The revised Swedish Match modified risk tobacco product application for General Snus fails to provide evidence that the claim is not misleading and will have a beneficial effect on the population as a whole

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BACKGROUND

Swedish Match originally submitted a Modified Risk Tobacco Product Application (MRTPA) in June 2014 to permit it to market eight sub-brands of General Snus with warning label statements different from those required by law for other commercially marketed smokeless tobacco products. In its MRTPA, Swedish match cited Swedish and international evidence to support its claim that Swedish smokers who switch completely to snus derive individual health benefits, and that the high prevalence of snus usage among men in Sweden has contributed to a lower frequency of tobacco-related disease and mortality than is found in comparable populations with higher cigarette smoking rates. The MRTPA was based on the proposition that if Swedish Match were permitted to make modified risk claims, it would lead smokers who would not otherwise quit smoking to switch completely to a Swedish match snus product, and would not lead to dual use or significant use among youth.

In December 2016, the FDA[1] denied Swedish Match's request to remove a currently required warning stating that the products can cause gum disease and tooth loss, and deferred final action on the company's other requests to remove or revise two additional currently required warnings (that the products can cause mouth cancer and that the products present "substantially lower risks to health than cigarettes"), and issued a response with advice on how the company may consider amending their applications to better align with existing evidence. FDA determined that the MRTPAs did not contain sufficient evidence to demonstrate that, as actually used by consumers, the snus products sold with modified risk claims would significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole. However, FDA stated it believed the MRTPAs could be amended to provide sufficient evidence to support issuance of MRTP orders.

In September 2018 Swedish Match submitted an amendment in response to the three deficiencies enumerated in FDA's December 2016 letter, and submitted a second amendment in November 2018[2] in response to FDA's October 2018 Advice and Information Request Letter. Regarding

[1] https://www.fda.gov/downloads/TobaccoProducts/Labeling/MarketingandAdvertising/UCM533236.pdf
[2] https://www.fda.gov/TobaccoProducts/Labeling/MarketingandAdvertising/ucm533454.htm

the first two deficiencies, the company's September 2018 amendment accepted FDA's recommendations to retain the warnings stating that the product "can cause mouth cancer" and "is not a safe alternative to cigarettes." In response to the third deficiency, Swedish Match conducted a new consumer perception study entitled "Perceptions and Behavioral Intentions Study" to address the issues with its previous consumer perception study that the FDA identified. Based on the results of this study and other research, Swedish Match proposed the following modified risk claim for the General Snus:

> "Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis."

Among other things, Swedish Match's November 2018 amendment provides copies of advertising, marketing, promotional, training, and educational materials the company plans to use to communicate modified risk information to consumers, as well as clarifications of the company's analyses of the data from the Perceptions and Behavioral Intensions Study.

REQUIREMENTS FOR AN MRTP ORDER

To be granted an MRTP order permitting Swedish Match to market its products with its proposed modified risk claim, the company must demonstrate that the product, *as actually used by consumers*, will both:

1) Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and

2) Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.[3]

This two-pronged statutory requirement means that Swedish Match must submit evidence about the way consumers use the product, including whether consumers typically use snus together with cigarettes and/or other combustible tobacco products. Additionally, even if Swedish Match can meet the first prong of the statutory test and demonstrate that marketing snus with the proposed modified risk claim will significantly reduce the risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis to individual users, the MRTPA fails if marketing snus with the proposed modified risk claim will not benefit the health of the population as a whole, including youth and other people who currently do not use tobacco products.

COMMENTS ON SWEDISH MATCH AMENDMENTS TO MRTP APPLICATION

- **Adult consumers are likely to understand the claim "instead of cigarettes" as compatible with dual use.**

[3] Family Smoking Prevention and Tobacco Control Act, section 911(g)(1), Public Law 111-31, 21 USC 387k (June 22, 2009).

Tobacco Control Act section 911(h)(1) requires that any advertising or labeling concerning modified risk products "enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products." The scientific studies submitted by the MRTP applicant "should inform FDA's evaluation of the product's marketing on consumer perception and understanding, including:

- The ability of consumers to understand the modified risk claims and the significance of the information in the context of one's health;
- Consumers' beliefs about the health risks of using the product relative to other tobacco products, including those within the same class of products;
- Consumer beliefs about the health risks of using the product relative to cessation aids; and
- Consumer beliefs about the risks of using the product relative to quitting all tobacco use."[4]

In particular, "the scientific studies submitted by the applicant should inform FDA's evaluation of the tobacco product's impact on tobacco use behavior, including:

- The likelihood that current tobacco product users will start using the product;
- The likelihood that tobacco users who adopt the product will switch to or switch back to other tobacco products that present higher levels of individual health risk;
- The likelihood that consumers will use the product in conjunction with other tobacco products;
- The likelihood that users who may have otherwise quit using tobacco products will instead use the product; and
- The likelihood that consumers will use the product as intended or designed."[5]

However, the application fails to demonstrate that adult consumers understand that the mode of use described in the claim ("instead of cigarettes") means a complete switch to General Snus, not a dual use with cigarettes or other tobacco products.

Swedish Match evaluated "comprehension" of the claim by asking:

> For General Snus to put you at a lower risk of disease, how many cigarettes can you smoke on a day when you also use General Snus?
>
> 1 Zero (0) cigarettes
> 2 Up to 5 cigarettes
> 3 Up to 20 cigarettes
> 4 As many as you want to smoke

[4] FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, Draft Guidance, March 2012. Available at: https://www.fda.gov/downloads/TobaccoProducts/Labeling/UCM297751.pdf
[5] FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, Draft Guidance, March 2012. Available at: https://www.fda.gov/downloads/TobaccoProducts/Labeling/UCM297751.pdf

5 None of the above
99 Don't know
999 Decline to answer[6]

The wording of this question is problematic because it implies that switching on some days while continuing to smoke on other days is compatible with complete switching. Furthermore, only between 37.4% and 56.2% of participants selected the correct number (zero cigarettes) (Table 1). (The detailed breakdown of proportions for other answer options has only been provided for current smokers after FDA requested it, but examining the raw data shows that across all groups, among other answers, the largest proportions were for "don't know" and "none of the above".)

Table 1. Proportion of participants who selected "zero cigarettes" in response to the question regarding the number of cigarettes one can smoke a day to lower risk of disease when using General Snus.

Participant category	Test (claim 1)	Control	p-value
Never tobacco users - legal age to 24 years	42.3%	37.2%	0.055
Never tobacco users – older than 24 years	37.4%	31.2%	0.020**
Former cigarette smokers - legal age and older	49.7%	37.0%	<0.001***
Current cigarette smokers - legal age to 24 years	56.2%	45.0%	<0.001***
Current cigarette smokers - older than 24 years of age	43.7%	33.9%	0.001*
Current smokeless tobacco users - legal age and older	53.9%	49.4%	0.160

Source: pp. 155-160, 04-study-smna-report-section-01-through-16_Redacted.pdf
P-values were reported from one-tailed independent two-sample proportion tests. Statistical significance was adjusted according to the Holm procedure, whereby p-values ordered from lowest to highest are compared (in that order) against target, adjusted p-values of *** - $p<0.017$, ** - $p<0.025$, and * - $p<0.050$, respectively. Testing ends with the first non-significant comparison.

In addition, consumer understanding of the phrase "instead of cigarettes" has been tested in Copenhagen Moist Snuff MRTP application.[7] It was found that: "some 21–34-year old adult smokers who do not reject MST [moist smokeless tobacco] disliked Prefix, 'Using this product instead of cigarettes…,' because it connoted ideas of switching to MST from cigarettes. A few participants in this group, however, thought 'instead of' was as open-ended as 'alternative to' and found the phrasing acceptable as a way of suggesting choice."[8] In the Copenhagen MRPT qualitative study, participants understood "alternative" to be compatible with continued smoking and not necessarily requiring complete switching from cigarettes to the smokeless tobacco product ("Across the board, the participants in this study tended to prefer a prefix that frames MST as an alternative to cigarettes rather than a replacement"[9]).

The quantitative findings from the Swedish Match study that users will not understand the message that they need to stop smoking all cigarettes are corroborated with results of a

[6] Kantar Health, General Snus MRTPA Study, p. 30, 04-study-smna-report-section-172_Release in Full.pdf
[7] Altria Client Services. (2018). *USSTC MRTP Application for Copenhagen Snuff Fine Cut: 6.2.: Effect of Marketing on Consumer Understanding and Perceptions*. Available at http://digitalmedia.hhs.gov/tobacco/static/mrtpa/Copenhagen/6-2-risk-perceptions_Release%20in%20Full.pdf
[8] Copenhagen MRTP application, 7.3.3-1: CS-01- Claims Qualitative Study; p. 17, app-7-3-3-1-cs-01-claims-qual-study_Redacted.pdf
[9] Copenhagen MRTP application, 7.3.3-1: CS-01- Claims Qualitative Study; p. 6, app-7-3-3-1-cs-01-claims-qual-study_Redacted.pdf

qualitative study from Copenhagen moist snuff MRTP application.[10] ***Together, they indicate that at least some adult consumers are likely to understand "instead of cigarettes" to mean using snus in addition to smoking cigarettes, a behavior that does not carry reduction in harm but likely increases harm to the users.***

- **Videos only showed mint and wintergreen products, not the other products for which the Swedish Match is seeking MRTP authorization.**

In Swedish Match's "Perceptions and Behavioral Intentions Study," "videos rotated evenly between mint and wintergreen flavors, which were chosen because they comprise roughly 70% of General Snus product sold in the US (internal sales data on file)".[11] However, it is unclear whether the effects of the claim will extend to other General Snus products (e.g., General Loose, General Portion Original Large, General Portion White Large).

Furthermore, the application did not address the appeal of flavors to youth. This is especially critical since youth are likely to use flavors. Adolescents' decisions to adopt use of any tobacco product are based on several considerations, including whether the product appeals to them, the product's flavors, smell and taste, the product's perceived harm reduction, and the ease and location of use.[12]

In order to attract young and new users, the tobacco industry adds characterizing flavors like mint, menthol, fruit, and candy to tobacco products,[13] including smokeless tobacco products.[14] These flavors appeal to new users by masking the harsh taste of tobacco. Additionally, tobacco products with a characterizing flavor including fruit-flavored e-cigarettes[15] and menthol cigarettes[16] are perceived to be less harmful than unflavored or tobacco-flavored products. In addition, there is some evidence that menthol cigarettes are harder to quit.[17] General Snus is no exception in how tobacco flavors and packaging elements affect youths' harm perceptions: Youth shown packages for smokeless tobacco with or without a flavor descriptor (primarily for snus and dissolvable tobacco) were more likely than older adults to associate the flavor descriptor

[10] Copenhagen MRTP application, 7.3.3-1: CS-01- Claims Qualitative Study; app-7-3-3-1-cs-01-claims-qual-study_Redacted.pdf

[11] MRTPA Response Amendment for MR0000020-MR0000022, MR0000024-MR0000025, and MR0000027-MR0000029; p. 12, 02-response-document_Release in Full.pdf

[12] McKelvey, K., Ramos, M., Roditis, M., Ramamurthi, D., Halpern-Felsher, B. A Qualitative Analysis of Adolescents' Appeal of Various Tobacco Products. In preparation.

[13] Brown JE, Luo W, Isabelle LM, Pankow JF. Candy flavorings in tobacco. N Engl J Med. 2014;370(23):2250-2252.

[14] Kostygina G, Ling PM. Tobacco industry use of flavourings to promote smokeless tobacco products. Tob Control. 2016 Nov;25(Suppl 2):ii40-ii49.

[15] Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. Tob Control. 2016;25(Suppl 2):ii62-ii66. doi:10.1136/tobaccocontrol-2016-053174.

[16] Brown JE, Luo W, Isabelle LM, Pankow JF. Candy flavorings in tobacco. N Engl J Med. 2014;370(23):2250-2252.

[17] Pletcher MJ, Hulley BJ, Houston T, Kiefe CI, Benowitz N, Sidney S. Menthol cigarettes, smoking cessation, atherosclerosis, and pulmonary function. 2006;166.
Trinidad DR, Pérez-Stable EJ, Messer K, White MM, Pierce JP. Menthol cigarettes and smoking cessation among racial/ethnic groups in the United States. Addiction. 2010;105(SUPPL.1):84-94. doi:10.1111/j.1360-0443.2010.03187.x.

with better taste, more appeal, and lower health risks.[18] ***Swedish Match ignored this evidence and failed to address how youth will perceive the flavors in the Snus products, that youth will perceive lower risk associated with General Snus due to the flavors, and that such flavored Snus products will result in greater likelihood for initiation of General Snus among non-users.***

- **No effects on dual users were examined.**

In Swedish Match's "Perceptions and Behavioral Intentions Study," submitted as part of the amendment to the MRTP application, participants were either non-users, exclusive cigarette smokers, or exclusive smokeless users. Dual users were not included. However, it is important to include dual users in participants given that dual use of smokeless tobacco (ST) products (including snus) and other products is common. According to an analysis of the 2012-14 National Adult Tobacco Survey, 3.6% of U.S. adults aged 18+ were current ST users and 52.4% of these current ST users concurrently used one or more other tobacco products.[19] Dual use also increases the risk of myocardial infarction more than cigarette smoking alone.[20]

General Snus has been on the US market for several years, since Swedish Match North America (SMNA) received market authorization for General Snus in November 2015. ***Given that it has been over three years since General Snus has been authorized to be sold in the US, Swedish Match should present updated epidemiological data demonstrating real-world use of the product, particularly the rates of initiation, switching, dual use, and cessation.***

- **Post-market surveillance program needs to be evaluated before MRTP authorization.**

In the application, Swedish Match states: "If modified risk orders are issued for the eight General Snus products, Swedish Match looks forward to presenting a post-market surveillance program that will generate valid, real-life data on actual use behaviors and perceptions."[21] However, the plan for post-market surveillance program should be presented at the time of the application to allow the FDA and the research community to comment on its adequacy and to point out the issues needed to be monitored for.

- **Swedish Match presents no evidence that the proposed modified risk claim will make current smokers completely switch to General Snus.**

Swedish Match's "Perceptions and Behavioral Intentions Study" aimed to assess the impact of the proposed claim on behavioral intentions among non-users, former users, current smokers, and current smokeless tobacco users. ("Objective 1: Compare the likelihood of various usage

[18] Adkison SE, Bansal-Travers M, Smith DM, O'Connor RJ, Hyland AJ. Impact of smokeless tobacco packaging on perceptions and beliefs among youth, young adults, and adults in the U.S: findings from an internet-based cross-sectional survey. Harm Reduct J. 2014 Jan 17;11:2. doi: 10.1186/1477-7517-11-2.
[19] See Table 2, Sung HY, Wang Y, Yao T, Lightwood J, Max W. Polytobacco Use and Nicotine Dependence Symptoms Among US Adults, 2012-2014. Nicotine Tob Res. 2018;20(suppl_1):S88-S98. PMCID: PMC6093419.
[20] Teo KK, Ounpuu S, Hawken S, et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. Lancet. 2006;368(9536):647–658.
[21] MRTPA Response Amendment for MR0000020-MR0000022, MR0000024-MR0000025, and MR0000027-MR0000029; p. 16, 02-response-document_Release in Full.pdf

intentions and behaviors related to General Snus and cigarettes after having viewed a single General Snus video."[22]) A modified risk claim might have a population-level benefit if smokers otherwise not willing to quit switched to General Snus completely. However, the study does not assess the intentions to switch completely. Instead, it measures smokers' likelihood of buying General Snus for themselves ("How likely are you to buy General Snus® for yourself if sold in a store where you usually shop?" Responses were on 11-point Juster scale where 0= no chance, almost none [1 in 100] to 10= certain, practically certain [99+ in 100].) Even then, the study found only one significant difference (only smokers older than 24 had greater intentions to buy General Snus in the test condition (Mean=2.04) than in the control condition (Mean=1.49).

Furthermore, exposure to the modified risk claims did not change intentions to quit smoking, reduce the number of cigarettes, or seek smoking cessation aid.[23] ***Thus, the revised application provides no evidence that the proposed modified risk claim will affect current smokers' switching behavior in a way that would be protective of public health.***

- **Swedish Match presents no information on the effect of their proposed modified risk claims might have on youth**

The revised Swedish Match application does not provide any reliable information on whether adolescents would be interested in using General Snus, especially after viewing the claims, if adolescents would initiate nicotine use with General Snus, if adolescents would switch from another tobacco product to General Snus, or if adolescents would use it along with other tobacco products.

One way to obtain information on adolescents' interests and behavior is to conduct studies with adolescents. However, no tobacco company should be permitted to conduct research on youth below the legal age for tobacco use (21, to be conservative) because they could use such information to design marketing campaigns to attract youth to their products. A different way to get at adolescents' interest and behavior is relying on research on other, similar products, such as electronic cigarettes, conducted with no direct or indirect involvement of tobacco companies or their agents.[24]

Our recent research with California youth (Wave 6 of an ongoing prospective cohort study that began in 2014-2015 with 9th and 12th graders) showed that youth exposed to modified risk claims perceived the target tobacco product as lower in risk compared to the non-exposure controls and only 70% understood that "switching completely" is incompatible with continued smoking.[25] This study tested the claims proposed in the PMI's MRTP for IQOS: a) *"Scientific studies have shown that switching completely from conventional cigarettes to IQOS system can reduce the risks of tobacco related-diseases;"* (reduced risk claim), and b) *"Scientific studies have shown that switching completely from cigarettes to the IQOS system significantly reduces your body's*

[22] Protocol SMNA 17-01GEN: Observational Study Report, p. 69, 04-study-smna-report-section-01-through-16_Redacted.pdf
[23] Protocol SMNA 17-01GEN: Observational Study Report, pp. 76-81, 04-study-smna-report-section-01-through-16_Redacted.pdf
[24] Institute of Medicine. 2012. *Scientific Standards for Studies on Modified Risk Tobacco Products*. Washington, DC: The National Academies Press. https://doi.org/10.17226/13294.
[25] Halpern-Felsher, B. and UCSF TCORS, unpublished data.

exposure to harmful or potentially harmful chemicals." Nonetheless, the findings might be applicable to other modified risk claims and indicate that such claims have significant effect in lowering youth's perceived risk of tobacco products. As extensive body of research has documented, lower perceived risks are associated with increased trial and use of tobacco products.[26] This indicates that the proposed claim will likely have negative impact on youth.

Because the application did not consider the impact of smokeless tobacco on adolescent use, it did not demonstrate that the product,* as actually used by consumers*, will benefit the health of the population as a whole, including current non-users; in particular, it did not provide any scientific evidence regarding the effect that this product and its marketing would have on increasing the likelihood that adolescents who are currently not tobacco users will start using smokeless.

Despite section 911(g)'s requirement, this application failed to provide adequate scientific evidence demonstrating that their Snus products would "benefit the health of the population as a whole," in particular non-users (including adolescents) as well as current users of other tobacco products.

- **Proposed modified risk claim misleads consumers about risks of General Snus**

The proposed modified risk claim is misleading because participants who saw the modified risk claim were more likely to say that General Snus is less harmful than never using any tobacco products compared to the control group, and were less likely to say that General Snus is equally or more harmful than never using any tobacco products compared to the control group. For example, among young never tobacco users (legal age to 24 years), in the control group, 10.1% believed that using General Snus daily has "a much lower chance" or "a lower chance" of "serious health problems" compared to never having used any tobacco products while 89.9% believed that using General Snus daily has "the same chance", "a higher chance", or "a much higher chance" of "serious health problems" compared to never having used any tobacco products. In the test group (claim 1, the proposed modified risk claim), the corresponding proportions were 18.7% and 81.3%, respectively.[27] Among older cigarette smokers (over 24 years old), in the control group, 24.6% believed that using General Snus daily has "a much lower chance" or "a lower chance" of stroke compared to never having used any tobacco products while 75.4% believed that using General Snus daily has "the same chance", "a higher chance", or "a much higher chance" of "serious health problems" compared to never having used any tobacco products. In the test group (claim 1), the corresponding proportions were 39.0% and 61.0%, respectively.[28]

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[26] Halpern-Felsher, BL, Biehl, M, Kropp, RY, & Rubinstein, ML. Perceived risks and benefits of smoking: Differences between adolescents with different smoking experiences and intentions. Preventive Medicine. 2004 Sep; 39(3): 559-567. PMID: 15313096. Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, BL. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. Journal of Adolescent Health. 2016 May, 58(5):5558-66. PMID: 27107909. Chaffee BW, Couch ET, Urata J, Gansky SA, Essex G, Cheng J. Predictors of Smokeless Tobacco Susceptibility, Initiation, and Progression Over Time Among Adolescents in a Rural Cohort. Substance Use and Misuse. 2019 (In Press).

[27] Protocol SMNA 17-01GEN: Observational Study Report, p. 128, 04-study-smna-report-section-01-through-16_Redacted.pdf

[28] Protocol SMNA 17-01GEN: Observational Study Report, p. 137, 04-study-smna-report-section-01-through-16_Redacted.pdf

This pattern of findings in terms of direction and statistical significance is consistent across all 8 diseases examined (chronic bronchitis, emphysema, lung cancer, serious health problems, gum disease, heart disease, mouth cancer, and stroke) for both young and older never tobacco users, former smokers, and older cigarette smokers; and across 6 (emphysema, serious health problems, gum disease, heart disease, mouth cancer, and stroke) of the 8 diseases examined for younger cigarette smokers. The findings are in the same direction for current smokeless tobacco users, but are not significant due to the small sample size. The findings are generally the same when comparing daily use of General Snus to quitting all tobacco products[29] and when comparing daily use of General Snus to daily use of aids that help stop smoking.[30] These findings indicate that seeing the ***proposed modified risk claim makes some participants more likely to believe that General Snus has protective qualities***, since its use is less risky than never using any tobacco products or quitting tobacco products. This clearly exacerbates the misperception that some participants already have (including a large proportion of current smokers and smokeless tobacco users) that use of General Snus is less harmful than not using any tobacco products. This indicates that ***the proposed modified risk claim is misleading***.

Swedish Match glosses over this problem by stating that: "The test groups in the cohorts of non-TNP [tobacco/nicotine products] users and current smokers did not perceive that the relative risks of each health condition (respiratory and non-respiratory) were equal or higher than the control group in most of the comparisons, when comparing daily use of General Snus vs. never having used any TNP. However, all respondents across test and control groups perceived the daily use of General Snus to pose higher risk for each health condition than never having used any TNP."[31] There are two flaws in this statement. First, instead of saying "The test groups ….did not perceive …," the correct statement should be "The test groups ….**were less likely to** perceive …" Second, it is incorrect to say "all respondents … perceived the daily use of General Snus to pose higher risk for each health condition than never having used any TNP." The correct statement should be "**the proportion of** respondents … who perceived the daily use of General Snus to pose **equal or** higher risk for each health condition than never having used any TNP **is greater than the proportion of respondents who perceived the daily use of General Snus to pose lower risk for each health condition than never having used any TNP**."

The exposure to the proposed claim led to another misperception. The claim explicitly lists 6 diseases ("mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis"), but does not list "gum disease." However, the exposure to the modified risk claim significantly reduced the perceived risk of gum disease. This indicates that seeing this claim might make people erroneously believe that the risk of other diseases, not listed on the claim, is reduced as well. It might stem from the fact that so many diseases were listed in the claim ("mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis") that people reading this claim generalized the risk reduction to all diseases.

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[29] Protocol SMNA 17-01GEN: Observational Study Report, pp. 140-152, 04-study-smna-report-section-01-through-16_Redacted.pdf

[30] Protocol SMNA 17-01GEN: Observational Study Report, pp. 168, 196-209, 04-study-smna-report-section-01-through-16_Redacted.pdf

[31] Protocol SMNA 17-01GEN: Observational Study Report, p. 222, 04-study-smna-report-section-01-through-16_Redacted.pdf

- **Problems with the way hypotheses are worded and tested**

There are multiple problems with how hypotheses are worded and tested (using one-tailed instead of two-tailed tests).

Here is how Hypothesis 3.3 is presented in the application:

> **Hypothesis 3.3:** The test groups will perceive the relative risk of each health condition as equal or higher than the control group when comparing daily use of General Gnus vs. never having used any TNPS.

Problem 1: Incorrect wording.

The way H3.3 is worded makes it sound like the measure of relative risk is continuous; however, it is measured as:

- a much lower chance
- a lower chance
- the same chance
- a higher chance
- a much higher chance.

It is then dichotomized into "a much lower/a lower chance" and "the same chance/a higher chance/a much higher chance." Therefore, the hypothesis should be stated in terms of proportions:

> **Reworded Hypothesis 3.3:** Greater or same proportion of participants in the test group than in the control group will perceive the relative risk of each health condition as equal or higher when comparing daily use of General Gnus vs. never having used any TNPS.

We are including "or same proportion" here because that is how these hypotheses are tested in the study. For example, in a grid on p. 99 (below), the Hypothesis 3.3 is listed as "Supported" (green X) for chronic bronchitis for "current smokers Legal – 24". The results on p. 134 (next panel below) show non-significant result (p=0.032). (Note that the result is non-significant due to the Holm correction for multiple testing.) Thus, they are holding lack of significant difference as evidence of equivalence and present is as support for their hypothesis 3.3. This leads us to the second problem.

Objective 3 Hypotheses	Never TNP Legal-24			Never TNP >24			Former Smokers			Current Smokers Legal-24			Current Smokers >24			Current Smokeless Tobacco		
	T1 vs. C	T2 vs. C	T3 vs. C	T1 vs. C	T2 vs. C	T3 vs. C	T1 vs. C	T2 vs. C	T3 vs. C	T1 vs. C	T2 vs. C	T3 vs. C	T1 vs. C	T2 vs. C	T3 vs. C	T1 vs. C	T2 vs. C	T3 vs. C
3.3 T≥C	Test groups will perceive the relative risks of each health condition (respiratory and non-respiratory) as equal or higher than the control group, when comparing daily use of *General* Snus vs. never having used any TNP. Specifically, the health conditions are:																	
Chronic bronchitis	O	O	X	O	O	O	O	O	O	X	X	X	O	O	O	X	X	X
Emphysema	O	O	X	O	O	O	O	O	X	O	O	O	O	X	X	X	X	X
Lung cancer	O	X	X	O	O	O	O	O	O	X	X	X	O	O	O	X	X	X
Serious health problems	O	O	X	O	O	O	O	O	O	O	O	O	O	O	O	X	X	X
Gum disease	O	O	X	O	O	O	O	O	X	O	X	X	O	O	O	O	X	X
Heart disease	O	O	X	O	O	O	O	O	O	O	O	O	O	O	O	O	X	X

d. Current cigarette smokers - legal age to 24 years

		Control Vs. Claims (1/2/3)								p-value (C1 vs. control)
		Claim 1 (N= 454)		Claim 2 (N= 457)		Claim 3 (N=455)		Control (N=462)		
		%	n	%	n	%	n	%	n	
Relative risk of chronic bronchitis	A much lower chance/A lower chance	28.1%	121	25.8%	111	25.3%	110	22.6%	99	0.032
	The same chance/A higher chance/A much higher chance	71.9%	310	74.2%	320	74.7%	325	77.4%	339	
	Don't Know	-	23	-	23	-	19	-	22	-
	Decline to Answer	-	0	-	3	-	1	-	2	-

Problem 2: Stating hypothesis of equivalence but testing it with nil-null hypothesis testing.

Hypothesis 3.3 is essentially a hypothesis of equivalence, which is aimed at finding evidence of no difference.[32] However, it is tested using null hypothesis of no effect (nil-null hypothesis); the test procedure is known as nil-null hypothesis significance testing (nil-NHST).[33] As typically used, the familiar independent samples t-test is an example of a nil-NHST. To test H3.3, the Swedish Match used "one-tailed independent two sample proportion tests," which are also an example of nil-NHST. As a result, they used non-significant finding (as in the example above with chronic bronchitis and current cigarette smokers between legal age and 24) as evidence of support for their hypothesis. This is wrong. An equivalence test should have been used instead. However, as we argue below, a much simpler solution should have been used.

Problem 3: Using one-tailed tests of significance is inappropriate and two-tailed tests should have been used instead.

[32] Levine, T. R., Weber, R., Park, H. S., & Hullett, C. R. (2008). A communication researchers' guide to null hypothesis significance testing and alternatives. Human Communication Research, 34, 188–209..
[33] Weber, R., & Popova, L. (2012). Testing Equivalence in Communication Research: Theory and Application. *Communication Methods and Measures, 6*(3), 190-213.

In testing the proposed hypotheses about effects of the modified risk claim on perceptions and behavioral intentions, one-tailed tests of significance were used. Instead, two-tailed tests should have been used. One-tailed tests make it easier to reach statistical significance. They are appropriate when researchers are interested only in studying one direction of differences. However, FDA is interested in significant changes in both directions – for example, not only in whether the modified risk claim increases intentions to quit smoking but also if they decrease intentions to quit smoking. The two-tailed hypotheses are the ones that matter for the protection of public health.

Overall, instead of coming up with these complicated and unnecessarily convoluted hypotheses, the study should have used simple two-tailed tests to answer the question: What effect does exposure to modified risk claim have on various populations?

- **The Dynamic Population Model used by Swedish Match is inappropriate to assess the population health impact of the proposed modified risk claim for a product which is already in the U.S. market.**

Although FDA encourages the development and application of computational models to forecast the harm to public health from the use of an MRTP applicant's product, FDA recommends that studies and analyses conducted to support an MRTP application have the following characteristics:

- Clearly articulated objectives and hypotheses;
- Protocols that employ standardized and validated methods of analysis;
- Sample sizes that permit for robust statistical analyses;
- Designs that permit valid comparisons with appropriate controls for the testing of study hypotheses (selection of the control group(s) should be based on the endpoint or effect to be evaluated);
- Procedures to minimize bias on the part of observers and analysts of the data and prevent undue influences on the results and interpretation of the study data, such as blinding, masking, random assignment to condition, etc.;
- Procedures for the selection of human subjects to allow for generalizability of study results to the U.S. population;
- Methods for assigning subjects to different comparator groups that are appropriate for making comparisons between groups with respect to pertinent variables;
- Oversampling of populations that are particularly likely to be affected, positively or negatively, by the marketing of the product;
- Protocols that allow for conditions of use of the product that are reflective of how the product will actually be used by consumers when it is marketed;
- A study duration to allow for adequate assessment of selected endpoint(s) and/or effects;[34] and

[34] Fn 17 from FDA guidance on MRTP:
[17] For example, a study of the product's effect on cessation from tobacco use would likely require greater duration than a study to assess the topography of product use or consumer perception of the product.

- Analyses that adequately address the effects of the product on the study measures, endpoints or outcomes.[35]

The Dynamic Population Model (DPM) estimates the difference in population-level survival between a counterfactual scenario that allows the use of a higher risk product and/or a lower risk product, and a ***base case scenario that only allows the use of the higher risk product***.[36] [37] For the purposes of the General Snus MRPTA, a variant of the model was used in which only cigarettes are available for use in the base case and one new product (General Snus) is added in the counterfactual scenario.[38] However, General Snus has been sold in the U.S. for several years. In this amendment, Swedish Match is seeking an authorization to market General Snus with a modified risk claim. In order to be granted this authorization, the FDA must determine whether marketing General Snus as MRTP will have a net benefit or harm for the health of the population as a whole compared to marketing General Snus without the MRTP claim. For this purpose, ***Swedish Match should construct a statistical model which compares the difference in population health between a base case that includes two products (cigarettes, and General Snus without the MRTP claim) and a counterfactual scenario that is the same as the base case except allowing for marketing General Snus as MRTP.*** The current DPM does not permit two products to be included in the base case, and hence is inappropriate to assess the impact of the proposed claim on U.S. population health***.***

- **The impact of the proposed claim on tobacco use behaviors should be used as the input parameters of the statistical model to forecast the resulting impact on population health.**

Although the FDA application guidelines recommend that the potential impact on mortality and morbidity be assessed for seven population groups and exposure patterns,[39] the Swedish Match used the DPM model to assess the impact of the proposed claim on mortality only for the following three groups/patterns: 1) cigarette smokers who switch to the MRTP completely instead of continuing to smoke, 2) cigarette smokers who opt to use the MRTP rather than quitting smoking, 3) never tobacco users who initiate the MRTP instead of remaining as never tobacco users. The model also examined never tobacco users who initiate the MRTP instead of initiating cigarette smoking. The model left out: 1) tobacco users and non-users who, after adopting the proposed product, switch to or switch back to other tobacco products that may present higher levels of individual health risk; 2) tobacco users who opt to use the proposed product rather than an FDA-approved tobacco cessation medication; 3) tobacco users who use the product in conjunction with other tobacco products; and 4) non-users who experience health

[35] FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, Draft Guidance, March 2012. Available at: https://www.fda.gov/downloads/TobaccoProducts/Labeling/UCM297751.pdf

[36] Bachand AM, Sulsky SI. A dynamic population model for estimating all-cause mortality due to lifetime exposure history. Regulatory Toxicology and Pharmacology 2013;67(2):246-51.

[37] Bachand AM, Sulsky SI, Curtin GM. Assessing the likelihood and magnitude of a population health benefit following the market introduction of a modified-risk tobacco product:
enhancements to the Dynamic Population Modeler, DPM(+1). Risk Analysis 2018;38(1):151-62.

[38] MRTPA Response Amendment for MR0000020-MR0000022, MR0000024-MR0000025, and MR0000027-MR0000029, p. 17, 02-response-document_Release in Full.pdf

[39] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products. Guidance for industry. modified risk tobacco product applications. Draft Guidance, 2012, p. 22.

risks from the product ***Therefore, their assessment does not fully satisfy FDA guidelines for MRTP applications.***

Furthermore, even for the four population groups and tobacco use patterns considered, Swedish Match fails to incorporate the findings from their "Perceptions and Behavioral Intentions Study" as input parameters of the statistical model to make a comprehensive assessment of how the changes in tobacco use behaviors that may result from the proposed claim would affect the population health.

- **Swedish Match provides no explanation to ascertain the direction and magnitude of the net effect on U.S. population health that may result from the proposed modified risk claim.**

Swedish Match did not revise their estimation of the DPM model. The results[40] shown in Appendix 1 "Dynamic Population Model" were redacted from their original MRTP application in 2014,[41] and all the tables presented in Appendix 1 were copied from the original MRTP applications.[42] As in the original application, Appendix 1 in this amendment does not provide clear description about the net effect (including direction and magnitude) of the proposed modified risk claim on population health after considering all the potential harmful and beneficial effects simulated under various hypothetical scenarios of switching rates (such as 1%, 5%, and 10%) for the four population groups and tobacco use patterns. ***Therefore, the results of this model cannot be used to support that allowing a modified risk claim would benefit the public health.***

- **Some of the messaging infringes on FDA's anti-tobacco efforts**

One of the Facebook posts that Swedish Match posted for General Snus used the tagline "Stay Fresh"[43] that is very similar to "Keep It Fresh", the slogan that FDA's anti-tobacco campaign Fresh Empire is using[44] (see Figure 1 below). Fresh Empire is the FDA's campaign to prevent and reduce tobacco use among multicultural youth. Using a similar tagline in advertisements that promote tobacco use undermines the anti-tobacco brand of the Fresh Empire campaign. ***The FDA should prohibit Swedish Match from using the "Stay Fresh" as a tagline in advertisements for tobacco products to avoid confusion with the FDA campaign and avoid the possibility that readers would misunderstand this as a health message.***

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[40] MRTPA Response Amendment for MR0000020-MR0000022, MR0000024-MR0000025, and MR0000027-MR0000029, pp. 20-26, 02-response-document_Release in Full.pdf

[41] pp. 17-35, "Consequences of Marketing Modified Risk Tobacco Product: Population Effects Estimated with the Dynamic Population Modeler", See: 24 appendix-6g-environ-tipping-point-analysis-2014.pdf

[42] pp. 740-743, "Information about Swedish Match North America's Modified Risk Tobacco Product Applications, See: 01 application narrative summary_Redacted.pdf.

[43] FDA Registration Brand Consumer Communications, p. 49, air-response-03-appendix-1_Release in Full.pdf.

[44] Fresh Empire Campaign, https://www.fda.gov/TobaccoProducts/PublicHealthEducation/PublicEducationCampaigns/FreshEmpireCampaign/default.htm

Figure 1. A Facebook post for General Snus (left) and the logo for Fresh Empire, the FDA's anti-tobacco campaign (right). Both use similar taglines: "STAY FRESH" and "KEEP IT FRESH."

Conclusion

FDA acted appropriately in December 2016, when FDA[45] denied Swedish Match's request to remove a currently required warning stating that the products can cause gum disease and tooth loss. FDA also determined that the MRTP application did not contain sufficient evidence to demonstrate that, as actually used by consumers, the snus products sold with modified risk claims would significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole. However, FDA issued a response with advice on how the company may consider amending their applications to provide sufficient evidence to support issuance of MRTP orders.

Swedish Match's September 2018 and a second amendment in November 2018[46] accepted FDA's recommendations to retain the warnings stating that the product "can cause mouth cancer" and "is not a safe alternative to cigarettes." As discussed earlier in this comment, Swedish Match's new consumer perception study "Perceptions and Behavioral Intentions Study" does not support the FDA permitting Swedish Match to market General Snus with its proposed modified risk claim "Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis." ***FDA should not issue a marketing order approving this modified risk claim because doing so would not improve public health and might harm public health by promoting more use (including more dual use with cigarettes).***

[45] https://www.fda.gov/downloads/TobaccoProducts/Labeling/MarketingandAdvertising/UCM533236.pdf
[46] https://www.fda.gov/TobaccoProducts/Labeling/MarketingandAdvertising/ucm533454.htm