on ''Postmarket Safety Reporting for Combination Products.'' It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. This guidance is not subject to Executive Order 12866.

IV. Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The collections of information in 21 CFR 314.80(c) and (e), as well as for 21 CFR 314.81(b) are approved under OMB control numbers 0910–0001, 0910–0230, and 0910–0291. The information collection provisions for 21 CFR 600.80 and 600.81 are approved under OMB control number 0910–0308. Those for 21 CFR 606.170 are approved under OMB control number 0910–0116. Those for 21 CFR 606.171 are approved under OMB control number 0910–0458. The information collection provisions for 21 CFR 803.50, 803.53, and 803.56 are approved under OMB control numbers 0910–0291 and 0910–0437. The information collection provisions for 21 CFR 806.10 and 806.20 are approved under OMB control number 0910–0359. The information collection provisions for 21 CFR 4.102, 4.103, and 4.105 are approved under OMB control number 0910–0834.

V. Electronic Access

Persons with access to the internet may obtain the draft guidance at either *https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm109110.htm* or *https://www.regulations.gov*.

Dated: March 15, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–05687 Filed 3–20–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 1100, 1140, and 1143

[Docket No. FDA–2017–N–6565]

RIN 0910–AH60

Regulation of Flavors in Tobacco Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing this advance notice of proposed rulemaking (ANPRM) to obtain information related to the role that flavors play in tobacco products. Specifically, this ANPRM is seeking comments, data, research results, or other information about, among other things, how flavors attract youth to initiate tobacco product use and about whether and how certain flavors may help adult cigarette smokers reduce cigarette use and switch to potentially less harmful products. FDA is seeking this information to inform regulatory actions FDA might take with respect to tobacco products with flavors, under the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act). Potential regulatory actions include, but are not limited to, tobacco product standards and restrictions on sale and distribution of tobacco products with flavors.

DATES: Submit either electronic or written comments by June 19, 2018.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before June 19, 2018. The *https://www.regulations.gov* electronic filing system will accept comments until midnight Eastern Time at the end of June 19, 2018. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov*. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov*.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2017–N–6565 for ''Regulation of Flavors in Tobacco Products.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information

redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov*. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf*.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Laura Rich or Katherine Collins, Center for Tobacco Products, Food and Drug Administration, Document Control Center, 10903 New Hampshire Ave., Bldg. 71, Rm. G335, Silver Spring, MD 20993, 1–877–CTP–1373, *ctpregulations@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

I. Background

A. The Tobacco Control Act

The Tobacco Control Act (Pub. L. 111–31) was enacted on June 22, 2009, amending the FD&C Act and providing FDA with the authority to regulate tobacco products. Specifically, the Tobacco Control Act amends the FD&C Act by adding a new chapter that provides FDA with authority over tobacco products. Section 901(b) of the FD&C Act (21 U.S.C. 387a(b)), as amended by the Tobacco Control Act, states that the new chapter in the FD&C Act (chapter IX—Tobacco Products) (21 U.S.C. 387 through 387u) applies to all cigarettes, cigarette tobacco, roll-your-own tobacco, smokeless tobacco, and any other tobacco products that the Secretary of Health and Human Services by regulation deems to be subject to chapter IX. In the **Federal Register** of May 10, 2016 (81 FR 28973), FDA issued a final rule deeming all products that meet the statutory definition of ''tobacco product'' in section 201(rr) of the FD&C Act (21 U.S.C. 321(rr)), except accessories of deemed tobacco products, to be subject to FDA's tobacco product authority (the deeming rule). The products now subject to FDA's tobacco product authority include electronic nicotine delivery systems (ENDS), cigars, waterpipes, pipe tobacco, nicotine gels, dissolvables that were not already subject to chapter IX of the FD&C Act, and other products that meet the statutory definition of ''tobacco product'' (other than accessories) that may be developed in the future.

B. Flavors and Tobacco Product Standards

Section 907 of the FD&C Act (21 U.S.C. 387g) gives FDA the authority to establish tobacco product standards. To establish a tobacco product standard, FDA must find that the standard is appropriate for the protection of the public health, taking into consideration scientific evidence concerning the risks and benefits to the population as a whole, including users and nonusers of tobacco products; the increased or decreased likelihood that existing users of tobacco products will stop using such products; and the increased or decreased likelihood that those who do not use tobacco products will start using such products (section 907(a)(3)(A) and (B) of the FD&C Act). Thus, under section 907, FDA may issue product standards respecting the construction, components, ingredients, additives, constituents, and properties of tobacco products (section 907(a)(4)(B)(i)) and restricting their sale and distribution (section 907(a)(4)(B)(v)).[1]

The Tobacco Control Act includes a ''Special Rule for Cigarettes,'' which prohibits cigarettes from containing characterizing flavors other than tobacco or menthol (section 907(a)(1)(A)). The statute also authorizes the Agency to issue additional product standards, including to address flavors in tobacco products (see section 907(a)(3)) and preserves FDA's authority to act with respect to menthol (section 907(e)(3)). The deeming rule did not include provisions relating to flavors in tobacco products. Nevertheless, FDA explained that it did intend to consider the issues surrounding the role of flavors in tobacco products, including the role flavors play in youth and young adult use, as well as the existence of preliminary data that some adults may use flavored noncombusted tobacco products to transition away from combusted tobacco use. See 81 FR 28973 at 29014 and 29055.

C. The Role of Flavors in Tobacco Products Use

Adolescence (under 18, also referred to as youth) and young adulthood (age 18 through 24) represent a time of heightened vulnerability to both the initiation of tobacco product use and the development of nicotine dependence (Ref. 1). Furthermore, flavors in tobacco products increase the appeal of those tobacco products to youth, and promote youth initiation (Ref. 2). Thus, the availability of tobacco products with flavors at these developmental stages attracts youth to initiate use of tobacco products and may result in lifelong use (Ref. 2). Researchers examining the impact of the Special Rule for Cigarettes have concluded that, while the prohibition of characterizing flavors in cigarettes has reduced adolescent tobacco product use, the continued availability of menthol cigarettes and other flavored tobacco products likely diminish the effects (Ref. 3). Researchers estimated a 6 percent reduction in the probability of using any tobacco product after implementation of the Tobacco Control Act (2009–2013), and observed the reductions to be significantly associated with the Special Rule for Cigarettes (Ref. 3).

The adverse health effects associated with tobacco product use by youth have been well documented. Nicotine exposure and smoking during adolescence can have unique adverse consequences on brain development (Refs. 2 and 4). For example, smoking cigarettes during adolescence is associated with lasting cognitive and behavioral impairments, including effects on working memory in smoking teens (Ref. 5) and alterations in the prefrontal attentional network in young adult smokers (Ref. 6). Furthermore, the nonclinical data related to nicotine exposure and epidemiologic studies related to smoking cigarettes during adolescence taken together suggest an age-dependent susceptibility to nicotine (Ref. 1).

Use of tobacco products, which is facilitated by nicotine exposure and dependence, puts youth and young adults at greater risk for future health issues, such as coronary artery disease, cancer, and other known tobacco-related diseases (Refs. 1 and 4). Youth and

[1] As set forth above, section 907(a)(4)(B)(v) provides that product standards ''shall, where appropriate for the protection of the public health, include—. . . (v) a provision requiring that the sale and distribution of the tobacco product be restricted but only to the extent that the sale and distribution of a tobacco product may be restricted under a regulation under section 906(d).'' Section 906(d) gives FDA authority to require restrictions on the sale and distribution of tobacco products by regulation if the Agency determines that such regulations would be appropriate for the protection of the public health. See section 906(d)(1) of the FD&C Act.

young adult tobacco product users, particularly cigarette smokers, also are at increased risk for future marijuana and illicit drug use, developmental and mental health disorders, reduced lung growth and impaired function, increased risk of asthma, and early abdominal aortic atherosclerosis (Ref. 1).

Nicotine is highly addictive. The use of nicotine can lead to nicotine dependence, and makes quitting tobacco products very difficult (Ref. 1). Achieving tobacco cessation after nicotine addiction is a long and difficult process. Smokers may try quitting 30 or more times before succeeding (Ref. 7). According to data from the 2015 National Health Interview Survey, 68 percent of adult smokers in the United States wanted to quit smoking and 55.4 percent made at least one quit attempt in the past year; however, only 7.4 percent actually quit within the 6 to 12 months preceding the survey (Ref. 8).

1. The Appeal of Flavors Generally and in Tobacco Products Specifically

Flavor is a multisensory perception consisting of taste, aroma, and chemesthetic (*e.g.,* cooling, burning) sensations in the mouth and throat (Ref. 9). A robust body of literature in food consumer science demonstrates that flavors impact the appeal of consumable products (Refs. 10 and 11), and that flavor preferences drive food selection and vary across age groups (Refs. 12 and 13). Certain flavors are particularly appealing to children and youth; for example, youth have a heightened preference for sweet food tastes and greater rejection of bitter food tastes. These preferences generally diminish with age (Refs. 14 through 17). Flavor compounds, such as sugar, are used to enhance flavor or mask undesirable tastes (*e.g.,* bitter) in food. (Ref. 18).

Research on the appeal of flavors in food informs the understanding of the appeal and the public health impact of flavors in tobacco products. In fact, many of the same compounds that are added to food are also added to tobacco products to enhance flavor or mask undesirable tastes (Refs. 19, 27, and 28). As with food products, flavors are added to tobacco products to, among other things, improve flavor and taste, such as by reducing the harshness, bitterness, and astringency of tobacco during inhalation (Refs. 19 and 20). Studies involving cigarettes have shown that the addition of sweet flavors increases the appeal of these products, especially to youth (Refs. 19 to 21). In addition, the sensory qualities of menthol flavor produce an analgesic or ''cooling'' effect, which can reduce feelings of pain or discomfort (Refs. 22 and 23), or increase sensations of respiration ease (Refs. 22 through 26).

Documents from the tobacco industry show that food flavors, such as fruit and candy, were used to attract new users, primarily youth (Ref. 1). Laboratory research has confirmed that tobacco products contain flavor chemicals at the same level per serving as defined by the studies, or higher than, popular candy and drink products (Refs. 27 and 28). Flavors in food products can trigger reward pathways in the brain and influence decision-making (Ref. 29). Flavors in tobacco products can also trigger reward pathways in the brain and additionally enhance the rewards of nicotine (Refs. 30 and 31).

2. Tobacco Product Use Patterns by Youth

a. *Overall tobacco product use.* According to National Youth Tobacco Survey (NYTS) data, the current use of e-cigarettes among U.S. youth increased significantly between 2011 and 2015 (Ref. 32). While use dropped in 2016, e-cigarettes remain the most commonly used tobacco product by youth (Refs. 33 and 34). Current use of waterpipes among U.S. youth increased significantly between 2011 and 2014, but declined in 2015 and 2016 (Ref. 33). The use of cigarettes, cigars, and smokeless tobacco has generally declined among youth in recent years, although these products remain popular among certain youth subpopulations (Refs. 1, 33, and 35).

b. *Use of tobacco products with flavors.* Data regarding use of menthol cigarettes and non-cigarette tobacco products among youth from 2013–2014 show widespread appeal of flavored tobacco products [2] (Refs. 36 through 38). Results from the 2014 NYTS on flavored tobacco product use in the past 30 days among middle and high school students show that an estimated 3.26 million youth tobacco product users (12 percent of all youth) reported using a flavored tobacco product in the past 30 days (Ref. 39). By product, an estimated 1.58 million reported using a flavored e-cigarette, 1.02 million reported using flavored waterpipe tobacco, 910,000 reported using flavored cigars, 900,000 reported using menthol cigarettes, 690,000 reported using flavored smokeless tobacco (defined as chewing tobacco, snuff, dip, snus, or dissolvables), and 120,000 reported using flavored pipe tobacco (Ref. 39). Among youth (12–17 years) who participated in the Population Assessment of Tobacco and Health (PATH) Study in 2013–2014, 88.7 percent of youth who have ever used (*i.e.,* ever tried even one or two times) waterpipe tobacco, 81 percent of e-cigarette ever-users, and 65.4 percent of cigar ever-users reported that the first product they used in these categories was flavored (Ref. 36). Similarly, 79.8 percent of youth who reported being current tobacco product users in the PATH Study reported using a flavored tobacco product in the past 30 days, including 89 percent of waterpipe users, 85.3 percent of e-cigarette users, and 71.7 percent of cigar smokers (Ref. 36). Data regarding use of flavored little filtered cigars also demonstrate appeal to youth and young adults. For example, 2017 Monitoring the Future data show that among 8th, 10th, and 12th grade students, 60 percent of current little cigar users reported using flavored little cigars (Ref. 40). In addition, data from the PATH Study show that among current filtered cigar users, 79.3 percent of young adults aged 18–24 years and 56.2 percent of adults aged 25 years and older report current flavored use (Ref. 37). Moreover, both youth and young adults identified flavors as a major reason for their e-cigarette use (Refs. 36 through 38). In addition, youth consistently reported product flavoring as a reason for using waterpipes, cigars, and smokeless tobacco (including snus products) (Refs. 36 and 37).

While the prevalence of cigarette smoking among youth generally has declined, rates of menthol smoking among youth remained stable between 2004 and 2014 (Ref. 41). Youth and young adult smokers are disproportionately more likely to smoke menthol than nonmenthol cigarettes, as compared to older adult smokers; in 2014, 52.4 percent of youth smokers aged 12–17 years, 50.5 percent of young adult smokers aged 18–25 years, and 36.3 percent of adult smokers aged 26 years or older, reported smoking menthol cigarettes (Ref. 42). Multiple studies show a greater use of menthol cigarettes by younger smokers and less usage among older smokers (Refs. 42 through 45).

3. Flavors and Perceptions of Harm and Likelihood of Tobacco Product Use

Perceptions about tobacco harm (*i.e.,* beliefs about the health risks of tobacco) can influence tobacco product use behavior as research suggests that adolescents who perceive lower harms from using tobacco products are more likely to initiate use (Ref. 46). Two systematic reviews report findings from studies assessing participants'

[2] For the purposes of this ANPRM, the terms ''flavored tobacco product'' and ''flavors in tobacco products'' are used interchangeably.

(including youth, young adults, and adults) harm perceptions of flavored tobacco products. Some findings show that each age group perceived flavored tobacco products as less harmful than unflavored products (Refs. 47 and 48).

4. Flavors and Progression to Regular Use

The association between initiation with flavored tobacco products and current tobacco product use was examined in Wave 1 of the PATH Study data, which indicated that 81 percent of youth (12–17 years of age) and 86 percent of young adult (18–24 years of age) ever tobacco users (*i.e.,* those who have used a tobacco product even once or twice in their lifetimes) reported that the first tobacco product they used was flavored, compared to 54 percent of adults aged 25 years and older (Ref. 37). Controlling for other factors associated with tobacco product use, youth ever tobacco users who reported their first tobacco product was flavored had a 13 percent higher prevalence of current tobacco product use compared to youth whose first product was not flavored. Adult ever users reporting that the first tobacco product they used was flavored had a 32 percent higher prevalence of current established tobacco product use (Ref. 37).

In addition, a longitudinal examination of youth indicated that youth who initiate smoking with menthol cigarettes may be at greater risk for progression from experimentation to established smoking and nicotine dependence than youth who initiate with nonmenthol cigarettes (Ref. 49).

5. Youth and Young Adult Flavor Preferences

As mentioned in section I.C.1. of this document, youth generally prefer sweet flavors (Refs. 14 through 17). Researchers reviewed the flavor chemicals and levels in several brands of candy and Kool-Aid drink mix and concluded that the chemicals used in these products largely overlapped with those in similarly labeled ''cherry,'' ''grape,'' ''apple,'' ''peach,'' and ''berry'' tobacco products (Ref. 27).

Results from studies show that flavored e-cigarettes appeal to youth and young adults; however, these data may not reflect the flavor preferences among all U.S. youth and adults. In a survey conducted in four high schools and two middle schools in Connecticut in 2013, 70.7 percent of the lifetime e-cigarette users (adolescents who had tried an e-cigarette) interviewed reported having used sweet flavors and 22.1 percent reported having used menthol-flavored e-cigarettes. In terms of preferred flavors, 56.8 percent reported preferring sweet flavors, while 8.7 percent preferred menthol e-cigarettes (Ref. 50). Additional results from the same research found that the top three reasons for e-cigarette experimentation among ever e-cigarette users, regardless of cigarette smoking status and school level, were curiosity (54.4 percent), the availability of appealing flavors (43.8 percent), and friends' influence (31.6 percent) (Ref. 51). Another cross-sectional study, in which 1,567 young adults (18–34 years) were recruited through Facebook ads, reported that the most commonly used flavors among current e-cigarette users were fruit (66.9 percent), candy (35.1 percent), and caramel/vanilla/chocolate/cream (33.3 percent) (Ref. 38). E-cigarette flavor preferences also varied by cigarette smoking status with former or never cigarette smokers preferring flavors more frequently than current cigarette smokers (Ref. 38).

Qualitative findings reveal differences in e-cigarette flavor preferences as well. Research from a 2016 laboratory study of young adult cigarette smokers who used e-cigarettes for the study reported fruit flavored (green apple) and dessert flavored (chocolate) e-cigarettes were more satisfying and rewarding than unflavored e-cigarettes (Ref. 52). Furthermore, participants puffed flavored e-cigarettes approximately 40 times compared with approximately 23 times for unflavored e-cigarettes (Ref. 52). Similarly, other research has shown that sweet-flavored e-cigarettes produce higher appeal ratings among youth than non-sweet and flavorless e-cigarettes (Ref. 53).

For cigars/cigarillos/little cigars, waterpipe, and smokeless tobacco products, limited evidence exists that differentiates types of flavors preferred (*e.g.,* menthol, fruit) among young adults. Among young adults (18–24 years of age), the 2013–2014 National Adult Tobacco Survey (NATS) reported the top three flavor types used by product. Young adult flavored smokeless tobacco product users reported using menthol/mint (80.6 percent), fruit (13.9 percent), and clove/spice/herb (7.7 percent) (Ref. 54). Young adult flavored waterpipe users reported using fruit (73.5 percent), menthol/mint (18 percent), and candy/chocolate/other sweet (17.3 percent). Young adult flavored cigar/cigarillo/little cigar users reported using fruit (61.4 percent), alcohol (21.9 percent), and candy/chocolate/other sweet (20.8 percent) (Ref. 54).

6. Adults' Use of Flavors in Tobacco Products

Cross-sectional data from Wave 1 of the PATH Study (Ref. 37) indicate that adult (25 years or older) established tobacco product users also often use flavored products (44.8 percent). Specifically, 35.6 percent of cigarette smokers (menthol), 63.2 percent of ENDS users, 47.8 percent of cigar smokers, 68.7 percent of waterpipe users, and 48.7 percent of smokeless tobacco product users reported use of flavored products at Wave 1 (2013–2014). Among established users of cigarettes and other tobacco products (polyusers), 68.9 percent use at least one flavored product.

The 2013–2014 NATS study data (among adults aged 18 years or older) suggested that the tendency to use flavored e-cigarettes and flavored cigars differed by cigarette smoking status. Never cigarette smokers tended to use flavored e-cigarettes more than other groups. Specifically, findings indicated that, among users of non-cigarette tobacco products, never-cigarette smokers had the highest proportion of flavored e-cigarette use (84.8 percent), followed by 78.1 percent of recent quitters and 63.2 percent of current cigarette smokers. The study also indicated, among users of non-cigarette tobacco products, that 43.8 percent of current cigarette smokers reported smoking flavored cigars, with 30.8 percent of never smokers and 38.9 percent of recent former smokers reporting smoking flavored cigars (Ref. 54). The 2013–2014 NATS study also reported flavor types used by product among adults aged 18 and over. Users of flavored smokeless tobacco reported using menthol/mint (76.9 percent), clove/spice/herb (12.3 percent), fruit (10.8 percent), and candy/chocolate/other sweet (4.5 percent) (Ref. 54). Flavored waterpipe users reported using fruit (74 percent), menthol/mint (18.9 percent), candy/chocolate/other sweet (17.4 percent), clove/spice/herb (4.3 percent), alcohol (3.2 percent), and other flavored (3 percent). Flavored e-cigarette users reported using fruit (44.9 percent), menthol/mint (43.9 percent), candy/chocolate/other sweet (25.7 percent), clove/spice/herb (7 percent), other flavored (6.1 percent), and alcohol flavors (4 percent) (Ref. 54). Flavored cigar, cigarillo, and little cigar users reported using fruit (52.4 percent), candy/chocolate/other sweet (22 percent), alcohol (14.5 percent), menthol/mint (12.9 percent), clove/spice/herb (8.1 percent) and other flavors (2.9 percent). Flavored pipe smokers reported using fruit (56.6

percent), candy/chocolate/other sweet (26.5 percent), and menthol/mint (24.8 percent) (Ref. 54).

Among adult e-cigarette users, a study with experienced exclusive e-cigarette and dual (e-cigarette and cigarette) users (aged 18 years or older) found that bitterness and harshness are negatively associated with liking e-cigarettes, while sweetness and ''coolness'' are positively associated with liking them (Ref. 55). In addition, sweetness appeared to have a greater impact than coolness on liking (Ref. 55).

7. Flavors May Contain or Form Toxic Compounds

Evidence exists regarding the toxicity of flavors, specifically certain ingredients in those flavors that have been used in tobacco products. Of particular concern for combusted or heated tobacco products is that toxicity also may result from the chemicals formed when flavors are heated or burned (Refs. 56 through 60). Diacetyl and acetyl propionyl, which are flavor ingredients that have been found in e-liquids, are highly irritating volatile organic compounds (Refs. 56 and 60). There is scientific evidence showing a link between repeated inhalation exposures to these flavor ingredients and adverse respiratory health outcomes in humans (Ref. 60). Finally, we note that certain substances may be authorized as a food additive or may be considered ''generally recognized as safe'' (GRAS) for certain uses in food. However, being authorized as a food additive or being considered GRAS, in and of itself, does not mean that the substances are safe when used in a tobacco product. The food additive approval or GRAS status of a substance applies only to specific intended uses in food, and are not supported by studies that account for inhalation toxicity. Importantly, exposure to chemicals via the inhalation route can have very different effects from oral exposure, and most tobacco products are inhaled (Ref. 61). For example, direct ''portal of entry'' effects to the respiratory tract, which is relatively more sensitive than the gastrointestinal tract, can occur upon inhalation exposure. There are also important metabolic differences between the two routes of exposure: After oral ingestion, a substance can be detoxified through ''first-pass metabolism'' in the liver before reaching systemic circulation. By contrast, substances introduced into the body via inhalation go directly into systemic circulation without the same potential for detoxification (Ref. 61).

D. The Potential Role of Flavors in Facilitating Transition From Cigarettes to Tobacco Products That May Pose Less Risk

FDA also is aware of self-reported information suggesting that the availability of flavors in some noncombusted tobacco products (*e.g.,* ENDS) may help some adult users decrease their cigarette use and transition away from combusted products to potentially less harmful products (Refs. 62 and 63). Reports from a focus group of eleven e-cigarette users, nine of whom switched to e-cigarettes from smoking a half-pack per day or more of cigarettes, suggest that the ability of consumers to personalize their e-liquids by mixing and matching flavors could contribute to e-cigarette appeal among cigarette smokers (Ref. 62). In one survey using an online convenience sample (*i.e.,* self-selected respondents recruited from online vape forums), respondents indicated that flavor variety was ''very important'' in reducing or quitting smoking (Ref. 63). Almost half of the respondents in that survey indicated that a reduction in available flavors would ''increase craving[s] for tobacco cigarettes and would make reducing or completely substituting smoking less likely'' (Ref. 63).

The issues surrounding the use of flavors in tobacco products involve various considerations. While data show significant youth appeal and continued growth in youth and young adult use of flavored tobacco products, which can lead to lifelong tobacco product use, self-reported information from a study (Ref. 63) shows that some flavors in ENDS may play a positive role in helping some adults transition away from cigarettes to potentially less harmful products. In addition, we note that, currently, no ENDS have been approved as effective cessation aids. In the preamble to the deeming rule, FDA discussed the evidence available to date, and found that some systematic reviews found insufficient data to draw a conclusion about the efficacy of e-cigarettes as cessation aids (81 FR 28973 at 29037). A recent systematic review by the National Academies of Sciences, Engineering, and Medicine found ''limited evidence that e-cigarettes may be effective aids to promote smoking cessation,'' and that ''there is moderate evidence from observational studies that more frequent use of e-cigarettes is associated with increased likelihood of cessation,'' thus, the evidence remains inconclusive (Ref. 64).

II. Requests for Comments and Information

FDA is seeking comments (including comments on this document and the data presented), data, research results, and other information related to the following topics. Please explain your responses and provide any evidence or other information supporting them.

- For the purposes of the questions in this ANPRM, when seeking comments, data, research results, and other information on ''flavors,'' FDA is seeking information relating to the following (as applicable): (1) Artificial or natural flavor additives, compounds, constituents, or ingredients or any other flavoring ingredient in a tobacco product, including its components or parts; (2) the multisensory experience of a flavor during use of tobacco products; (3) flavor representations (including descriptors), either explicit or implicit, in or on the labeling, advertising, and packaging of tobacco products; and (4) any other means that impart flavor or represent that tobacco products are flavored. The foregoing is intended only to provide guidance to commenters and is not intended to limit or restrict the information they may submit. Additionally, for purposes of the questions in the ANPRM:
- ''Youth'' means under age 18; and
- ''Young adult'' means ages 18 through 24.

FDA intends to use the information submitted in response to this **Federal Register** document, its independent scientific knowledge, and other appropriate information to inform regulatory actions FDA might take with respect to flavors in tobacco products. When submitting information, provide evidence by product class (*e.g.,* cigarettes, cigars, pipes) for each topic, when available. If it exists, discuss the influence of flavors by flavor type/category (*e.g.,* fruit, candy, menthol) for each topic. Also, provide information regarding any positive or negative effects that may result from a regulatory action FDA might take with respect to flavors in tobacco products, including, but not limited to, health implications and economic impacts. We ask that commenters clearly identify the section and question number associated with their responsive comments and information.

A. The Role of Flavors (Other Than Tobacco) in Tobacco Products

1. Provide studies or information regarding the role of flavors (other than tobacco) generally in tobacco products. If the response relies on research in other areas (*e.g.,* consumer products),

discuss the appropriateness of extrapolating from such research to tobacco products.

B. Flavors (Other Than Tobacco) and Initiation and Patterns of Tobacco Product Use, Particularly Among Youth and Young Adults

2. Provide studies or information regarding the role of flavors (other than tobacco) in initiation and/or patterns of use of combusted tobacco products, particularly among youth and young adults.

3. Provide studies or information regarding the role of flavors (other than tobacco) in initiation and/or patterns of use of noncombusted tobacco products, particularly among youth and young adults.

4. Provide studies or information regarding the role of flavors (other than tobacco) in noncombusted tobacco products on initiation of tobacco product use or progression to use of other tobacco products (for example, from noncombusted to combusted tobacco products), particularly among youth and young adults.

C. Flavors (Other Than Tobacco) and Cessation, Dual Use, and Relapse Among Current and Former Tobacco Product Users

5. Provide studies or information regarding the role of flavors (other than tobacco) in helping adult cigarette smokers reduce cigarette use and/or switch to potentially less harmful tobacco products.

6. Provide studies or information regarding the role of flavors (other than tobacco) in noncombusted tobacco products on the likelihood of: (1) Cessation of combusted tobacco products use, (2) cessation of all tobacco product use, and (3) uptake of dual use of combusted and noncombusted tobacco products among current and former tobacco product users. Include information from, and define, all populations: Youth, young adults, and adults (and any subgroup thereof, if applicable).

7. Provide studies or information regarding the role of flavors (other than tobacco) in noncombusted products on the likelihood of: (1) Delayed or impeded cessation among users who would have otherwise quit combusted tobacco product use, or (2) delayed or impeded cessation among users who would have otherwise quit all tobacco product use. Include information from, and define, all populations: Youth, young adults, and adults (and any subgroup thereof, if applicable).

8. Provide studies or information regarding the role of flavors (other than tobacco) in noncombusted tobacco products on the likelihood that former combusted tobacco product users relapse. Include information from, and define, all populations: Youth, young adults, and adults (and any subgroup thereof, if applicable).

D. Additional Public Health Considerations

9. Provide studies or information regarding the potential toxicity or adverse health effects to the user or others from any flavors (*e.g.,* flavor additives, compounds, or ingredients) in tobacco products. These adverse health outcomes may include, but are not limited to, cancer or adverse respiratory, cardiac, or reproductive/development effects. Of particular interest are studies or information on inhalation exposure to any flavor. Provide studies or information on what, if any, toxic chemicals might be formed from the heating or burning of tobacco products with flavors and the potential toxicity or health risks that might result from these formed chemicals.

10. Provide studies or information on the impact, whether intended or unintended, of public health efforts by local jurisdictions, States, and members of the international community to impose restrictions on the manufacture, marketing, sale or distribution of all or a subset of tobacco products with flavors (other than tobacco), including but not limited to cigars, ENDS, menthol cigarettes, and smokeless tobacco products.

11. Provide studies or information regarding consumer perceptions of the health risks of tobacco products with flavors (other than tobacco) when compared to other tobacco products, both with and without flavors. Include information from, and define, all populations: Youth, young adults, and adults (and any subgroup thereof, if applicable).

12. Provide studies or information regarding consumer perceptions, if any, of the addictiveness of tobacco products with flavors (other than tobacco). Include information from, and define, all populations: Youth, young adults, and adults (and any subgroup thereof, if applicable).

E. Tobacco Product Standards

13. All Flavors:

a. Are there any specific flavors for which FDA should establish a tobacco product standard? If so, which flavors (*e.g.,* flavor additives, compounds, or ingredients) and why?

b. With respect to your response to the previous question, what level (*e.g.,* maximum, minimum, prohibition) should FDA establish to protect the public health, and why?

14. If FDA were to establish a tobacco product standard prohibiting or restricting flavors, to which types of tobacco products should the standard apply (*e.g.,* combusted, noncombusted, both), and why?

15. Menthol Flavor:

a. FDA has carefully reviewed the data it received in response to the 2013 ANPRM on menthol in cigarettes (78 FR 44484, July 24, 2013). Provide any additional data or information about the role of menthol in cigarettes, particularly regarding the role menthol plays in smoking initiation and in the likelihood of smoking cessation for all populations (youth, young adult, adult).

b. What additional evidence exists on the likelihood that smokers would completely switch to another tobacco product, or start dual use with another product, in the event of a tobacco product standard prohibiting or limiting menthol in cigarettes?

c. What is the role, if any, that menthol plays in use of tobacco products other than cigarettes, including, but not limited to, cigars and ENDS?

F. Sale or Distribution Restrictions

16. FDA may consider restrictions on the sale and distribution of flavored tobacco products. Possible restrictions could include restrictions on the advertising and promotion of tobacco products with flavors; on access to tobacco products with flavors; and/or on the label, labeling, and/or packaging of tobacco products with flavors. These restrictions could include requirements to bear warnings or disclosure statements. What such restrictions, if any, should FDA consider and why?

G. Other Actions and Considerations

17. To the extent that flavors may pose both (1) potential benefits to adult smokers who might consider switching to a noncombusted flavored tobacco product with lower individual risk and (2) potential risks to nonusers who might initiate use of tobacco products through flavored tobacco products or to current users who might progress to flavored tobacco products with higher individual risks, how should FDA assess and balance these benefits and risks?

18. Provide studies or information on the role of tobacco flavor in tobacco products in initiation, patterns of use of tobacco products (particularly with respect to progression from non-combusted to combusted tobacco products or from combusted to non-combusted), reduction in use of

combustible tobacco products and cessation of tobacco products. Include information from, and define, all populations: Youth, young adults, and adults (and any subgroup thereof, if applicable).

19. Provide information on whether manufacturing process(es) affect product flavor. Describe any such manufacturing process(es), including the specific products that use the process(es), as well as specific flavors used in the process(es).

20. Provide analyses regarding any other tobacco product standard, regulatory action, or other action that FDA could implement that you believe would more effectively reduce the harms caused by flavors in tobacco products to better protect the public health than the tobacco product standards or other regulatory actions discussed in the preceding questions.

21. Discuss any other tobacco product standard, regulatory action, or other activity that FDA could pursue that would complement or increase the effectiveness of the potential tobacco product standards or other regulatory actions discussed in the preceding questions.

22. Are there any flavors that especially appeal to youth, young adults, or other specific age group? If so, how are such flavors distinguished from other flavors?

23. To the extent that you have identified a tobacco product standard or other regulatory action in response to the prior questions, provide additional information and comments on: (1) The technical achievability of compliance with the tobacco product standard or other regulatory action you identified; and (2) how FDA could maximize compliance and public health benefits.

24. If FDA were to establish a tobacco product standard prohibiting or restricting flavors in tobacco products, what evidence is there, if any, that consumers would start to flavor their own tobacco products?

25. What data may be used to assess and analyze the range and variety of flavored tobacco products that are currently available to consumers? How can available sources of information, such as manufacturer registrations and/or product listings with FDA, be used in this assessment?

III. References

The following references are on display in the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *https://www.regulations.gov.* FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

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Dated: March 15, 2018.

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DEPARTMENT OF THE INTERIOR

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25 CFR Part 273

RIN 1076–AF24

Education Contracts Under Johnson-O'Malley Act

AGENCY: Bureau of Indian Affairs, Interior.

ACTION: Proposed rule.