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REVIWER'S GUIDE

This reviewer's guide is provided to assist with navigation of the premarket tobacco product application (PMTA) for ZYN®, a tobacco-free, smoke-free, and spit-free nicotine pouch manufactured and marketed by Swedish Match USA, Inc. (Swedish Match). This guide covers all 20 ZYN products representing 20 stock keeping units (SKUs) (ten flavors × two nicotine strengths [3 and 6 mg]). Each SKU listed in Table 1.

Table 1 ZYN SKUs

ZYN Product Flavor	Unique ID	
	US	SE
Cool Mint 3 mg Cool Mint 6 mg	900510 900520	8105 8106
Peppermint 3 mg Peppermint 6 mg	901510 901520	8107 8108
Spearmint 3 mg Spearmint 6 mg	902510 902520	8109 8110
Wintergreen 3 mg Wintergreen 6 mg	903510 903520	8111 8112
Citrus 3 mg Citrus 6 mg	907510 907520	8122 8123
Coffee 3 mg Coffee 6 mg	904510 904520	8124 8125
Cinnamon 3 mg Cinnamon 6 mg	906510 906520	8128 8129
Smooth 3 mg Smooth 6 mg	914510 914520	8134 8135
Chill 3 mg Chill 6 mg	920510 920520	8136 8137
Fresh 3 mg Fresh 6 mg	921510 921520	8140 8141

ID=identifier; SE=Kungälv, Sweden, manufacturing site; SKU=stock keeping unit; US=Owensboro, Kentucky, United States, manufacturing site.

This submission is aligned with the *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems Guidance for Industry* (June 2019) and is also reflective of the proposed rule for PMTAs. The structure is shown in Table 2. This reviewer's guide is organized in the same manner and introduces the information and data provided in each section of the submission.

Table 2 PMTA Structure Versus Reviewer's Guide

PMTA Structure	Reviewer's Guide Location
Section A, General Information	Section 5
Section B, Table of Contents	NA
Section C, Descriptive Product Information	Section 6
Section D, Product Samples	Section 7
Section E, Product Packaging and Labeling	Section 8
Section F, Product Environmental Assessment	Section 9
Section G, Summary of All Research Findings	Section 10
Section G.1, Introduction	Section 10.1
Section G.2, Product Design Summary	Section 10.2
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Section H, Scientific Studies and Analyses	Section 11
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NA=not applicable; PMTA=premarket tobacco product application.

1 PROPOSED USE

ZYN is a non-heated, tobacco-free, smoke-free, and spit-free nicotine pouch for oral use with an appearance similar to Swedish snus products. ZYN is intended for adult tobacco and nicotine consumers. Use of ZYN does not involve any inhalation of smoke or vapor. ZYN is intended to be used under the upper lip for up to 60 minutes and is then discarded, as the product is not intended to be swallowed or reused.

2 REGULATORY BACKGROUND

Swedish Match and staff from the Food and Drug Administration (FDA)'s Center for Tobacco Products met to discuss Swedish Match's plan to submit this PMTA for ZYN on the following dates:

- 7 December 2016 (STN TC0001638) – This was an informational meeting only, and no meeting minutes were distributed.

- 13 September 2017 (STN TC0002533) – This meeting was held to discuss the consumer perception study proposed for Swedish Match's Modified Risk Tobacco Product Application (MRTPA) for the General Snus products (Section A.4 FDA Meeting Minutes, 12 October 2017 – TC0002533). Since General Snus and ZYN are similar pouched products, feedback from this meeting was used to design and conduct the two consumer perception studies performed for this PMTA for ZYN.

3 FILE NAMING CONVENTION

As the eSubmitter tool does not allow the use of folders within a submission package, the PMTA uses a standardized file naming convention to organize the files within the application. This convention also ensures that, in cases where multiple files with the same name might otherwise be included within the application, those files are uniquely named to avoid confusion.

The file naming convention is as follows:

> [section letter/number]-[brief title of the document or the study number]-[additional descriptor (as needed)].file extension
>
> **Note**: The colors used here are for illustration purposes only.

For example, for a clinical study, the files would be named along the lines of:

- h-3-1-2-1-study-abc-123-report-body.pdf
- h-3-1-2-1-study-abc-123-appendix-16-1.pdf

4 APPROACH TO THE REDACTION OF CONFIDENTIAL INFORMATION IN ITS APPLICATION

Using statutory provisions, regulations, and FDA guidance documents and policies as a guide, Swedish Match has identified two categories of confidential information within all modules of the application that have been redacted. The first category meets the definition of trade secrets or confidential commercial information (CCI). Items redacted as CCI may include any

commercially valuable plan, product formula, and manufacturing process or design that can be the end product of either innovation or substantial efforts. CCI that is privileged or confidential means valuable data or information that is used in one's business, is of a type customarily held in strict confidence, and is exempt from public disclosure. Therefore, this type of information has been redacted. The second category is personally identifiable information (PII). The disclosure of PII would constitute an unwarranted invasion of personal privacy for the company, vendor personnel, as well as for the individuals that participated in the clinical studies. Signatures and direct contact information have been redacted for all individuals. Names and initials for company and vendor personnel have also been redacted, except for certain individuals in an authorized contact role. For the individuals that participated in the clinical studies, their unique identifiers and individually identifiable health information have been redacted to protect their privacy.

5 GENERAL INFORMATION (PMTA SECTION A)

Table 3 lists the documents provided in Section A.

Table 3 Section A Documents

Document Type	Location in PMTA
Cover letter including the certification statement in accordance with § 1114.7(m)	Section A.1 Cover Letter
Executive Summary in accordance with § 1114.7(h)	Section A.2 Executive Summary
Reviewer's Guide	Section A.3 (this document)
FDA correspondence	Section A.4 FDA Meeting Minutes, 12 October 2017 – TC0002533
Foreign language certification	Section A.5
TPMF letter of authorization	Section A.5 TPMF Letters of Authorization

FDA=Food and Drug Administration; TPMF=tobacco product master file.

6 DESCRIPTIVE PRODUCT INFORMATION (PMTA SECTION C)

Section C Descriptive Product Information of the submission provides an executive summary of the chemistry, manufacturing, and controls (CMC) of the following PMTA sections: Section G.2 Product Design Summary, Section G.3 Product Manufacturing and Controls Summary, and Section G.4 Product Composition Summary. Detailed information for all components of the ZYN products is provided in Sections E, F, G, and H.1 of the submission.

7 PRODUCT SAMPLES (PMTA SECTION D)

ZYN is sold as 15 pouches in a can. For shipping, there are five cans per roll and 18 rolls per case. Upon request, Swedish Match is prepared to provide product sample lots of half a case (ie, 45 cans) of each flavor and strength of ZYN for all 20 SKUs listed in Table 1 from the United States [US] plant. The powder was manufactured and the product was packaged at the Owensboro, KY, US plant.

8 PRODUCT PACKAGING AND LABELING (PMTA SECTION E)

Packaging and labeling for each of the 20 SKUs are provided in Section E.1 Product Packaging and Labeling.

The marketing plan is provided in Section E.2 Marketing Plan.

9 PRODUCT ENVIRONMENTAL ASSESSMENT (PMTA SECTION F)

The environmental assessment is provided in Section F Environmental Assessment.

10 SUMMARY OF ALL RESEARCH FINDINGS (PMTA SECTION G)

Section G includes six summaries as described in the following sections. Key questions addressed in the Section G summaries and the corresponding location in the PMTA are provided in Table 4.

Table 4 Key Questions and Location in the PMTA

Key Question	Location in PMTA
Summary of the nonclinical studies relevant to the PMTA	Section G.5 Nonclinical Evaluation Summary
Summary of the clinical studies relevant to the PMTA	Section G.6 Human Health Impact Evaluation Summary
The relative health risks of the product for both users and nonusers compared to other tobacco products on the market, including tobacco products within the same product category as it may be expected that consumers of current products within the same product category may switch to using a newly marketed product, and the health risks compared to never using tobacco products	Section G.6 Human Health Impact Evaluation Summary
The chemical and physical identity of the product	Section G.2 Product Design Summary Section G.3 Product Manufacturing and Controls Summary Section G.4 Product Composition Summary
The use patterns within which consumers are likely to use the product	Section G.6 Human Health Impact Evaluation Summary
The likelihood, based on the research information contained in your application, of current nonusers of tobacco products initiating or reinitiating tobacco use by using the product	Section G.6 Human Health Impact Evaluation Summary
The likelihood, based on the research information contained in your application, that consumers will adopt the product and then switch to other tobacco products that may present higher levels of risk, such as cigarettes	Section G.6 Human Health Impact Evaluation Summary
The likelihood, based on the research information contained in your application, of consumers using the product in conjunction with other tobacco products	Section G.6 Human Health Impact Evaluation Summary

Key Question	Location in PMTA
The likelihood, based on the research information contained in your application, of current tobacco product users switching to the product instead of ceasing tobacco product use or using an FDA-approved tobacco cessation product (because use of the product includes inherent risk above quitting altogether or the use of an FDA-approved NRT)	Section G.6 Human Health Impact Evaluation Summary
Assessment of abuse liability (ie, the addictiveness, abuse, and misuse potential of the new product and the exposure to nicotine during product use)	Section G.6 Human Health Impact Evaluation Summary
Assessment of user topography (how individual users consume the product), the frequency with which consumers use the product, and the trends by which users consume the product over time	Section G.6 Human Health Impact Evaluation Summary
A discussion demonstrating how the data and information contained in your PMTA establish that permitting the marketing of the new tobacco product would be APPH.	Section G.1 Introduction Section G.5 Nonclinical Evaluation Summary Section G.6 Human Health Impact Evaluation Summary

APPH=appropriate for the protection of the public health; FDA=Food and Drug Administration; NRT=nicotine-replacement therapy; PMTA=premarket tobacco product application.

10.1 Section G.1 Executive Summary

Section G.1 Introduction provides an executive summary of the nonclinical and clinical sections, which are provided in Section G.5 Nonclinical Evaluation Summary and Section G.6 Human Health Impact Evaluation Summary, respectively. The executive summary of the CMC information for ZYN is located in Section C Descriptive Product Information. Links to the corresponding PMTA sections and subsections are provided in the sections that follow.

10.2 Section G.2 Product Design Summary

Section G.2 Product Design Summary presents the principles of operation, including formulations and intended function of each ingredient, packaging components and intended function of each component, and product use.

10.3 Section G.3 Product Manufacturing and Controls Summary

Section G.3 Product Manufacturing and Controls Summary presents the manufacturing (eg, manufacturing and testing sites, flavor suppliers, formulations, and manufacturing process) and the properties (eg, ingredients, flavor components, routine release specifications, and stability).

10.4 Section G.4 Product Composition Summary

Section G.4 Product Composition Summary includes the composition for each flavor of the ZYN finished products as well as the description of the packaging (ie, primary, secondary, and tertiary container closure systems). Refer to Section A5 TPMF Letters of Authorization for a copy of the

(b) (4) Tobacco Products Master File letter of authorization for details of the nicotine manufacturer and specifications.

10.5 Section G.5 Nonclinical Evaluation Summary

Section G.5 Nonclinical Evaluation Summary summarizes the nonclinically relevant research findings, including the analyses of harmful and potentially harmful constituents (HPHCs), quantitative health risk assessments, and results from the *in vitro* toxicology (mutagenesis/genotoxic) studies (Section H.2.3 Study (b) (4) Report). This work was also supplemented by *in vitro* and *in vivo* data from the published literature.

10.6 Section G.6 Human Health Impact Evaluation Summary

Section G.6 Human Health Impact Evaluation Summary summarizes all clinically related research findings, including the product's health risks, the product's effect on tobacco use behavior among current users, the product's effect on tobacco use initiation among non-users, and the product's effect on the population as a whole. The summary includes findings from clinical studies conducted with ZYN, supplemented by data from the published literature on Swedish snus, a relevant comparator product.

A total of four clinical and two consumer research studies were conducted in support of the PMTA for ZYN:

- Three clinical pharmacology studies:
  - Study SM 17-01 was an open-label, randomized, 14-way, cross-over, single-dose study in 20 healthy subjects designed to evaluate the in vivo extraction of nicotine and flavor compounds from ZYN compared with conventional, tobacco-based Swedish snus in healthy daily snus users. A full copy of the study report and all appendices are provided in Section H.3.1.2.1.
  - Study SM 17-02 was an open-label, randomized, five-way, cross-over, single-dose study in 18 healthy subjects to assess nicotine pharmacokinetics (PK) and subjective effects of a single dose of ZYN compared with conventional, tobacco-based Swedish snus among current healthy daily snus users. A full copy of the study report and all appendices are provided in Section H.3.1.3.1.
  - Study SM 18-01 was an open-label, randomized, seven-way, cross-over, single-dose study in 36 healthy subjects to assess nicotine plasma concentrations and PK of a single dose of ZYN compared with conventional, tobacco-based Swedish snus and American moist snuff among current healthy daily snus users. A full copy of the study report and all appendices are provided in Section H.3.1.2.3.
- One oral safety clinical study:
  - Study SM 17-03 was an observational 2-part study of oral health associated with the use of ZYN among current daily snus users. Part 1 was an open-label, randomized, four-way cross-over, single administration (60 minutes) study in 20 healthy subjects. Part 2 was an open-label, observational, six-week, follow-up study in 59 healthy subjects during which subjects were encouraged to substitute as much as possible of their snus with ad

libitum use of the ZYN of their choice. A full copy of the study report and all appendices are provided in Section H.3.1.2.2.

- One likelihood of use consumer research study

  – Study (b) (4) was an observational, consumer research study with a pre-/post-exposure, repeated-measures study design in (b) (4) US residents. A full copy of the study report and all appendices are provided in Section H.3.1.1.2.

- One patterns of use consumer research study

  – Study (b) (4) was a consumer research study in US residents designed for a descriptive analysis of ZYN users' and ZYN non-users' patterns of use and perceptions of health risk in the absolute, relative to other tobacco/nicotine products (TNPs), and in combination with ZYN and consisted of two distinct phases:

    o Retrospective Study, which utilized a cross-sectional design to measure recalled TNP usage among ZYN users and ZYN non-users ((b) (4))

    o Prospective Study, which longitudinally evaluated TNP patterns of use among ZYN users and ZYN non-users over a (b) (4) observation period ((b) (4))

    A full copy of the study report and all appendices are provided in Section H.3.1.1.1.

11 SCIENTIFIC STUDIES AND ANALYSES (PMTA SECTION H)

Section H provides the source documentation for the Section G summaries as noted below.

Section H.1 Product Analysis and Manufacturing provides documentation supporting product analysis and manufacturing, including properties, specifications, analytical procedures, batch analyses, stability, and packaging. These results are summarized in Section G.2 Product Design Summary, Section G.3 Product Manufacturing and Controls Summary, and Section G.4 Product Composition Summary.

Section H.2 Nonclinical Evaluation provides the following:

- quantitative risk assessment reports performed for select HPHCs and a flavor component (b) (4)) (Section H.2.1)
- assessments of HPHCs and analytes (Section H.2.2)
- the mutagenesis/genotoxic Study (b) (4) report (Section H.2.3)

Results from Section H.2 are summarized in Section G.5 Nonclinical Evaluation Summary.

Section H.3 Human Health Impact Evaluation provides the study reports for the four clinical and two consumer research studies conducted in support of the ZYN PMTA. Results from the clinical and consumer research studies are summarized in Section G.6 Human Health Impact Evaluation Summary (see Section 10.6 for details of studies).

12 REFERENCES (PMTA SECTION I)

Section I includes three systematic literature review reports (Section I.1) and all copies of references (Section I.2) cited throughout the PMTA.

The three systematic literature review reports conducted by (b) (4) and provided in this submission are as follows:

- Section I.1 (b) (4), which was previously conducted for the General Snus MRTPA and included a comprehensive review of the available literature on snus through December 2012 and also selected important new publications as available through April 2013.
- Section I.1 Health Effects and Meta-Analysis Update Report, which identified and evaluated all original primary scientific studies published since 01 December 2012 through 28 July 2017, and not included in the previous review, and to comprehensively update previous conclusions contained within the following specific sub-sections of the (b) (4):
  - Section 4: Non-clinical toxicological studies with snus
  - Section 5: Human health effects of snus (including all previous and new endpoints)
  - Appendix VI (to Section 5): Relative risks among snus users and smokers compared to nontobacco users
  - Appendix VII (to Section 5): Comparison of risks from dual use, switching, and quitting
- Section I.1 Use Behavior Update Report, which identified and evaluated all original primary scientific studies published since 01 December 2012 through 28 July 2017 and not included in the previous review, and to comprehensively update previous conclusions contained within the following specific sub-sections of the (b) (4):
  - Section 6.2: Effect on tobacco use behavior among current users
  - Section 6.3: Effect on tobacco use initiation among non-users
  - Sections 6.4.1.1 to 6.4.1.2: Consumers' beliefs about the health risks of using the product

When relevant, additional literature published after 28 July 2017 was included in Section I.2.