PROPOSED PRODUCT STANDARDS FOR REDUCED RISK TOBACCO PRODUCTS IN THE UNITED STATES

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EXECUTIVE SUMMARY

The success of tobacco harm reduction in the United States hinges on a navigable regulatory framework that allows manufacturers to provide adult tobacco consumers ("ATCs") with potentially reduced risk tobacco products ("RRPs"). The Family Smoking Prevention and Tobacco Control Act ("FSPTCA") gives the Food and Drug Administration ("FDA" or the "Agency") authority to regulate the manufacture, distribution and marketing of tobacco products in the United States. Regulation benefits ATCs by establishing a common set of rules for all tobacco manufacturers and providing scientific evaluation of potentially less harmful tobacco products.

To receive market authorization for a new tobacco product, the FSPTCA established three distinct product authorization pathways. New tobacco products, those not commercially marketed in the United States as of February 15, 2007, are subject to FDA review through one of three product pathways: Substantial Equivalence ("SE") to a product commercially marketed as of or before February 15, 2007; Exemption from Demonstrating Substantial Equivalence ("SEE") for products with a minor change to a predicate product; or a Premarket Tobacco Product Application ("PMTA"), the most rigorous science- and evidence-based evaluation and the primary avenue for innovative, RRP authorization.

Tobacco product manufacturers and ATCs benefit from foundational product standards, *i.e.*, product standards that, when met, would define a baseline for safety and quality for potential RRPs. This proposal has two goals: 1) to encourage FDA to promulgate foundational product standards under section 907(a)(3) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), as amended by the FSPTCA, that enhance product safety and quality industry wide; and 2) provide industry and regulators with a more efficient PMTA pathway for RRPs.

We propose product standards for three tobacco product categories – Oral Tobacco Derived Nicotine ("OTDN"), Electronic Nicotine Delivery Systems ("ENDS") and Heated Tobacco Products ("HTP") – for which the practical pathway to market is a PMTA. While smokeless tobacco products are also reduced risk as compared to combustible cigarettes, these products are out of scope due to successful authorizations through the SE pathway. Moreover, unlike OTDN, ENDS and, to some extent, HTPs, traditional smokeless products are subject to agricultural variation that makes establishing technically achievable product standards more difficult. For purposes of this document, the term "RRP" refers to novel reduced risk products that cannot use the SE pathway. We provide extensive background to facilitate discussion with a variety of stakeholders.

Product standards currently exist for certain novel RRPs, the majority of which are voluntary standards issued outside of the United States, covering topics from ingredients to testing methodology and battery safety to device performance. We performed an extensive review of these standards as we built our proposed framework. We also considered products currently marketed in the United States for which PMTAs have been authorized, or for which applications are pending, and considered future product development work. It is impossible to create a

universal product standard for every possible iteration of every product, especially for those that are not yet invented. Accordingly, our proposal seeks to establish standards that should be foundational for each product category.

Table I: Summary of Proposed RRP Product Standards

	Oral Tobacco Derived Nicotine	Electronic Nicotine Delivery Systems	Heated Tobacco Products
Nicotine / Nicotine Salts	Pharmaceutical grade	Pharmaceutical grade	N/A (agricultural product)
Product Ingredients and/or Product Components*	Standard toxicological risk assessments (food) Generally Recognized as Safe ("GRAS") for oral consumption Toxicological risk assessment (food) Full quantitative disclosures of ingredients from suppliers	Standard toxicological risk assessments Full quantitative disclosures of ingredients from suppliers Toxicological risk assessment for inhalation (hazard and dose)	Standard toxicological risk assessments Full quantitative disclosures of ingredients from suppliers Toxicological risk assessment for inhalation (hazard and dose)
Constituent / Emission Testing	Nicotine Others as guided by toxicological risk assessment (food)	HPHC testing as recommended in FDA Guidance[+] Others as guided by ingredient and materials risk assessment[+]	HPHC testing (abbreviated list) as recommended in FDA Draft Guidance[++] Combustion markers (CO; NO; NO_x) Others as guided by ingredient and materials risk assessment
Electrical Components / Batteries	N/A	Assessment of potential hazards[+] Certification through industry standard, UL 8139[**]	Assessment of potential hazards Certification through industry standard, UL 8139[**]
Product Stability	Nicotine and nicotine degradants Others as guided by standard toxicological assessment	Nicotine and nicotine degradants Others as guided by standard toxicological assessment	As guided by standard toxicological assessment

* The product standards proposed herein encompass only components that are part of the "tobacco product" as defined by the TCA. They do not reach components that are separate and distinct from the tobacco product.

[+] FDA Guidance for Industry, *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems* (June 11, 2019).

[**] ANSI/CAN/UL 8139 – Electrical Systems of Electronic Cigarettes and Vaping Devices

[++] FDA Draft Guidance for Industry, *Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke* Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act (April 3, 2012).

Under this proposal, FDA would implement foundational product standards, pursuant to Section 907(a)(3) for OTDN, ENDS and HTPs. These product standards will define a baseline for safety and quality for potential RRPs and provide the basis for an abbreviated marketing authorization pathway, satisfying specific statutory PMTA requirements. Congress clearly intended that different levels of regulation would be appropriate for different categories of tobacco products[1] and FDA is sufficiently equipped to implement such accelerated or modified PMTA pathways. FDA has similarly utilized statutory authority in the past to develop flexible approval policies, modified processes, and enforcement discretion policies for certain classes of drugs, medical devices, and other products.

Our proposed framework is designed to facilitate productive engagements with FDA, other tobacco manufacturers, and public health stakeholders that will lead to implementation of these standards, a multi-year process. A successful effort will, ultimately, enhance product safety and provide FDA and tobacco product manufacturers with a more efficient, predictable PMTA process that encourages the development and authorization of RRPs. While there are other factors considered by the Agency in the PMTA process, (*e.g.*, full description of the manufacturing process, human studies for abuse potential, consumer perception, marketing plan and environmental assessment) the product standards proposed here focus only on the safety and quality of the product itself.

[1] For example, § 907(a)(I)(A), establishes special rules for cigarettes, § 907(e) specifically addresses menthol cigarettes, and Section 907(f) specifically addresses dissolvable tobacco products. Additionally, § 911 establishes a separate regime for "modified risk" tobacco products.

INTRODUCTION

FDA regulation of tobacco products is, at its core, intended to protect the public health. FDA pursues this, in part, by implementing policies and programs intended to reduce the use of tobacco products. FDA's vision statement leaves no doubt as to the ambitious nature of this role, stating a goal "[t]o make tobacco-related death and disease part of America's past, not America's future and, by doing so, ensure a healthier life for every family."[2] Establishing a marketplace of satisfying, FDA-authorized, non-combustible products, backed by stakeholder communications about the relative risks of those products, is an essential step towards realizing this goal.

Today, a public health consensus recognizes that there is a continuum of risk among tobacco products, and that products lower in risk than cigarettes have an important role to play in reducing harm for Adult Smokers ("AS").[3] In 2017, FDA announced the Comprehensive Plan for Tobacco and Nicotine Regulation ("Comprehensive Plan"),[4] where the Agency recognized, for the first time, a "continuum of risk" among various nicotine-containing products. That continuum "ranges from combustible cigarettes at one end, to medicinal nicotine products at the other."[5] Then-FDA Commissioner Scott Gottlieb acknowledged "the nicotine in cigarettes is not directly responsible for the cancer, lung disease, and heart disease that kill hundreds of thousands of Americans each year . . . it's the other chemical compounds in tobacco, and in the smoke created by setting tobacco on fire, that directly and primarily cause the illness and death, not the nicotine."[6]

The Comprehensive Plan demonstrated bold leadership by FDA, as the Agency embraced tobacco harm reduction and the goal of converting AS who cannot, or will not, quit combustible cigarettes, to less harmful products. These RRPs, which generally must be authorized through the PMTA pathway, are expected to have lower health risks compared to conventional tobacco

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[2] FDA, Center for Tobacco Products Overview, https://www.fda.gov/tobacco-products/about-center-tobacco-products-ctp/center-tobacco-products-overview (last visited Aug. 11, 2020).

[3] *See, e.g.,* Sherine El-Toukhy, PhD, Kelvin Choi, PhD, MPH, A Risk-Continuum Categorization of Product Use Among US Youth Tobacco Users, *Nicotine & Tobacco Research*, Volume 18, Issue 7, July 2016, Pages 1596–1605, https://doi.org/10.1093/ntr/ntw008; Remarks by Scott Gottlieb, M.D., *Protecting American Families: Comprehensive Approach to Nicotine and Tobacco* (June 28, 2017), *available at* https://www.fda.gov/news-events/speeches-fda-officials/protecting-american-families-comprehensive-approach-nicotine-and-tobacco-06282017 ("[W]e must acknowledge that there's a continuum of risk for nicotine delivery.").

[4] *See* Press Release, FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death (July 27, 2017), *available at* https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regulatory-plan-shift-trajectory-tobacco-related-disease-death; FDA's Comprehensive Plan for Tobacco and Nicotine Regulation, https://www.fda.gov/tobacco-products/ctp-newsroom/fdas-comprehensive-plan-tobacco-and-nicotine-regulation; Scott Gottlieb & Mitchell Zeller, Perspective, A Nicotine-Focused Framework for Public Health, *New Engl. J. Med.*, 2017; 377:1111-1114. DOI: 10.1056/NEJMp1707409.

[5] Remarks by Scott Gottlieb, M.D., *Protecting American Families: Comprehensive Approach to Nicotine and Tobacco* (June 28, 2017), *available at* https://www.fda.gov/news-events/speeches-fda-officials/protecting-american-families-comprehensive-approach-nicotine-and-tobacco-06282017.

[6] *Id.*

products,[7] and certainly as compared to combustible tobacco products, like cigarettes. To be effective in converting AS, RRPs must provide superior sensory experiences and nicotine satisfaction. FDA recognized this fact in evaluating the IQOS® PMTA, where the Agency states, "Nicotine exposures appear sufficient to provide user satisfaction, which can facilitate partial or complete switching to [IQOS]."[8] FDA also stated "[pharmacokinetic] studies show Marlboro, Smooth Menthol, and Fresh Menthol Heatsticks have nicotine delivery, addiction potential, and abuse liability similar to CC [combustible cigarettes]. This is potentially beneficial for smokers trying to switch to IQOS as they are more likely to have satisfactory results and not resume CC smoking."[9]

AS are looking for a range of different product formats, flavors, and nicotine levels, and each of these play a key role in transitioning AS to non-combustible products. To facilitate switching to RRPs, AS must also have access to accurate product risk information. This includes decoupling the significant risk of death and disease caused by smoking from the low risk posed by nicotine itself. This also includes understanding that potential RRPs, while not safe, may pose significantly reduced individual risk of premature death and disease, thus providing a significant benefit to overall public health.[10]

At Altria, our 10-year vision is to responsibly lead the transition of adult smokers to a non-combustible future.[11] To achieve our vision, we are committed to advancing tobacco harm reduction, and we view RRPs as a compelling opportunity for AS and the public health. Reasonable science- and evidence-based RRP standards, combined with a regulatory framework that respects the rights of consumers to accurate and truthful information, to inform product choices, is a critical step in building ATC confidence in RRPs and advancing harm reduction.

FDA Product Pathways and Authority to Establish Product Standards

The FSPTCA established three distinct product authorization pathways, each with unique roles and burdens.[12] These pathways demonstrate Congress' intent to prevent the introduction of new tobacco products that pose greater risk than the existing conventional tobacco products (*e.g.*,

[7] *See* Tobacco Product Marketing Orders, https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/tobacco-product-marketing-orders#1 ("Marketing orders are given to Premarket Tobacco Product Applications that have demonstrated that the new tobacco product is appropriate for the protection of the public health, which is determined with respect to the risks and benefits to the population as a whole, including users and non-users of tobacco products.").

[8] CTP Technical Project Lead Review (TPL) Review of IQOS PMTA: PM0000424, PM0000425, PM0000426, and PM0000479 (April 29, 2019), *available at* https://www.fda.gov/media/124247/download at 49.

[9] *Id.* at 11.

[10] Abrams D, Glasser A., Pearson J., Villanti A., Collins L., and Niaura, R. 2018. Harm Minimization and Tobacco Control: Reframing Societal Views of Nicotine Use to Rapidly Save Lives. Annual Reviews of Public Health. 39:193–213.

[11] Altria, Our 10-Year Vision, https://www.altria.com/about-altria/our-10-year-vision.

[12] FDA released a pre-publication notice for the final SE and PMTA rules on January 19, 2021. FDA subsequently withdrew the pre-publication notices on January 20, 2021 for review and approval by the new administration. FDA should issue final rules and implement the pathways in a manner that advances tobacco harm reduction, clarifies key terms and requirements, and avoids unnecessary review delays. There must be clear rules of the road which allow manufacturers to develop new, potential reduced risk products and invest in scientific research.

combustible cigarettes, smokeless tobacco products and cigars), while also providing market access to innovative RRPs, such as OTDN products, ENDS and HTPs.[13] A more modern and flexible regulatory approach, informed by product standards, would foster the innovation of RRPs and further Congress' intent.

All "new tobacco products," not on the market as of February 15, 2007, must receive FDA authorization through one of these pathways, prior to entering the marketplace. The three pathways are:

1. **Substantial Equivalence ("SE")** – Manufacturers must demonstrate that the new tobacco product (a) has the same characteristics as the predicate tobacco product, or (b) has different characteristics than the predicate tobacco product but does not raise different questions of public health.[14] As implemented by FDA, this pathway requires manufacturers to compare a new tobacco product to a predicate tobacco product or a product previously found by FDA to be substantially equivalent. Congress designed this pathway to be more streamlined and less burdensome than the more exhaustive PMTA pathway. The SE pathway is the primary avenue to market a new conventional tobacco product.
2. **SE Exemption ("SEE")** – Manufacturers must demonstrate that the product has a "minor" change to a tobacco product additive, as compared to a predicate tobacco product.[15] Congress created this pathway to provide an alternative, less burdensome pathway to SE.
3. **Premarket Tobacco Product Application ("PMTA")** – Manufacturers must demonstrate that marketing of the new tobacco product "is appropriate for the protection of the public health."[16] This showing must be made "with respect to the risks and benefits to the population as a whole," taking into account "the increased or decreased likelihood that existing users of tobacco products will stop using such products . . . [and] that those who do not use tobacco products will start using such products."[17] This pathway is intended for entirely new products – those so different from those on the market when the FSPTCA was introduced that they require submission of the most extensive information and data. The PMTA pathway is both the most rigorous and the primary avenue for innovative, RRP authorization.

Moving forward, FDA will consider product applications for a variety of new tobacco products. Some products will merit authorization through the SE pathway because they have the "same

[13] Pub. L. 111-31 (June 22, 2009) §§ 3(4)(7) (purposes of the Act include "continu[ing] to permit the sale of tobacco products to adults in conjunction with measures to ensure that they are not sold or accessible to underage purchasers" and establishing a regulatory framework for promoting "efforts to develop, introduce, and promote less harmful tobacco products").
[14] Federal Food, Drug, and Cosmetic Act ("FDCA") § 910(a)(3)
[15] § 905(j)(3)
[16] § 910(c)(4)
[17] *Id.*

characteristics" as a predicate tobacco product or do not raise "different questions of public health." Other products will warrant authorization through the PMTA pathway under the more demanding "appropriate for the protection of the public health" standard. Since the public health standards for SE and PMTA differ, the information requirements and filing burdens should differ as well, with the burden associated with SE being far less than the science and evidence required for a PMTA.

FDA proposed a PMTA rule[18] and has issued several guidance documents,[19] which collectively articulate FDA's expectations for a successful PMTA. PMTAs must contain extensive product-specific information to satisfy FDA scientific review. A selection of PMTA requirements includes:

- Detailed documentation of the product, including its design, materials, and ingredients;
- Analyses of constituents and emissions, if applicable;
- Assessment of the impact of the product on tobacco use initiation by non-users, including youth;
- Effect of marketing the product on the population as a whole;
- The pharmacological profile of the product, including the impact of nicotine in clinical studies;
- Toxicological profile of the product, which may include preclinical testing for genotoxicity, carcinogenicity, and reproductive toxicity;
- Studies of consumer perception and intent to use;
- Information about how consumers actually use the product and whether users switch from more harmful tobacco products;
- Comprehensive literature search; and
- Detailed description of manufacturing processes.

The differences in information requirements between SE and PMTA result, in part, from the reality that traditional tobacco products have been available for decades, substantial amounts of scientific research describe their risks and use patterns, and versions of traditional tobacco products submitted through the SE pathway are highly similar to their predicate tobacco product counterparts. None of this is the case for RRPs, which must navigate the PMTA pathway. This results in combustible tobacco products, such as cigarettes, facing a lighter regulatory burden and an easier and faster path to market than RRPs. In other words, it is easier, cheaper, and faster to put a new cigarette on the market than an RRP. This is not to suggest that the SE pathway should be made more burdensome. Rather, FDA should take steps to alleviate the regulatory

[18] *See* Premarket Tobacco Product Applications and Recordkeeping Requirements, 84 Fed. Reg. 50,566 (September 25, 2019). FDA released a pre-publication notice for the final PMTA rule on January 19, 2021. FDA subsequently withdrew the pre-publication notice on January 20, 2021 for review and approval by the new administration.
[19] *See, e.g.*, Draft Guidance for Industry, *Applications of Premarket Review of New Tobacco Products* (September 27, 2011), *available at* https://www.fda.gov/media/81821/download; Guidance for Industry, *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems* (June 2019), *available at* https://www.fda.gov/media/127853/download.

burden associated with seeking authorization of RRPs while keeping the scientific rigor of the process.

Today, more than half of AS in the United States are interested in satisfying, less harmful alternatives to cigarettes.[20] This equates to approximately 17 million AS that are interested in RRPs. Congress intended for ATCs to have the ability to choose or switch to RRPs, subject to effective FDA oversight.[21] However, it remains unclear how many of these products will gain market authorization through the PMTA process, as the deadline to submit premarket applications for many of these products was significantly accelerated.[22]

FDA should exercise its authority under section 907(a)(3) of the FDCA, as amended by the FSPTCA, to create product standards for RRPs. These product standards should be class-specific and include science- and evidence-based product stewardship principles that evolve with product innovation. FDA should immediately issue an Advance Notice of Proposed Rulemaking ("ANPRM") to begin the important process of engaging with major stakeholders, including industry and the scientific community.

Compliance with RRP standards would benefit ATCs, manufacturers and the Agency. ATCs benefit from products compliant with foundational safety features and product innovation, manufacturers benefit from clearer regulatory expectations, and the Agency meets its mandate to protect the public health by authorizing a marketplace of tobacco products lower on the continuum of risk than combustible products, while reducing its administrative burden of product application reviews.

To establish a tobacco product standard, FDA must demonstrate that the proposed product standard is "appropriate for the protection of the public health ("APPH"),"[23] when considering all countervailing effects, and is technically achievable. Product standards can bring clarity and efficiency to the PMTA process by setting baseline parameters for an APPH determination. Product standards currently exist for certain novel RRPs, the majority of which are voluntary standards issued outside the United States (*see* Appendix A for a representative sampling). Here, we provide a science- and evidence-based framework for RRP standards and discuss, in detail, some examples of reasonable and achievable RRP standards.

[20] ALCS analysis of PATH Wave 1 data, Sept. 12, 2013 – Dec. 14, 2014; Response to question – "If a tobacco product made a claim that it was less harmful to health than other products, how likely would you be to use that product?"
[21] *See* FSPTCA § 3(4); FDCA § 911.
[22] *See American Academy of Pediatrics, et al. v. U.S. Food and Drug Admin.* No. 8:18-cv-00883-PWG (D. Md. July 12, 2019).
[23] FDCA § 907(a)(3)

I. FDA SHOULD ADOPT A REGULATORY APPROACH, INFORMED BY PRODUCT STANDARDS, THAT MAXIMIZES THE HARM REDUCTION POTENTIAL OF REDUCED RISK PRODUCTS

While no tobacco product is safe, efforts should be made to reduce the risk associated with tobacco product use. As observed more than 40 years ago, and as recognized by FDA in 2017,[24] "[p]eople smoke for nicotine but they die from the tar."[25] In satisfying their desire for nicotine, smokers subject themselves to increased risks of premature death and disease (*e.g.*, heart attack, stroke, cancer, chronic obstructive pulmonary disease) through their continued use of combustible tobacco products, predominantly cigarettes. It is here, in the manner of nicotine delivery, where the greatest potential for reducing or minimizing the harm caused by cigarettes lies.

FDA's Comprehensive Plan acknowledges that AS, who cannot or will not quit, should have access to acceptable RRP alternatives that are substantiated through science and evidence.[26] RRP standards will enhance product safety and quality and, if implemented correctly, allow these products to move through the pathways more effectively. This alone, will not be enough to convert AS; rather, ATCs must find these products satisfying, and they must receive accurate relative risk information to inform product choices.

FDA should implement product standards that facilitate the innovation of potential RRPs and allow such products to enter the market more rapidly. FDA noted in the Deeming Rule that the "majority of ENDS submissions will be PMTAs."[27] Other potential RRPs, such as OTDN products, HTPs, and any other future innovative products, will require the PMTA pathway as well. Therefore, a manufacturer's ability to navigate the PMTA pathway is central to tobacco

[24] *See* Press Release, FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death (July 27, 2017), *available at* https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regulatory-plan-shift-trajectory-tobacco-related-disease-death; Remarks by Scott Gottlieb, M.D., *Protecting American Families: Comprehensive Approach to Nicotine and Tobacco* (June 28, 2017), *available at* https://www.fda.gov/news-events/speeches-fda-officials/protecting-american-families-comprehensive-approach-nicotine-and-tobacco-06282017; FDA's Comprehensive Plan for Tobacco and Nicotine Regulation, https://www.fda.gov/tobacco-products/ctp-newsroom/fdas-comprehensive-plan-tobacco-and-nicotine-regulation; Scott Gottlieb & Mitchell Zeller, Perspective, A Nicotine-Focused Framework for Public Health, *New Engl. J. Med.*, 2017; 377:1111-1114. DOI: 10.1056/NEJMp1707409.

[25] *See* Russell MA. 1976. Low-tar medium-nicotine cigarettes: a new approach to safer smoking. British Medical Journal 1:1430–33. pp 1431.

[26] Press Release, FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death (July 27, 2017), *available at* https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regulatory-plan-shift-trajectory-tobacco-related-disease-death ("Envision[] a world . . . where adults who still need or want nicotine could get it from alternative and less harmful sources. . .").

[27] FDA, Deeming Tobacco Products to be Subject to the Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Regulations Restricting the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Product Packages and Advertisements; Final Regulatory Impact Analysis; Final Regulatory Flexibility Analysis; Final Unfunded Mandates Analysis, Docket No. FDA-2014-N-0189 at 78, *available at* https://www.fda.gov/media/97875/download.

harm reduction. The PMTA pathway must maintain scientific rigor while not being so burdensome that it prevents innovative RRPs from entering the market.[28]

Similarly, FDA should avoid product standards that are overly restrictive as this would severely undermine tobacco harm reduction by simply preventing successful innovation. Product standards that are overly restrictive or place impractical regulatory hurdles could also feed an illicit market. In 2018, FDA recognized that banning or limiting products may drive illegal activity, soliciting public comment regarding "the potential for illicit trade markets to develop in response to a tobacco product standard."[29]

In the Proposed PMTA Rule, FDA recognized the importance of providing an accelerated authorization process for modifications to products that have been previously determined to be "appropriate for the protection of the public health."[30] FDA should continue to develop PMTA format alternatives that "would reduce the burden associated with the submission and review of an application."[31]

FDA's interpretation of the APPH standard is central to its implementation of the PMTA pathway. The standard must be clearly articulated and predictably applied. Product standards can bring clarity and efficiency to the PMTA process by setting baseline parameters for an APPH determination. Similarly, demonstrating compliance with a specific product standard (through a manufacturer's certification or otherwise) may alleviate the amount of product-specific information required in a PMTA. For example, a manufacturer of an OTDN product using pharmaceutical grade nicotine and Generally Recognized as Safe ("GRAS") ingredients may not need to provide Harmful and Potentially Harmful Constituent ("HPHC") testing (other than nicotine) or a full toxicological evaluation of ingredients. This does not alleviate the manufacturer from submitting a PMTA or providing sufficient information and data to demonstrate that the product is APPH or reduce the overall scientific burden of the PMTA process. It merely reduces the administrative burden on the manufacturer and facilitates a more efficient review by FDA, who otherwise would have to provide and review data or other scientific evidence for a PMTA product information requirement that could be evaluated by showing compliance with a product standard.

Additionally, manufacturers should not be required to submit a new PMTA, Supplemental or otherwise, to demonstrate that an FDA-authorized product, or a product that FDA has already

[28] The FDA recognizes that regulatory burdens limit market access. The final Regulatory Impact Analysis for the Deeming Rule predicts that "54 percent of delivery systems and somewhere between 50 and 87.5 percent of e-liquids will not submit a marketing application and will exit the market." FDA, Deeming Tobacco Products to be Subject to the Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Regulations Restricting the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Product Packages and Advertisements; Final Regulatory Impact Analysis; Final Regulatory Flexibility Analysis; Final Unfunded Mandates Analysis, Docket No. FDA-2014-N-0189 at 78, *available at* https://www.regulations.gov/document?D=FDA-2019-N-2854-0070.
[29] 83 Fed. Reg. 11,754 (March 16, 2018).
[30] 84 Fed. Reg. at 50,611-13.
[31] 84 Fed. Reg. at 50,611.

determined to be "appropriate for the protection of the public health," complies with a ***new*** product standard – a standard that was implemented ***after*** the Agency reached its "appropriate for the protection of the public health" determination. FDA will have already determined that the standard is "appropriate for the protection of the public health" for the products to which it applies. Modifications to comply with an applicable new standard will not require the same evaluation as a typical PMTA or Supplemental PMTA. Rather, manufacturers should be allowed to certify that modifications were made to comply with an applicable product standard, if implemented.

Adopting such a policy is consistent with FDA Guidance, which recognized the importance of providing efficient premarket pathways for modifications that enhance safety.[32] In November 2019, FDA announced that it would exercise enforcement discretion for product modifications that satisfy a specific battery standard because it would encourage manufacturers to comply with an established standard that "enhances consumer safety, minimizes battery-related injuries and mitigates potential risks."[33] Importantly, under this Guidance, FDA provided manufacturers the opportunity to modify products to comply with this standard without a PMTA submission requirement, demonstrating how product standards can inform flexible pathway execution.[34] Any requirement beyond a certification of compliance would be needlessly burdensome and would unnecessarily delay consumer access to RRPs that are appropriate for the protection of the public health and satisfy the new product standard.

II. FDA SHOULD PROMULGATE FOUNDATIONAL SCIENCE- AND EVIDENCE-BASED PRODUCT STANDARDS FOR REDUCED RISK PRODUCTS THAT REFLECT A PRODUCT STEWARDSHIP APPROACH

Novel RRPs are fundamentally different than traditional tobacco products in their form and function. Even within the broader RRP category, products range in complexity from simple products containing only tobacco derived nicotine and flavor in an inert base (*e.g.*, OTDN) to complex electrical devices with liquids containing tobacco derived nicotine or a tobacco substrate (*e.g.*, ENDS, HTPs).

FDA should promulgate product standards to maximize the harm reduction potential of RRPs.[35] For RRP standards to be effective in protecting public health, the standards must be supported by science and evidence. Product stewardship principles are key to enhancing RRP safety and quality industry wide.

Product stewardship is a broad description of a process by which to manage product lifecycle from design to disposal.[36] Here, we focus on a toxicological framework for minimizing potential

[32] Guidance for Industry, *Compliance Policy for Limited Modifications to Certain Marketed Tobacco Products* (November 26, 2019), *available at* https://www.fda.gov/media/133009/download.
[33] *Id.*
[34] *Id*.
[35] Lee PA. 2020. Estimating the population health impact of recently introduced modified risk tobacco products: a comparison of different approaches. Nicotine & Tobacco Research. 2020. https//:doi.org/10.1093/ntr/ntaa102
[36] *See* What is Product Stewardship, *available at* https://www.productstewardship.us/.

RRP risks by pragmatically evaluating product ingredients and product components (*e.g.*, flavors, carriers, components of ENDS in contact with e-liquids) and the resulting chemical characterization of the products. A systematic quantitative risk assessment of each product ingredient and product component followed by a quantitative risk assessment of exposure to constituents (*e.g.*, TSNAs, nicotine, formaldehyde, as appropriate) is the backbone of any toxicological review for product stewardship. For each RRP category, we demonstrate how these concepts are applied consistently throughout the toxicological assessment.

Risk assessment is highly dependent on two factors. First, the route of exposure to the product is paramount. Toxicological concerns differ between oral exposure and inhalation. One example – acetaldehyde – is listed by FDA as a HPHC in combustible products but is designated as GRAS for use in food.[37, 38] The route of exposure toxicity must be evaluated. In the case of OTDN products, GRAS designation followed by a quantitative risk assessment may suffice. On the other hand, inhaled products may require further examination, specifically related to inhalation effects. Second, the consumption patterns of the product are integral to the exposure assessment of any product. In quantitative risk assessments, less exposure produces less risk.

While there are inherent differences in toxicological concern between oral and inhaled products/aerosols, in the sections below we first discuss products using tobacco derived nicotine (OTDN and ENDS where applicable), followed by HTPs. We outline reasonable, science- and evidence-based product stewardship principles and their application to RRPs, beginning with the least complex, OTDN products, since many of these principles will also apply to more complex categories like ENDS and HTPs.

III. PROPOSED PRODUCT STANDARDS FOR ORAL TOBACCO DERIVED NICOTINE (OTDN) PRODUCTS

OTDN products do not contain tobacco. Today, these products exist in several formats – pouch, lozenge or gum. OTDN products are designed to be placed into the oral cavity and are either held or masticated for a period of time; then, the products are either removed to discontinue use or may be designed to be fully ingested. Since OTDN products are neither combusted nor contain tobacco, tobacco-related and combustion-related HPHCs, with the exception of nicotine, are not applicable.[39]

Manufacturers, without Agency guidance on HPHCs for this product category, have compared HPHCs in OTDN products to combustible and smokeless tobacco products, in order to demonstrate the APPH standard for PMTA authorization. The resulting data demonstrated either

[37] *See* Draft Guidance for Industry, *Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act* (April 3, 2012), *available at* https://www.fda.gov/media/83375/download at 4;
[38] Generally Recognized as Safe (GRAS) FDA Voluntary Program, https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras.
[39] Draft Guidance for Industry, *Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act* (April 3, 2012), *available at* https://www.fda.gov/media/83375/download.

substantially lower or absent HPHCs compared to mainstream cigarette smoke and smokeless tobacco products, including snus, which has received MRTP authorization.[40]

FDA should consider four key principles in developing RRP standards for OTDN products. These principles, discussed in detail in subsequent sections, are as follows.

- Nicotine and/or nicotine salts used in OTDN products should be pharmaceutical grade;
- OTDN ingredients should be GRAS and of suitable quality for use in food (i.e., food grade);
- Manufacturers should evaluate OTDN product stability.

A new OTDN product that can demonstrate compliance with these principles, through a manufacturer's certification, reduces the regulatory burden for the applicant and FDA, and may be authorized through the PMTA pathway if the remaining statutory requirements are met.

A. Nicotine and/or nicotine salts used in OTDN products should be pharmaceutical grade

USP grade nicotine conforms to the International Conference on Harmonization ("ICH") Guidance Q3B(R2).[41] This standard minimizes contaminants and ensures nicotine content consistency. While nicotine has the potential to be acutely toxic at high levels, its toxicity is dose-limiting. Symptoms such as nausea, vomiting and dizziness provide feedback to modify behavior.[42, 43, 44]

B. OTDN ingredients should be GRAS and of suitable quality for use in food (*i.e.*, food grade)

The route of exposure to OTDN products is the same as for food. Decades of toxicological data and assessments exist for this category. Therefore, ingredients, including natural extracts, with acceptable purity (*e.g.*, pharmaceutical, food grade ingredients deemed as GRAS and produced according to current Good Manufacturing Practices ("cGMPs"), should be used in the manufacture of OTDN products.[45]

These designations guarantee that ingredients are manufactured according to a quality system that ensures consistency, adherence to manufacturing specifications, establishes traceability and

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[40] *FDA Authorizes Modified Risk Tobacco Products,* https://www.fda.gov/tobacco-products/advertising-and-promotion/fda-authorizes-modified-risk-tobacco-products.

[41] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), *Impurities in New Drug Products*, (July 2006) Revision 2.

[42] Aubin et al., Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomized open-label trial. Thorax 2008; 63:717–724.

[43] Greenland et al, A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. Drug Safety1998; 18:297-308.

[44] Marsh et al., Safety profile of a nicotine lozenge compared with that of nicotine gum in adult smokers with underlying medical conditions: A 12-week, randomized, open-label study. Clin. Ther. 27:1571-1587.

[45] 21 CFR 117 - Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls For Human Food; *accessible at* https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=117&showFR=1

minimizes potential contamination during their manufacture, storage, and shipping. Further, any compounds that have been identified as carcinogenic, mutagenic or toxic to reproduction ("CMR") or teratogenic should not be used. Additionally, any chemical listed by the International Agency for Research on Cancer ("IARC") as a Group 1, 2A or 2B carcinogen should not be used. There may be some limited exceptions – for example, while ethanol is listed as a Group 1 carcinogen based on its overuse in alcoholic beverages, it is a common solvent for flavors, and the dose should be used to determine its suitability for use as it is clearly a threshold carcinogen.

Additionally, full quantitative disclosures of each ingredient as well as all the vendor documentation attesting to material quality and suitability for use in food/USP should be obtained. Quantitative disclosures are necessary to complete quantitative risk assessments as flavor recipes from suppliers can be comprised of a multitude of different chemical entities, and some of these entities may overlap between different formulations. It is important to produce a precise quantitative "roll-up" of each separate chemical entity to perform a risk assessment.

Even though each ingredient should be GRAS or pharmaceutical grade, the basis for the GRAS designation may not be based on toxicological data.[46] Therefore, a thorough literature review should be conducted on each chemical entity in the quantitative "roll-up." In this hazard identification and dose-response assessment, Acceptable Daily Intake ("ADI") levels set by JECFA, PADIs disseminated by FEMA and any other relevant determinations of safety-in-use (*e.g.*, Point of Departure ("PODs"), No-Observed-Adverse-Effect-Levels ("NOELs") - accompanied by appropriate uncertainty factors) should be used for the purposes of risk characterization. In some cases, it may be necessary to consider a sum total class of compounds (meaning multiple flavor chemicals with similar structures) to develop a relative margin of safety. Margins of safety for each compound or class of specific compounds should be greater than 1.[47]

The toxicological assessment of ingredients for OTDN products should be closely guided by the same process applied within the food industry. Within Part 21 of the Code of Federal Regulations ("CFR"), FDA has identified chemicals that are safe for use as food additives, as set forth in the appropriate section of Part 21 for their material type. For instance, any polymeric ingredients should conform to 21 CFR 177, and the supplier of these ingredients should be able to produce food grade statement documents as well as compliance with cGMPs.

C. Manufacturers should evaluate OTDN product stability

The toxicological assessment of ingredients, including the potential for ingredient chemistry, determines the necessity for, and extent of, stability studies. For products in which pharmaceutical grade nicotine is the nicotine source, nicotine impurities and degradants should

[46] Costigan, S. and Meredith, C. An approach to ingredient screening and toxicological risk assessment of flavors in e-liquids. Regulatory Toxicology and Pharmacology. 72 (2015) 361-369.
[47] The margin of safety is calculated using the ratio of the derived reference dose (*i.e.*, ADI RfD, NDEL) to the predicted, or estimated human exposure level or dose.

be measured throughout the product retail shelf life to ensure nicotine impurities or degradants remain within acceptable ranges (*i.e.*, for accurate labeling). FDA should promulgate product standards, with appropriate guidance, to inform manufacturers on the evaluation of product/nicotine impurities. While OTDN products are not pharmaceutical, an approach consistent with the International Conference on Harmonization ("ICH") Guidance Q3B(R2),[48] is a reasonable and appropriate approach for evaluating nicotine stability and establishing a threshold of acceptable levels for possible degradation products in the absence of direct guidance by FDA. Other FDA centers, including the Center for Drug Evaluation and Research ("CDER") and the Center for Biologics Evaluation and Research ("CBER") have adopted this guidance. Total nicotine-related impurities should be based on specifications of the European Pharmacopeia Council of Europe (2012). At reasonable stability protocol intervals, evaluation of stability for OTDN products may include pH, major ingredients, nicotine degradants, and microbial activity, if applicable.

Any analytical testing for chemical constituents should use internationally recognized or consensus methods. When not available, methods should be validated as suitable for use. In addition, testing should occur in laboratories following internationally recognized standards (*e.g.*, ISO/IEC 17025) and accredited by a recognized accreditation body (*e.g.*, American Association for Laboratory Accreditation).[49] As discussed above, OTDN products are neither combusted nor contain tobacco, and as such, tobacco-related and combustion-related HPHCs, with the exception of nicotine, are not applicable.

IV. PROPOSED PRODUCT STANDARDS FOR ELECTRONIC NICOTINE DELIVERY SYSTEMS (ENDS)

The basic components of ENDS are a power source (*i.e.*, battery), a heating element, and a liquid reservoir, which is filled with an e-liquid formulation ("e-liquid"). The interaction of the e-liquid, the materials that contact both the aerosol and the e-liquid, and the energy management of the device (*e.g.*, battery voltage) dictate the aerosol composition. Consumers are exposed to this aerosol ("e-vapor") when they use an ENDS as intended. Three distinct facets of ENDS are integral to its nonclinical evaluation: device, e-liquid(s), and the ENDS product (*i.e.*, the combination of a device and e-liquid).

FDA Guidance states that "knowing the full assessment of the toxicological effects of your ENDS product (*e.g.*, ingredients, product components, use of the product) is important to assess the health effects on users and nonusers."[50] Additionally, in order to evaluate health effects of the products, Section VI(H)(2) of the Guidance recommends that "(i)nformation on both nonclinical and clinical investigations should be provided, including, but not limited to, any

[48] ICH Guidance Q3B(R2) – Impurities in New Drug Products, July 2006 Revision 2 (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2006)
[49] ISO/IEC 17025
[50] Guidance for Industry, *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (ENDS)* (June 11, 2019), *available at* https://www.fda.gov/media/127853/download at 12.

studies assessing constituents of tobacco, tobacco smoke, or aerosol, toxicology, consumer exposure, and consumer use profiles."[51] ENDS should be designed using rigorous design principles, including toxicological assessment of formulation ingredients and product components and, operation consistency, proprietary connection, limited battery output, failure mode effects, hazards assessment and overall product stability, when deemed appropriate by toxicological assessment.

FDA should consider four key principles in developing RRP standards for ENDS.[52] These principles, discussed in detail in subsequent sections, are as follows.

- Nicotine and/or nicotine salts used in ENDS should be pharmaceutical grade;
- ENDS ingredients should follow standard toxicological assessments;[53]
- ENDS emissions should be characterized over a range of operating conditions; and
- Manufacturers should evaluate ENDS stability.

A new ENDS that can demonstrate compliance with these principles, through a manufacturer's certification, reduces the regulatory burden for the applicant and FDA, and may be authorized through the PMTA pathway if the remaining statutory requirements are met.

A. Nicotine and/or nicotine salts used in ENDS should be pharmaceutical grade

Standardization of nicotine purity minimizes contaminants and ensures nicotine content consistency. While nicotine has the potential to be acutely toxic at high levels, dose-limiting toxicity (*e.g.*, nausea, vomiting and dizziness) from nicotine may be expected.[54,55,56]

B. ENDS ingredients and ENDS components should follow standard toxicological assessments

[51] *Id.* at 31.
[52] A recent publication of the Administration's Unified Regulatory Agenda ("URA") included a potential product standard for ENDS. *See* "ENDS Safety Standards, Including Standards for Toxicants and Impurities in Nicotine, Propylene Glycol, and Vegetable Glycerin Used in E-Liquids; Tobacco Product Standard," https://www.reginfo.gov/public/do/eAgendaViewRule?pubId=202004&RIN=0910-AI06. This rule, if finalized, would implement "regulations to establish tobacco product standards for electronic nicotine delivery systems (ENDS), to include, among other things, standards for nicotine, propylene glycol, and vegetable glycerin purity in e-liquid. This rule, if finalized, would, among other things, establish limits on the level of toxicants and impurities found in nicotine, propylene glycol, and vegetable glycerin. Toxicants and impurities found in nicotine, propylene glycol, and vegetable glycerin can cause death or other adverse health effects, and this rule would establish limits on the level of those toxicants that are appropriate for the protection of public health." *Id.*
[53] The product standards proposed herein encompass only components that are part of the "tobacco product" as defined by the TCA. They do not reach components that are separate and distinct from the tobacco product.
[54] Aubin et al., Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomized open-label trial. Thorax 2008; 63:717–724.
[55] Greenland et al, A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. Drug Safety1998; 18:297-308.
[56] Marsh et al., Safety profile of a nicotine lozenge compared with that of nicotine gum in adult smokers with underlying medical conditions: A 12-week, randomized, open-label study. Clin. Ther. 27:1571-1587.

While GRAS designations do not exist for inhalable products, the process described above for ingredients in OTDN products should serve as a best practice guide to begin the toxicological review process for e-vapor product ingredients. As with OTDN products, full quantitative disclosures of each ingredient as well as all the vendor documentation attesting to quality and suitability for use in food/USP should be obtained. Quantitative disclosures are necessary to complete quantitative risk assessments, as flavor recipes from suppliers can be comprised of a multitude of different chemical entities, and some of these entities may overlap between different formulations. It is important to produce a precise quantitative "roll-up" of every separate chemical entity to perform a risk assessment.

E-vapor aerosols are inhaled. Thus, route of exposure and local (*i.e.*, lung specific) effects must be considered. Costigan and Meredith (2015) outlined general considerations for e-vapor ingredients, including the steps outlined here, as well as recommendations on excluding ingredients that are respiratory sensitizers, and minimizing the use of natural flavor ingredients (*e.g.*, oils, oleoresins, extracts) due to the complexity of characterizing these ingredients on a chemical basis as well as consistency over time, as they are derived from agricultural products.[57]

If sufficient safety-in-use data for an ingredient via inhalation does not exist, either ingredient or final product aerosol toxicological studies will be necessary to demonstrate that there is no biologically significant increase in toxicity, compared to cigarettes. Standard toxicological assays, in particular the Ames reverse mutation assay,[58] the neutral red uptake cytotoxicity assay,[59] the in vitro micronucleus assay,[60] and the 90-day in vivo inhalation assay,[61] provide valuable toxicological data that develop the weight of evidence for the safety-in-use of ingredients. Expert judgement in the application of these assays should dictate which assay or combination of assays is necessary to answer the particular toxicological question(s).

FDA should invest in the development and utilization of *in vitro*-based toxicity testing, according to FDA's Tox21 roadmap and 3R's principle of reducing the use of animal testing. FDA's involvement in the development of these methodologies must culminate with the acceptance of these methods in their regulatory review process for new tobacco product applications. A significant opportunity exists to develop, through curating the publicly available inhalation data as well as data supplied to FDA in the form of applications, a list of ingredients where sufficient data exist such that further *in vivo* testing may not be required.

The overall risk assessment of each ingredient integrates the hazard identification and dose response assessments with estimated human exposure data from behavioral or market data. These data can then be compared to acceptable daily intakes, thresholds of concern or other measures of human health impact. Examples of such comparators are health-based occupational

[57] Costigan, S. and Meredith, C. An approach to ingredient screening and toxicological risk assessment of flavors in e-liquids. Regulatory Toxicology and Pharmacology. 72 (2015) 361-369.
[58] OECD TG 471 www.oecd.org
[59] OEC TG 129/432 www.oecd.org
[60] OECD TG 487 www.oecd.org
[61] OECD TG 413 www.oecd.org

exposure values, derived no adverse effect levels from inhalation studies, and the threshold of toxicological concern of 1.5 µg/day which is used across regulated industries as an acceptable level of lifetime exposure to chemicals – including mutagenic compounds – and is applicable to all routes of exposure. Margins of safety for each compound or class of specific compounds should be greater than 1.[62] Like flavor and non-flavor ingredients, ENDS components should be closely guided by toxicological risk assessment and/or physical testing (*e.g.,* leachable and extractables testing) to demonstrate the absence of toxicological concern for each device component under use conditions. For example, ENDS components in contact with e-liquid should have acceptable levels of potentially toxic impurities (*e.g.,* lead) and the product manufacturer should confirm appropriate supplier controls are in place to ensure device component quality. Device component-specific testing may be used to pre-screen materials prior to completing more intensive analytical and biological investigations and determine material interchangeability (*i.e.,* equivalence between different suppliers of the same device component).[63]

C. ENDS emissions should be characterized over a range of operating conditions

FDA recommends providing "the chemical and physical identity and quantitative levels of the emission of aerosols under the range of operating conditions (*e.g.*, various temperature, voltage, wattage settings) and use patterns (*e.g.*, intense and non-intense use conditions) within which consumers are likely to use the new tobacco product."[64] The Agency has also provided a list of 33 chemicals commonly found in ENDS.[65] This type of information can be provided by measuring constituent or chemical yields in the product or, where the constituent or chemical recommended by the agency are ingredients, *e.g.*, nicotine, providing the quantity added to the e-liquid.

Testing should reflect the range of operating conditions (*e.g.,* various temperature, voltage, wattage settings) and use patterns (*e.g.,* intense and non-intense use conditions) within which consumers are likely to use the product. Evaluating new tobacco products under a range of conditions, including both non-intense (*e.g.,* lower levels of exposure and lower volumes of aerosol generated) and intense (*e.g.,* higher levels of exposure and higher volumes of aerosol generated), enables the Agency to understand the likely range of delivery of emissions. The two regimens provide the Agency with information about possible different deliveries of constituents, including the range of quantities of constituents.

[62] The margin of safety is calculated using the ratio of the derived reference dose (*i.e.*, ADI RfD, NDEL) to the predicted, or estimated human exposure level or dose.

[64] Guidance for Industry, *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems* (June 11, 2019), *available at* https://www.fda.gov/media/127853/download.
[65] *Id.*

Knowledge physiochemical properties of product ingredients and product components and whole product performance can be used to determine if additional testing, such as Non-Targeted Analysis, is necessary. Non-Targeted Analysis ("NTA") may become necessary to assess additional compounds not directly measured during targeted analyses, such as potential degradation or reaction products created during typical use conditions. NTA is a semi-quantitative screening study, and complementary NTA techniques, such as gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry, may be necessary to achieve a comprehensive aerosol characterization. If NTA is employed, compounds identified should be evaluated by a toxicological risk assessment. If compounds identified do not have robust data from which to draw compound-specific toxicological data, QSAR, read across and derived values such as a threshold of toxicological concern ("TTC") such as 1.5 µg/day as established by ICH (2014) should be used to complete the risk assessment. The TTC is used across regulated industries as an acceptable level for lifetime exposures (*i.e.*, 70 years) to chemicals, including mutagenic compounds, and is applicable to all routes of exposure, including inhalation.

D. Manufacturers should evaluate ENDS stability

We agree with FDA's Guidance regarding the type of requested stability data for PMTAs, and that ENDS product stability should be demonstrated over the product's retail shelf life.[66] Full characterization of ENDS, including changes in aerosol delivery, pH, microbial activity, and chemical composition (liquid and aerosol), if deemed necessary, should be conducted to ensure product stability. Knowledge of ingredient physiochemical properties as well as device material composition and performance should be used to determine if additional testing is necessary during stability studies. FDA should promulgate product standards, with appropriate guidance, to inform manufacturers on the evaluation of ENDS product stability. As with OTDN products, nicotine and nicotine impurities or degradants for ENDS should be measured throughout stability testing to ensure accurate labeling. FDA should promulgate product standards, with appropriate guidance, to inform manufacturers on the evaluation of product/nicotine impurities (*see* OTDN section above).

V. PROPOSED PRODUCT STANDARDS FOR HEATED TOBACCO PRODUCTS (HTPs)

HTPs are products containing a tobacco substrate that is designed to be heated and not combusted by a separate source (*e.g.*, electrical, aerosol, carbon) to produce a nicotine-

[66] *Id.* ("The following information will aid in satisfying the statutory requirement under the FD&C Act and help FDA to determine whether permitting the marketing of the new tobacco product would be APPH…Stability information for the new tobacco product. This information should include the established shelf life of the product and changes in pH and constituents (including HPHCs and other toxic chemicals) over the lifespan of the product, such as the factors that determine the shelf life (e.g., volume of e-liquid, power supply, atomizer, coil); how stability is affected by the storage conditions, such as moisture and temperature; full reports of all stability testing; and how the product's performance may significantly decline (e.g., decrease in aerosol flow rate or change in aerosol constituents) over the product's lifetime.").

containing aerosol.[67] Commercialization of these products prompted Cooperation Centre for Scientific Research Relative to Tobacco ("CORESTA") to create an HTP task force to develop standardized terminology, aerosol generation and collection methodologies and potential chemical constituents.[68] HTPs (also referred to as heat-not-burn or non-combustion cigarettes ("NCC")) heat tobacco at much lower temperatures than combustion thus significantly reducing levels of HPHCs in the aerosol compared to combustible cigarette smoke.[69] FDA recently granted, through the PMTA process and rigorous science-based review, a market authorization of a HTP, IQOS®, manufactured by Philip Morris International ("PMI").[70] The PMTA was submitted in March 2017 and market authorization was granted April 2019. PMI also submitted an MRTPA for IQOS® in December 2016 and FDA authorized marketing IQOS® with a reduced exposure claim in July 2020. The PMTA market order for IQOS® took over two years and the MRTPA claim authorization took approximately 3.5 years. Product standards for this class of RRPs would facilitate quicker FDA review and provide an additional non-combustible alternative for AS.

FDA should consider four key principles in developing RRP standards for HTPs. These principles, discussed in detail in subsequent sections, are as follows.

- Product standards for nicotine are not applicable for HTPs because nicotine is generated from an agricultural product;
- Product ingredients and product components used in HTPs should follow standard toxicological assessments;[71]
- Emissions testing for HTPs should be based on FDA's "abbreviated list;" and
- Manufacturers should evaluate HTP stability, only if deemed necessary.

A new HTP that can demonstrate compliance with these principles, through a manufacturer's certification, reduces the regulatory burden for the applicant and FDA, and may be authorized through the PMTA pathway if the remaining statutory requirements are met.

A. Product standards for nicotine are not applicable for HTPs because nicotine is generated from an agricultural product

Nicotine in HTPs is delivered to the consumer via inhalation of aerosol generated by heating a tobacco containing substrate. Tobacco used for HTPs should follow the same crop protection

[67] CORESTA Heated Tobacco Products Task Force Technical Report – "Heated Tobacco Products (HTPs): Standardized Terminology and Recommendations for the Generation and Collection of Emissions" July 2020
[76] *Id.*
[69] "Comparative assessment of HPHC yields in the Tobacco Heating System THS2.2 and commercial Cigarettes" Regulatory Toxicology and Pharmacology. Volume 90, Pages 1-8. 2017.
[70] *FDA Permits Sale of IQOS Tobacco Heating System through Premarket Tobacco Product Application Pathway* (April 30, 2019) *available at* https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway.
[71] The product standards proposed herein encompass only components that are part of the "tobacco product" as defined by the TCA. They do not reach components that are separate and distinct from the tobacco product.

agent standards as other tobacco products. Where Guidance Residue Levels ("GRLs") for crop protection agents are not available, the association group, CORESTA has published guidance.[72]

B. HTP ingredients and HTP components should follow standard toxicological assessments

Tobacco and tobacco derived ingredients used for HTPs must deliver supported levels of TSNAs through toxicological risk assessment. Additional ingredients used in the tobacco portion of HTPs should be GRAS, not CMR or respiratory sensitizers. Ingredients should not increase addictiveness or toxicity, relative to combustible tobacco products. Ingredients or reaction products reasonably expected to be delivered to the consumer should be evaluated by a toxicological risk assessment. Knowledge of ingredient physiochemical properties as well as device material composition and performance should be used to determine if additional testing is necessary.

Additionally, full quantitative disclosures of added ingredient(s), as well as all vendor documentation attesting to material quality and suitability for use in food/USP, should be obtained. Quantitative disclosures are necessary to complete quantitative risk assessments, as flavor recipes from suppliers can be comprised of a multitude of different chemical entities, and some of these entities may overlap between different formulations. It is important to produce a precise quantitative "roll-up" of every separate chemical entity to perform a risk assessment.

Even though each ingredient should ideally be GRAS or pharmaceutical grade, the basis for the GRAS designation may not be based on toxicological data. Therefore, a thorough literature review should be conducted on each chemical entity in the quantitative "roll-up." In this hazard identification and dose-response assessment, ADI levels set by JECFA, PADIs disseminated by FEMA and any other relevant determinations of safety-in-use (*e.g.*, PODs, NOELs) - accompanied by appropriate uncertainty factors) should be used for the purposes of risk characterization. In some cases, it may be necessary to consider a sum total class of compounds (meaning multiple flavor chemicals with similar structures) to develop a relative margin of safety. Margins of safety for each compound or class of specific compounds should be greater than 1.[73] Like flavor and non-flavor ingredients, HTP non-tobacco components should be closely guided by toxicological risk assessment and/or physical testing (*e.g.*, leachable and extractables testing) to demonstrate the absence of toxicological concern for each component under use conditions. For example, product components should have acceptable levels of potentially toxic impurities (*e.g.*, lead) and the product manufacturer should confirm appropriate supplier controls are in place to ensure component quality. Component-specific testing may be used to pre-screen materials prior to completing more intensive analytical and biological investigations and

[72] Cooperation Centre for Scientific Research Relative to Tobacco, CORESTA Guide No. 1. "*The concept and implementation of CPA guidance residue levels.*" Nov 2019. https://www.coresta.org/agrochemical-guidance-residue-levels-grls-29205.html (last visited July 22, 2020).

[73] The margin of safety is calculated using the ratio of the derived reference dose (*i.e.*, ADI RfD, NDEL) to the predicted, or estimated human exposure level or dose.

determine material interchangeability (*i.e.*, component equivalence between different suppliers of the same material).

C. Emissions testing for HTPs should be based on FDA's "abbreviated list"

Since HTPs contain heated tobacco, emissions testing should include HPHCs as listed in FDA's "abbreviated list."[74] In addition, HTP emissions of CO, NO and NO_x should be below specified thresholds to demonstrate non-combustion of tobacco.[75]

D. Manufacturers should evaluate HTP stability, if deemed necessary

Generally, combustible tobacco products, like cigarettes and roll-you-own tobacco products ("RYO"), are not labeled with an expiration date. Instead, tobacco containing combustibles are commonly managed through distribution. Even though HTPs contain tobacco, FDA's recently proposed PMTA rule[76] recommends stability data for HTP products, including microbial and chemical endpoints. The toxicological assessment of ingredients and determination of potential ingredient chemistry or microbial activity performed during product development may be used to determine product shelf life and the necessity and extent of stability studies. Stability studies, if deemed necessary, may include HPHC analysis, microbial activity, water content and/or oven volatiles ("OV").

VI. ENDS AND HTPs SHOULD MEET CERTAIN BASIC SAFETY PRODUCT REQUIREMENTS FOR PRODUCTS WITH ELECTRICAL COMPONENTS

Design features of ENDS and most HTPs include battery-operated electrical systems not present in typical combustible or oral tobacco products. The Agency's consideration of these unique features is important when promulgating product standards. FDA should establish class-specific standards to reduce risks associated with the electrical components used in ENDS and HTPs. The Agency previously recognized that various aspects of device batteries can cause health risks and recommended manufacturers provide testing certificates for voluntary battery standards,[77] such as UL 8139.[78]

FDA should consider three key principles in developing product standards for electrical product components. These principles, discussed in detail in subsequent sections, are as follows.

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[74] Draft Guidance for Industry, *Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act* (April 3, 2012), *available at* https://www.fda.gov/media/83375/download.

[75] Absence of the combustion of heated tobacco: CO $\leq$ 0.3 mg/100 cm3; NO $\leq$ 4.0 ug/100 cm3; $NO_x \leq 5$ ug/100 cm3; with 25% CI for all three. *See* BSI Publicly Available Specification (PAS) PAS 8852:2020, *Non-Combustible Tobacco Products – Heated Tobacco Products and Electrical Tobacco Heating Devices – Specification* https://standardsdevelopment.bsigroup.com/projects/2019-01574#/section

[76] *See* Premarket Tobacco Product Applications and Recordkeeping Requirements, 84 Fed. Reg. 50,566 (September 25, 2019). FDA released a pre-publication notice for the final PMTA rule on January 19, 2021. FDA subsequently withdrew the pre-publication notice on January 20, 2021 for review and approval by the new administration.

[77] *See* Guidance for Industry, *Compliance Policy for Limited Modifications to Certain Marketed Tobacco Products* (November 26, 2019), *available at* https://www.fda.gov/media/133009/download.

[78] ANSI/CAN/UL 8139 – Electrical Systems of Electronic Cigarettes and Vaping Devices

- General safety requirements for ENDS and HTPs should include considerations for reducing potential residual risks to the consumer;
- Electrical components should be reliable under conditions of both normal use and foreseeable misuse; and
- RRPs that use batteries should be certified through voluntary industry standards (*e.g.*, UL 8139).

A. General safety requirements for ENDS and HTPs should include considerations for reducing potential residual risks to the consumer

General safety requirements are determined by intended use, due to use error and/or due to intentional or unintentional misuse.[79] General safety requirements include:

- Physical (*e.g.*, sharp corners or edges);
- Mechanical (*e.g.*, kinetic or potential energy from a moving object);
- Thermal (*e.g.*, high-temperature components);
- Electrical (*e.g.*, electrical current, electromagnetic interference (EMI));
- Chemical (*e.g.*, toxic chemicals);
- Radiation (*e.g.*, ionizing and non-ionizing); and
- Biological hazards (*e.g.*, allergens, bio-incompatible agents and infectious agents).

Proper assessment of chemical hazards, as discussed below, should consist of adequate material and ingredient toxicological risk assessment, including extractables/leachables testing and emissions testing per the Agency's Draft Guidance HPHCs.[80] Both device and associated charger(s) should have sufficient structural integrity (*i.e.*, strength and rigidity) to reduce risk of fire, rupture or injury during the product's intended use. All metal parts should be corrosion resistant both to environmental and electrochemical action.

B. Electrical components should be reliable under conditions of both normal use and foreseeable misuse

Products should be designed to prevent inadvertent shorting, reverse polarity and misalignment. Soldered connections should have redundant fixation to ensure soldering is not the sole fixation for connection. No loosening or disconnection of electrical connections should occur during or

[79] Food and Drug Administration. (2016). Applying human factors and usability engineering to medical devices: Guidance for industry and Food and Drug Administration staff. Washington, DC: FDA.
[80] *See, e.g.*, for list of HPHCs for ENDS, Guidance for Industry, *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (ENDS)* (June 11, 2019), *available at* https://www.fda.gov/media/127853/download.

after device performance tests.[81] Devices should have protection against accidental activation (unless this action creates no hazard).

C. RRPs that use batteries should be certified through voluntary industry standards (*e.g.*, UL 8139)

Lithium-ion batteries are widely used as a power source in portable electrical products and have become ubiquitous in our home and business environment. Lithium-ion batteries power most ENDS. While the rate of failure associated with their use is small, several well-publicized incidents related to lithium-ion batteries in actual use have raised concerns about their overall safety.[82]

Over the past 20 years, rechargeable lithium- ion battery technologies have evolved, providing increasingly greater energy density, greater energy per volume, longer life cycles and improved reliability. Commercial lithium-ion batteries now power a range of electrical and electronic devices, including medical devices, mobile phones, digital cameras, laptop computers, industrial equipment and automotive applications. We concur with the Agency's recommendations for testing and certification with voluntary standards, like UL 8139. Specific battery performance standards are fundamental to ensuring consumer safety. These may include a functioning venting mechanism that ensures in the event of a malfunction the resulting pressure wave is directed opposite the mouthpiece and protective circuits/controls to limit charging or discharging of the device when outside the device's normal operating limits. Accessories such as device chargers and battery chargers should meet industry standards for overheating and compatibility.

Voluntary standards for ENDS, such as UL 8139, mandate a number of individual tests designed to assess specific safety risks associated with the use of lithium-ion batteries.[83] An ENDS battery system design that does not recognize and accommodate battery cell performance boundaries can force a potentially safe cell into hazardous operating conditions. A systematic device hazards analysis can identify instances where device demands on a battery cell do not align with the capabilities of the battery cell and enable mitigation of inadvertently designed-in hazards.

The safety and quality of ENDS and HTPs is of paramount importance. A comprehensive hazards analysis process to evaluate device electronic safety is critical.[84] This comprehensive process includes understanding product requirements during development, a third-party failure analysis (FMEA) and review utilizing recognized standards such as the Institute of Electrical and Electronic Engineers ("IEEE") Standard 1725, and human factors analysis to facilitate a comprehensive evaluation of potential modes of consumer interaction.

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[81] Examples of device performance tests and acceptable/unacceptable results are described in ANSI/CAN/UL 8139 – Electrical Systems of Electronic Systems and Vaping Devices, Sections 17-31.
[82] Brownson et al. "Explosion Injuries from E-Cigarettes" N Eng J Med 2016; 375:1400-1402.
[83] ANSI/CAN/UL 8139 – Electrical Systems of Electronic Systems and Vaping Devices, Sections 17-31.
[84] *See* ALCS Comments on Docket No. FDA-2016-N-4232, "Battery Safety Concerns in Electronic Nicotine Delivery Systems (ENDS) Public Workshop" (submitted May 22, 2017).

VII. APPROPRIATE CONTROLS FOR MANUFACTURING SHOULD BE PROMULGATED IN TPMPs, NOT PRODUCT STANDARDS

FDA has not yet promulgated tobacco Good Manufacturing Practice ("GMP") regulations, otherwise known as Tobacco Product Manufacturing Practices ("TPMPs"). Compliance with TPMPs, once established, will be enforced during routine FDA inspections and site licensure. FDA should not regulate manufacturing controls through product standards or any other regulatory action.

The intent of TPMPs is to prescribe a general framework to tobacco product manufacturers for establishing adequate manufacturing controls, consistent with section 906(e) of FDCA. The language of Section 906(e) (which references, for example, hazard analysis and critical control point methodology, or "HACCP") indicates that TPMPs are intended to be traditional manufacturing controls. Traditional manufacturing controls protect the public health by helping to ensure that the manufacturing of tobacco products does not result in such products being adulterated or misbranded. This primarily means that the products are manufactured in a way, and under conditions, that will help ensure they are not contaminated and meet product specifications.

CONCLUSION

The potential for RRPs to benefit the public health, by providing AS with alternatives, is clear. Millions of AS have transitioned from cigarette smoking to use of ENDS. While the long-term health consequences of ENDS are unknown, those health risks are almost certainly lower than those caused by cigarette smoking. More recently, we have seen a rapid increase in the use of OTDN products, such as ZYN® or on!®, among users of traditional smokeless tobacco products. Internationally, HTPs, such as IQOS®, have converted millions of AS to a product with vastly lower levels of toxic constituents. As we noted at the outset, millions of ATCs are interested in satisfying, less harmful alternatives to combustible tobacco products. The examples above demonstrate that when such RRPs become available, ATCs will switch to these products, to the benefit of both the individual user and the public health. To further facilitate switching to RRPs, it will also be important to provide ATCs with clear, FDA-authorized relative information about these products.

Despite the numbers of adults who have adopted RRPs in place of conventional tobacco products, cigarette smoking remains the dominant form of tobacco use and conventional tobacco products, including cigarettes, smokeless tobacco products, and cigars, comprise the vast majority of tobacco products sold. We do not believe this is because ATCs are unwilling to switch to lower risk alternatives. Rather, we believe that a wide array of lower risk tobacco and nicotine containing products is needed to provide a sufficient range of alternatives for a diverse

set of ATCs. That array of alternative, RRPs is not yet available, and will not become available without FDA authorization through the PMTA pathway.

We recognize the need for, and reiterate our support for, comprehensive FDA regulation of all tobacco products. We further recognize FDA's concern about the potential unintended consequences that may accompany the introduction of new tobacco products into the market. For example, we share FDA's concern over the recent sharp rise in youth use of e-vapor products, and with the issues associated with unsafe batteries in some ENDS. Therefore, what we propose here is not intended to weaken FDA oversight of new, alternative RRPs; rather, we believe that should FDA adopt reasonable, science-based product standards for RRPs, so that the PMTA pathway can become more efficient and thereby increase the speed-to-market for RRPs.

To that end, FDA should explore product standards for a variety of non-combustible product categories, including OTDN, ENDS and HTPs. These product standards should be class-specific and include science- and evidence-based product stewardship principles that evolve with product innovation. FDA should immediately issue an ANPRM to begin the important process of engaging with major stakeholders, including industry and the scientific community.

APPENDIX A: SUMMARY OF SELECTED PRODUCT STANDARDS

A.1 Summary of content from a representative selection of RRP product standards and/or technical standards

	European Union Tobacco Product Directive (TPD) 201/40/EU[85]	**Swedish Institute for Standards (SIS) Technical Standard SIS/TS 72:2020**[86]	**BSI Publicly Available Specification (PAS) 8850:2020**[87]	**BSI Publicly Available Specification (PAS) 54115:2015**[88]	**ANFOR XP D90-300-1**[89]	**UL-8139:2018**[90]
Oral Tobacco Derived Nicotine		Ingredients Materials Product Information/Labelling				
Electronic Nicotine Delivery Devices	Ingredients Emissions Packaging/Labelling Other			Ingredients Emissions Packaging/Labelling	Ingredients Electrical/Device Safety Packaging/Labelling	 Materials Electrical/Device Safety
Heated Tobacco Products	Ingredients Packaging/Labelling Other		Tobacco Ingredients Materials Emissions Electrical/Device Safety Shelf Life Packaging/Labelling			 Materials Electrical/Device Safety

[85] Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products and repealing Directive 2001/37/ https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1598897772361&uri=CELEX:32014L0040
[86] Swedish Institute for Standards SIS/TS 72:2020 "Nicotine-Containing, tobacco-free oral products – Safety and quality related requirements" https://www.sis.se/produkter/jordbruk-0faca7db/tobak-tobaksprodukter-och-tillhorande-utrustning/sists-722020/
[87] BSI Publicly Available Specification PAS 8852:2020 "Non-Combustible Tobacco Products – Heated Tobacco Products and Electrical Tobacco Heating Devices – Specification" https://standardsdevelopment.bsigroup.com/projects/2019-01574#/section
[88] BSI Publicly Available Specification 54115:2015 "Vaping products, including electronic cigarettes, e-liquids, e-shisha and directly-related products - manufacture, importation, testing and labeling - Guide" https://standardsdevelopment.bsigroup.com/projects/2014-01418#/section
[89] ANFOR General Safety Requirements for ENDS XP D90-300-1 "Electronic cigarettes and e-liquids - Part 1: Requirements and test methods"
[90] ANSI/CAN/UL-8139:2018 "Electrical Systems of Electronic Cigarettes and Vaping Devices" available at https://standardscatalog.ul.com/ProductDetail.aspx?productId=UL8139

A.2.1 Detail from Swedish Institute for Standards SIS/TS 72:2020[91] for Nicotine-Containing Tobacco-Free Oral Products

Nicotine	Limit of 20 mg nicotine per consumable
Ingredients	Disclosures from ingredient suppliers Ingredients that are carcinogens, mutagens or reproductive toxicants, (CMR) are prohibited Nicotine shall meet appropriate pharmaceutical grade purity requirements Flavorings and additives restricted to substances allowed in food and/or assessed as GRAS unless the weight of evidence from a toxicological risk assessment shows the toxicological endpoint is not relevant for the exposure level and route.
Product	Final product shall be subject to a toxicological risk assessment Limit of 20 mg nicotine per consumable pH limit of 9.1 Water activity greater than 0.7 requires additional toxicological risk assessment for microbiological activity
Materials	Materials and packaging in contact with product must meet food contact requirements
Product Information and Labelling	Nicotine warnings as prescribed by local legislation Technical labelling must be conspicuous, prominent, legible and not obscured by external wrapping Include manufacturing date and/or "best before" or expiry date Manufacturer contact information for feedback and adverse event reporting Allergy and contact sensitizers labeled, as appropriate

[91] Swedish Institute for Standards SIS/TS 72:2020 "Nicotine-Containing, tobacco-free oral products – Safety and quality related requirements" https://www.sis.se/produkter/jordbruk-0faca7db/tobak-tobaksprodukter-och-tillhorande-utrustning/sists-722020/

A.2.2 Detail from a selection of existing standards for Electronic Nicotine Delivery Systems

	European Union Tobacco Product Directive (TPD) 201/40/EU	**BSI Publicly Available Specification (PAS) 54115:2015**	**ANFOR XP D90-300-1**	**ANSI/CAN/UL-8139:2018**
Nicotine	Volume Limit: 10 mL for refills; 2 mL for disposables; Concentration Limit: 20 mg/mL			
Ingredients	Ingredients used in the nicotine-containing liquid cannot pose a risk to human health in heated or unheated form Requires toxicological data regarding the product's ingredients and emissions, including when heated, referring in particular to their effects on the health of consumers when inhaled and taking into account, *inter alia*, any addictive effect	Must meet requirements of European Pharmacopoeia (Ph. EUR.) or American Pharmacopoeia (USP) Tobacco extracts allowed but must measure TSNAs in tobacco extracts and reduce to toxicologically supportable levels. Natural extracts must undergo toxicological risk assessment (TRA).	Vitamins and minerals restricted to food supplements No active molecule at the pharmaceutical level other than nicotine (narcotic, anabolic steroid, psychotropic substances, stimulants) Formaldehyde releasers (including preservatives e.g., Quaternium 15, Imidazolidinyl Urea, Sodium hydroxymethylglycinate) Preservatives including triclosan, phenoxyethanol, long chain parabens, isothiazolinone No oils or fats of mineral origin	
Specific Ingredient / Contamination Callouts	Vitamins or other ingredients intended to create an impression of health prohibited Caffeine, Taurine or other ingredients associated with energy or vitality prohibited Ingredients intended to color emissions prohibited Ingredients that are CMR prohibited	Diethylene glycol (DEG) and ethylene glycol < 0.1% Cadmium, Chromium, Iron, Lead, Mercury, Nickel should not be present above toxicologically supportable levels (via TRA) Formaldehyde prohibited as an ingredient, but may be present	Specific Chemical Limits: Diacetyl, formaldehyde, and acrolein: 22 mg/L; Acetaldehyde: 200 mg/L; Lead: 10 mg/L; Arsenic: 3 mg/L; Cadmium: 1 mg/L, Mercury: 1 mg/L; Antimony: 5 mg/L Based on limits applied to aromas in Directive 88/388/EC[92] Radioactive per Directive 96/29/Euratom[93]	

[92] Council Directive 88/388/EEC of 22 June 1988 on the approximation of the laws of the Member States relating to flavourings for use in foodstuffs and to source materials for their production, available at https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A31988L0388

[93] Council Directive 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation, available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A31996L0029

	European Union Tobacco Product Directive (TPD) 201/40/EU	BSI Publicly Available Specification (PAS) 54115:2015	ANFOR XP D90-300-1	ANSI/CAN/UL-8139:2018
		below a toxicologically supportable level		
Materials				Enclosure of the device or charger interface shall have the strength and rigidity required to resist the possible physical abuses that it will be exposed to during its intended use Non-metallic material serving as an enclosure of the device shall comply with CAN/CSA-C22.2 No. 0.17 [94,95] ; Flammability with a minimum rating of V-2; Mechanical Relative Thermal Index (RTI) suitable for the application;; Resistance to Moisture Ingress with a minimum IP rating of IPX4; Resistance to Impact; Crush Resistance not less than 45.4 kg (100 lbsf); Resistance to Mold Stress Relief Distortion Metal parts should be corrosion resistant
Emissions	Deliver nicotine at consistent levels during use	TRA to consider emissions, to include carbonyls, metals, silica particles		
Electrical Components and Device Safety			Must not provoke overheating of power source or vaporizing chamber; Minimize risk of cutting or injuring and risk of explosion Must be shock – resistant and pass drop test; Chemical risks must be minimized Coatings must not release any allergenic or toxic substances or cause burns	Conductive parts in contact at terminals and connections not subject to corrosion due to electrochemical action. Electrical connections reliable and suitable for the application under normal use and foreseeable misuse. An external terminal of the device, battery, charger, charger interface, or other accessory designed to prevent inadvertent shorting, reverse polarity, and misalignment.

[94] CAN/CSA-C22.2 No. 0.17 Standard for Evaluation of Properties of Polymeric Materials

[95] Exceptions for non-metallic materials that are part of, or in contact with, consumables, and to small consumables with a mass less than 4 g or a volume less than 1750 mm^3

	European Union Tobacco Product Directive (TPD) 201/40/EU	BSI Publicly Available Specification (PAS) 54115:2015	ANFOR XP D90-300-1	ANSI/CAN/UL-8139:2018
				Internal wiring routed, supported, clamped or secured to reduce excessive strain on wires and terminal connections; and loosening of terminal connections; and/or damage of conductor insulation. Soldered terminations must have secondary support. Insulated wires passing through a metal wall protected via a smoothly rounded bushing or other smooth surfaces, free of burrs, fins, sharp edges, and the like Power supplies (for charging) comply with UL8139 Protection from accidental activation, unless the device creates no hazards Reliable venting mechanism that channels the pressure wave in the direction where the harm is minimized. Printed wiring boards comply with the Standard for Printed-Wiring Boards, UL 796, for a minimum flame rating of V-1 and maximum operating temperature suitable for the application Protection against overcharge and over discharge (anticipated normal and abnormal use) and short circuit conditions. Appropriate limiting or shut down function to prevent battery/device excursions beyond operating limits. Protective circuits and controls of device, battery, power supply and any other associated parts that withstand single fault conditions (specified in the standard).

	European Union Tobacco Product Directive (TPD) 201/40/EU	**BSI Publicly Available Specification (PAS) 54115:2015**	**ANFOR XP D90-300-1**	**ANSI/CAN/UL-8139:2018**
Whole device / Packaging / Labelling	Child and tamper proof Refills must be leak proof (ref Q2 2016 technical stds)	Child and tamper proof Refills must be leak proof (ref Q2 2016 technical standards)	Icons created to prevent use of incompatible devices	

A.2.3 Detail from a selection of existing and draft Heated Tobacco Products standards

	European Union Tobacco Product Directive (TPD) 201/40/EU	**BSI Draft PAS 8850:2020**	**ANSI/CAN/UL-8139:2018**
Tobacco		Crop protection agent (CPA) levels using CORESTA Guide No 1.[96]	
Ingredients	Vitamins or others intended to create an impression of health prohibited Caffeine, Taurine or others associated with energy or vitality prohibited Ingredients that are CMR are prohibited	Food grade[97] Prohibited: CMR, respiratory sensitizers and respiratory toxicants and substances with confirmed toxicity when inhaled (e.g., diacetyl and 2,3-pentanedione) Toxicological risk assessment for all ingredient (literature review and relevant toxicity tests of the heated tobacco aerosol) Certificate of analysis/certificate of conformity from ingredient supplier in combination with routine audits of the heated tobacco ingredient immediate supplier by the provider. Provider/manufacturer must know composition of compounded ingredients	
Materials		Toxicological risk assessment of all non-tobacco materials in contact with the heated tobacco product or the heated tobacco aerosol under intended use conditions Materials used for electronic tobacco heating devices meet local requirements or harmonized standards that examine the use of hazardous substances in electrical and electronic equipment, e.g., IEC 63000 (technical documentation requirements) and relevant parts of IEC 62321 series (the determination of certain hazardous substances).	Enclosure of the device or charger interface shall have the strength and rigidity required to resist the possible physical abuses that it will be exposed to during its intended use Non-metallic material serving as an enclosure of the device shall comply with CAN/CSA-C22.2 No. 0.17 [98,99] • Flammability with a minimum rating of V-2 • Mechanical Relative Thermal Index (RTI) suitable for the application; • Resistance to Moisture Ingress with a minimum IP rating of IPX4 • Resistance to Impact • Crush Resistance not less than 45.4 kg (100 lbsf)

[96] Cooperation Center for Scientific Research Relative to Tobacco (CORESTA), CORESTA Guide No 1 "The Concept and Implementation of CPA Guidance Residue Levels" November 2019, available at https://www.coresta.org/sites/default/files/technical_documents/main/Guide-No01-GRLs5th-Issue-Nov19.pdf

[97] Direct addition to food according to European Union Regulation (EC) no 1333/2008 or European Union Regulation (EC) No 1334/2008

[98] CAN/CSA-C22.2 No. 0.17 Standard for Evaluation of Properties of Polymeric Materials

[99] Exceptions for non-metallic materials that are part of, or in contact with, consumables, and to small consumables with a mass less than 4 g or a volume less than 1750 mm^3

	European Union Tobacco Product Directive (TPD) 201/40/EU	BSI Draft PAS 8850:2020	ANSI/CAN/UL-8139:2018
			• Resistance to Mold Stress Relief Distortion Metal parts should be corrosion resistant
Emissions		Substances confirmed to be released into the aerosol shall be the subject of the toxicological risk assessment Absence of the combustion of heated tobacco (CO $\leq$ 0.3 mg/100 cm3; NO $\leq$ 4.0 ug/100 cm3; $NO_x \leq$ 5 ug/100 cm3; 25% CI for all three) Comparison of the following with cigarette smoke to strengthen the differentiation of HTP to cigarettes: acetaldehyde, acrolein, formaldehyde, NNK, NNN, benzo[a]pyrene, 1,3-butadiene, and benzene; measured in units of ng/100 cm3 or µg/100 cm3. Aerosol generation using BS ISO 20778, or relevant parts of ISO 20768 (if puff is dependent on the flow rate or pressure drop) Testing to occur across user conditions e.g., variable power, external air supply. Additional HPHCs shall be measured under at least one more intense puffing regime with a larger puff volume and/or longer puff duration as defined by the manufacturer.	
Electrical Components and Device Safety		Requirements for electrical safety, electromagnetic compatibility, wireless technology and restriction on the use of hazardous substances shall be met. Tobacco heating systems shall comply with the standard BS EN 60335-1. The secondary batteries of electronic tobacco heating devices shall comply with the standard BS EN 62133. Tobacco heating devices shall meet the applicable requirements of EMC standards CISPR 14-1 for emissions and CISPR 14-2 for immunity for the appliance When an external power supply is provided, the charging assembly (AC power adapter with docking station and tobacco heating system) shall also be compliant to BS EN IEC 61000-3- 2 and BS EN IEC 61000-3-3.	Conductive parts in contact at terminals and connections shall not be subject to corrosion due to electrochemical action. Electrical connections shall be reliable and suitable for the application under normal use and foreseeable misuse specified in this standard. An external terminal of the device, battery, charger, charger interface, or other accessory shall be designed to prevent inadvertent shorting, reverse polarity, and misalignment. Internal wiring shall be routed, supported, clamped or secured to reduce excessive strain on wires and terminal connections; and loosening of terminal connections; and/or

	European Union Tobacco Product Directive (TPD) 201/40/EU	BSI Draft PAS 8850:2020	ANSI/CAN/UL-8139:2018
		External power supplies shall conform to BS EN IEC 61558-1 with the relevant parts of BS EN IEC 61558-2.	damage of conductor insulation. Soldered terminations must have secondary support. insulated wires passing through a metal wall protected via a smoothly rounded bushing or other smooth surfaces, free of burrs, fins, sharp edges, and the like Power supplies (for charging) comply with UL8139 Protection from accidental activation, unless the device creates no hazards Reliable venting mechanism that channels the pressure wave in the direction where the harm is minimized. Printed wiring boards shall comply with the Standard for Printed-Wiring Boards, UL 796, for a minimum flame rating of V-1 and maximum operating temperature suitable for the application Protection against overcharge and over discharge (anticipated normal and abnormal use) and short circuit conditions. Appropriate limiting or shut down function to prevent battery/device excursions beyond operating limits. Protective circuits and controls of device, battery, power supply and any other associated parts that withstand single fault conditions (specified in the standard).
Shelf Life/Stability		Appropriate stability studies, as defined by the manufacturer quality management system, toxicological risk assessment and relevant consumer endpoints, shall be conducted to determine the shelf life of the heated tobacco product A confirmatory stability study shall be performed on a representative heated tobacco product configuration under relevant climatic conditions extending at minimum to the shelf life. As a minimum, temperature and humidity in accordance with ISO 3402 shall be considered. If water activity exceeds 0.7, additional toxicological risk assessments shall be performed considering microbiological	

	European Union Tobacco Product Directive (TPD) 201/40/EU	BSI Draft PAS 8850:2020	ANSI/CAN/UL-8139:2018
		endpoints, in particular afla- and ochratoxin levels in the heated tobacco.	
Packaging / Labelling	Unique identifier for traceability, e.g., date, time and place of manufacture Tamper-proof security features	Tobacco heating devices shall be traceable so that if an issue is identified in subsequent testing, the affected products can be effectively identified, and corrective actions implemented in accordance with applicable general product safety laws in the countries where the products are on sale	
Other	Manufacture and importers submit notification of a novel tobacco product and provide: (a) available scientific studies on toxicity, addictiveness and attractiveness of the novel tobacco product, in particular as regards its ingredients and emissions. (b) available studies, executive summaries thereof and market research on the preferences of various consumer groups, including young people and current smokers. (c) other available and relevant information, including a risk/benefit analysis of the product, its expected effects on cessation of tobacco consumption, its expected effects on initiation of tobacco consumption and predicted consumer perception		