Section X Post-Market Surveillance Program

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X. Post-market Surveillance Program

A. Background

The Family Smoking Prevention and Tobacco Control Act directs the Food and Drug Administration to require post-market surveillance and studies from applicants that receive an exposure reduction order (§ 911(g)(2)(C)(ii)). The FDA has provided recommendations for post-market surveillance and studies in the Draft Guidance for Industry on Modified Risk Tobacco Product Applications. This FDA MRTP Draft Guidance describes the need for the FDA to understand the short- and long-term impacts of the authorization of MRTPs on consumer perception, behaviors, and health through post-market surveillance and studies. As stated in the FDA MRTP Draft Guidance, "… post-market surveillance is a very important tool for monitoring the effects of the MRTP on individual and population health" that can allow for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."

B. Post-market Surveillance Program

22nd Century proposes a multi-faceted program to collect both qualitative and quantitative data about how consumers use VLN™ as well as tracking potential adverse experiences with the products. This program will enable the identification and collection of unanticipated and undesired health-related events associated with the use of VLN™, as well as determine the related tobacco use behaviors. Protocols for the various studies are included in with this application (file names Protocols_Consumer_Study_18Dec2018_V1.0.pdf, Protocols_Post_Market_Tob_Reduction_18Dec2018_V1.0.pdf, and Protocols_Product_Complaints_Syst_18Dec2018_V1.0.pdf) .

The post marketing surveillance program will be made up of five parts:

1. Serious and unexpected adverse event reporting
2. A cross-sectional survey of knowledge and use of VLN™ cigarettes
3. A prospective non-interventional study to evaluate reduction in cigarette use
4. Manufacturing deviations
5. Annual reporting

1. Serious and Unexpected Adverse Event Reporting

22nd Century proposes to hire a third-party company experienced in monitoring adverse events for pharmaceutical products. A dedicated telephone number and email address for reporting of product complaints will be implemented and published on 22nd Century's website and on promotional material relating to 22nd Century's products, e.g. press releases, advertisements in newspapers and magazines, internet advertisements, etc. In addition, 22nd Century's employees will receive training on the recognition of product complaints and will be

required to forward to the dedicated contact information any product complaints they become aware of during discussions with users or healthcare professionals. Any vendors or commercial partners also will be required to forward product complaints, with such requirements included into their contracts with 22nd Century.

The telephone number and email address will be monitored during routine business hours in the Eastern time zone, with the telephone number providing voicemail facilities for after hours. Users and healthcare professionals will be able to report any product complaints, safety concerns or 'adverse experiences' via these contact information pathways.

The monitoring will be performed by an experienced team of information professionals accustomed to collecting adverse experience reports for a wide range of products across the pharmaceutical industry. Reporters will be questioned to determine all available information about each user's experience, including important comorbidities.

All calls and emails received will be entered into an information database and assessed by an experienced staff member to see if they contain an adverse experience (i.e. an adverse event as defined by ICH E2D).

Each adverse experience will be entered into a safety database and reviewed by a safety physician. The safety physician will determine if additional information is required to understand the user's experience and follow-up information will be requested from the reporter to build a robust database of information about the VLN™ cigarettes.

Reconciliation between the information database and safety database will be performed at regular intervals to ensure that all adverse experiences have been appropriately identified and transferred to the safety database.

Each adverse experience report will be assessed to determine if there is a potential relationship between the symptoms experienced by the user and the VLN™ cigarettes. If the reporter considers there is a relationship, a positive causality will be assumed by 22nd Century. If the reporter does not provide an opinion or considers there is no relationship, a further assessment of causality will be made by the safety physician involved in the processing of the adverse experience in the safety database. If either the reporter or the safety physician considers there is a possibility that VLN™ cigarettes caused the user's symptoms, or there is insufficient information to make a conclusion about a relationship, a report about the user will be submitted to the US Food and Drug Administration (FDA).

Reports will be submitted as ICH E2B electronic reports via the FDA's Safety Reporting Portal as follows:

- Adverse experiences that meet ICH E2D criteria for 'serious' will be submitted within 15 calendar days of receipt as expedited safety reports;
- Adverse experiences that do not meet the above criteria (i.e. are 'non-serious') will be submitted within 90 calendar days of receipt as periodic safety reports.

Trend analysis will be performed on the safety database at quarterly intervals to identify if there are emerging trends in the safety data collected. Each adverse experience term categorized as a MedDRA Preferred Term will be evaluated to determine if the reporting rate for the current quarter is more than 3 standard deviations away from the historical quarterly reporting rate for that Preferred Term, assuming that the safety data collected has a normal distribution. If a Preferred Term is more than 3 standard deviations from the historical reporting rate, a potential safety issue will be highlighted and investigated. The data will be reviewed by a

Safety Committee that includes professionals accustomed to evaluating safety data. If an emerging trend or potential safety issue is identified, an action plan will be agreed upon that may include one or more of the following actions depending on the nature of the trend identified:

- No action when safety data conforms with the current understanding of the safety profile of VLN™ cigarettes or is confounded by other factors that create a statistical abnormality;
- Continued monitoring to see if future data received confirms or refutes the trend;
- Development of a communication plan for users and/or healthcare professionals;
- Updates to published information for the VLN™ cigarettes;
- Discussions with the FDA regarding suitable actions;
- Changes to the legal/registered status of the VLN™ cigarette.

2. A cross-sectional survey of knowledge and use of VLN™ cigarettes

22nd Century proposes to conduct a 6-month cross-sectional study in 1000 subjects, assessing product knowledge, use, and attitudes of VLN™ users. The study will be conducted among U.S. individuals who have initiated VLN™ cigarettes within the past 6 months. The target number of users completing the study is 1000.

Users will be recruited from the general population in the U.S. The specific objectives are:

- Primary objectives
  - assess knowledge of VLN™ cigarettes product characteristics
  - assess usage patterns of VLN™ cigarettes

- assess demographic (age, gender, ethnicity, three-digit zip code) characteristics of VLN™ cigarette users

- Secondary objectives:
  - assess use of other tobacco products used at time of initiation of VLN™ cigarettes
  - describe how user learned about VLN™ cigarettes
  - describe personal factors motivating initiation to VLN™ cigarettes

The user population will be asked to complete an online data collection form at enrollment. Demographic questions, questions about nicotine/tobacco usage, and questions about knowledge and usage of VLN™ will be asked. The primary analysis population will include all subjects who have completed the survey. Generally, categorical outcomes will be described by the absolute and relative (%) frequency of each outcome and number of missing data. Missing data will be taken into account in the percentage calculation. If appropriate, 95% Confidence Intervals for proportions will be calculated for the key categorical outcomes. Quantitative variables generally will be described by their mean, standard deviation, median, and number of missing data. Results for some quantitative variables may also include ranges (minimums and maximums).

3. A prospective non-interventional study to evaluate reduction in cigarette use

22nd Century proposes to conduct a 12-month prospective study in 300 subjects, tracking cigarette use behavior and consumption. This longitudinal cohort study will evaluate reduction of smoking and tobacco use among new users of VLN™ cigarettes who have initiated the product.

The study will be conducted in the U.S. among smokers who have initiated VLN™ cigarettes. The target number of users completing the study is 300. Users will be recruited from users of VLN™ cigarettes who have agreed to participate in a cross-sectional survey of knowledge and use of VLN™ cigarettes which is also being submitted to the FDA as part of the post-approval study requirements for VLN™ cigarettes. Users who have completed the cross-sectional study will be asked to participate in this longitudinal cohort study. The specific objectives are:

- Primary objectives:
    - assess use of VLN™ cigarettes (number per day)
    - assess use of all other types of cigarettes (type of cigarette, number per day)
    - assess use of all other types of smoked and non-smoked tobacco product (type of product, frequency used per day)
    - assess use of any other nicotine containing product (type of device, frequency and amount of usage per day)
- Secondary objectives:
    - assess subjects' stated desire to quit or reduce tobacco use
    - describe cigarette, tobacco, and nicotine containing product use prior to initiation of VLN™ cigarettes
    - describe tobacco reduction rates by levels of prior tobacco use and user demographic characteristics (age, gender, geography)

The user population will be asked to complete an online data collection form at enrollment and every 2 months for 12 months after enrollment (2, 4, 6, 8, 10, 12 months). The primary analysis population will include all subjects who have completed at least four of the assessments inclusive of the enrollment assessment, the two- or four-month assessment, the six- or eight-month assessment and the final assessment. Frequency distributions and means (with standard deviation) will be used to report information reported as ordinal data (i.e. number of cigarettes smoked). Information on and decline in tobacco and nicotine delivery device use will be reported as proportions (with 95% confidence intervals) of the total population enrolled in the study at each time point after the enrollment visit.

4. Manufacturing Deviations

22nd Century will promptly investigate all manufacturing deviations, including but not limited to those associated with processing, testing, packing, labeling, storage, holding, and distribution of VLN™ products. For products that have already been distributed, if the deviation may negatively impact public health, the Company will promptly identify and report that deviation to the Center for Tobacco Products.

5. Periodic Reporting

The Company will submit a post-marketing annual report under Section 910(f) of the FD&C Act, to contain the following information:

- A single submission with a cover letter that includes the Submission Tracking Number (STN) and corresponding tobacco product name, applicant name, date of report, reporting period and marketing order status outside the United States.

- A summary of how the tobacco product continues to be appropriate for the protection of the public health which includes:
    - A status report of ongoing studies and a summary of completed studies about the tobacco product conducted by or on behalf of, the applicant.
    - A summary of significant findings in publications not previously reported and including the full articles. Any new scientific data (published or otherwise) will be reported categorized by current users of any tobacco products, former users of any tobacco product, and youth and young adults.
    - A summary of adverse experiences with the tobacco product providing a listing and analysis of all adverse experiences, including those serious and unexpected adverse experiences reported previously.
    - A summary of sales and distribution of the product: Total U.S. sales reported in dollars, units and volume, with breakdowns by channels in which the product is sold.
- A description of each change made to the manufacturing facilities or controls during the reporting period, including:
    - A comparison of each change to what was described in the PMTA/MRTPA.
    - The rationale for making each change.
    - A certification that the reported change did not result in any modification of the tobacco product; and the basis for concluding that each change did not result in any modification to the final product.

- A summary of manufacturing deviations, including those associated with processing, testing, labeling, storage and any deviation that may affect the characteristics of the final product.
- Full-color copies of all advertising for the product that has not been previously submitted, along with the original date the advertisements were first disseminated.

A description of any or all labeling changes and full color final printed labeling.

C. Bibliography

Certara USA, Inc. 2018. "A Simulation Model to Evaluate the Impact of VLN™ Cigarettes on the Population as a Whole."

US Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products. 2012. "Modified Risk Tobacco Product Applications Draft Guidance."