

6.1.6 Abuse Liability

6.1.6.1 Background and Objectives

The 2012 FDA MRTPA Draft Guidance states that applications should contain evidence to inform FDA's evaluation of whether a candidate MRTP, as actually used by consumers, will:

- “Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- 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taking into account both users of tobacco products and persons who do not currently use tobacco products” ([FDA MRTPA Draft Guidance 2012, p. 3](#)).

FDA further recommends:

- “Nonclinical and/or human studies to assess the abuse liability and the potential for misuse of the product as compared to other tobacco products on the market” ([FDA MRTPA Draft Guidance 2012, p. 19](#)).

FDA defines “abuse liability” in this context as:

- “...the likelihood that individuals will develop physical and/or psychological dependence on the tobacco product. Physical dependence is characterized by the development of tolerance to tobacco product use and/or the onset of withdrawal symptoms upon stopping use of the tobacco product. Psychological dependence is characterized by persistent tobacco-seeking and tobacco-use behaviors, impairment in behavioral control, craving, and inability to abstain consistently” ([FDA MRTPA Draft Guidance 2012, p. 19, footnote 11](#)).

In accordance with FDA's MRTPA Draft Guidance, RJRT commissioned a review and analysis of published and unpublished scientific data pertinent to the abuse liability of Camel Snus as part of this Application. Based upon its established expertise in this area, RJRT retained PinneyAssociates (Bethesda, Maryland) to review the available data with respect to the abuse liability of Camel Snus and prepare a report. PinneyAssociates' final report, titled *An Assessment of Camel Snus Abuse Liability* ([Henningfield et al. 2017](#)) (“Abuse Liability Report”) and submitted with this Application, constitutes a formal assessment of the abuse liability of the six Camel Snus products that are the subject of this MRTPA. The chemical composition, nicotine delivery kinetics and usage characteristics of Camel Snus comprise core points of comparison to the abuse liability of other nicotine-delivering products including cigarettes, conventional smokeless tobacco products, and NRT. The authors describe the balance, with respect to abuse liability, that must be achieved for an MRTP to provide a benefit to users and the population as a whole:

“[t]o be useful and provide benefit to the user, non-combustible MRTPs must provide some level of consumer appeal and deliver enough nicotine to attenuate withdrawal in smokers, but not so much as to be locally toxic or aversive, maintain nicotine dependence at an unnaturally elevated level, or lead to initiation by non-tobacco users” (Henningfield *et al.* 2017).

A primary purpose of the analysis is to provide a science-based determination of how well Camel Snus conforms to this ideal point of balance.

6.1.6.2 Underlying Concepts

The PinneyAssociates Abuse Liability Report includes a discussion of fundamental concepts in this field, including the differences in terminology and perspectives that have been advanced by different regulatory, scientific and advisory bodies to distinguish a given product’s simple appeal from those characteristics that contribute to abuse liability. Henningfield *et al.* describe differences in terminology that have been used by CDER and CTP with respect to abuse liability:

“At the FDA, evaluation of abuse liability occurs in the Center for Drug Evaluation and Research (CDER), and CDER uses the term ‘abuse potential’. The FDA Center for Tobacco Products (CTP) determined that it would use the term ‘abuse liability.’ By either term, abuse liability assessment refers to the portfolio of scientific methods that can be used before a product is marketed to determine the risk that self-administration or consumption will lead to pharmacologically-based dependence.” (Henningfield *et al.* 2017).

Whereas explicit FDA guidance on methods for assessment of the abuse liability of tobacco products is not currently available, the existing guidance and recommendations for such evaluations of drug products provide a broadly applicable framework for similar assessments of tobacco products (*e.g.*, FDA 2010; NIDA 1984). A proposed translation of such broad guidance for the abuse liability assessment of drugs into analogous assessments of MRTPs has been advanced (Carter *et al.* 2009), with a recommendation that specific laboratory and clinical investigations be tailored to address the design, composition and manner of use of a candidate MRTP. Therefore, an evaluation of the abuse liability of Camel Snus was based primarily on published scientific data from other nicotine products, including tobacco products and nicotine replacement medicines, to provide comparators to Camel Snus, as well as Camel Snus-specific product information. Some additional data (*e.g.*, certain chemical analyses of other U.S. tobacco products) that were unavailable in the published literature were developed through new analyses that were performed, documented and included in this submission. Categories of information considered included product chemical analyses, non-clinical studies, clinical studies of the deliveries and effects nicotine, and product usage information. A review of the published literature on the comparative abuse liability of cigarettes, smokeless tobacco and NRT products provides a contextual basis for evaluation of the Camel Snus-specific data. In addition to published studies identified in the authors’ literature search, additional scientific evidence pertaining specifically to the abuse liability of Camel Snus was made available to Henningfield *et al.* for consideration, discussion and summarization in the Abuse Liability Report.

There is a general recognition that all nicotine-delivering products may have some potential for dependency from use, that is, some level of abuse liability; but also an emerging appreciation that different nicotine-delivering products, ranging from combustible cigarettes to smokeless tobacco and pharmaceutical NRT, manifest very different degrees of abuse liability (Henningfield *et al.* 1997; Henningfield and Keenan 1993; Henningfield *et al.* 2011; Fagerström and Eissenberg 2012; Stitzer and de Wit 1998; USDHHS 2010, Ch. 4.). Available evidence indicates that the acute kinetics of nicotine delivery to the user's system is a significant factor in determining the relative abuse liability of different tobacco and nicotine products. The 2014 report of the Surgeon General stated that, among all tobacco products, "[c]igarettes carry the highest risk of addiction following initiation" (USDHHS 2014, p. 783). The Surgeon General's conclusion summarizes the findings of a large body of experimental and observational evidence that the risk of dependence and the difficulty in achieving cessation are greater for combustible cigarettes than for smokeless tobacco or any other nicotine-delivering products.

Certain aspects of the abuse liability of tobacco products are relatively straightforward to assess, such as the measurement of nicotine content and speed of nicotine delivery to the user. The Abuse Liability Report presents the scientific foundations of abuse liability assessment for Camel Snus as it relates to a spectrum of nicotine-delivering products encompassing combustible cigarettes, conventional U.S. smokeless tobacco, and therapeutic nicotine replacement products. Other aspects such as the actual uptake of use in the community are influenced by many factors; including pharmacologic, sensory and social elements, as well as exposure to communications (*e.g.*, FDA-approved and other communications; see Henningfield *et al.* 2011). Henningfield *et al.* present these perspectives in conjunction with a review and discussion all available published and unpublished product chemistry, product formulation, nonclinical, human clinical and population-level evidence pertinent to the topic in order to develop a science-based assessment of the abuse liability of Camel Snus. Related topics such as evaluations of consumers' perceptions and the likelihood of use by both present users and non-users of tobacco products are also considered, with full detail on all of these underlying data resources presented and available for review elsewhere in this Application.

6.1.6.3 Abuse Liability of Camel Snus as an individual tobacco product

As summarized in the Abuse Liability Report (Henningfield *et al.* 2017):

- Mouth level nicotine exposure and acute systemic nicotine delivery kinetics that accompany the use of Camel Snus have been characterized in human clinical evaluations. Consistent with prior published and discussed literature developed from broadly similar smokeless products and cigarettes, peak plasma nicotine values (C_{max}) and time to attainment of peak values (T_{max}) are lower and slower, respectively, for Camel Snus than for cigarettes (see Abuse Liability Report, Figures 16 & 19). Over the course of daily use of Camel Snus, total systemic nicotine delivery can be comparable to that provided by cigarettes.

(b) (4)

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These findings are summarized in the Abuse Liability Report (see Figures 3-6 therein).

- Other aspects of the composition of Camel Snus that have been suggested to be potential contributors to the abuse potential of other tobacco products (*e.g.*, acetaldehyde and content of minor alkaloids such as nornicotine and anabasine) are, respectively, far lower than those found in cigarette smoke and broadly similar to those of other U.S. smokeless tobacco products, including other Swedish-style snus sold in the U.S. (see Abuse Liability Report, Table 4, Figures 7-11).
- The capacity of Camel Snus to relieve cigarette smoking urges in abstinent smokers, as demonstrated in clinical study evaluations, was found to (b) (4) (see Abuse Liability Report, Figures 17, 18, 20, 21). Similar findings have been reported previously for NRT products.

(b) (4)

In summary, all of these main findings are consistent with a conclusion that the abuse liability of Camel Snus is lower than that of cigarettes, and are also consistent with a body of published, peer-reviewed literature developed from other broadly similar smokeless tobacco products.

6.1.6.4 Abuse Liability of Camel Snus compared to combustible cigarettes, other smokeless tobacco products, and nicotine replacement therapy (NRT) products

In alignment with FDA's 2012 MTRPA Draft Guidance and the concepts and main findings itemized above, the Abuse Liability Report ([Henningfield *et al.* 2017](#)) offers several main conclusions. These are:

1. The abuse liability of Camel Snus is lower than that of combustible cigarettes, yet sufficient to position the product as a viable alternative to cigarettes for some smokers; and
2. The moderate abuse liability of Camel Snus is higher than the very low abuse potential that has been extensively documented for nicotine replacement therapy (NRT) products, suggesting that Camel Snus can serve as a viable alternative to cigarettes for some smokers who have found NRT products to be unacceptable or inadequate to sustain smoking cessation.

Henningfield *et al.* considered the chemical composition, product formulations, nicotine delivery kinetics and manner of use of Camel Snus by consumers in developing these additional conclusions:

1. The abuse potential of Camel Snus is lower than that of some other conventional smokeless tobacco products on the U.S. market, or is at most similar to that of some others; but is unlikely to be higher in abuse potential than the majority of currently popular U.S. smokeless tobacco products;
2. The abuse liability of Camel Snus does not differ among the six product varieties that are the subject of this Application; and
3. The abuse liability profile of Camel Snus is appropriate with respect to its potential to function as an acceptable MRTP and thereby serve the public health goal of contributing to the reduction of combustible tobacco product use, as was advocated by the 2014 Surgeon General's report ([USDHHS 2014](#)).

6.1.6.5 Camel Snus Abuse Liability Profile and Designation as a MRTP

PinneyAssociates' abuse liability assessment of Camel Snus supports a designation of the product as a MRTP. After review of the available data, the authors conclude that, based on the abuse liability profile of Camel Snus, it will serve as an acceptable and beneficial MRTP. This designation reflects the fact that the abuse liability of Camel Snus is substantially less than that of traditional cigarettes and likely higher than that of FDA-approved over-the-counter nicotine replacement therapy (NRT) medications. Thus, Camel Snus is expected to benefit smokers who are concerned about the risks of smoking, but find medicinal NRT products unacceptable and who will continue to use some form of tobacco product. The authors note that while the ultimate population impact of Camel Snus as an MRTP will depend on factors beyond abuse liability, Camel Snus appears to fall in the general "midrange" for a viable harm reduction product. A midrange harm reduction product is one that manifests moderate abuse liability and acceptability to current smokers while providing a substantial potential to reduce the risks that attend cigarette smoking (see [Figure 1 in Henningfield *et al.* 2017](#)).