FLAVOR AND EXTRACT MANUFACTURERS ASSOCIATION OF THE UNITED STATES
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July 19, 2018

Via Electronic Transmission

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Food and Drug Administration Docket No. FDA-2017-N-6565: Regulation of Flavors in Tobacco Products; Advanced Notice of Proposed Rulemaking. 83 *Fed. Reg*. 12294 (March 21, 2018)

Dear Sir or Madam:

On behalf of the Flavor and Extract Manufacturers Association of the United States (FEMA), we appreciate the opportunity to submit comments in response to the U.S. Food and Drug Administration's (FDA) Advanced Notice of Proposed Rulemaking requesting comments and information regarding the regulation of flavors in tobacco products, 83 *Fed. Reg*. 12294 (March 21, 2018).

I. Introduction

FEMA, founded in 1909, is the Washington, D.C.-based national association of the U.S. flavor industry. FEMA's members include flavor manufacturers, flavor users, flavor ingredient suppliers and others interested in assuring the supply of safe flavoring materials. FEMA members manufacture or market more than 95% of all flavors sold in the United States and create flavors for use in a wide variety of food and beverage products. FEMA is in its 109th year of existence and has a long history of working collaboratively with regulatory authorities, including the FDA.

II. Background

Section 101(b) of the 2009 Family Smoking Prevention and Tobacco Control Act (Pub. L. 111-31) amended the Federal Food Drug and Cosmetic Act (FD&C Act) by providing FDA with the authority to regulate tobacco products. Specifically, Section 901 of the FD&C Act as amended (21 U.S.C. §387a) extended FDA's regulatory authority to "all cigarettes, cigarette tobacco, roll-your-own tobacco and smokeless tobacco and to any other tobacco products that the Secretary [of Health and Human Services] by regulation deems" to be subject to the FD&C Act.[1] As such, in May 2016, FDA issued a final rule deeming additional products that meet the definition of "tobacco product" to be subject to FDA's tobacco product regulatory authority, (81 *Fed. Reg*. 28973 (May 10, 2016). As a result of FDA's 2016 deeming rule, the products now subject to FDA's tobacco product regulatory authority include electronic nicotine delivery systems (ENDS), cigars, waterpipes, pipe tobacco, nicotine gels and dissolvables, and their components. Although FDA's final deeming rule did not prohibit the use of flavors in these products, FDA designated flavors as "components" of ENDS and explained that the agency intended to consider a proposed

[1] *See also* 21 CFR §901(a).

standard that would prohibit characterizing flavors in deemed tobacco products, including ENDS. On March 21, 2018, FDA took its first step to consider such regulatory action by publishing an Advanced Notice of Proposed Rulemaking (ANPR) seeking information from stakeholders on the role flavors play in tobacco products (83 *Fed. Reg*. 12294 (March 21, 2018)).

In recent years, new types of tobacco products like e-cigarettes and other ENDS products have become increasingly popular. These products involve a delivery device through which the user inhales vapor from a mixture of constituents typically including nicotine, flavor and other materials. FDA's ANPR reflects the agency's concern about the increase in use of flavored tobacco products, including ENDS, among American youth as well as the ability of ENDS and other flavored tobacco products to help adult users transition from combustible cigarette use. The agency has important public health issues to consider and FEMA appreciates the opportunity to share the following comments and information with the FDA.

III. The FEMA GRAS Program Does Not Evaluate Flavor Ingredients for Use in Products Other than in Food

In the U.S., the vast majority of flavor ingredients are added to food consistent with the "generally recognized as safe" (GRAS) provision of the FD&C Act. The GRAS provision of Section 201(s) of the FD&C Act applies, however, only to food as defined in Section 201(f) of the Act. For the purposes of the GRAS provision, food is defined as "(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article."[2] More than fifty years ago, FEMA began a program to assess the safety and GRAS status of flavor ingredients under the authority of the 1958 Food Additives Amendment to the FD&C Act.[3] In accordance with the statute, the FEMA GRAS program provides the primary route to achieve regulatory authority to use flavor ingredients in food in the U.S. It is important to note that a FEMA GRAS determination for a flavor ingredient does not constitute "approval" of that substance by FDA.

The FEMA Expert Panel evaluates the safety of flavor ingredients only under their conditions of intended use in food, including beverages and chewing gum. Therefore, the Expert Panel only evaluates flavor ingredients for exposure through ingestion. The Expert Panel does not evaluate flavor ingredients for use in tobacco products such as e-cigarettes or other ENDS devices, other products that are not food, or products that result in exposures other than by ingestion. Therefore, FEMA GRAS status for the use of a flavor ingredient in food does not provide regulatory authority to use the flavor ingredient in e-cigarettes, ENDS devices or other tobacco products in the U.S.

In addition, there are a variety of programs in various countries and geographic regions that evaluate the safety of flavor ingredients, and like the FEMA GRAS program, all of these programs evaluate the safety of flavor ingredients under their conditions of use in food. In Europe, flavor ingredients are evaluated by the European Food Safety Authority (EFSA) solely for their use in food. Also consistent with this principle is the global food safety evaluation program conducted by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) that also evaluates the safety of flavor ingredients solely for their use in food. None of these primary global

[2] 21 U.S.C. §321(f) (2012).

[3] John B. Hallagan and Richard L. Hall, *FEMA GRAS – A GRAS Assessment Program for Flavor Ingredients*, 21 REGULATORY TOXICOLOGY AND PHARMACOLOGY 422, 422 – 430 (1995); John B. Hallagan and Richard L. Hall, *Under the Conditions of Intended Use – New Developments in the FEMA GRAS Program and the Safety Assessment of Flavor Ingredients*, 47 FOOD AND CHEMICAL TOXICOLOGY 267, 268 (2009).

safety assessment programs for flavor ingredients, including the FEMA GRAS program, evaluate flavor ingredients for use in products other than in food and as such evaluate flavor ingredients only for safety upon ingestion.

FEMA has made publicly available on its website a long-standing statement that flavor ingredients are not evaluated by the FEMA Expert Panel for safety and GRAS status for any uses other than use in food (https://www.femaflavor.org/safety-assessment-and-regulatory-authority-use-flavors-focus-electronic-nicotine-delivery-systems). Therefore, use in ENDS and other tobacco products must have separate safety assessments to assure safety and establish regulatory authority to use flavors in such products. FEMA has periodically updated this statement to reflect new regulatory activity related to flavored tobacco products, and to include citations to recent publications known to FEMA regarding flavors and ENDS devices.

IV. Information Relevant to the FDA's Evaluation of the Use of Flavors in Tobacco Products – the Opportunity to Cooperate and Collaborate

Because the FEMA Expert Panel's GRAS evaluations apply only to the conditions of intended use of flavor ingredients in food, FEMA does not focus on scientific information within the FEMA GRAS program related to inhalation exposure to flavors or their use in tobacco products. However, FEMA has collected voluminous scientific information on flavor ingredients over the years and would be pleased to discuss with FDA how FEMA and the agency may cooperate and collaborate on sharing relevant information. A FEMA resource that will be of value to the agency is the FEMA Flavor Ingredient Library on the public portion of the FEMA website (www.femaflavor.org). The Library contains an inventory of all FEMA GRAS flavor ingredients plus supporting information.

While FEMA does not focus on the use of flavors in tobacco products we have followed recent developments and are aware that e-cigarettes and other ENDS devices have generated increasing interest among academic and government researchers, and that many publications are available. In Appendix I, we have listed the citations for a small sample of publications which are known to us that may be helpful to FDA as the agency considers issues related to the use of flavors in tobacco products.

V. Conclusion

FEMA appreciates the opportunity to comment on FDA's Advanced Notice of Proposed Rulemaking regarding the Regulation of Flavors in Tobacco Products and would be pleased to address additional concerns directly with the FDA Office of Tobacco Products.

Sincerely,

John B. Hallagan
Senior Advisor

APPENDIX I

Recent Publications of Interest

Allen J.G., Flanigan S.S., LeBlanc M., Vallarino J., MacNaughton P., Stewart J.H. and Christiani D.C. Flavoring chemicals in e-cigarettes: diacetyl, 2,3-pentanedione, and acetoin in a sample of 51 products, including fruit-, candy-, and cocktail-flavored e-cigarettes. *Environmental Health Perspectives*. 124, 733. 2016.

Anders M.W., Diacetyl and related flavorant α-diketones: Biotransformation, cellular interactions, and respiratory-tract toxicity. *Toxicology*. 388, 21. 2017.

Behar R.Z., Wentai L., McWhirter K.J., Pankow J.F., and Talbot P. Analytical and toxicological evaluation of flavor chemicals in electronic cigarette refill fluids. *Scientific Reports*. May 29, 2018. Available at https://www.nature.com/articles/s41598-018-25575-6.

Canistro, D., Vivarelli F., Cirillo S., Babot Marquillas C., Buschini A., Lazzaretti M., Marchi L., Cardenia V., Rodriquez-Estrada M.T., Lodovici M., Cipriani C., Lorenzini A., Croco E., Marchionni S., Franchi P., Lucarini M., Longo V., Della Croce C.M., Vornoli A., Colacci A., Vaccari M., Sapone A., and Polini M. E-cigarettes induce toxicological effects that can raise the cancer risk. *Scientific Reports*. May 17, 2017. Available at https://www.nature.com/articles/s41598-017-02317-8.

Farley S.M., Schroth K.R., Grimshaw V., Luo W., DeGagne J.L., Tierney P.A., Kim K., and Pankow J.F. Flavor chemicals in a sample of non-cigarette tobacco products without explicit flavor names sold in New York City in 2015. *Tobacco Control*. 27, 170. 2018.

Fetterman J.I., Weisbrod R.M., Feng B., Bastin R., Tuttle S.T., Holbrook M., Baker G., Roberson R.M., Conklin D.J., Bhatnagar A., and Hamburg N.M. Flavorings in Tobacco Products Induce Endothelial Cell Dysfunction. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 7. 2018.

Ganapathy V., Manyanga J., Brame L., McGuire D., Sadhasivam B., Floyd E., Rubenstein D.A., Ramachandran I., Wagener T., Queimado L. Electronic cigarette aerosols suppress cellular antioxidiant defenses and induce significant oxidative DNA damage. *PLoS ONE*. 12, 5. 2017.

Kaur G., Pinkston R., Mclemore B., Dorsey W.C., and Batra S. Immunological and toxicological risk assessment of e-cigarettes. *European Respiratory Review*. 27. 2018.

National Academies of Sciences, Engineering and Medicine. Public health consequences of e-cigarettes. The National Academies Press. 2018. Available at https://www.nap.edu/catalog/24952/public-health-consequences-of-e-cigarettes.

Russell C., McKeganey N., Dickson T., and Nides, M. Changing patterns of first e-cigarette flavor used and current flavors used by 20,836 adult frequent e-cigarette users in the USA. *Harm Reduction Journal*. 15. 2018.

Sommerfeld, C.G., Weiner D.J., Nowalk A., and Larkin A. Hypersensitivity Pneumonitis and Acute Respiratory Distress Syndrome from e-cigarette use. *Pediatrics*. 141, 6. 2018.

Staudt M.R., Salit J., Kaner R.J., Hollmann C., and Crystal R.G. Altered lung biology of healthy never smokers following acute inhalation of e-cigarettes. *Respiratory Research*. 19, 78. 2018.

Tzortzi A., Teloniatis S.I., Matiampa G., Bakelas G., Vyzikidou V.K., Vardavas C., Behrakis P.K., Fernandez E. Passive exposure to e-cigarette emissions: Immediate respiratory effects. *Tobacco Prevention & Cessation.* 4, 18. 2018.

Zhu S.-H., Sun J.Y., Bonnevie E., Cummins S.E., Gamst A., Yin L., and Lee M. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tobacco Control*. 23, iii3. 2016.

Zwack L.M., Stefaniak AS.B., and LeBouf R.F. Evaluation of chemical exposures at a vape shop. NIOSH Health Hazard Evaluation Program. HHE Report 2015-0107-3279. 2018.