. Retrieved from

http://c.ymcdn.com/sites/www.casro.org/resource/resmgr/Code/Code_of_Standards_and_Ethics.pdf

Etter, J. F., & Sutton, S. (2002). Assessing 'stage of change' in current and former smokers. *Addiction, 97*(9), 1171-1182.

International Chamber of Commerce/ESOMAR. (2008). ICC International code on market and social research. Retrieved from https://www.esomar.org/uploads/public/knowledge-and-standards/codes-and-guidelines/ICCESOMAR_Code_English_.pdf

International Epidemiological Association. (2007). IEA guidelines for proper conduct in epidemiologic research. Retrieved from http://ieaweb.org/good-epidemiological-practice-gep/

Liu, G., Wasserman, E., Kong, L., & Foulds, J. (2017). A comparison of nicotine dependence among exclusive E-cigarette and cigarette users in the PATH study. *Prev Med*. doi:10.1016/j.ypmed.2017.04.001

Pepper, J. K., Emery, S. L., Ribisl, K. M., Rini, C. M., & Brewer, N. T. (2015). How risky is it to use e-cigarettes? Smokers' beliefs about their health risks from using novel and traditional tobacco products. *J Behav Med, 38*, 318-326.

Richardson, A., Pearson, J., Xiao, H., Stalgaitis, C., & Vallone, D. (2014). Prevalence, harm perceptions, and reasons for using noncombustible tobacco products among current and former smokers. *Am J Public Health, 104*, 1437-1444.

Strong, D. R., Pearson, J., Ehlke, S., Kirchner, T., Abrams, D., Taylor, K., . . . Foulds, J. (2017). Indicators of dependence for different types of tobacco product users: Descriptive findings from Wave 1 (2013-2014) of the Population Assessment of Tobacco and Health (PATH) study. A comparison of nicotine dependence among exclusive E-cigarette and cigarette users in the PATH study. *Drug Alcohol Depend, 178*, 257-266.

United States Department of, H., Human Services. National Institutes of Health. National Institute on Drug, A., United States Department of, H., Human Services, F., & Drug Administration. Center for Tobacco, P. (2017). *Population Assessment of Tobacco and Health (PATH) Study [United States] Restricted-Use Files*. Retrieved from: http://doi.org/10.3886/ICPSR36231.v13

Vangeli, E., Stapleton, J., Smit, E. S., Borland, R., & West, R. (2011). Predictors of attempts to stop smoking and their success in adult general population samples: a systematic review. *Addiction, 106*(12), 2110-2121. doi:10.1111/j.1360-0443.2011.03565.x

Zhou, X., Nonnemaker, J., Sherrill, B., Gilsenan, A. W., Coste, F., & West, R. (2009). Attempts to quit smoking and relapse: factors associated with success or failure from the ATTEMPT cohort study. *Addict Behav, 34*(4), 365-373. doi:10.1016/j.addbeh.2008.11.013