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Food and Drug Administration
Division of Dockets Management
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Rockville, MD 20852
Via <https://www.regulations.gov>

Re: Docket No. FDA-2017-N-6189: Tobacco Product Standard for Nicotine Level of Combusted Cigarettes

This submission is in response to the Advance Notice of Proposed Rule Making on Tobacco Product Standards for Nicotine Levels of Combusted Cigarettes. We provide information relevant to Section IV.F.4 of the ANPRM, which asks the following.

FDA hypothesizes that, based on currently available research, nicotine levels like those levels that FDA would consider with a possible nicotine tobacco product standard would be self-limiting (i.e. smokers would be unable to obtain their nicotine dose form cigarettes no matter how they smoke them and eventually would stop trying to do so). Do any peer-reviewed studies demonstrate that lowering the nicotine content of cigarettes to minimally addictive levels might encourage consumers to smoke more VLNC cigarettes to achieve the higher nicotine doses currently delivered by NNC cigarettes?

What is compensation? When faced with a potential reduction of nicotine availability, smokers may try to adjust their smoking behavior (either by smoking their cigarettes more intensely, or by increasing the number that they smoke) to maintain desired levels of nicotine intake. In addicted cigarette smokers there appears to be an optimal level of daily intake of nicotine that provides the desired rewards from smoking, including avoidance of nicotine withdrawal symptoms.(N. Benowitz, 2008) Thus, smokers tend to take in a similar amount of nicotine from their cigarettes day after day. Compensation is seen when smokers switch from normal nicotine to low nicotine yield commercial cigarettes (i.e., light cigarettes) and when the number of cigarettes one can smoke is limited.

Compensation for reduced nicotine yield cigarettes is relatively easy because the nicotine content of the tobacco filler (generally between 10 and 15 mg) is similar for normal and low nicotine yield commercial cigarettes. They are considered low yield based on smoking machine testing, which consists of taking a standard number of puffs of fixed duration and at fixed intervals until the cigarettes burns to the filter overwrap. Low yield commercial cigarettes are engineered to burn more quickly and/or to have greater ventilation via changes in the cigarette paper and/or ventilation holes in the filter, compared to normal nicotine yield cigarettes.(National Cancer Institute (US), 2001) The smoker can easily compensate by inhaling more deeply, taking more frequent puffs, blocking ventilation holes with fingers or mouth and/or smoking more cigarettes per day. Compensation occurs with minimal effort and often without the smoker being aware of the change in behavior.

Compensation for smoking fewer cigarettes per day occurs by taking in more smoke from each cigarette, by inhaling more deeply, and/or taking more puffs per cigarette. Assuming a cigarette contains 10-15 mg of nicotine, and the smoker takes in a systemic dose of 1 mg nicotine (both typical values), then the bioavailability is only about 6-10%. A smoker can, by puffing more frequently and more intensively

increase bioavailability 3-4 fold, such that a dose of 3-4 mg nicotine can be obtained per cigarette, effectively maintaining nicotine exposure even when the number of cigarettes smoked is reduced.(N. L. Benowitz, Jacob, Kozlowski, & Yu, 1986)

Is it possible to engage in compensatory smoking behavior when switching to Very Low Nicotine Content (VLNC) cigarettes? Effectively compensating to maintain nicotine exposure is virtually impossible when switching to cigarettes with minimally addictive nicotine content. The amount of nicotine needed to make cigarettes minimally addictive appears to be 0.4 to 0.5 mg nicotine per gram of tobacco in the tobacco rod (this may be different for other combusted products such as cigars).(Donny et al., 2015) This represents a reduction of nicotine content of 95% or more compared to currently available commercial cigarettes. Assuming the tobacco in a cigarette weighs 0.7 gm, a cigarette containing 0.4 mg/gm tobacco would contain 0.28 mg nicotine. Assuming the usual level of bioavailability, the systemic dose per cigarette would be around 0.025 mg. Assuming the most intensive compensatory inhalation of a 4-fold increase, the maximal systemic dose per cigarette would be about 0.1 mg. These doses are in contrast to the 1 mg or more taken systemically from a currently marketed cigarette. Assuming that a 10 cigarette per day smoker is trying to maintain an intake of 10 mg nicotine per day, and assuming the most intensive compensation, it would require that the smoker smoke 100 cigarettes per day to achieve full compensation. It is likely impossible that a person could smoke 100 cigarettes per day at maximal intensity, so full compensation would be impossible. More likely, the smoker would try to smoke more intensively and smoke more cigarettes per day at first, find compensation impossible, and give up. As nicotine intake falls, one would predict that the level of nicotine dependence would likewise decline, and eventually the smoker would find the cigarette unrewarding and quit. Alternatively, the smoker may seek other available forms of nicotine to satisfy their need for nicotine.

Is there evidence of compensation in VLNC clinical trials? A number of clinical trials have assessed compensation across a variety of measures when smokers are switched from Normal Nicotine Content (NNC) to VLNC cigarettes and found minimal compensatory smoking behavior. Compensation has been assessed by measuring cigarettes smoked per day, nicotine intake (blood levels of nicotine and cotinine or urine total nicotine equivalents), by exposure to tobacco combustion toxicant biomarkers (carbon monoxide, polycyclic aromatic hydrocarbons) and tobacco specific nitrosamines (NNAL), and by smoking topography. Trials have been done with single reduced nicotine content cigarettes, with switching from periods of 4 weeks to one year, and with gradual and immediate reduction of nicotine content levels.(Neal L. Benowitz et al., 2007, 2012, 2015; Donny et al., 2015; Hatsukami et al., 2010) In a study of smokers smoking a single cigarette of different nicotine content on separate days, the intake of nicotine based on area under the plasma nicotine concentration time curve was highly correlated with the nicotine content of the cigarette.(Neal L. Benowitz, Jacob, & Herrera, 2006) Compensation when smoking the lowest nicotine content cigarette (0.6 mg nicotine per cigarette) compared to a 10 mg nicotine content cigarette was 33% with no difference in carbon monoxide exposure). Furthermore, a study by MacQueen indicated that increases in total puff volume were confined to the first few cigarettes and quickly returned to control levels.(Macqueen et al., 2012) Several studies have looked at switching smokers to VLNC for weeks or up to one year.(Neal L. Benowitz et al., 2007, 2012, 2015; Donny et al., 2015; Hatsukami et al., 2010, 2013) These studies were quite consistent, showing a reduction of plasma cotinine or urine total nicotine equivalent levels of about 60 to 70% (data synthesized by Hatsukami, 2015).(Hatsukami, Donny, Koopmeiners, & Benowitz, 2015) Overall, at the end of the study period, there was a significant decrease in cigarettes smoked per day, although with gradual reduction there was a slight increase in cigarettes per day compared to baseline at medium nicotine content level, then a decline in cigarettes per day as nicotine content was further decreased. Expired carbon monoxide and polycyclic aromatic hydrocarbon exposure was unchanged by condition, indicating no harmful over-smoking. Urine NNAL levels decreased in all reduced nicotine content cigarettes studies compared to baseline, but this does not inform compensation because the NNK levels in reduced nicotine content cigarettes are lower than currently marketed commercial cigarettes. One study found that total puff volume when smoking a single cigarette was significantly lower when smoking 0.4 mg/gm tobacco cigarettes compared to baseline.(Donny et al., 2015) The observation that with gradual reduction there was evidence consistent with some compensatory smoking with more cigarettes per day when cigarettes contained medium levels of nicotine, supports the idea that nicotine levels need to be reduced to lower levels at which compensatory smoking is not feasible.

An unpublished analysis focused on solanesol, a long-chain terpenoid that is naturally occurring in tobacco, deposited in the cigarette butt during smoking, and serves as a marker for mainstream smoke exposure.(Polzin et al., 2009) Solanesol levels were analyzed in discarded cigarettes butts from a clinical trial in which participants were randomly assigned to receive research cigarettes with one of five nicotine contents (15.8 (control), 5.2, 2.4, 1.3, or 0.4 mg nicotine / g tobacco).(Donny et al., 2015) Two groups received the lowest nicotine content, and one of them had an increased tar content compared to the other cigarettes. The solanesol levels in cigarette butts smoked during the sixth week of the trial showed reduced mainstream smoke exposure in the reduced nicotine cigarettes compared to the control group (unpublished data, see attachment). These data are consistent with the data described above showing that very low nicotine content cigarettes do not result in compensatory smoking.

Are there limitations in the interpretation of clinical trials that switch smokers to VLNC cigarettes?

The main limitation in interpreting the switching studies with respect to compensation is the non-compliance with research VLNCs. Based on biochemical assessments, non-compliance with study cigarettes is as high as 80%.(Nardone et al., 2016) Non-compliance is unavoidable in real world studies because usual brand cigarettes are readily available. Compliance is partial such that, as described above, nicotine intake decreases to 30 – 40% of baseline, but this decline is less than expected based on the extent of nicotine reduction. Smokers typically smoked a few normal nicotine content cigarettes per day. Presumably, these cigarettes provide some of the nicotine that the addicted smoker cannot get from the VLNC. We do not yet know the extent of compensatory smoking behavior that would occur if higher nicotine content cigarettes were unavailable, as would be the case if all cigarettes were mandated to be VLNC. However, when confined to a residential research facility for 11 days, participants smoked fewer cigarettes per day and had lower exhaled carbon monoxide when randomized to very low nicotine vs. control cigarettes.(Donny, Houtsmuller, & Stitzer, 2007)

Another potential limitation is that experimental studies include subjects who have volunteered to participate. It is possible that more highly addicted smokers who might have trouble with nicotine reduction would not have volunteered to participate, or would have dropped out of studies.

Conclusions: The available research on switching from NNC to VLNCs shows minimal evidence of compensatory smoking, such that smokers do not smoke more cigarettes per day and are not exposed to higher levels of tobacco combustion toxicants. Furthermore, mathematical estimations based on the nicotine availability in VLNCs compared with NNC cigarette with consideration of potential increases in bioavailability that could occur with intensive smoking suggest that substantial compensation would be impossible. It is much more likely that smokers who are unable to tolerate the extent of proposed nicotine reduction would switch to other sources of nicotine, rather than try to compensate by smoking more VLNC cigarettes more intensively.

Sincerely,

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