Preface and Introduction to FDA

Pursuant to Section 910(c)(1)(A)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), Swedish Match USA, Inc. (Swedish Match) requests marketing authorization in this Premarket Tobacco Product Application (PMTA) for ZYN®. ZYN is sold in 10 different flavors (Cool Mint, Peppermint, Spearmint, Wintergreen, Coffee, Cinnamon, Citrus, Smooth, Chill, and Fresh) and two nicotine strengths (3 and 6 mg per pouch).

This is a brief form summary made in accordance with the requirements outlined in Proposed Rule, Premarket Tobacco Product Applications and Record Keeping Requirements (Proposed Rule) (84 FR 50566). Under the Proposed Rule, FDA will create a new section, 21 C.F.R. 114.7(h), and require a summary to "help reviewers understand the product and scientific data more quickly" (*id*. at 50583). Additionally, FDA asked for a "unified document" that will serve as a "briefing document that highlights the most important aspects of the application" to demonstrate that the product "would be . . . APPH [i.e., appropriate for the protection of public health]" (*id*.). FDA requested that the following information be addressed in the summary: (1) a summary of the product formulation; (2) a summary of the product manufacturing processes; (3) a summary of the health risks including youth assessments of behavior, user and non-user trends and changes, and abuse scenarios; (4) a discussion of the validity of the science relied upon; and (5) a concluding section discussing risks to the population as a whole, adverse events, mortality and morbidity, and how granting marketing authorization for ZYN would be appropriate for the protection of public health (*id*.). In accordance with the Proposed Rule, the following summary presents to FDA why the ZYN products are appropriate for the protection of public health. Where needed to facilitate FDA's review, this summary cites to other portions of the PMTA.

I. Product Formulation

In the Proposed Rule, FDA requested that applicants provide information summarizing the degree to which, based on its formulation, ZYN would likely be appropriate for the protection of public health. ZYN is a tobacco-free, smoke-free, and spit-free nicotine pouch intended for oral use and with an appearance similar to that of Swedish snus products that is intended for adult tobacco and nicotine consumers. ZYN is produced using high-purity nicotine bitartrate dihydrate (nicotine salt), complying with the purity criteria of the United States Pharmacopeia. Moreover, the nicotine used in ZYN is in a granulated salt form, rather than the liquid freebase form, in order to enhance product stability.

ZYN's common ingredients are a sweetener, a stabilizer, fillers, nicotine salt, pouch material fiber, pH adjusters, and flavorings (Section G.4 Product Composition Summary Section 1.1). The chemical composition of ZYN results in fewer HPHCs than are present in General Snus products, which have been granted PMTA marketing authorizations and MRTP marketing orders (Section G.1 Introduction Section 1.2.1). Ingredients in the ZYN product include acesulfame K, maltitol, sodium bicarbonate and sodium carbonate at levels safe for human consumption. ZYN only contains ingredients that are approved by health authorities (Section G.4 Product Composition Summary Section 1.1). The product is contained in a container with a twisting lid design and perforated breakable label (Section G.2 Product Design Summary Section 1.2).

To confirm that the flavors used in ZYN do not pose a public health risk, a Quantitative Health Risk assessment (QRA) was conducted for the flavor component (b) (4), (b) (4) which is specific to ZYN Wintergreen. Based on the QRA, the low level of (b) (4) is unlikely to have an adverse effect on public health (Section G.5 Nonclinical Evaluation Summary, Section 4.3). Further, *in vitro* testing of all 10 flavors of ZYN showed no mutagenic or genotoxic response, which indicates a low potential for carcinogenic effects. (Section G.5 Nonclinical Evaluation Summary, Section 7). Further, the flavors found in ZYN are not responsible for and had no effect on nicotine delivery (Section G.1 Introduction, Section 4.2.1). All the material in the pouch fabric complies with the following FDA regulations for indirect food additives: Paper and paperboard components (21 C.F.R. 176.170) and Adhesive (21 C.F.R. 175.105).

II. Manufacturing

As noted above, a relevant comparator product for the purposes of this PMTA is General Snus. As FDA has noted, one of the topline reasons for granting PMTA marketing authorization of General Snus included the fact that General Snus is manufactured under the GOTHIATEK® quality standard. For ZYN manufacturing, Swedish Match employs a chemical quality control program that confirms that almost none of the HPHCs governed by the GOTHIATEK standard can be detected in the ZYN products; and none exceeds the GOTHIATEK limits. During manufacturing of ZYN products, the ingredients, (b) (4) (b) (4) (Section G.5 Nonclinical Evaluation Summary, Section 3.1). As part of this quality control program, samples are collected on the line (Section G.5 Nonclinical Evaluation Summary, Section 3.2). The results of laboratory chemical testing showed that HPHCs were lower in ZYN than in General Snus products, except for a slight increase in formaldehyde. Many of the HPHCs were at unquantifiable levels (Section G.5 Nonclinical Evaluation Summary, Section 3.3).

III. Validity of Scientific Evidence

The evidence relied upon for ZYN is valid scientific evidence. Swedish Match's reliance on well-controlled scientific trials, acceptable laboratory testing standards, and a systematic review of relevant literature exemplifies our commitment to demonstrating that ZYN is appropriate for the protection of public health. For these and the reasons that follow, the evidence used in the PMTA to demonstrate that ZYN is appropriate for the protection of public health should be viewed as both valid and reliable for FDA decision makers.

In the Proposed Rule, FDA asks for substantiation that evidence used within the PMTA is valid scientific evidence. In the Guidance for Industry, Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems, June 2019 (ENDS Guidance), FDA defines valid scientific evidence as based on "well-controlled investigations [which] are generally those that are designed and conducted in such a way that minimizes or controls for bias, confounding variables, and other factors that may render the results unreliable." Throughout the application, Swedish Match has relied upon internationally accepted standards and research practices in order to show that ZYN is appropriate for the protection of public health.

The testing conducted by Swedish Match to show that ZYN is appropriate for the protection of public health consisted of *in vivo* testing in human subjects regarding nicotine uptake (Section G.6 Human Health Impact Evaluation Summary, Section 4.1.1). Additionally, a systematic literature review of *in vivo* studies of smokeless tobacco in humans and animals was conducted for toxicological data (Section G.5 Nonclinical Evaluation Summary, Section 6.4). A majority of the HPHC testing was performed by Swedish Match's (b) (4) and third-party laboratory (b) (4). Both laboratories hold an International Standards (ISO)/International Electrotechnical Commission (IEC) 17025 accreditation (Section G.5 Nonclinical Evaluation Summary, Section 3.2). For human toxicology assessments, the studies relied upon the health-based threshold limit values from credible sources such as European Commission Exclusive Scientific Committees, European Food Safety Authority (EFSA), World Health Organization (WHO), Joint Food and Agriculture Organization of the United Nations (FAO), WHO Expert Committee on Food Additives (JECFA), and US Environmental Protection Agency (EPA) (Section G.5 Nonclinical Evaluation Summary, Section 4.1). For oral toxicology studies, meaningful exposure was calculated using EFSA, WHO, JECFA and EPA values for a risk category of a chemical substance (Section G.5 Nonclinical Evaluation Summary, Section 4.1). The mutagenicity assay was based on the requirements of the Organization for Economic Co-operation and Development (OECD) Guideline Number 471 and those of the Health Canada official test method T-501, Second Edition, *Bacterial Reverse Mutation Assay for Mainstream Tobacco Smoke* (Section G.5 Nonclinical Evaluation Summary, Section 5.1.1). Finally, Swedish Match conducted a systematic review of relevant literature, the results of which are relied upon throughout the PMTA. This scientific literature was pulled from PubMed/MedLine (http://www.pubmed.com), Scopus (http://www.scopus.com/), and ClinicalTrials.gov (http://clinicaltrials.gov/). All studies conducted were completed under controlled conditions using acceptable methods of scientific evaluation and assessment.

IV. Health Risks: Tobacco Use Behavior with Respect to Nonusers and Users

As summarized below, this PMTA includes detailed information regarding the impact ZYN product marketing will have on changes in tobacco use behavior. For example, two consumer research studies demonstrated, among other findings supportive of the public health, that the likelihood of initiation of ZYN by non-users (b) (4) and former TNP users was low (Section G.6 Human Health Impact Evaluation Summary, Section 7.6). Moreover, cigarette smokers intending to quit were more likely to buy ZYN than cigarette smokers not intending to quit. Literature regarding Swedish snus indicates that snus, a relevant comparator product to ZYN in this regard, is commonly and intentionally used as a smoking cessation aid in Sweden and other countries (Section I.1. Use Behavior Update Report, Section 2.5). One large set of longitudinal data of Swedes reported that over three-quarters of smokers who picked up snus as a secondary daily tobacco product completely quit smoking. The potential health benefits of snus as a smoking cessation aid will likely apply with equal force to smokers seeking to quit with the assistance of ZYN.

With regard to switching, literature reflects that the proportion of snus users who picked up smoking habits was small compared to the proportion of smokers who then added snus use as a habit (Section I.1. Use Behavior Update Report, Section 3.2). Furthermore, those who started daily tobacco use with snus had a lower probability of acquiring a daily smoking habit compared

to those who did not initiate daily tobacco use with snus. Swedish Match expects these patterns to hold true, or improve from a public health perspective, for ZYN as well.

When assessing the perception of health risk across all absolute risk metrics, a consistent pattern evolved. Respondents found that cigarettes presented the greatest risk of harm. Usage of ZYN was associated with some risk of health conditions, but a lower rate than cigarettes. Never using TNP was generally deemed to carry the lowest risk (Section G.6 Human Health Impact Evaluation Summary, Section 7.7.1). In the consumer research, *Likelihood of Use Study* (b) (4) (b) (4), the majority of respondents comprehended the ZYN product label (Section G.6 Human Health Impact Evaluation Summary, Section 7.4).

ZYN also has a low misuse potential and poses virtually no threat of secondary or tertiary harm to non-users. ZYN is a tobacco-free, smoke-free, and spit-free nicotine pouch. It is intended to be placed between the gum and the upper lip and enjoyed for up to 60 minutes, then discarded, as the product is not intended to be swallowed or reused. If swallowed, the nicotine salt and other food-grade (or higher) ingredients found in ZYN are not harmful to adults if consumed in small quantities. A person would have to swallow (b) (4) in order to overdose, in which case the nicotine may cause nausea and vomiting (Section G.6 Human Health Impact Evaluation Summary, Section 7.8). ZYN does not emit any emissions or contaminants into the atmosphere like smoke from combustible cigarettes or vapor from e-cigarettes. Therefore, there is no secondary or tertiary harm to non-users while ZYN is consumed as intended. In addition, as noted above, the nicotine salt and other ingredients found in ZYN are not harmful to adults if consumed in small quantities (eg, accidental swallowing) (Section G.6 Human Health Impact Evaluation Summary, Section 8).

V. Health Risks: Cancer, Heart Disease, Stroke, Cardiopulmonary, and Adverse Events Associated with Use

Within the Proposed Rule, FDA asks for a summary of the PMTA's evaluation of the risk of cancer and cardiopulmonary diseases from the use of ZYN. Overall health risks associated with the use of ZYN are either not quantifiable or reflect a reduction in risk when compared to other tobacco products, and only marginal increase in risk when compared to tobacco non-use. In fact, ZYN is in a unique category, compared to other smokeless products, in terms of improved health profile. Tobacco based snus products have different levels of N-nitrosonornicotine (NNN) and 4-methylnitrosamino-1-(3-pyridyl)-1-butanone (NNK), which are the suspected carcinogenic constituents in tobacco products. Because ZYN has fewer HPHCs than General Snus, the present literature and studies associated with tobacco-based snus indicate that the overall health risk of General Snus would be even lower if using ZYN as the investigational product. For example, General Snus has been found by FDA and empirical scientific research to offer lower risks of respiratory disease and cancers compared to smoking. It is therefore logical to assume ZYN would present even lower risks of respiratory disease and cancers.

Out of 93 measurable HPHCs identified in cigarette smoke, only seven—with lower or similar levels to General Snus—were found in ZYN (Section G.6 Human Health Impact Evaluation Summary, Section 1.2). NNN and NNK were at levels below quantification in ZYN. Moreover, the levels of quantifiable HPHCs (formaldehyde, acetaldehyde, coumarin, naphthalene,

(b) (4) and (b) (4)) in ZYN were below health-based thresholds (Section G.5 Nonclinical Evaluation Summary, Section 4; Section G.6 Human Health Impact Evaluation Summary, Section 1.2). The chemical profile of ZYN would not result in increased cancer or cardiopulmonary disease risks and is appropriate for the protection of public health. The difference between ZYN and smoked tobacco is dramatic with cigarette smoke containing dangerous levels of most HPHCs. As noted above, ZYN contains fewer HPHCs than General Snus at levels that are not quantifiable and/or do not pose a risk to health. When compared to CRP2.1, an American-style loose moist snuff ST product manufactured for use in scientific studies as a reference standard product, the reduction in HPHCs provides even more compelling evidence that ZYN is appropriate for the protection of the public health (Section G.5 Nonclinical Evaluation Summary, Section 3.3).

Carcinogenic substances including NNN, NNK, and B(a)P are not quantifiable in ZYN. Since ZYN exposes the user to similar levels of nicotine to those found in snus but generally has reduced or non-measurable levels of unwanted HPHCs, the health effects of snus, which contain very low levels of NNN, NNK, and B(a)P, were considered to be a measure of maximum health risks. Since there is no literature on the effects of ZYN and its adverse health effects, a systematic review of the literature on the health effects of Swedish snus, a relevant comparator product, was conducted. Limited/suggestive evidence of no association was found between snus and cardiovascular (IHD, MI, heart failure, CVD, atrial fibrillation, and stroke), cancer (head and neck, pancreatic, stomach, and lung), metabolic, or GI effects. From the literature reviewed for this PMTA, the current evidence suggests an approximately 30% decreased risk of all-cause mortality in snus users compared to smokers. There is also no evidence that snus causes lung cancer, a major contributor to smoking mortality in the US (CDC 2018, CDC 2008). Use of snus or ZYN is not associated with secondary exposure and therefore decreases risk for both users and non-users. Some studies provided evidence for an increased risk in dual users (i.e., snus and cigarettes) and switchers (i.e., switched from cigarette use to snus use) compared to never tobacco users; however, most studies also provided evidence of decreased or statistically non-significant risks in dual users and switchers compared to smokers (Section G.6 Human Health Impact Evaluation Summary, Section 3).

VI. Conclusion

Given the totality of evidence, Swedish Match believes that the information provided in this PMTA supports that the continued marketing of ZYN would be appropriate for the protection of the public health based on the following:

- Appropriate quality systems together with the fact that there is no tobacco in the product ensure that HPHC levels are well below the GOTHIATEK standard.

- The levels of carcinogenic substances such as TSNAs (eg, NNN and NNK) and B(a)P are below limits of quantification in ZYN.

- The levels of HPHCs are generally similar to or lower than the levels of General Snus products, which have received both PMTA marketing authorizations and MRTP marketing orders from FDA. Based on the QRAs performed for measurable HPHCs in ZYN, the HPHC levels in ZYN were below health-based thresholds. Thus, the toxicological safety profile of ZYN represents a significant improvement over General Snus and CRP2.1 (moist

snuff reference product). The HPHC results and QRAs suggest that the exposure of an individual, under reasonably foreseeable conditions of use of ZYN, would be less than that with other marketed products such as General Snus and considerably less than with smoking combustible cigarettes. The HPHC levels in ZYN do not raise concern from a public health perspective and support that ZYN is appropriate for the protection of the public health.

- The non-clinical Ames and *in vitro* micronucleus assays demonstrated no evidence of genotoxic or mutagenic effect.

- As ZYN exposes the user to levels of nicotine similar to those found in snus but generally has reduced or non-measurable levels of unwanted HPHCs, the health effects of snus could be considered to be a measure of maximum health risks. From a systematic review of the literature, there was limited/suggestive evidence of no association found between Swedish snus, a relevant comparator product to ZYN, and cardiovascular, cancer, metabolic, or gastrointestinal effects. There is also no evidence that snus causes chronic obstructive pulmonary disease, a major contributor to smoking mortality in the US.

- A comprehensive clinical program was conducted that included PK, pharmacodynamics (including changes in (b) (4) and (b) (4)), AEs, and oral safety and demonstrated that:

    - There were no differences in time to maximum plasma concentration (approximately 1 hour) across products.

    - (b) (4)

    - The abuse potential for ZYN is similar to other marketed ST products.

    - No safety issues, including oral safety, were identified.

- Two consumer research studies, robustly designed and conducted based on FDA guidance and feedback, demonstrated that:

    - The likelihood of initiation of ZYN by non-users (b) (4) and former TNP users was low.

    - Cigarette smokers intending to quit were more likely to buy ZYN than cigarette smokers not intending to quit.

    - Dual use of ZYN and cigarettes was low.

    - Respondents including ZYN non-users and users conveyed an understanding of a continuum of risk ranging from low/minimal absolute risks for never having used

any TNPs, low-to-moderate absolute risks for using only ZYN, and moderate-to-very high absolute risks for smoking cigarettes.

- ZYN users perceived a lower relative risk of daily use of only ZYN compared with cigarettes, e-cigarettes, moist snuff, chewing tobacco, snus, and dual use of ZYN and cigarettes.

In summary, findings from the aforementioned research program support that use of ZYN is likely associated with substantially lower health risks among individual consumers than most, or even all, of the tobacco products that currently dominate the US tobacco market (cigarettes and moist snuff). These conclusions are mainly based on the substantially more favorable toxicological profile of ZYN and the method of use that does not involve inhalation of smoke or vapor:

- ZYN offers a less risky alternative to combusted tobacco products.
- ZYN offers additional options for less toxic smokeless products, thereby potentially decreasing the negative health impact from tobacco use.
- It is anticipated that there is a low likelihood of non-user uptake of these products, decreased or delayed cessation, or other significant shifts in user demographics.

References

Centers for Disease Control and Prevention (CDC). Smoking-attributable mortality, years of potential life lost, and productivity losses--United States, 2000-2004. Morb Mortal Wkly Rep. 2008;57:1226-1228.

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