

Module 4: Nonclinical

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1. TABULAR LISTING OF ALL NONCLINICAL STUDIES

We do not provide new nonclinical study information or data compared to the corresponding PMTAs.

(b) (4)

¹

2. NONCLINICAL STUDIES

Data in the corresponding PMTAs² demonstrate the overall toxicological safety profile of the *proposed MRTPs* is significantly improved compared to the *authorized MRTPs* and thus, combusted cigarettes. The *authorized MRTPs* contain tobacco leaf, while the *proposed MRTPs* contain tobacco-derived nicotine, resulting in an even greater reduction in exposure to HPHCs. Nevertheless, differences in nicotine formulation do not result in different nicotine delivery and uptake. Additionally, *in vitro* testing showed no mutagenic or genotoxic response to any variety of the *proposed MRTPs*, whereas data from cigarette Total Particulate Matter (TPM) showed a positive genotoxic response in two different assays (Ames and micronucleus assays) compared to the control samples. The *proposed MRTPs* demonstrated a lack of mutagenic or genotoxic effects, indicating a low potential for the *proposed MRTPs* to produce carcinogenic effects. Meanwhile, combusted cigarettes demonstrated both mutagenicity and genotoxicity in the same studies and are known to produce carcinogenic effects. Therefore, these data support authorization of the same reduced risk claim for the *proposed MRTPs* as for the *authorized MRTPs*, as it demonstrates toxicological risks, and thereby disease risks, are significantly lower with use of the *proposed MRTPs* compared to use of the combusted cigarettes. (b) (4)

³

3. NONCLINICAL BEHAVIORAL STUDIES

As FDA has already authorized the proposed claim for use in marketing the *authorized MRTPs*, there is both pre- and post-market data for the *authorized MRTPs* demonstrating a high level of comprehension of the claim language.⁴ The *proposed MRTPs* are used in the same manner as the *authorized MRTPs*, and the *proposed MRTPs* will be marketed with the same modified risk claim as in the *authorized MRTPAs*. There are no new nonclinical behavioral studies, so to evaluate comprehension of the claim language when used with the *proposed MRTPs*, we conducted a new tobacco product perceptions and intentions to use (TPPI) study.⁵ Given the data included in Module 6 of these MRTPAs⁶, it is reasonable to expect commercializing the *proposed MRTPs* with the same reduced risk claim as the *authorized MRTPs* will promote the public health and benefit both the health of individual users and the population as a whole.

4. NONCLINICAL ABUSE LIABILITY STUDIES

We do not provide nonclinical study data to assess abuse liability potential of the *proposed MRTPs*. Clinical abuse liability studies and all other clinical studies pertaining to the individual health effects associated with the *proposed MRTPs* compared with the *authorized MRTPs* and combusted cigarettes are discussed in Module 5 of these MRTPAs.

¹ The referenced information is in (b) (4)

² PM0000593–PM0000612

³ The referenced information is in (b) (4)

⁴ Post-market surveillance and studies (PMSS) for the *authorized MRTPs* have been provided to FDA since 2019. See "Attachment C" of the solicited response for General Snus MRTP Renewal MR0000256.PD1-PD9 submitted January 30, 2024.

⁵ See all attachments associated with Module 6.2 of these MRTPAs.

⁶ See Module 6: Clinical Population Health of these MRTPAs.

5. NONCLINICAL STUDY MODEL OR ANALYSIS

No new information or data compared to the corresponding PMTAs.⁷

6. NONCLINICAL LITERATURE REVIEW

At the time of submission of the original PMTAs for the *proposed MRTPs*, only limited nicotine pouch literature was available, so a comprehensive and systematic review of published literature related to snus was provided.⁸ Since the original PMTA submission, more extensive literature has been published specific to nicotine pouches. A comprehensive and systematic review of published nonclinical literature related to nicotine pouches, including the *proposed MRTPs*, is in the cross-referenced (b) (4), owned by (b) (4).⁹ A brief summary of this literature was also in the October 2023 amendment to the original PMTAs.¹⁰

7. OTHER DOCUMENTS RELATING TO RESEARCH [911(d)(5)]

We are not providing any new information or data related to the provisions of Section 911(d)(5) of the FD&C Act in these MRTPAs.

⁷ (b) (4)

⁸ (b) (4)

⁹ (b) (4)

¹⁰ The referenced information is in (b) (4)