

FDA's proposed regulation establishes reasonable tobacco product manufacturing practice requirements that could help minimize the risks of products, especially to youth and young adults

Docket No. FDA-2013-N-0227
Requirements for Tobacco Product Manufacturing Practice

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FDA's proposed regulation¹ establishing tobacco product manufacturing practice requirements for manufacturers of finished and bulk tobacco products is designed to establish controls to prevent or minimize some risks inherent in tobacco products, ensure that products are manufactured in conformance with established specifications, minimize the likelihood that nonconforming tobacco products are manufactured and distributed, require investigating and addressing nonconforming products, prevent contamination of tobacco products, and establish traceability to account for all components and parts, ingredients, additives, and materials to aid in investigations of nonconforming products.

We generally agree with the proposed requirements to the extent that they control the manufacturing and treatment of contaminated or otherwise nonconforming products and prevent mislabeling of products that could confuse or mislead consumers, especially youth and young adults. In particular, we support the proposed approach which ensures that manufacturers consistently produce products that meet all applicable statutory and regulatory requirements, that require packaging and labeling to accurately indicate the nicotine concentration levels in nicotine products, and that requires manufacturers to identify, prevent distribution of, and take other necessary corrective actions for nonconforming, adulterated, or misbranded products.

We offer specific comments on six areas of the proposed regulation that we believe are especially important to protect public health.

- 1. We strongly support finalizing section 1120.92 because it will help prevent the manufacture and distribution of e-liquids and e-cigarettes that contain nicotine concentration levels that differ from the amounts indicated on the labels and will help protect the public health, especially of youth and young adults.**

¹ Food and Drug Administration, Requirements for Tobacco Product Manufacturing Practice, Proposed Rule. 88 FR 15174 (March 10, 2023). Available: <https://www.federalregister.gov/documents/2023/03/10/2023-04591/requirements-for-tobacco-product-manufacturing-practice>

Section 1120.92 is essential to help protect the public health, especially of youth and young adults. This provision requires manufacturers to establish and maintain procedures to control packaging and labeling to ensure that all packaging and labeling comply with all applicable FDA regulations as well as all requirements of the manufacturer's master manufacturing record (MMR), which lays out its tobacco products' established specifications, including all packaging, labeling, and labels approved by the manufacturer for use with the tobacco product. This is especially important to ensure that nicotine concentration labels on e-liquids and e-cigarettes accurately describe the nicotine concentration levels that are contained in the e-liquid and e-cigarette products themselves.

There is considerable evidence that actual nicotine concentrations in e-liquids frequently vary considerably from the labeled concentrations. For example, in a study² of 35 popular e-liquid samples with labels indicating 18 mg/mL nicotine, the samples measured between 11.6 and 27.4 mg/mL nicotine, i.e., the range was from 35% less nicotine to 52% more nicotine than indicated on the labels. In the 35 samples labeled 0 mg/mL, nicotine was detected in 91.4% of the samples, with six samples labeled 0 mg/mL from two manufacturers found to contain nicotine in amounts ranging from 5.7 mg/mL to 23.9 mg/mL. A systematic review³ of peer reviewed articles published worldwide on e-liquid nicotine content accuracy found that 48.3% of samples (277/574) had an analyzed nicotine concentration more than 10% above or below the labeled nicotine concentration. Many studies found that some liquids varied from the label by more than 50%⁴ and some by more than 100%.^{5, 6, 7, 8} Samples purchased from the U.S. had more variation in nicotine content than samples purchased from other countries, with 55% (159/289) of samples from the US mislabeled.

² Raymond BH, Collette-Merrill K, Harrison RG, Jarvis S, Rasmussen RJ. The Nicotine Content of a Sample of E-cigarette Liquid Manufactured in the United States. *J Addict Med.* 2018 Mar/Apr;12(2):127-131. doi: 10.1097/ADM.0000000000000376. PMID: 29280749.

³ Miller DR, Buettner-Schmidt K, Orr M, Rykal K, Niewojna E. A systematic review of refillable e-liquid nicotine content accuracy. *J Am Pharm Assoc* (2020). 2021 Jan-Feb;61(1):20-26. doi: 10.1016/j.japh.2020.09.006. Epub 2020 Oct 2. PMID: 33012670.

⁴ M.C. Guy, P. Pokhrel, T.A. Herzog, et al. How much nicotine is in your electronic cigarette flavored liquid? *Tob Regul Sci*, 5 (1) (2019), pp. 15-26

⁵ Buettner-Schmidt K, Miller DR, Balasubramanian N. Electronic cigarette refill liquids: child-resistant packaging, nicotine content, and sales to minors. *J Pediatr Nurs.* 2016;31(4):373e379.

⁶ Famele M, Palmisani J, Ferranti C, et al. Liquid chromatography with tandem mass spectrometry method for the determination of nicotine and minor tobacco alkaloids in electronic cigarette refill liquids and second-hand generated aerosol. *J Sep Sci.* 2017;40(5):1049e1056.

⁷ Goniewicz ML, Gupta R, Lee YH, et al. Nicotine levels in electronic cigarette refill solutions: a comparative analysis of products from the U.S., Korea, and Poland. *Int J Drug Policy.* 2015;26(6):583e588.

⁸ Raymond BH, Collette-Merrill K, Harrison RG, Jarvis S, Rasmussen RJ. The nicotine content of a sample of E-cigarette liquid manufactured in the United States. *J Addict Med.* 2018;12(2):127e131.

Of further concern, many studies^{9, 10, 11, 12, 13, 14} show that young e-cigarette users frequently misunderstand the strength of nicotine in e-cigarettes and are uncertain whether the e-liquids they use even contain nicotine. These studies show that adolescents and young adults have difficulty understanding nicotine concentrations labeled using the common metrics mg/mL and percent nicotine. Young users often rate concentrations presented as mg/mL as stronger, more addictive, and more harmful than equivalent concentrations presented as percent nicotine.¹⁵ Adults who use e-cigarettes also have difficulty understanding nicotine concentrations presented as either mg/mL or percent nicotine.¹⁶ Clear and accurate labeling is a first step to mitigate this problem.

Inaccurate and ineffective labeling leads to misunderstanding, confusion, and possibly disregard about nicotine in e-cigarette products. Adolescents and young adults often underestimate nicotine strength, which could lead to inadvertent exposure to high nicotine levels.¹⁷ E-liquids that contain a greater amount of nicotine than the label indicates can put the consumer at risk of inhaling more nicotine than intended^{18, 19, 20, 21} increasing the likelihood of addiction.

⁹ Morean ME, Wackowski OA, Eissenberg T, Delnevo CD, Krishnan-Sarin S. Adolescents and Young Adults Have Difficulty Understanding Nicotine Concentration Labels on Vaping Products Presented as mg/mL and Percent Nicotine. *Nicotine Tob Res.* 2021 Aug 4;23(8):1389-1397. doi: 10.1093/ntr/ntab007. PMID: 33433626; PMCID: PMC8496508.

¹⁰ Morean ME, Bold KW, Kong G, et al. Adolescents' awareness of the nicotine strength and e-cigarette status of JUUL e-cigarettes. *Drug Alcohol Depend.* 2019;204:107512

¹¹ McKelvey, Karma, and Bonnie Halpern-Felsher. "How and why California young adults are using different brands of pod-type electronic cigarettes in 2019: implications for researchers and regulators." *Journal of Adolescent Health* 67.1 (2020): 46-52.

¹² Willett JG, Bennett M, Hair EC, et al. Recognition, use and perceptions of JUUL among youth and young adults. *Tob Control.* 2019;28(1):115-116.

¹³ Gorukanti, Anuradha, et al. "Adolescents' attitudes towards e-cigarette ingredients, safety, addictive properties, social norms, and regulation." *Preventive medicine* 94 (2017): 65-71.

¹⁴ Morean ME, Kong G, Cavallo DA, Camenga DR, Krishnan-Sarin S. Nicotine concentration of e-cigarettes used by adolescents. *Drug Alcohol Depend.* 2016;167:224-227.

¹⁵ Morean ME, Wackowski OA, Eissenberg T, Delnevo CD, Krishnan-Sarin S. Adolescents and Young Adults Have Difficulty Understanding Nicotine Concentration Labels on Vaping Products Presented as mg/mL and Percent Nicotine. *Nicotine Tob Res.* 2021 Aug 4;23(8):1389-1397. doi: 10.1093/ntr/ntab007. PMID: 33433626; PMCID: PMC8496508.

¹⁶ Morean ME, Wackowski OA, Eissenberg T, Delnevo CD, Krishnan-Sarin S. Adults who use e-cigarettes have difficulty understanding nicotine concentrations presented as mg/ml and percent nicotine. *Addict Behav* 2021;120:106965

¹⁷ Morean ME, Wackowski OA, Eissenberg T, Delnevo CD, Krishnan-Sarin S. Adolescents and Young Adults Have Difficulty Understanding Nicotine Concentration Labels on Vaping Products Presented as mg/mL and Percent Nicotine. *Nicotine Tob Res.* 2021 Aug 4;23(8):1389-1397. doi: 10.1093/ntr/ntab007. PMID: 33433626; PMCID: PMC8496508.

¹⁸ Buettner-Schmidt K, Miller DR, Balasubramanian N. Electronic cigarette refill liquids: child-resistant packaging, nicotine content, and sales to minors. *J Pediatr Nurs.* 2016;31(4):373e379.

¹⁹ Czoli CD, Goniewicz ML, Palumbo M, White CM, Hammond D. E-cigarette nicotine content and labelling practices in a restricted market: findings from Ontario, Canada. *Int J Drug Policy.* 2018;58:9e12.

²⁰ Kosmider L, Sobczak A, Szołtysek-Bołdys I, et al. Assessment of nicotine concentration in electronic nicotine delivery system (ENDS) liquids and precision of dosing to aerosol. *Przegl Lek.* 2015;72(10):500e504.

²¹ Srbinoska M, Kavrakovski Z, Rafajlovska V, Simonovska J. Determined and declared nicotine content in refill liquids for electronic cigarettes marketed in North Macedonia. *Arh Hig Rada Toksikol.* 2019;70(2):130-133.

Therefore, incorrect nicotine labeling, whether it is labeling that does not accurately reflect the amount of nicotine in the product or labeling that leads to misperceptions, poses a significant risk to consumers, especially adolescents and young adults. As FDA correctly stated in its rationale for the proposed regulation, “this potential variability in nicotine concentration, in which an e-liquid product contains significantly higher levels of nicotine than what is stated on the label, could be misleading to consumers concerned about nicotine delivery levels, potentially intensifying or prolong their addiction and potentially exposing users to increased toxins [references omitted].”²²

To protect the public health, and especially the health of adolescents and young adults, FDA should finalize section 1120.92 of the proposed regulation requiring manufacturers to make sure that all packaging and labeling comply with all applicable FDA regulations as well as with all the tobacco products’ established specifications laid out in their master manufacturing record. These controls will help to prevent mix-ups and to ensure that e-liquid and e-cigarette labels accurately reflect the nicotine concentrations contained in the products.

2. We strongly support finalizing section 1120.44(a)(3) requiring manufacturers to establish and maintain a master manufacturing record (MMR) to keep manufacturers accountable and protect public health.

Proposed section 1120.44(a)(3) would require manufacturers to establish and maintain a master manufacturing record (MMR) containing the established specifications for their tobacco products, including all packaging, labeling, and labels approved by the manufacturer for use with the tobacco product. This provision would help to ensure that the tobacco products are manufactured in conformance with the specifications established in the MMR, comply with all other Family Smoking Prevention and Tobacco Control Act (FSPTCA) requirements, are consistent with specifications contained in the relevant tobacco product applications (including modified risk applications), and comply with tobacco product standards.

The premarket tobacco product application (PMTA) process (FSPTCA Act sections 905 and 910) and the modified risk tobacco product (MRTP) application process (FSPTCA section 911) are cornerstones of the Family Smoking Prevention and Tobacco Control Act. These provisions require manufacturers to demonstrate before selling their products that the marketing of their new tobacco products would be appropriate for the protection of the public health, i.e., would produce net benefits, considering their impacts on current users, former users, and non-users, including adolescents and young adults. PMTA and MRTP applications include detailed descriptions of the products and their components and ingredients, and in the case of modified risk products, include details intended to demonstrate that the product is less harmful or exposes consumers to reduced levels of some toxicants. These provisions would be completely ineffective and meaningless if the actual products manufacturers put on the market do not comply with the specifications detailed in their applications.

²² Food and Drug Administration, Requirements for Tobacco Product Manufacturing Practice, Proposed Rule. 88 FR 15174 at 15179 (March 10, 2023).

We agree with FDA's statement in the preamble to the proposed rule:

"Because the content and design of a tobacco product can directly (e.g., by increasing harmful emissions) or indirectly (e.g., by increasing the addictiveness and the amount of use) contribute to the harm of a product, tobacco products that are manufactured inconsistently with established specifications may cause increased harm to the public health beyond what is normally associated with the product [reference omitted]. Requiring manufacturers to establish product specification and manufacture products that meet those specifications helps minimize harm to public health associated with nonconforming products."²³

Additionally, the proposed regulation would help ensure that the products comply with other regulations under the Tobacco Control Act, including requiring submission and testing of ingredients, additives, and harmful and potentially harmful constituents (FSPTCA sections 904 and 915), complying with applicable tobacco product standards, e.g., a standard prohibiting menthol along with other flavors, a standard setting a reduced level of nicotine) (FSPTCA section 907). Products that are found to be out of compliance could be found to be adulterated (FSPTCA section 902) and/or misbranded (FSPTCA section 903) and face enforcement action.

It is essential to keep manufacturers accountable and ensure that the products they market do, in fact, confer the public health benefits described in their PMTA and MRTP applications and comply with FDA's regulations. Therefore, we support finalizing proposed section 1120.44.

3. We support the risk prevention, mitigation, and treatment requirements included in section 1120.42(a)(1)(ii).

Proposed section 1120.42(a)(1)(ii) would require manufacturers to ensure: (a) their products are consistent with the specifications identified in their marketing authorization applications and orders; (b) their products comply with all regulations under the Tobacco Control Act; and (c) their products conform to the specifications and requirements established in any applicable tobacco product standard. Additionally, this provision would require that each finished and bulk manufacturer treat all identified risks, including risks addressed in applicable tobacco product standards, in a manner that would conform to the specifications and requirements established in the tobacco product standard.

FDA specifically requested comment on whether these are appropriate risks for which risk prevention or mitigation should be required. They are.

Tobacco product standards under FSPTCA section 907 such as flavor restrictions and maximum nicotine levels are created to protect the public health by discouraging initiation, reducing the likelihood of continued use and addiction, encouraging cessation, and otherwise reducing the harms associated with tobacco use. These standards are particularly important to decrease the likelihood that adolescents and young adults, as well as non-users and former users of any tobacco product, do not initiate nicotine use, continue use, and progress to or maintain

²³ Food and Drug Administration, Requirements for Tobacco Product Manufacturing Practice, Proposed Rule. 88 FR 15174 at 15211 (March 10, 2023).

nicotine addiction. We support the proposed regulation because it would help ensure that tobacco products conform to applicable tobacco product standard and help protect public health, especially that of youth and young adults.

4. Proposed section 1120.102 requiring the establishment and maintenance of procedures to ensure that tobacco products are handled and stored under appropriate conditions should be strengthened to require the setting, public disclosure, and enforcement of explicit specifications in the MMR addressing shelf life to ensure that tobacco products that have degraded and/or deteriorated are taken off store shelves and that consumers are notified not to consume the products after the expiration date.

Proposed section 1120.102 requires manufacturers to establish and maintain procedures to ensure that tobacco products are handled and stored under appropriate conditions to prevent nonconforming products as well as mix-ups, deterioration, contamination, adulteration, and misbranding of tobacco products. Requiring manufacturers to establish product specifications and manufacturing methods and procedures is important because it could help reduce the chances of product degradation or adulteration that could render the products harmful to health.

For example, e-cigarettes have finite shelf lives because they become more toxic over time. E-cigarettes often become contaminated with bacteria and fungus that grow while the e-cigarettes sit on the shelf.^{24,25} Additionally, the chemicals in the e-liquid continue reacting with each other after they are mixed,²⁶ growing more toxic over time.²⁷

For these reasons and to protect the public health, proposed section 1120.102 should be strengthened to require the setting of explicit specifications in the MMR describing the specific shelf life to prevent the degradation and/or deterioration of ingredients in tobacco products, especially e-liquids and e-cigarettes. The intended shelf life should also be required to be included in e-liquid and e-cigarette labels. These labels would be required to conform to the specific packaging and labeling controls laid out in proposed section 1120.92.

Including a specific expiration date would allow removal of deteriorated products from store shelves and would warn consumers not to consume the products after a certain date.

²⁴ Lee MS, Allen JG, Christiani DC. Endotoxin and [Formula: see text] Contamination in Electronic Cigarette Products Sold in the United States. *Environ Health Perspect*. 2019 Apr;127(4):47008. doi: 10.1289/EHP3469. PMID: 31017484; PMCID: PMC6785222.

²⁵ Lee MS, Christiani DC. Microbial Toxins in Nicotine Vaping Liquids. *Am J Respir Crit Care Med*. 2020 Mar 15;201(6):741-743. doi: 10.1164/rccm.201911-2178LE. PMID: 31816248; PMCID: PMC7068821.

²⁶ Erythropel HC, Jabba SV, DeWinter TM, Mendizabal M, Anastas PT, Jordt SE, Zimmerman JB. Formation of flavorant-propylene Glycol Adducts With Novel Toxicological Properties in Chemically Unstable E-Cigarette Liquids. *Nicotine Tob Res*. 2019 Aug 19;21(9):1248-1258. doi: 10.1093/ntr/nty192. PMID: 30335174; PMCID: PMC6698951.

²⁷ Jabba SV, Diaz AN, Erythropel HC, Zimmerman JB, Jordt SE. Chemical Adducts of Reactive Flavor Aldehydes Formed in E-Cigarette Liquids Are Cytotoxic and Inhibit Mitochondrial Function in Respiratory Epithelial Cells. *Nicotine Tob Res*. 2020 Dec 15;22(Suppl 1):S25-S34. doi: 10.1093/ntr/ntaa185. PMID: 33320255; PMCID: PMC8224836.

5. Proposed sections 1120.144 should be strengthened to require FDA to refer any petitions for exemption or variance to TPSAC, and to make the petitions available for public comment.

The provisions of Subpart J (proposed sections 1120.140-1120.148) describe the procedures that manufacturers must follow to petition FDA for an exemption or variance from the requirements for tobacco product manufacturing practice. FDA requested specific comment on the kinds of information and/or evidence that would be helpful in determining whether a petition should be granted.

These provisions should be strengthened to explicitly require manufacturers to support their petitions for exemption or variance with scientific data and evidence demonstrating that the requested exemption is appropriate to protect the public health, especially the health of youth and young adults. Of particular concern, any exemption or variance to provisions designed to ensure that product labeling indicating nicotine concentrations accurately reflect the actual nicotine content in the products could be especially harmful to adolescents, young adults, and other new users of e-cigarettes.

Further, proposed section 1120.144 currently provides that FDA “*may*” refer such petitions for exemption or variance to the Tobacco Products Scientific Advisory Committee (TPSAC). This provision should be strengthened to *require* FDA to refer any such petitions to TPSAC, and to make the petitions available for public review and comment.

6. We support FDA’s proposed two-year compliance date.

FDA proposed²⁸ that any final rule become effective two years after the date the final rule publishes in the Federal Register, and specifically requested comment regarding this proposed effective date. We support FDA’s proposed two-year effective date. As FDA describes in the section of the preamble describing the “Development of the Proposed Regulation,”²⁹ manufacturers have been involved in helping FDA develop these regulations since January 2012 so have had more than 11 years to develop and put in place manufacturing controls. As FDA described, the proposed regulations were in fact based on recommendations submitted by the manufacturers. Further, while given these facts, one year would be more than enough time, two years is a reasonable and sufficient period of time for manufacturers to comply.

Conclusion

We generally support FDA’s proposed requirements for tobacco product manufacturing practice which establish reasonable controls for the manufacture, preproduction design validation, packing, storage, and labeling of tobacco products because they will help to protect

²⁸ Food and Drug Administration, Requirements for Tobacco Product Manufacturing Practice, Proposed Rule. 88 FR 15174 at 15239 (March 10, 2023).

²⁹ Food and Drug Administration, Requirements for Tobacco Product Manufacturing Practice, Proposed Rule. 88 FR 15174 at 15182 (March 10, 2023).

public health by taking steps to ensure that tobacco products conform with the manufacturers' stated specifications and are in compliance with existing regulations.

In particular, we offer specific comments on six areas that we believe are especially important to provide greater public health protections, especially to youth and young adults:

1. We strongly support finalizing section 1120.92 because it will help prevent the manufacture and distribution of e-liquids and e-cigarettes that contain nicotine concentration levels that differ from the amounts indicated on the labels and will help protect the public health, especially of youth and young adults.
2. We strongly support finalizing section 1120.44(a)(3) requiring manufacturers to establish and maintain a master manufacturing record (MMR) to keep manufacturers accountable and protect public health.
3. We support the risk prevention, mitigation, and treatment requirements included in section 1120.42(a)(1)(ii).
4. Proposed section 1120.102 requiring the establishment and maintenance of procedures to ensure that tobacco products are handled and stored under appropriate conditions should be strengthened to require the setting, public disclosure, and enforcement of explicit specifications in the MMR addressing shelf life to ensure that tobacco products that have degraded and/or deteriorated are taken off store shelves and that consumers are notified not to consume the products after the expiration date.
5. Proposed sections 1120.144 should be strengthened to require FDA to refer any petitions for exemption or variance to TPSAC, and to make the petitions available for public comment.
6. While one year would provide more than enough time, we support FDA's proposed two-year compliance date.