FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTAs

New Products Subject to this Review[1]	
Submission tracking numbers (STNs)	PM0000529.PD1-PM0000531.PD1, PM0000535.PD1-PM0000537.PD1, PM0000540.PD1-PM0000541.PD1
Common Attributes	
Submission date	August 19, 2019
Receipt date	August 19, 2019
Applicant	Logic Technology Development LLC
Product manufacturer	Logic Technology Development LLC
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	Closed E-Liquid, ENDS Component
Cross-Referenced Submissions	
All STNs	(b) (4)
Supporting FDA Memoranda Relied Upon in this Review	
All STNs	• Medical Consultation Memorandum finalized on 6/28/2021 • Tobacco Product Surveillance Team Consultations finalized on 5/24/2021 and 2/2/2022 • OHCE Consultation finalized on 11/22/2021
Recommendation	
Issue marketing granted orders for the new tobacco products subject to this review.	

Technical Project Lead (TPL):

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Megan J. Schroeder, Ph.D.
Supervisory Pharmacologist
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Signatory Decision: Concur with TPL recommendation and basis of recommendation

Digitally signed by Matthew R. Holman -S
Date: 2022.03.23 14:57:44 -04'00'

Matthew R. Holman, Ph.D.
Director
Office of Science

[1] Product details, amendments, and dates provided in the Appendix. PMTA means premarket tobacco application(s).

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1. EXECUTIVE SUMMARY

Based on the information provided in the application and other scientific data, as described in this Technical Project Lead review, I find that permitting the marketing of the eight new products listed above ("new products") is appropriate for the protection of the public health (APPH) (subject to certain marketing restrictions) and that none of the other denial grounds specified in section 910(c)(2) apply. Accordingly, I recommend that marketing granted orders be issued for the new products, subject to the marketing restrictions and post-market requirements.

1.1. APPH STANDARD

Section 910 of the FD&C Act requires that, for a product to receive a premarket tobacco product application (PMTA) marketing authorization, FDA must conclude, among other things, that permitting the product to be marketed would be APPH. Section 910(c)(2)(A). The statute specifies that, in assessing APPH, FDA must consider the risks and benefits to the population as a whole, including both tobacco users and nonusers, taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products and the increased or decreased likelihood that those who do not use tobacco products will start using such products. Section 910(c)(4). FDA interprets the APPH standard to require a showing that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole, which includes youth, young adults, and other vulnerable populations. In determining whether permitting the marketing of a new tobacco product would result in a net benefit to public health, FDA weighs the potential negative public health impacts (e.g., harm from initiation and use among nonusers, particularly youth) against the potential positive public health impacts (e.g., benefit from adult users of more harmful tobacco products completely switching).

In making the APPH assessment for a noncombustible tobacco product such as an electronic nicotine delivery system (ENDS) FDA weighs, among other things, the negative public health impact stemming from youth initiation and use of the product against the potential positive public health impact stemming from adult cigarette smokers transitioning away from combustible cigarettes to the ENDS product. In order to show that an ENDS is APPH, an applicant must show that the benefits, including those to adult smokers, outweigh the risks, including those to youth, resulting in a net benefit to the public health. As the known risks of the product increase or decrease, the burden of demonstrating a substantial enough benefit likewise increases or decreases. For flavored ENDS[2] (i.e., ENDS with e-liquid flavors other than tobacco or menthol, such as fruit), there is a known and substantial risk of youth initiation and use; accordingly, an applicant has a higher burden to establish that the likely benefits to adult smokers outweigh that risk. For tobacco-flavored ENDS the risk to youth is lower; accordingly, a lesser showing of benefit may suffice. Assessments for menthol-flavored ENDS will be addressed separately. When it comes to evaluating the risks and benefits of a marketing authorization, the assessment for menthol ENDS, as compared to other flavored ENDS, raises unique considerations.

[2] Throughout this document, we use the term "flavored ENDS" to refer to ENDS with flavors other than tobacco or menthol. We use the term "menthol-flavored ENDS" or "menthol-ENDS" to refer to ENDS flavored to impart a menthol flavor and the term "tobacco-flavored ENDS" or "tobacco ENDS" to refer to ENDS flavored to impart a tobacco flavor.

In making the APPH assessment for a flavored ENDS, FDA has determined that it is appropriate to compare flavored ENDS with tobacco-flavored ENDS. Tobacco-flavored ENDS may offer the same type of public health benefit as flavored ENDS, i.e., increased switching and/or significant reduction in smoking, but do not pose the same degree of risk of youth uptake. Whether other products, such as tobacco-flavored ENDS, give adult smokers comparable options for switching or cigarette reduction bears on the extent of the public health benefit that the new products arguably provide to that population. Therefore, in making the APPH determination for a flavored ENDS, FDA considers whether the applicant has provided acceptably strong evidence of an added benefit relative to that of tobacco-flavored ENDS in facilitating smokers in completely switching from or significantly reducing their smoking.

Before determining that permitting the marketing of a new tobacco product would be APPH, FDA also considers the impact of marketing restrictions and other mitigation efforts that aim to reduce the risk of youth initiation and tobacco use. Such mitigation efforts include advertising and promotion restrictions (e.g., measures such as limiting advertising to platforms that are predominantly used by adults and using advertising content and methods that are not known to resonate with youth); sales access restrictions (e.g., measures such as selling products only in face to face interactions, in adult-only facilities, or via websites that require robust age verification); and device access restrictions (e.g., technologies that require adult user identification by fingerprint or other biometric parameters in order to unlock and use a tobacco product). FDA evaluates these measures in the context of the overall public health evaluation of the product, weighing the known risks to youth against the benefit to adults. In the case of flavored ENDS, the risk of youth initiation and use is well documented and substantial. Experience shows that advertising and promotion restrictions and sales access restrictions cannot mitigate the substantial risk to youth from flavored ENDS sufficiently to reduce the magnitude of adult benefit required to demonstrate APPH.[3] Rather, for flavored ENDS, only the most stringent mitigation measures – specifically device access restrictions – have such mitigation potential.[4] In contrast, the risk of youth initiation and use with tobacco-flavored ENDS is lower. Restrictions on advertising and promotion and sales access for tobacco-flavored ENDS could mitigate that more limited risk and impact the overall new benefit assessment. In addition, restrictions on advertising and promotion and sales access are important to include in MGOs because they can help ensure that the marketing of a new tobacco product remains APPH after authorization. FDA has included such restrictions in MGOs issued to date.

Finally, before determining that permitting the marketing of a tobacco product would be APPH, FDA also takes into account whether the applicant has provided sufficient information regarding product design, chemistry, stability, manufacturing controls including process controls and quality assurance procedures, toxicology, abuse liability, and other factors that can impact the product's risks and benefits to individual users, including relative to those of other tobacco products on the market.

[3] *See* FDA, *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised): Guidance for Industry* 44 (Apr. 2020) ("The reality is that youth have continued access to ENDS products in the face of legal prohibitions and even after voluntary actions by some manufacturers."); *see also id*. at 45 (noting "data that many youth obtain their ENDS products from friends or sources in their social networks").

[4] Device access restrictions are novel and rare. To the extent flavored ENDS applicants purport to have device access restrictions (which, as components or parts of the product, would be discussed in the product formulation and engineering sections of a PMTA, rather than solely in the marketing plan), FDA's approach is to engage in further scientific review of those applications.

1.2. SUBJECT APPLICATIONS

FDA's evaluation of these PMTAs determined that these PMTAs contain sufficient information to characterize the products' designs and that there are adequate process controls and quality assurance procedures to help ensure the devices and e-liquids are manufactured consistently. Based on the information provided in the PMTAs, the new products' abuse liability—i.e., ability to promote continued use, addiction, or dependence—is lower than combusted cigarettes (CC) and is similar to, or lower than, that of other ENDS. The overall toxicological risk to the users of the new products is lower compared to CC due to significant reductions in aerosol Harmful and Potentially Harmful Constituents (HPHCs) of the new products compared to CC and similar to representative ENDS due to similarities in their aerosol HPHCs, as evidenced by results of nonclinical studies. In vitro toxicology data suggest aerosols from the new products are less mutagenic, genotoxic, and cytotoxic compared to smoke from CC under the conditions tested. In addition, the effects of in vivo exposure to all new products were typically both reversible and less severe compared to the effects of exposure to mainstream CC smoke, which produced toxic effects that were more severe and often irreversible. In the clinical studies, most participants (in new product cohorts) substantially decreased cigarettes per day (CPD), cutting down from an average of 13-16 CPD at screening to 1-2 CPD by Day 59 (greater than 80% reduction). (Study enrollees were current CC smokers, not dual users.) Between 60-63% of study participants reported dually using one of the new products and CC in the Exit Interviews. Given the substantial reduction in CPD, dual use was sufficient to decrease most biomarkers of exposure (BOE) (e.g., volatile organic compounds [VOCs], tobacco-specific nitrosamines [TSNAs], and polycyclic aromatic hydrocarbons [PAHs]) in CC smokers who used the new products compared to CC smoking cohorts.

In the Consumer Perception Studies, adult dual users reported the greatest interest in purchase, trial, and use of all Logic Vapeleaf, Pro, and Power products, followed by current tobacco users, and then former and never users, suggesting the highest likelihood of uptake by CC smokers and dual users of ENDS and other tobacco products. Therefore, the applicant has sufficiently demonstrated that current tobacco users will use the new products to significantly decrease CC consumption and that non-tobacco users are unlikely to initiate with the tobacco-flavored new products. These new products have the potential to benefit CC users who reduce CC use through either dual use or exclusive use of the new products. Because reductions in CC consumption are other found to increase the likelihood of successful CC cessation (Hughes & Carpenter, 2006), decreases in CPD associated with the use of the new products may promote CC quit attempts and lead to successful CC cessation among CC smokers who are interested in quitting; however, these outcomes are not assessed in the current PMTAs.

In terms of the risks to nonusers, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood and thus youth are at particular risk of tobacco initiation. Existing evidence consistently indicates that, among youth, use of tobacco-flavored ENDS is less common compared to non-tobacco flavored ENDS. Furthermore, 2019 National Youth Tobacco Survey (NYTS) data indicated a limited market penetration among high school-aged youth by the applicant's brand, and the applicant-submitted Consumer Perception Studies concluded that intent to use among former and never tobacco users was low. (The NYTS 2020 data had unstable estimates for youth Logic brand use, so updated estimates are not available.) Likewise, due to the relatively low abuse liability associated with these tobacco-flavored ENDS and their low youth appeal (Section 3.4.1.3.), adults who initiate use of the new products are less likely to progress to regular use of the new products than they would with CC. Nonetheless, given the strong

evidence regarding the impact of youth exposure to marketing on youth appeal and initiation of tobacco use, any marketing authorization should include marketing restrictions and postmarket requirements to help ensure that youth exposure to tobacco marketing is limited. Together, based on the information provided in the PMTAs and the available evidence, the potential to benefit smokers who switch completely or significantly reduce their CC use would outweigh the risk to youth, provided the applicant follows post-marketing requirements aimed at reducing youth exposure and access to the products.

All new products were designed to prevent consumers from adjusting or altering parameters. The e-liquids are closed cartridges to prevent product tampering, and all new products were designed to have unique connections between them and their associated battery units to mitigate misuse and promote intended product usage. Furthermore, the new products were designed to prevent consumers from adjusting or altering performance parameters. Several safety features are incorporated into the new products' design to mitigate misuse and promote intended product usage, including puff-activation controls, unique connections between battery unit and USB charger as well as between e-liquid cartridges and battery unit, and overcurrent discharge.

The applicant provided complete shelf life data sets for all finished new products and the intermediate bulk e-liquids for PM0000530.PD1, PM0000535.PD1, and PM0000540.PD1 under long-term (25°C, 60% relative humidity; 24 months for bulk e-liquids, 18 months for finished products) and accelerated conditions (40°C, 75% relative humidity, 6 months for all bulk and finished products). This data is sufficient to demonstrate satisfactory microbial and chemical stability and engineering functionality/safety of the new products over the applicant-proposed shelf lives.

Together, based on the information provided in the PMTAs and the available evidence, I find that permitting the marketing of the new products, subject to certain marketing restrictions, would be APPH. The potential of the new products to benefit smokers who significantly reduce their CC use (or who switch completely and experience CC cessation) outweighs the risk to youth, provided that the applicant follows post-marketing requirements and implements marketing restrictions to reduce youth exposure to marketing of the new products and youth access to the new products.

FDA has examined the environmental effects of finding the new products APPH and made a Finding of No Significant Impact (FONSI).

2. BACKGROUND

2.1. NEW PRODUCTS

The applicant submitted information for the eight new tobacco products listed on the cover page and with more detail in Appendix A, sold under the brand names Logic Vapeleaf, Logic Pro, and Logic Power. Briefly, the applicant stated that the new products are "designed for adult combusted tobacco smokers", and their user guides state that the new products are not smoking cessation products. Logic Vapeleaf products are three-piece closed ENDS composed of an e-liquid and heating module cartridge, a replaceable capsule containing granulated tobacco, and the tobacco vapor system, which includes a rechargeable battery unit and a Universal Serial Bus (USB) charger. The Logic Vapeleaf e-liquid is nicotine free and has no flavor (unflavored). The tobacco capsule is marketed in "Regular" and has a tobacco characterizing flavor. Logic Pro products are three-piece closed ENDS composed of a battery unit, a replaceable e-liquid capsule, and a capsule case. The Logic Pro e-liquid contains nicotine and a "Tobacco"

characterizing flavor. Logic Power products are two-piece closed ENDS composed of a rechargeable battery unit and a replaceable e-liquid cartridge with mouthpiece. The Logic Power e-liquid contains nicotine and a "Tobacco" characterizing flavor.

2.2. REGULATORY ACTIVITY

On August 19, 2019, FDA received eight PMTAs (PM000029.PD1-PM0000531.PD1, PM0000535.PD1-PM0000537.PD1, PM0000540.PD1, and PM0000541.PD1 [see Appendix A]) from Logic Technology Development LLC (Logic) consisting of three product sub-brands: Logic Vapeleaf, Logic Pro and Logic Power products. On September 18, 2019, FDA issued an Acceptance letter. On October 7, 2019, FDA issued a Samples Request letter. On October 18, 2019, FDA issued a Filing letter. On October 24, 2019, FDA issued an Inspection Request letter and conducted three site inspections at manufacturing facilities between January 6, 2020 and January 16, 2020. On June 26, 2020, FDA issued a Deficiency letter. On August 13, 2020, FDA issued a correction letter rescinding Deficiency 8 described in the Deficiency letter dated June 26, 2020.

Refer to Appendix B for a complete list of amendments received by FDA.

2.3. SCOPE OF REVIEW

This review captures all compliance and scientific reviews completed for the new products subject to this review.

The applicant-submitted amendment (PM0004435) in response to the Deficiency letter was reviewed by engineering, chemistry, toxicology, social science, epidemiology, and environmental science disciplines. Medical and Behavioral and Clinical Pharmacology (BCP) disciplines did not identify deficiencies in the 1st review cycle and, therefore, did not review PM0004435. The microbiology discipline did not identify deficiencies in the 1st review cycle but reviewed new stability data received in PM0004435 during the 2nd review cycle.

Two cross-referenced TPMFs (b) (4) and (b) (4)) were reviewed by the chemistry and toxicology disciplines to support these new products. Because the chemistry discipline identified deficiencies in the 1st review cycle, the amendments submitted by the TPMF owners were reviewed by the chemistry discipline.

Table 1. Disciplines reviewed

Discipline	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
Engineering	Rashele Moore and Morgan Lee	6/24/2020	Mohammad Ali	3/21/2022
Chemistry	Margaret Schmierer	6/24/2020	Margaret Schmierer	3/17/2022
Microbiology	Almaris Alonso Claudio	6/24/2020	Prashanthi Mulinti	3/17/2022
Toxicology	Guy Lagaud	6/24/2020	Kimberly Stratford	3/22/2022

Discipline	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
Behavioral and Clinical Pharmacology	Carolina Ramoa	6/24/2020	Colin Cunningham	3/17/2022
Medical	Omoye Imoisili	6/24/2020	Dara Lee	3/17/2022
Epidemiology	Michael Sawdey	6/23/2020	Ibrahim Zaganjor	3/17/2022
Social science	Izabella Zandberg	6/24/2020	Stephanie Pitts	3/18/2022
Environmental Science	Shannon Hanna	6/23/2020	Bria Martin	3/18/2022
OCE – BIMO[5]	Julian Moore	6/23/2020	N/A	N/A
OCE – manufacturing/lab[5]	Abraham Agyapong	6/24/2020	N/A	N/A

Table 2. Consultations

Discipline or Office	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
Statistics	N/A	N/A	N/A	N/A
OCE – DPAL	Melissa View	1/16/2020	N/A	N/A
OHCE	None	N/A	Emily Talbert	11/22/2021
Tobacco Product Surveillance Team	Susan Rudy	N/A	Susan Rudy	5/24/2021 and 2/2/2022

3. SCIENTIFIC REVIEW

3.1. COMPARISON PRODUCTS

3.1.1. Discipline key findings

The following discussion is based on key findings provided in the discipline reviews:

Per the chemistry review:

- Several products were included as possible comparison products: Pall Mall Red Kings (CC), VUSE Vibe ("tank style" ENDS) Original flavor, blu PLUS (ENDS used with disposable cartridge) Classic Tobacco flavor.
- Justification for ENDS comparison products was that they were similar style ENDS to the new products. The applicant did not specify which representative ENDS product was meant to be similar style to which new product, so all new product data was compared to all representative ENDS product data submitted. Further descriptive information about the representative ENDS products (e.g., ingredient listings, device power, nicotine source) was not provided. However, the information provided was adequate for review from a chemistry perspective because the product characteristics of the submitted representative ENDS products are similar to the

[5] Second cycle review was not necessary as there was no additional data that required review by this discipline.

product characteristics of the assembled new products (e.g., VUSE Vibe is from the same product category as the assembled Logic Pro product; blu PLUS is from the same product category as the assembled Logic Power product) and thus, the assembled Logic Pro and Logic Power products are expected to have comparable aerosol emissions with the representative ENDS products. Based on product design characteristics (presence of tobacco capsule), the aerosol emissions from the assembled Logic Vapeleaf product are more appropriate to be compared with the submitted CC comparison product.

Per the toxicology review:

- The applicant provided comparisons between the new products and CC (Pall Mall Red Kings) as well as reference cigarette 3R4F for in vitro mutagenicity, cytotoxicity and genotoxicity studies. The applicant conducted a separate in vivo 90-day inhalation study for the comparison products and provided in vitro mutagenicity, cytotoxicity and genotoxicity studies. All new products were compared to other ENDS (VUSE Vibe Original and blu PLUS Classic Tobacco). The applicant's rationale for this comparison is based on the premise that adverse health outcomes are reduced when CC smokers switch completely to new products. Therefore, from a toxicological perspective, the applicant's rationale for using CC as a comparator is appropriate.

Per the BCP review:

- The applicant compared all of the new products to usual brand (UB) CC in applicant-submitted clinical studies that provided data on abuse liability, use behaviors, and biomarkers of exposure (BOE; LP001-LP005). From a BCP perspective, CC are an appropriate comparison product, as the applicant's stated intended user population for the new products is current CC smokers interested in switching to ENDS.
- The applicant also provided comparisons of some of the new products with other ENDS (PM0000529.PD1 compared to blu PLUS Classic Tobacco, 2.4% nicotine, LP001; PM0000540.PD1, PM0000541.PD1 compared to VUSE Vibe Original with an unknown nicotine content, LP003), nicotine gum (PM0000529.PD1, PM0000535.PD1 compared to Nicorette White Ice Mint, 2 mg nicotine, LP001 and LP002), or nicotine inhaler (PM0000540.PD1 compared to NICOTROL, 4 mg nicotine delivered per 10 mg nicotine cartridge, LP004) in the clinical studies to provide context for how abuse liability, use behaviors, and BOE associated with use of the new products might compare to other nicotine-containing products. Furthermore, ad libitum use of all new products was compared to continued use of usual brand CC; Logic Vapeleaf and Power (PM0000529.PD1, PM0000540.PD1) product use was also compared to tobacco cessation (no tobacco product use). Thus, while CC are the most appropriate comparison products from the BCP perspective, these representative ENDS and nicotine replacement therapy (NRT) products provide context for where the new products may fit within tobacco products' abuse liability continuum.

Per the medical review:

- The applicant compared usual brand CC to the new products in all clinical studies that provided data on AEs, health effects, and biomarkers of potential harm (BOPH). In nicotine pharmacokinetic/pharmacodynamic single center randomized cross-over studies (LP001-LP003), there were also additional comparisons of:

  - Logic Vapeleaf products (PM0000529.PD1) to nicotine gum
  - Logic Pro products (PM0000535.PD1) to a closed ENDS and nicotine inhaler
  - Logic Power products (PM0000540.PD1) to a closed ENDS and nicotine gum
- The selection of these comparison and representative products is appropriate.
- The applicant provided a literature review of studies that typically used either CC or closed ENDS for evaluating effects on BOPH and health effects.

Per the epidemiology review:

- The new products are closed ENDS. Since adult CC smokers are a likely user population, comparisons between the new products and CC are appropriate.

Per the social science review:

- The information provided by the applicant suggests that adult CC users are likely users of the new products. Therefore, from the social science perspective, comparisons between the new products and CC are appropriate.

3.1.2. Synthesis

The aerosol data from all new products were primarily compared to data provided for CC comparison products, the Pall Mall Red Kings. These data were also compared to two representative ENDS: VUSE Vibe Original and blu PLUS Classic Tobacco. In the applicant-submitted clinical studies (LP001-LP005), the new products were compared to usual brand CC. Some new products were compared to the representative ENDS as well as NRT products.

CC are the primary comparison products because the applicant stated that the new products are intended for CC smokers. Evidence from the applicant-submitted clinical and Consumer Perception Studies, as well as the peer-reviewed ENDS literature, suggests that CC smokers will most likely use the new products to support decreased CPD and dual use (see Section 3.4.1.2.). Therefore, the totality of evidence suggests that CC are appropriate comparison products. The applicant submitted HPHC comparison data to one CC with significant U.S. market share, Pall Mall Red Kings. As TPL, I find this approach to be reasonable and appropriate, and agree with the relevant scientific discipline reviews.

Representative products, including the in-class ENDS and NRT, are helpful to define where the new products fit within the continuum of risk among nicotine-containing products. The comparison of actual use behaviors associated with Logic Vapeleaf and Power (PM0000529.PD1, PM0000540.PD1) products to tobacco cessation (NRT was available upon request) is helpful to determine the risks associated with use of the new products compared to tobacco cessation.

3.2. PRODUCT CHARACTERIZATION

3.2.1. Discipline key findings

The following discussion is based on key findings provided in the discipline reviews:

3.2.1.1. Product design and composition

Per the engineering review:

- Logic Vapeleaf (PM0000529.PD1–PM0000531.PD1) products:

- The Logic Vapeleaf product is a three-piece closed ENDS composed of an e-liquid and heating module cartridge (PM0000530.PD1), a replaceable tobacco capsule (PM0000529.PD1), and the tobacco vapor system (PM0000531.PD1), which includes a rechargeable battery unit and a Universal Serial Bus (USB) charger. The battery is composed of a rechargeable battery cell and printed circuit board (PCB) for output voltage control. The user activates the battery output by inhaling air from the mouthpiece end. The inhalation of air creates a pressure differential that is detected by a pressure sensor, which activates a switch to allow current to flow to the cartridge heating module. The purpose of the printed circuit board assembly (PCBA) is to maintain constant power to the heating coil by controlling the output voltage to the heater. The USB charger is used to charge the battery from a standard USB port. The USB charger is connected to the battery unit by a standard screw connector, which connects the positive and neutral circuitry. Maximum output specifications for the USB charger are 4.2 V and 210 mA (180mA ±30mA).
- PM0000529.PD1, the tobacco capsule, acts as the mouthpiece and is composed of the capsule, filter plug, and capsule end piece, which is filled with the tobacco granules (material). The capsule is the container that holds the tobacco material; about (b) (4) mg of flavored tobacco granules are in the capsule. The filter plug prevents the tobacco material from falling out of the assembled tobacco capsule. The filter plug is made of (b) (4) (b) (4) (b) (4), (b) (4) total denier), plasticizer (b) (4)), and plug wrapper paper; the seams are glued using a (b) (4) or (b) (4) glue. The end piece acts as a cap for the tobacco capsule and prevents the filter from falling out of the capsule.
- PM0000530.PD1 contains 1.125 mL of e-liquid with an integral heating module. The heating module consists of a wicking material of (b) (4) (b) (4) cord without coating that is in contact with the e-liquid inside the reservoir and a (b) (4) 80 heating coil wrapped around the wicking material. When power is applied from the battery unit, a constant voltage is applied to the coil, heating the e-liquid and consequently forming an aerosol.

- Logic Pro (PM0000535.PD1–PM0000537.PD1) products:
  - The Logic Pro products are three-piece closed ENDS composed of a battery unit (PM0000537.PD1), a replaceable e-liquid capsule (PM0000535.PD1), and a capsule case (PM0000536.PD1). A USB charger is used to recharge the battery unit and is included in the Logic Pro Capsule Tank System. The battery unit consists of a rechargeable lithium-ion battery cell, a PCBA, which includes a microcontroller, a charging integrated circuit (IC), a battery protection IC, and a button for user activation. The user is able to unlock the product by pressing the button five times within three seconds. Once unlocked, the product can be activated by pressing the button. Locking the product requires the same pattern of five presses in three seconds. Once activated by the user, the battery unit provides controlled output voltage to the replaceable coil through the screw connections and a spring-style pin. The PCBA controls the functionality of the product (e.g., charging, discharging). The USB charger is used to charge the battery unit from limited

power source USB ports with a target charging time of approximately 100 minutes. The USB charger is connected to the battery unit by a screw connector, which connects the positive and negative circuitry. The connection mating the battery unit to the USB charger was designed to be unique, preventing other brands of USB chargers from being used.

- PM0000536.PD1, the capsule case, is an assembly of the capsule outer housing and the mouthpiece. The capsule case is designed to allow insertion of the replaceable capsule in the correct orientation for further assembly and operation. The capsule case is also designed to render the product non-operable (i.e., no electrical connectivity of the capsule to the battery unit) upon incorrect insertion of the capsule.
- PM0000535.PD1, the replaceable capsule, is a closed (nonrefillable) system containing approximately 1.5 mL of e-liquid and an integral heating module. The heating module comprises a (b) (4) wick that is in contact with the e-liquid in the reservoir and wrapped by a (b) (4) coil. When the user takes a puff from the assembled product, power from the battery unit is applied to the coil at a constant voltage (3.45 V), which heats the liquid and generates aerosol that exits the capsule through the mouthpiece. The product is designed to use software to provide a fixed power output by applying a constant voltage to the heating coil.

- Logic Power (PM0000540.PD1 and PM0000541.PD1) products:
  - The Logic Power products are two-piece closed ENDS composed of a rechargeable battery unit (PM0000541.PD1) and a replaceable e-liquid cartridge with mouthpiece (PM0000540.PD1). A USB charger is used to recharge the battery unit and is included in the Logic Power Rechargeable Kit.
  - PM0000541.PD1, the battery unit, is composed of a lithium-ion battery cell and an airflow sensor for user activation. The user activates the battery by inhaling air from the mouthpiece of the assembled product. An airflow sensor detects the negative pressure caused by the inhalation. A constant voltage is then applied to the cartridge heating module through the positive and neutral terminals. Functionality of the battery unit is controlled by a PCBA, which includes an application-specific integrated circuit (ASIC), a pressure sensor, and an LED. The USB charger is used to charge the battery unit from a standard USB port. The USB charger is connected to the battery unit by a screw connector, which connects the positive and negative circuitry. The battery is designed to charge in approximately 180 minutes.
  - PM0000540.PD1, the replaceable e-liquid cartridge, is a (non-refillable) closed system containing approximately 1.2 mL of e-liquid and an integrated heating module. The heating module comprises a (b) (4) wick that is in contact with the e-liquid in the reservoir and a (b) (4) coil that encircles the wick. When the user takes a puff from the assembled product, power from the battery unit is applied to the coil at a constant voltage, which heats the e-liquid and generates aerosol that flows through the (b) (4) tube and exits the cartridge into the mouthpiece.
- For all new products, the applicant provided an adequate product description and sufficient information for all necessary design parameters.

- The applicant provided sufficient information regarding software/firmware descriptions and functionality, requirements, verification and validation, and revision level history for all new products. These data confirm that the puff activation sensor starts providing power to the heating coil when the air pressure differential crosses a threshold but will stop providing power to the heating coil when the air pressure drops below the threshold in order to prevent accidental activation. Additionally, the information regarding software/firmware verifies that the software can maintain the battery maximum discharging current, charging temperature limits, or discharging temperature limits all of which are set by the battery cell manufacturer.
- The applicant provided appropriate information regarding the tobacco filler and filter plug for PM0000529.PD1.
- The applicant submitted results from child-resistance packaging test for Logic Pro and Power e-liquids (PM0000535.PD1, PM0000540.PD1) to demonstrate that these e-liquids have appropriate child-resistant packaging. The Logic Vapeleaf e-liquid (PM0000530.PD1) is a closed system and does not contain nicotine, and therefore the products do not require[6] child-resistant packaging. The Logic Vapeleaf e-liquid is packaged with the Logic Vapeleaf tobacco capsule (PM0000529.PD1) that contains nicotine and has appropriate tamper evident packaging, which is sufficient from an engineering perspective.
- The batteries (PM0000531.PD1, PM0000537.PD1, and PM0000541.PD1) are not UL 8139 certified; however, the applicant tested these batteries to different international and internal battery standards: All batteries were certified to, or appropriately tested against, IEC 60335-1, IEC 62133, IEC 60950-1. The combination of testing necessary for these standards is sufficient to minimize risks associated with battery safety.
- For PM0000531.PD1, PM0000537.PD1, and PM0000541.PD1, applicant provided the appropriate battery capacity target values and range limits, nominal voltage, as well as battery size, battery chemistry, battery type, number of cells, and target cycle life.
- Assessment of the Tobacco Product Surveillance Team (TPST) Adverse Event report did not identify any issues for Engineering associated with the new products. As such, the TPST Adverse Event report does not modify any conclusions in the engineering review.

Per the chemistry review:

- Logic Vapeleaf (PM0000529.PD1–PM0000531.PD1) products:
  - The product design is such that the e-liquid is heated and flows through the tobacco capsule, extracting compounds from the tobacco capsule and then producing an aerosol.
  - PM0000529.PD1 is a tobacco capsule, which contains (b) (4) mg total tobacco, flavorings, and casings. The tobacco blend is a mixture of (b) (4) and (b) (4) tobaccos and was fully identified. The "Regular" flavorings, (b) (4) (b) (4) , capsule, and capsule end piece ingredients were provided in a TPMF. This information was sufficient to characterize the new products from the chemistry perspective.

[6] Not an FDA requirement. Child-resistant packaging is required by the Consumer Protection Safety Commission.

  - PM0000530.PD1 is an unflavored, nicotine-free e-liquid, which contains only propylene glycol (PG), vegetable glycerin (VG), and water. The e-liquid is a 50:50 mixture of PG and VG/water. The information provided was sufficient to characterize the new product from the chemistry perspective.
  - PM0000531 is the Tobacco Vapor System. No ingredients for this structural component were provided, but extractable and leachable test data were provided to show which compounds from the structural components could reach users (see Section 3.2.1.3). The information provided was acceptable from a chemistry perspective.
- Logic Pro (PM0000535.PD1 –PM0000537.PD1) products:
  - PM0000535.PD1 is a tobacco-flavored e-liquid capsule, which contains a mixture of PG, VG, nicotine, and flavorings. PG, VG, and nicotine are sufficiently identified in the PMTA and flavoring ingredients were submitted in a TPMF. The PMTA and TPMF information was sufficient to characterize the new product from a chemistry perspective.
  - PM0000536.PD1 and PM0000537.PD1 are the Capsule Case and Capsule Case Tank System/battery used with the Logic Pro e-liquid capsules. No ingredient information for these structural components was provided, but extractable and leachable test data were provided to show which compounds from the structural components could reach users (see Section 3.2.1.3). The information provided was acceptable from a chemistry perspective.
  - During inspection of the (b) (4) manufacturing site, the applicant provided documentation indicating they received reports about leakage of the Logic Pro e-liquid capsule (PM0000535.PD1) and subsequently completed a corrective and preventative action (CAPA) report to investigate and fix the leakage issue.
- Logic Power (PM0000540.PD1 and PM0000541.PD1) products:
  - PM0000540.PD1 is a tobacco-flavored e-liquid cartridge, which contains a mixture of PG, VG, nicotine, and flavorings. PG, VG, and nicotine are sufficiently identified in the PMTA and flavoring ingredients were submitted in a TPMF. The PMTA and the TPMF information were sufficient to characterize the new products from a chemistry perspective.
  - PM0000541.PD1 is the Rechargeable Kit for each e-liquid, including the battery component. No ingredient information for the structural components were provided, but extractable and leachable test data were provided to show which compounds from the structural components could reach users (see Section 3.2.1.3). The information provided was acceptable from a chemistry perspective.

Per the microbiology review:

- PM0000530.PD1, PM0000535.PD1, and PM0000540.PD1 contain humectants (PG, VG, and/or water), which may impact microbial activity during the applicant-determined product shelf life. The applicant adequately addressed this concern by providing microbial counts data which showed total aerobic microbial count (TAMC) and total yeast and mold count (TYMC) values below the method limit of detection (<100 colony forming units [cfu]/mL) for all new products over the complete shelf life.

- PM0000529.PD1 includes a tobacco capsule component, which includes (b) (4) (b) (4) and (b) (4) tobaccos that are not fermented. Fermentation can impact microbial activity and potentially promote TSNA formation, thereby negatively affecting stability of the finished product during shelf life. Therefore, use of non-fermented tobacco improves stability from a microbiology perspective.

3.2.1.2. Manufacturing

Per the engineering review:

- For all new products, the applicant provides summaries of the manufacturing steps, including the source of all assemblies, facilities used, external vendor oversight strategies, and all associated quality control measures that are in place. The applicant provides evidence demonstrating that the new products are manufactured in a consistent manner to minimize variability in product quality. The available inspection documents also support product consistency.
- A product risk assessment was submitted for all products and their consumables using a failure mode and effects analysis (FMEA). The applicant stated that all the new products were designed to prevent consumers from adjusting or altering performance parameters without significant effort. PM0000530.PD1, PM0000535.PD1, and PM0000540.PD1 are closed e-liquid cartridges/capsules to reduce the likelihood of new product tampering. Further, several features are incorporated into the new products' design to mitigate misuse and promote intended product usage, including puff-activation controls, unique connections between battery unit as well as between USB charger and e-liquid cartridges and battery unit, and overcurrent discharge. The applicant submitted adequate risk analysis information for all new products. Furthermore, the applicant provided adequate instructions about how the new products should be used and warnings against misuse in the leaflets.
- The shelf-life/stability information provided for e-liquid relative density, aerosol generation, visual inspection, capsule/cartridge resistance, max loading time, battery capacity, battery output voltage, short circuit protection, and USB charger functionality is sufficient and appropriate to characterize all new products.
- The aerosol particle size delivered by all new products remains consistent over time.

Per the chemistry review:

- The applicant provided complete and detailed descriptions of manufacturing processes and standard operating procedures for all new products and components.
- Each incoming raw material and manufactured new product is controlled through the Japan Tobacco Inc. Quality Management System, raw material testing, in-process testing, and finished product testing.
- Quality and manufacturing of all new products and components is well controlled at all stages, and the applicant provided sufficient information to show all new products are consistently manufactured.
  Three manufacturing site inspections were performed: (b) (4) (b) (4), and (b) (4). Final Logic EIRs were completed with exhibits collected during each inspection. Findings from each manufacturing site inspection did not raise new issues, and therefore are adequate to suggest complete and appropriate manufacturing practices from a chemistry perspective.

Per the microbiology review:

- The applicant provided adequate descriptions of the manufacturing processes and standard operating procedures for all new products.
- Manufacturing was assessed via inspection in January 2020. The manufacturing of all new products is well controlled at all stages and the manufacturing controls demonstrate adequate environmental controls and storage conditions to ensure product quality. The findings of the inspection did not raise new issues, and therefore are adequate to suggest appropriate manufacturing practices from a microbiology perspective.

3.2.1.3. Product stability

Per the chemistry review:

- Complete method information was submitted for all stability studies. One stability method (photostability for PM0000535.PD1 –PM0000537.PD1) was provided in a TPMF.
- The applicant provided complete shelf life data sets for all finished new products and the intermediate bulk e-liquids for PM0000530.PD1, PM0000535.PD1, and PM0000540 under long-term (25°C, 60% relative humidity; 24 months for bulk e-liquids, 18 months for finished products) and accelerated conditions (40°C, 75% relative humidity, 6 months for all bulk and finished products).
- The applicant also submitted leachable and extractable data for all structural components, e-liquid, tobacco, and aerosol HPHC stability data under long-term and accelerated conditions, particle size stability data, and microbial stability data. Leachable and extractable data were adequate to suggest the container closure systems for the new products are stable for the intended shelf life of each new product.
- HPHC stability data and shelf life stability studies submitted were sufficient from chemistry perspective to support proposed finished product shelf lives.
- The studies showed that the new products are stable for up to 12 (for all bulk e-liquids and PM0000529.PD1–PM0000531.PD1) or 15 (PM0000535.PD1–PM0000537.PD1, PM0000540.PD1, and PM0000541.PD1) months.

Per the microbiology review:

- The microbial stability data are necessary for the proposed shelf life of the new products as bacterial communities change as a function of storage time (Chopyk et al., 2017; Djordjevic, Fan, Bush, Brunnemann, & Hoffann, 1993). Increased microbial growth over time can impact stability of the product and may result in an increased risk to public health as the new products sit in storage.
- The applicant provided stability data over shelf life of all new products. pH and moisture data were provided over the complete shelf life of PM0000529, PM0000530.PD1, PM0000535.PD1, and PM0000540.PD1. pH values of all new products were within the pH values observed in published literature for marketed e-liquids. Moisture content of all new products increased (65-107%) during storage, which could potentially affect microbial growth and TSNA levels in the finished products. The applicant adequately addressed this concern by providing complete microbial (TAMC, TYMC) and TSNA (N-Nitrosonornicotine [NNN] and 4-

(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK]) stability data for all new products.

- PM0000530.PD1, PM0000535.PD1, and PM0000540.PD1 showed TAMC and TYMC values below method limit of detection (<100 cfu/mL) at all time points tested over shelf life, which are acceptable from a microbiology perspective. Additionally, the NNN and NNK levels for all these products were below detection limits (b) (4) ng/g and (b) (4) ng/g, respectively) over shelf life.
- PM0000529.PD1 showed high microbial counts (TAMC (b) (4) cfu/mL and TYMC: (b) (4) cfu/mL) over shelf life, which was a potential microbiological concern. However, these high counts are not of concern due to the submitted TSNA data.
- The quantities of NNN (b) (4) ng/g) and NNK (b) (4) ng/g) in PM0000529.PD1 are lower than the quantities found in tobacco filler of marketed CC products available in the U.S. (median [range] for NNN and NNK in tobacco filler is (b) (4) ng/g [(b) (4) ng/g] and (b) (4) ng/g (b) (4) ng/g], respectively).
- From a microbiology perspective, the applicant provided adequate stability data to demonstrate a shelf life of 12 months for PM0000529.PD1 and PM0000530.PD1 and 15 months for PM0000535.PD1, and PM0000540.PD1.

3.2.1.4. Product test data

Per the engineering review:

- The applicant provided test data needed to fully characterize and evaluate the new products. The applicant provides test data for coil diameter, e-liquid viscosity, e-liquid boiling point, amount of wicking material, wicking rate, total coil length (uncoiled), coil surface area, coil temperature, coil temperature cut-off, current cut-off, and inhaled aerosol temperature for all new products. The product performance testing results adequately demonstrate all new product consistency.
- Adequate manufacturing processes and controls were used to ensure that all new products (including devices and replacement cartridges) meet manufacturer's specifications, and they will operate consistently throughout the life of the product.

Per the chemistry review:

- The applicant provided e-liquid, tobacco (PM0000529.PD1[7]), and aerosol HPHC data for all new products. Aerosol HPHC data were generated under CORESTA recommended method (CRM) 81 for all new products; a modified ISO3308 puff regimen for Logic Vapeleaf Regular (PM0000529.PD1), Logic Pro Tobacco (PM0000535.PD1), and Logic Power Tobacco (PM0000540.PD1) products; as well as a product-specific developed intense puff regimen for Logic Pro Tobacco (PM0000535.PD1) and Logic Power Tobacco (PM0000540.PD1) products. Additional aerosol data was not provided for the Logic Vapeleaf Regular (PM0000529.PD1) product under this product-specific developed intense puff regimen because the data generated under CRM81 already represented data generated under an intense regimen. The maximum puff duration for the Logic Vapeleaf Regular product is 2.4 seconds, which is lower than the puff duration of CRM81 (3 seconds), so all data

[7] For all instances where a complete ENDS is required, all components and parts are implied with the inclusion of the Logic sub-brand e-liquids' STN.

generated under the CRM81 is generated under more extreme conditions than the product would typically be used under.

- New product aerosol data generated under three puff regimens (CRM 81, a modified ISO3308, and a product-specific developed intense puff regimen) was compared to the Pall Mall Red Kings CC smoke yields. Generally, all aerosol yields for the new products were lower than the CC smoke yields. Most new product aerosol HPHC yields were lower than, or analytically equivalent to, the representative ENDS aerosol yields.
- Under the product-specific intense puff regimens, some formaldehyde yields were slightly higher than the corresponding CC smoke yield; however, this may have been the result of overestimating intense new product use and underestimating intense CC use. Additionally, the intense puff regimen conditions were based on the upper 2.5% of results of clinical data from LP004 and LP005 for different puff parameters, and represent conditions likely to be used only by the most intense users of all characterizing flavors of Logic Pro and Logic Power products (PM0000532.PD1-PM0000535.PD1, PM0000538.PD1-PM0000540.PD1, some not subject to this PMTA review). The data submitted is sufficient to characterize the new products from a chemistry perspective.
- Complete descriptions of analytical methods were provided in a TPMF and found sufficient to support the analytical testing from a chemistry perspective. In addition, the applicant provided complete information regarding the testing laboratory (b) (4)) and accreditation, sample storage, manufacture and test dates, and details of puff generation for each puff protocol. All of this information was found sufficient to support the analytical testing from a chemistry perspective.
- FDA verification testing was completed for NNN and NNK quantities in PM0000529.PD1; for nicotine, PG, VG, diethylene glycol, and ethylene glycol in PM0000530.PD1; and for nicotine, formaldehyde, acetaldehyde, and acrolein in the aerosol generated from PM0000529.PD1-PM0000531.PD1, PM00000536.PD1-PM0000537.PD1 (with PM00000532.PD1, not subject to this PMTA review) and PM0000541.PD1 (with PM0000538.PD1, not subject to this PMTA review). FDA testing verified the accuracy of the test results provided by the applicant.

3.2.2. Synthesis

As TPL, I agree with the engineering, chemistry, and microbiology conclusions that these PMTAs do contain sufficient information to characterize the ingredients and product design. The applicant submitted adequate processes and controls to ensure that the new products meet the manufacturer's specifications for consistent manufacturing. Furthermore, the NNN and NNK content within the tobacco capsule in PM0000529.PD1 were lower than median levels for quantities found in tobacco filler of marketed CC in the U.S., and the levels within the new products' aerosol were below the detection limit.

While the battery units for the Logic Vapeleaf, Pro, and Power products (PM0000531.PD1, PM0000537.PD1, and PM0000541.PD1, respectively) are not certified to the UL 8139 standards, the batteries were tested against several international and internal standards to minimize risks associated with battery safety. Furthermore, no reports of the new products' malfunction were reported in the TPST searches.

The applicant-submitted data are sufficient to demonstrate satisfactory microbial (Note: the microbiology discipline did not evaluate the stability data supporting the battery unit or capsule cases) and chemical stability and engineering functionality/safety over the new products' (evaluated for bulk-e-liquids, aerosol, batteries, and finished products) shelf lives:

- PM0000529.PD1-PM0000531.PD1: 12 months
- PM0000535.PD1-PM0000537.PD1, PM0000540.PD1, PM0000541.PD1: 15 months

The applicant conducted HPHC analyses in all new products' aerosols under two or three puff regimens for comparison with the comparison CC: CRM 81, modified ISO 3308 (for PM0000529.PD1-PM0000531.PD1, PM0000535.PD1-PM0000537.PD1, PM0000540.PD1, and PM0000541.PD1), and an intense puffing regimen that reflected the upper 2.5% of topography variables collected in LP004 and LP005 (for PM0000535.PD1-PM0000537.PD1, PM0000540.PD1, and PM0000541.PD1). As TPL, I agree with the chemistry review conclusions: most HPHCs and other constituents were lower in aerosol yields from all new products compared to CC smoke yields. The chemistry review noted that the constituent yields that slightly surpassed that of the CC (e.g., formaldehyde) are likely due to over-estimations of intense ENDS use. These risks associated with these slightly higher constituent yields are outweighed by larger decreases in other HPHCs. The toxicology review also evaluated these HPHC data from the toxicology perspective (see Section 3.5.1.1.). These HPHC yield data are supported by the lower BOE (compared to continued CC smoking) evident for all new products in the LP004 and LP005 clinical studies (see Section 3.5.1.2.) – indeed, exposure to non-nicotine HPHCs did not increase upon actual use of the new products (see Section 3.5.1.).

Data from an applicant-submitted child-resistance packaging study demonstrate adequate evidence to suggest Logic Pro and Power e-liquids (PM0000535.PD1 and PM0000540.PD1) have appropriate child-resistant packaging. Such tests were not conducted on the Logic Vapeleaf flavorless e-liquid (PM0000530.PD1; Logic Vapeleaf Regular Cartridge/Capsule Package) because it does not contain nicotine and is a closed system (where nicotine cannot be added); therefore, new product PM0000530.PD1 does not require[8] child-resistance packaging. However, it is packaged with tobacco capsules (PM0000529.PD1) which contain nicotine and have appropriate tamper evident packaging.

To better ensure proper usage and safety, the new products were designed to prevent consumers from adjusting or altering performance parameters. Several safety features are incorporated into the new products' design to mitigate misuse and promote intended product usage, including puff-activation controls, unique connections between battery unit and USB charger as well as between e-liquid cartridges/capsules and battery unit, and overcurrent discharge. Failure mode and effects analyses were conducted for all new products and were adequate from the engineering perspective. Product leakage was evident under a long-term and accelerated study in the Logic Pro product line and the applicant has received some complaints about leakage from the Logic Pro product line (PM0000535.PD1-PM0000537.PD1). The Logic Pro product leaflets contain a warning about possible leakage. I believe these steps appropriately respond to the low level of risk. If significant product leakage complaints for PM0000535.PD1-PM0000537.PD1 occur in the future, additional

[8] Not an FDA requirement. Child-resistance packaging is required by the Consumer Protection Safety Commission.

review may be warranted. Such complaints will be monitored through the required post-market reports.

3.3. ABUSE LIABILITY

The BCP review considered the five applicant-sponsored clinical studies in adult smokers. Three studies investigated the abuse liability of Logic Power Tobacco (PM0000540.PD1; LP001), Logic Vapeleaf Regular (PM0000529.PD1; LP002), and Logic Pro Tobacco (PM0000535.PD1; LP003) products under controlled laboratory conditions, compared to usual brand CC smoking, representative ENDS, and nicotine gum or inhaler. Nicotine exposure and exposure to non-nicotine BOE, as well as subjective effects, were evaluated in forced-switch, 60-day ad libitum use studies (PM0000529.PD1, PM0000540.PD1; LP004 and PM0000535.PD1; LP005); BOE were compared to continued CC smoking and, in one study, complete tobacco cessation (although NRT was provided, if requested).

3.3.1. Discipline key findings

The following discussion is based on key findings provided in the BCP review.

3.3.1.1. Current tobacco users

- 'Abuse liability' refers to the ability of the product to promote continued use and the development of addiction and dependence. This can be relevant to determining the likelihood that addicted users of one nicotine product would switch to another. For example, if a new tobacco product has a low abuse liability, current addicted tobacco users may find it to be an inadequate substitute for the product they are currently using. On the other hand, low abuse liability makes it less likely that new users will become addicted.
- Results of applicant-sponsored clinical laboratory studies (LP001, LP002, and LP003) show nicotine exposure is significantly and substantially lower following use of all new products relative to usual brand CC under controlled conditions among adult ENDS naïve CC smokers. The new products' relatively lower abuse liability compared to CC suggests two potential benefits: 1) a relatively low likelihood that new ENDS users will progress to regular use of the new products, and 2) reduced nicotine exposure may lead to lower nicotine dependence which may improve cessation outcomes in CC smokers who are motivated to quit.
- Data from all of the applicant-sponsored clinical studies show subjective effects (e.g., liking, satisfaction) were lower for PM0000540.PD1 and PM0000529.PD1 relative to usual brand CC, and subjective effects were similar or lower for PM0000535.PD1 relative to usual brand CC.
- The abuse liability of the Logic Vapeleaf Regular product (PM0000529.PD1) is substantially lower than usual brand CC and lower than nicotine gum in adult CC smokers.
- The abuse liability of the Logic Pro Tobacco product (PM0000535.PD1) is substantially lower than usual brand CC, similar to or greater than nicotine inhaler, and similar to or slightly higher than VUSE Vibe Original (a representative ENDS) in adult CC smokers.
- The abuse liability of the Logic Power Tobacco product (PM0000540.PD1) is substantially lower than usual brand CC, similar to or greater than nicotine gum, and similar to or slightly higher than blu PLUS Classic Tobacco (a representative ENDS) in

adult CC smokers.

- The abuse liability of all new products for regular ENDS users, former smokers, other tobacco product users, or never users was not assessed.
- Applicant-submitted evidence suggests the Logic Vapeleaf Regular product (PM0000529.PD1) may be less preferred than the Logic Vapeleaf non-tobacco-flavored products (not subject to this PMTA review), and the Logic Pro Tobacco product (PM0000535.PD1) may be less preferred than the Logic Pro non-tobacco-flavored products (not subject to this PMTA review). All Logic Pro product cohorts reported similar satisfaction as CC, whereas all Logic Vapeleaf product cohorts had lower subjective effects as CC.
- The abuse liability of the new products was slightly greater than, or comparable to, the abuse liability of 2mg nicotine gum and 4mg nicotine inhaler, which may increase the likelihood of use of and adherence to the new products compared to NRT in adult CC smokers interested in quitting all tobacco products.
- Although abuse liability of the new products may be expected to be higher in individuals with a history of ENDS use, results from the applicant-sponsored 60-day clinical studies showed that abuse liability of the new products was still lower than usual brand CC in adult smokers who were more familiar with the new products and who had used them regularly for several weeks.

3.3.2. Synthesis

As TPL, I agree with the BCP review conclusions that the nicotine pharmacokinetic profiles and lower positive subjective effects ratings for the new products indicate a lower abuse liability than usual brand CC, the comparison product. Furthermore, the abuse liability of the new products appears to be similar to representative ENDS with similar design features and e-liquid nicotine concentrations. However, it should be noted that the applicant-submitted clinical studies were conducted in CC smokers with little to no ENDS experience; among experienced ENDS users, the new products may have somewhat higher abuse liability, although it would not be expected to surpass the abuse liability of CC. Indeed, the new products maintained their relatively lower abuse liability in participants who used the new products during the 60-day clinical studies (LP004 and LP005) and became more experienced ENDS users throughout the process. These studies (although they do not represent real-world use behaviors) also suggest that nicotine exposure, upon dual use of the new products and usual brand CC, is unlikely to exceed that of the comparison product, usual brand CC.

All new products had relatively lower abuse liability than CC in adult smokers. The abuse liability of the Logic Vapeleaf Regular product is likely below that of 2mg nicotine gum. The BCP review notes that many CC smokers may be unlikely to use this new product because it does not deliver nicotine beyond that of NRT, has low subjective appeal, and is associated with little reinforcement. However, despite its low abuse liability profile, use of the Logic Vapeleaf Regular product did decrease CPD by approximately 80% and showed significantly lower BOE upon use (see Sections 3.4.1.2. and 3.5.1.2.). These data suggest that the Logic Vapeleaf Regular product may be a viable alternative to CC in some smokers (and means towards CC cessation).

Despite their relatively lower abuse liability profile than CC, the new products were successfully used in LP004 and LP005 to decrease nicotine exposure and significantly decrease CC smoking (see Section 3.4.1.2.) in adult CC smokers. Decreased nicotine exposure and CPD may help to facilitate CC cessation in CC smokers who are motivated to quit. Thus, CC smokers who choose to use the new products may experience the benefits of significantly reducing their nicotine exposure, reducing their exposure to BOE (see Section 3.5.1.2.), reducing their nicotine dependence, and facilitating smoking quit attempts and success.

3.4. USER POPULATIONS

The BCP review considered the five applicant-submitted clinical studies (LP001-LP005).

The social science review considered the following studies: Focus Groups (LOGIC-CMA-CPS-001), Cognitive interviews (LOGIC-CMA-CPS-002), Consumer Perception Studies (LOGIC-CMA-CPS-003; LOGIC-CMA-CPS-004; LOGIC-CMA-CPS-005), and Exit Interviews conducted with participants at the conclusion of two 60-day clinical studies (LOGIC-CMA-EI-001, participants from clinical studies LP004 and LP005).

The epidemiology review considered data from the Exit Interviews conducted with participants at the conclusion of two 60-day clinical studies (LOGIC-CMA-EI-001, participants from clinical studies LP004 and LP005).

3.4.1. Discipline key findings

The following discussion is based on key findings provided in the discipline reviews:

3.4.1.1. Intended user population(s) (target population)

Per the BCP, epidemiology, and social science reviews:

- The applicant stated that the intended population for the new products is adult CC smokers.

Per the BCP review:

- The applicant submitted five clinical studies that were conducted in current CC smokers, which provide sufficient evidence to inform use behavior in those populations.

Per the social science review:

- The information provided suggests that the likely users of the new products include current CC smokers and current ENDS users.

3.4.1.2. Current tobacco users

Per the BCP review:

- The abuse liability of all new products in adult smokers is lower than CC; dual use of the new products with CC is the most likely use behavior. Some CC smokers may temporarily adopt the new products before switching back to CC. These smokers may switch back to CC because the latter are rated higher in terms of liking and

satisfaction compared with the new products. CC smokers with the intent to quit smoking may use these new products as a means to transition away from CC smoking (reduce CPD or experience CC cessation).

- It is unclear from the information provided how many participants completely switched (i.e., completely quit CC use) to the new products in the applicant-submitted 60-day clinical studies (LP004, LP005).
- Most participants in all new product cohorts (LP004, LP005) substantially decreased CPD from an average of 13-16 CPD at screening to 1-2 CPD by Day 59 (greater than 80% reduction) in all new product cohorts[9]. CC consumption decreased to 1-2 CPD in all new product cohorts (regardless of Logic sub-brand). Dual use occurred despite free access to the new products and study instructions to solely use the new products.

Per the epidemiology review:

- The applicant did not provide studies or information from the peer-reviewed literature that contained prevalence of use estimates for the new products among adults. They relied on e-commerce sales data as a proxy for data on prevalence of use of their new products; however, e-commerce sales data is limited in its ability to characterize actual patterns of tobacco use, and thus, may not be an adequate proxy for describing prevalence of use. Evidence from the peer-reviewed literature suggests that adult use of closed ENDS, like the new products, is likely to be non-daily and concurrent with CC.
- The applicant emphasized results from the Exit Interviews, conducted among LP004 and LP005 clinical study participants who were smokers at baseline, which suggested that dual use was common (with nearly two-thirds reporting smoking a CC during one of the clinical studies). The applicant did not provide studies from the peer-reviewed literature that contained prevalence estimates of dual-use or poly-use of the new products with other tobacco products. The peer-reviewed literature indicates that, in general, ENDS use among CC smoking adults is common and that dual use is particularly common among young adults.
    - In the applicant-submitted 60-day clinical studies (L0004 and LP005), a large majority of participants in the full analysis set decreased self-reported CPD by 80%:
        - Logic Vapeleaf Regular (PM0000529.PD1): 73%-77%
        - Logic Pro Tobacco (PM0000535.PD1): 70%-80%
        - Logic Power Tobacco (PM0000540.PD1): 63%-72%

      However, the extent to which participants maintained their reduced CPD outside of the clinical study setting or completely switched from CC in these studies (i.e., CC cessation) was not described based on the study design.

[9] Determining whether marketing a new product is APPH includes evaluating the risks and benefits to the population as a whole. This requires FDA to balance, among other things, the negative public health impact for nonusers against the potential positive public health impact for current tobacco users. Accordingly, for marketing of a new product to be found to be APPH, any risks posed by a new product to youth would need to be overcome by a sufficient benefit to adult users, and as the known risks increase, so too does the burden of demonstrating a substantial enough benefit. In the case of a new flavored ENDS, the risk of youth initiation and use is substantial, given the clearly documented published evidence. In contrast, the risk of youth initiation for tobacco-flavored ENDS is less substantial, thus the level of evidence demonstrating benefit to adult smokers may not need to be as high.

Per the social science review:

- Results from the Consumer Perception Studies and Exit Interviews are limited in generalizability to describe the likelihood of actual use of the new products in the U.S. population due to methodological limitations, particularly among youth. These limitations were considered in the synthesis of this data.
    - The Consumer Perception Studies included current, former, and never tobacco using adults (> 21 years) who were assessed for product appeal and intent to use after viewing pictures of the new products. They did not use the products.
    - The Exit Interviews were conducted for study participants at the end of the longer clinical studies. The study participants were adult current CC smokers who were randomly assigned to use one of the new products during the study.
- Respondents within all tobacco-use status groups (dual users [those who dually use ENDS and other tobacco product], current users [those who currently use tobacco products], former users, and never users) in the Consumer Perception Studies rated the perceived health risks and addiction risks of all new products below CC, at a similar level or slightly above NRT, and above cessation. Current tobacco users and dual users rated all new products on health risks and addiction risks as "Moderate Risk."
- In the Consumer Perception Studies, for all new products, dual users reported the greatest interest in purchase, trial, and use of the new products, followed by current tobacco users and then former and never users, suggesting the highest likelihood of uptake by dual users of ENDS and other tobacco products. For all new products, between 31% to 64% of dual users responded "Likely" or "Definitely Likely" for the intentions items for the new products after viewing an image of the new products. In comparison, between 7.4% to 35% of current CC users responded "Likely" or "Definitely Likely" to the items assessing intentions to purchase, try, and use the new products. When presented with reasons why respondents would use the new products, more dual users endorsed intentions to use the new products to reduce current use of tobacco products than to use it to quit all forms of tobacco.
- The Consumer Perception Studies indicate that intent to use the tobacco-flavored new products among current users was 35.1% for PM0000529.PD1, 27.5% for PM0000535.PD1, and 26% for PM0000540.PD1. Current users were more likely to indicate intent to use the Logic Vapeleaf Regular product than Logic Vapeleaf products with non-tobacco flavors (not subject to this PMTA review). However, the Consumer Perception Studies only showed images of the new products and are also limited in generalizability due to methodological limitations, particularly among youth.
- Data obtained from the Consumer Perception Studies with adult dual users (those who dually use ENDS and another tobacco product) differed slightly in intent to use patterns from current users (those who currently use tobacco products). Intent to use Logic Vapeleaf Regular products (48%) if offered by a friend was the lowest among all Logic Vapeleaf products (all characterizing flavors, some not subject to this PMTA review). Intent to use Logic Power Tobacco products was 56%; intent to use Logic Pro Tobacco products was 64%. However, the Consumer Perception

Studies are limited in generalizability due to methodological limitations, particularly among youth.

3.4.1.3. Tobacco nonusers (including youth)

Per the BCP review:

- The applicant submitted five clinical studies (LP001-LP005) in adults indicating lower abuse liability for the tobacco-flavored new products among adult current tobacco users relative to CC. Although tobacco nonusers including youth were not included in the applicant-submitted clinical studies, the comparably low abuse liability of the new products relative to CC suggests progression to and sustained use of the new products among tobacco nonusers is likely to be lower than progression to and sustained use of tobacco products with greater abuse liability (e.g., CC).
- Due to the low abuse liability of the new products compared to CC, former and non-tobacco users (including youth) who initiate use of the new products are less likely to progress to regular use of the new products. The applicant did not submit clinical studies or reviewed literature addressing initiation or progression to regular use of the new products among tobacco nonusers or youth.

Per the social science review:

- Results from the Consumer Perception Studies and Exit Interviews were conducted in adults only and are limited in their ability to describe the likelihood of actual use of the new products in the U.S. population due to methodological limitations, particularly among youth. These limitations were considered in the synthesis of this data.
- The Consumer Perception Studies provided data on intent to use the new products: for adult never users by product: 2.6% were interested in trying the Logic Vapeleaf Regular product, 4.7% were interested in trying the Logic Power Tobacco product, and 5.3% were interested in trying the Logic Pro Tobacco product if recommended by a friend. However, the Consumer Perception Studies are limited in generalizability due to methodological limitations, particularly among youth.
- Taking into consideration the existing low prevalence of ENDS use by older adult (aged 25+ years) never tobacco users, and the findings from the Consumer Perception Studies, the likelihood of initiation of tobacco use with the new products by adult nonusers is low. These data also suggest that youth appeal for the new products is low (as further discussed in Sections 3.4.1.5. and 3.4.1.6.).
- In the Consumer Perception Studies, former tobacco users, on average, rated the new products as “Moderate Risk” to “High Risk,” while never users rated the new products as “High Risk.”
- The applicant did not submit any data from youth under age 21 and did not discuss the submitted data’s applicability to youth. This lack of applicant-submitted youth data and the lack of sufficient bridging information or information in the literature regarding the new products limited the social science review conclusions about whether young people will initiate ENDS use with the new products. However, other data relevant to youth use of Logic products has become available.
- In 2021, Logic products were not among the top five brands reported for use among youth despite being one of the options available for selection in the 2021 survey (Park-Lee et al., 2021). However, use of the new products by youth ENDS

users might substantially change, depending on the availability of other products on the market.

- The 2020 NYTS queried Logic brand use, but this analysis did not report on 2020 Logic brand use among youth due to unstable estimates, and therefore this reference cannot be used to provide updated prevalence of youth Logic brand use (Wang et al., 2021). The applicant did not cite results from the 2020 NYTS data because it was not available at the time the applicant provided a deficiency response.
- In 2021, 11.3% of high school students and 2.8% of middle school students reported current e-cigarette use (Park-Lee et al., 2021). It is possible that the number of youth who were current ENDS users was higher than reported in 2021; approximately half of students took the survey at home, which may have resulted in an under-reporting of tobacco use behaviors (Biglan, Gilpin, Rohrbach, & Pierce, 2004; HHS, 2012)). Longitudinal research using 2013-2015 U.S. Population Assessment of Tobacco and Health Study (PATH) data indicated that 42.2% of past 30-day youth ENDS users remained past 30-day ENDS users one year later (Stanton et al., 2019). These published findings indicate significant risk of ENDS use among youth. However, youth are less likely to initiate tobacco-flavored ENDS and subsequently progress to regular use than with non-tobacco-flavored ENDS. Youth are more likely to initiate non-tobacco-flavored ENDS and subsequently progress to regular use than with tobacco-flavored ENDS. For instance, in Wave 1 of the PATH Study from 2013-2014, over 80% of youth aged 12-17, 75% of young adults 18-24, and 58% of adults 25 and older reported that the first ENDS that they used was non-tobacco-flavored (Villanti et al., 2019). In another PATH study, more youth, young adults and adults who initiated ENDS use between Wave 1 and Wave 2 reported use of a non-tobacco-flavored product than a tobacco-flavored product (Rose et al., 2020). Finally, in PATH Wave 4 from 2016-2017, 93.2% of youth and 83.7% of young adult ever ENDS users reported that their first ENDS product was non-tobacco-flavored compared to 52.9% among adult ever users 25 and older (Rostron, Cheng, Gardner, & Ambrose, 2020). Additionally, existing literature on non-tobacco-flavored product use suggests that non-tobacco flavors not only facilitate initiation, but also promote established regular ENDS use. For example, regional studies have found that the use of non-tobacco-flavored ENDS was associated with a greater frequency of ENDS used per day among a sample of adolescents in Connecticut in 2014 (Morean et al., 2018) and continuation of ENDS use in a sample of adolescents in California from 2014-2017 (Leventhal et al., 2019). Use of non-traditional flavors (vs. tobacco, mint/menthol, flavorless) was associated with increased likelihood of continued use and taking more puffs per episode (Leventhal et al., 2019). Data from a regional survey in Philadelphia, PA found initial use of a non-tobacco-flavored (vs. unflavored or tobacco-flavored) ENDS was associated with progression to current ENDS use as well as escalation in the number of days ENDS were used across 18 months (Audrain-McGovern, Rodriguez, Pianin, & Alexander, 2019). Finally, similar effects have been found in the nationally representative PATH study among young adults (18-24 years), where “ever use” of non-tobacco-flavored ENDS at Wave 1 was also associated with increased odds of current regular ENDS use a year later at Wave 2 (Villanti et al., 2019). Collectively, these findings indicate that while all ENDS pose risks to youth, youth are less likely to initiate tobacco-flavored ENDS, and to

subsequently progress to regular use of such products, than with non-tobacco-flavored ENDS.

- The limitations of data on youth appeal in PM0000529.PD1-PM0000531.PD1, PM0000535.PD1-PM0000537.PD1, PM0000540.PD1, and PM0000541.PD1 do not rise to the level of a concern from the social science perspective. The e-liquids in these PMTAs are tobacco-flavored e-liquids or closed, unflavored e-liquids (with no known functionality for users to add flavors to the e-liquids and which have unique compatibility with the Logic Vapeleaf system, which has a tobacco characterizing flavor). The interest in tobacco-flavored products is low among youth. The available evidence (NYTS 2021) indicates that a higher proportion of middle and high school current users reported using flavored ENDS than unflavored ENDS (including tobacco flavor) (Park-Lee et al., 2021). Most youth (93.2%) report that their first ENDS use was with a flavor other than tobacco (Rostron, Cheng, et al., 2020). In 2020 NYTS data, 84.7% of high school ENDS users and 73.9% of middle school ENDS users reported using non-tobacco-flavored ENDS (Wang et al., 2020). Thus, the tobacco-flavored new products are unlikely to have significant youth appeal.
- According to NYTS 2021 data, 28.7% of middle and high school users reported prefilled or refillable pods or cartridges as the ENDS device types they used most often (Park-Lee et al., 2021). Sleek design, ability to use products discreetly, and user-friendly nature make pod-based (rechargeable cartridge-based ENDS) products appealing among youth. Although the new products are not pod-based, they are sleek and small in design, user friendly cartridge-based, and easily rechargeable. Although there is some risk of youth uptake of these products, in general, tobacco-flavored ENDS are less appealing to youth compared to non-tobacco-flavored ENDS, making the risk of youth initiation low for these products. NYTS data support that when FDA implemented the 2020 Enforcement Priorities Guidance ("Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised). Guidance for Industry," April 2020) to prioritize enforcement actions for pod-based flavored ENDS, youth switched to disposable ENDS with non-tobacco/non-menthol flavors rather than switch to tobacco- or menthol-flavored pod-based ENDS. These data suggest that flavor has greater influence on youth product selection compared to device type or design. Specifically, among youth ENDS users in 2021 NYTS data, 53.7% (95%CI: 48.7–58.6) stated they use disposable ENDS compared to 28.7% (95%CI: 25.1–32.6) who stated they use pod or cartridge based ENDS (Park-Lee et al., 2021), representing a change in device type use from earlier waves of data. NYTS 2019 and 2020 data further show that the percentage of youth ENDS users who select disposable ENDS increased coinciding with the enforcement prioritization, with use prevalence among youth ENDS users increasing from 3.0% (95%CI: 1.7-5.4) for middle school and 2.4% (95%CI: 1.6- 3.7) for high school in 2019 to 41.3% (95%CI: 31.9-51.4) for middle school and 26.5% (95%CI: 20.0- 34.2) for high school in 2020 (Wang et al., 2021b). NYTS 2020 and 2021 data show that during this time period where cartridge-based ENDS use decreased and disposable ENDS use increased, use of flavored ENDS among youth ENDS users remained stable (82.9% in 2020 and 84.7% in 2021) with fruit as the most prevalent flavor for both years (Park-Lee et al., 2021; Wang et al., 2020).
- Findings from a discrete choice experiment showed that non-tobacco flavors were associated with more curiosity, less perceived danger, and greater perceived ease-

of-use among high school students, compared to tobacco flavor (Chaffee et al., 2020). Additionally, the published literature indicates that youth report significantly higher preference for non-tobacco-flavored ENDS compared to tobacco-flavored ENDS (Groom et al., 2020; Harrell et al., 2017; Morean et al., 2018). Moreover, the evidence indicates that tobacco-flavored ENDS are less likely to be used by youth who initiate or regularly use ENDS compared to non-tobacco flavors. The findings from the 2020 MTF survey provide evidence that youth use of tobacco-flavored ENDS is less common compared to other flavored ENDS including mint (Miech et al., 2021). According to the 2020 MTF data, the prevalence of tobacco flavor was 2.9% among 10th and 12th graders while mint was the second most often used flavor (26.9%) after fruit (59.3%) (Miech et al., 2021).

Per the epidemiology review:

- The applicant presented information on intentions and perceptions from their Consumer Perception Studies in an attempt to discuss the likelihood of initiation of the new products; however, the applicant did not present actual use or initiation estimates. The applicant did not provide studies from the peer-reviewed literature containing information on the likelihood that adult or young adult nonusers of tobacco will start using the new products. The applicant provided a short review of published studies on youth initiating tobacco use with ENDS and suggested that estimates of youth ENDS initiation varied widely.
- In 2021, Logic products were not among the top five brands reported for use among youth (despite being one of the options available for selection in the 2021 NYTS survey) (Park-Lee et al., 2021). However, the data are not specific to the Logic products subject to these PMTAs and may represent other types and flavors of Logic ENDS.
- To address initiation of the new products, or ENDS generally, among former tobacco users, the applicant provided a summary of information from the literature and suggested that ENDS use among former smokers is relatively low. Studies suggest that some adult former smokers do use ENDS, but data from both the PATH and National Health Interview Survey (NHIS) suggest that ENDS use among adult former smokers is less common than among current adult smokers.
- The published literature shows that prevalence of youth use of tobacco-flavored ENDS is low and that tobacco-flavored ENDS are less likely to be used by youth who initiate or regularly use ENDS compared to non-tobacco flavors.

3.4.1.4. Vulnerable populations (other than youth)

Per the social science and epidemiology reviews:

- The applicant did not provide information on use of the new products among vulnerable populations—i.e., groups that are susceptible to tobacco product risk and harm due to disproportionate rates of tobacco product initiation, use, burden of tobacco-related diseases, or decreased cessation. Evidence from the published literature indicates that all age groups with substance use or mental health issues are more likely to use ENDS compared to those without these conditions (Cho et al., 2018; Conway et al., 2018; Riehm et al., 2019). Additionally, the prevalence of ENDS use is higher among other vulnerable populations (e.g., pregnant persons, and

lesbian, gay, and bisexual individuals) (Azagba, Latham, & Shan, 2019; Buchting et al., 2017; Hawkins, Wylie, & Hacker, 2020; Obisesan et al., 2020; Wheldon & Wiseman, 2019). While the evidence indicates that some vulnerable populations experience disproportionate ENDS use, there is a lack of currently available evidence to show whether the new products would help facilitate adult CC smokers from vulnerable populations to switch or reduce CPD.

Per the BCP review:

- No clinical studies were provided or reviewed by the applicant addressing use of the new products among vulnerable populations. The applicant submitted five clinical studies (LP001-LP005) indicating lower abuse liability among adult CC smokers for the new products relative to CC, which suggests the new products may not pose greater risk of progression to regular use and addiction among vulnerable populations other than youth compared to CC. However, these studies did not specifically assess vulnerable populations, and from a BCP perspective, this information is insufficient and the impact of the new products on abuse liability and product use behavior in vulnerable populations other than youth is unknown.

3.4.1.5. Actions taken to mitigate risk to nonusers, including youth

Per the OHCE consult:

- OHCE reviewed the relevant marketing submissions and drafted a consult dated 11/22/2021.
- The marketing plan information submitted by the applicant includes very limited information on its intended labeling, advertising, marketing, and promotion for the new products for at least the first year the products would be marketed after receiving an order. Furthermore, the applicant did not provide robust product-specific data on the degree to which its labeling, advertising, marketing, and promotion may influence youth perception, youth appeal, and the likelihood of youth initiation of tobacco use.
- The applicant stated that it intends to market its products to adult smokers and ENDS users aged 21 years and older. The applicant does not describe plans to further segment its target audience by demographic characteristics (e.g., race/ethnicity, geographic region), psychographic characteristics, or behaviors other than current tobacco use.
- The applicant's choice of marketing channels and tactics impacts youth exposure and appeal. Based on the limited information submitted by the applicant and review of publicly available information online, it appears that the applicant uses, or has used the following marketing channels and tactics: an owned e-commerce website; social media marketing (Facebook, Instagram, YouTube); TV and radio advertising; paid digital advertising; point-of-sale advertising; out-of-home advertising (e.g., mass transit, billboards, cinema); tradeshows; events; and sponsorships. Because the applicant did not describe its plans for marketing the products the first year after receiving an order in the subject applications, it is difficult for OHCE to assess whether the applicant plans to continue marketing via the above channels and tactics. The applicant has discontinued online sales of all Logic products from its website and has eliminated its social media accounts. Many of the advertising

examples found during a routine internet search were from 2015-2019, including the TV commercials. Thus, it is possible that the applicant may have altered its marketing approach. However, given that the applicant has not communicated definitively about its future marketing plans, OHCE is concerned that, absent robust marketing restrictions, the applicant could resume its use of marketing channels and tactics with significant youth reach and appeal.

- The applicant briefly described a few measures intended to restrict youth access to its products, minimize youth appeal, and limit youth exposure to its products' marketing, but did not provide a clear description of its approach to youth restrictions overall. Furthermore, the applicant did not describe plans to further segment its marketing audience by demographic characteristics (e.g., race/ethnicity, geographic region), psychographic characteristics, or behaviors other than current tobacco use. The applicant did not describe any past or future actions to limit youth exposure to its product marketing via the following channels and tactics: broadcast TV and radio; paid digital; out-of-home; tradeshows, events, or sponsorships.

- OHCE noted support for certain measures described in the application, including: the elimination of all social media accounts (which the applicant states it has done as of September 28, 2020); not currently paying social media or any other influencers to market or promote the products; not employing social media bots to market the products; using only models over the age of 30 in consumer marketing materials; not using characterizing words such as sweet, fruity, candy, juicy, iced, soda, mouthwatering, sugary, gummy, sour, tart, cool, or naturally flavored; not using cartoon imagery or images of foods marketed to youth; requiring adult consumers to confirm they are current tobacco or vapor users and to participate in mandatory age verification before any in-person interactions with Logic products; providing retail partners with the most advanced and up-to-date training to ensure only adult consumers can access the products; supporting the We Card program as a member of the Manufacturers' Advisory Council; discontinuation of online sales of all Logic products via the applicant's website (as of March 16, 2021).
- To address concerns identified by OHCE, including the applicant's past marketing practices, any MGOs for the new products should include specific marketing requirements, including restrictions on digital marketing and TV and radio advertising to protect youth. Additionally, any MGOs for the new products should include the requirement to submit 30-day advance notifications of marketing plans for a period of time. Any MGOs should also note support for certain aspects of the applicant's marketing practices (described above) and recommend that such practices be implemented to help further mitigate the risks to youth. Finally, any MGOs should recommend that the applicant take additional steps to limit youth exposure to any out-of-home, point-of-sale, or print advertising, including, for example, limiting advertising to print publications where 85% or more of the readership is 21 years of age or older and/or selecting publications that do not over-index for youth.

Per the social science review:

- As of March 16, 2021, Logic has discontinued online sales of all Logic products (https://www.logicvapes.us/ecommerce-closure-consumer-messaging). In addition, it appears that consumers must make an account by providing their personal

information including name, address, and last four digits of their social security number in order to view the applicant's website (as of April 02, 2021).

3.4.1.6. Labeling, packaging, and advertising

Per the social science review:

- Per 21 CFR 1143.3, packages and advertising of covered tobacco products other than cigars must bear the statement "WARNING: This product contains nicotine. Nicotine is an addictive chemical." (nicotine warning statement). As noted in the DPAL memo finalized on January 16, 2020, some of the submitted materials do not include the nicotine warning statement. The leaflet for Logic Power Rechargeable Kits do not bear the nicotine warning statement on any page (*e-1-2-tob-recharge-kit-leaflet-pwr*). (b)(4)
- On February 28, 2020, the applicant submitted new information about product labeling for Logic Pro and Power products, which included images of the Logic Power product user guide insert, Logic Pro product user guide insert, and Logic Pro Capsule Tank System carton. The amendment received on February 28, 2020 does not address the concerns raised in the DPAL memo about the required nicotine warning statement.
- DPAL recommends that any MGO for the new products include a reminder that the applicant must comply with all applicable requirements, including the nicotine warning statement for covered tobacco products required under 21 CFR 1143.3. Social science concurs with this recommendation.
- The leaflet/user guide submitted with the Logic Vapeleaf products described the product as "A unique combination of vapor technology and real tobacco provides satisfying taste with no smoke smell and no ash." In addition, the Point-of-Sale advertisement for the Logic Vapeleaf Regular products included a similar statement: "Real Tobacco. No Smoke Smell. No Ash." Also, the cartridge and capsules shelf carton show a statement "No Ash, No Smoke Smell" on one side of the package, above the image of the device. Based on the information presented at this time, there is insufficient information to conclude that the above statements on the Logic Vapeleaf materials submitted with the application, or any other information in the applicant's other labeling/advertising for Logic Vapeleaf products do in fact convey modified risk. Accordingly, Social Science does not conclude that this labeling/advertising would cause the new tobacco products to be modified risk tobacco products.
- The applicant assessed comprehension of overall package labeling and marketing materials (specifically, the warning label) for the new products in the Consumer Perception Studies. The overall comprehension score for the new products' labeling and marketing materials appears adequate.

[10] This sample was misidentified in the DPAL review as e-2-2-cap tank-system-pack-pro.

- As described below, the applicant provided proposed labeling. Based on the information presented at this time, we have not concluded that the proposed labeling is false or misleading in any particular.

In order to assess the statements "A unique combination of vapor technology and real tobacco provides satisfying taste with no smoke smell and no ash." and "Real Tobacco. No Smoke Smell. No Ash." on the Logic Vapeleaf packaging, a meeting with chemistry and engineering disciplines was held. The PMTA Internal Meeting Record dated December 17, 2019 with chemistry and engineering disciplines concluded:

- Because the tobacco is heated, and not combusted, it should not produce ash or a smoke smell under normal use conditions.
- The lower HPHC levels in the Logic Vapeleaf Regular product's aerosol (compared to CC) also suggest that the tobacco is not combusted and therefore will not produce ash or a smoke smell.
- Although CTP did not have specific data at the time to indicate that such statements are modified risk claims, they may convey modified risk.

3.4.2. Synthesis

As TPL, I agree with the epidemiology, social science, and BCP reviews which conclude that current CC smokers (who become dual users upon initiation of ENDS) are the most likely populations to use the new products. This conclusion is based on the applicant-submitted clinical study data on intentions to use the new products, actual use behavior, and abuse liability, as well as conclusions from the literature about ENDS in general.

The applicant's Consumer Perception Studies suggest that dual ENDS and other tobacco product users, followed by current tobacco users are the most likely user populations to purchase, try, and use the new products. Dual users endorsed using the new products to reduce current use of tobacco products rather than to quit all tobacco products, indicating the new products may initially facilitate dual use.

The applicant-submitted data indicate that use of the new products may reduce CC smoking by greater than 80% and thereby reduce nicotine exposure and dependence (see Section 3.3.). Most participants (CC smokers) in the clinical studies decreased their usual brand CPD to just 1-2 CPD, regardless of Logic sub-brand. Importantly, LP004 and LP005 required that CC smokers be randomized to a new product, and participants' usual brand CC preference (i.e., menthol or non-menthol CC) or ENDS characterizing flavor preference was not considered in the study's randomization scheme. Given that all study cohorts decreased CPD (following 60 days of new product use) to a similar degree, these data suggest that all new products are viable substitutes to CC smoking and a means to CC cessation among those interested in quitting.

These new product-specific data are in line with the current literature where studies suggest that CPD (and exhaled CO; see Section 3.5.1.2.) decreases among CC smokers who initiate ENDS use (e.g., (DeVito et al., 2019; Goniewicz et al., 2017; Hickling et al., 2019; Litt, Duffy, & Oncken, 2016; Masiero et al., 2019; Truman, Gilmour, & Robinson, 2018; Valentine et al., 2018). Thus, the new products are likely to promote significant decreases in CC consumption and nicotine exposure, which may facilitate smokers' transition away from CC smoking and

aid in successful CC cessation. As discussed in Section 3.5.1.2., the data also suggest that the dual use and reduced CC consumption lead to significant decreases in exposure to most non-nicotine BOE.

The applicant-submitted data do not suggest that the new products will promote CC cessation, at least in the 60 days assessed in LP004, LP005. But because they may facilitate incomplete switching (i.e., dual use) and decrease CPD, the new products may still promote CC quit attempts and, ultimately, CC cessation. In addition, there is no evidence to suggest that CC smokers will increase their overall tobacco use when initiating use of these new products.

I also agree with the epidemiology, social science, and BCP conclusions that the impact the new products, and ENDS in general, may have on promoting complete switching (i.e., CC cessation) is unclear. The applicant-submitted clinical studies do show a significant decrease in CPD upon all new products' initiation, although the implications of those findings are limited due to study design and limited applicability to real-world situations. Therefore, given that all study cohorts decreased CPD following 60 days of new product use to a similar degree (most participants decreased CPD by more than 80%), these data suggest that the tobacco-flavored new products (regardless of sub-brand) may be viable substitutes to CC.

As TPL, I have compared each new product to the appropriate comparison product, CC. I conclude that the totality of evidence suggests that the new products would benefit current smokers who substantially reduced their CC smoking or experienced CC cessation.

Regarding adult non-tobacco users, findings from the Consumer Perception Studies indicate low intent to use the new products; however, the findings are limited in generalizability and the Consumer Perception Studies did not evaluate intent to use among youth nonusers. Nonetheless, the published literature shows that prevalence of youth use of tobacco-flavored ENDS is low and that tobacco-flavored ENDS are less likely to be used by youth who initiate or regularly use ENDS compared to non-tobacco flavors.

The BCP review concluded that due to the relatively low abuse liability of the new products (compared to CC), non-tobacco users (including youth) who initiate use of the new products are less likely to progress to regular use of the new products. Although youth use of ENDS is concerning, as previously discussed, the published literature shows that prevalence of youth use of tobacco-flavored ENDS is low and that tobacco-flavored ENDS are less likely to be used by youth who initiate or regularly use ENDS compared to non-tobacco flavors. The findings from the 2020 MTF survey provide evidence that youth use of tobacco-flavored ENDS is less common compared to other flavored ENDS including mint (Miech et al., 2021). According to the 2020 MTF data, the prevalence of tobacco flavor was 2.9% among 10th and 12th graders while mint was the second most often used flavor (26.9%) after fruit (59.3%) (Miech et al., 2021). Although over a quarter of youth ENDS users reported using prefilled or refillable pods or cartridges most often in the 2021 NYTS data (Park-Lee et al., 2021), NYTS data suggest low youth prevalence rates associated with the Logic brand. The applicant did not cite recent results from analysis of 2020 NYTS data (which were unavailable at the time the applicant provided deficiency responses). The social science review stated that 2020 NYTS queried Logic brand use, but this analysis did not report on 2020 Logic brand use among youth due to unstable estimates, and therefore this reference cannot be used to

provide updated prevalence of youth Logic brand use (Wang et al., 2021). Based on the BCP, social science, and epidemiology conclusions, I agree that youth use of the tobacco-flavored e-liquids (and their associated devices) is likely low.

To further evaluate the new products' potential risk to youth, FDA examined the applicant's marketing plans and restrictions. The applicant has discontinued its sale of all new products directly to consumers (i.e., online), requires third-party verified accounts for age-restricted website access, and has eliminated all social media accounts (see Section 3.4.1.5.). The applicant did not clearly indicate whether and for how long it intends to keep these measures in place. These practices (and others described in Section 3.4.1.5.) in combination with other use mitigation strategies, reduce the potential for youth access to and product purchase from the applicant's website.

With respect to marketing, OHCE reviewed the marketing information provided by the applicant, including information about advertising and promotion and sales access. Notably, the marketing plan information submitted by the applicant included very limited information on its intended labeling, advertising, marketing, and promotion for the new products for at least the first year the products would be marketed after receiving an order. It was also unclear whether certain measures described by the applicant (e.g., discontinuation of online sales; elimination of all social media accounts) will be implemented on an ongoing basis. OHCE expressed concerns with certain aspects of the information that was provided and was supportive of other aspects. As TPL, I agree with OHCE's evaluation. I also agree that the marketing restrictions recommended by OHCE are necessary to mitigate the risk to youth. Accordingly, I recommend that the MGO letter include the marketing requirements and recommendations specified in the OHCE consult.

Regarding product labeling, packaging, advertising, there are insufficient data at this time to conclude that the statements "A unique combination of vapor technology and real tobacco provides satisfying taste with no smoke smell and no ash" and "Real Tobacco. No Smoke Smell. No Ash." are misleading, and the statements do not contain scientifically false information from an engineering or chemistry perspective. Therefore, I conclude that PM0000529.PD1-PM0000531.PD1 should not be denied under 910(c)(2)(C) of the FD&C Act (see Section 3.4.1.6. and 3.8.3.).

As TPL, I agree with the DPAL memo that the applicant must include the mandatory nicotine warning statements on packages and advertising for its covered tobacco products. However, as TPL I disagree with some of the samples cited in the DPAL memo. The contents of the Logic Pro package (e-1-1-cap-tank-system-pack-pro) are components/parts that do not contain nicotine, and therefore are not covered tobacco products subject to the mandatory nicotine warning statement in 21 CFR 1143.3. The leaflet for Logic Power Rechargeable Kit (PM0000541.PD1 packaged with PM0000540.PD1) (e-1-2-tob-recharge-kit-leaflet-pwr) consists primarily of user instructions for the product. Although the leaflet directs consumers to the Logic website, it appears to direct them there so that they can obtain further information about the product, based on the fact that it is listed under the "contact us" section along with a telephone number for a customer helpline. Therefore, I am unable to conclude at this time that the leaflet is advertising and that a nicotine warning statement is required.

(b) (4)

While the DPAL recommendation was for the MGO for the new products to include an explicit reminder that the applicant must comply with all applicable requirements, including the nicotine warning statements for covered tobacco products required under 21 CFR 1143.3, this statement is already covered. The main body of the order letter contains language reminding applicants of their responsibility to ensure the new products comply with all applicable statutory and regulatory requirements and notes that FDA monitors for compliance.

Lastly, I conclude that all product labeling and marketing information has appropriate comprehension scores.

3.5. TOXICANT EXPOSURE

The toxicology discipline evaluated in vitro genotoxicity and cytotoxicity studies that compared all new products to the 3R4F research cigarette. They also compared chemical constituents (HPHCs) from the new products' aerosol, the reference ENDS (VUSE Vibe Original and blu PLUS Classic Tobacco) and conduced a toxicity assessment.

The BCP discipline evaluated BOE from the forced switch, 60-day clinical studies (LP004, LP005).

3.5.1. Discipline key findings

The following discussion is based on key findings provided in the discipline reviews:

3.5.1.1. Toxicity

Per the toxicology review:

[11] Section 910(c)(2)(C) provides that FDA shall deny a PMTA if, "based on a fair evaluation of all material facts, the proposed labeling is false or misleading in any particular." (b) (4)

- The CC, Pall Mall Red Kings, used as a comparison product, did not induce genotoxicity in the in vivo micronucleus assay. This result is inconsistent with in vitro data showing that CC smoke from both the comparison product Pall Mall Red Kings and the reference cigarette 3R4F induced cytotoxicity and genotoxicity at the same cigarette smoke concentrations tested in vivo. Differences in results may be due to experimental issues related to the lack of systemic exposure leading to low sensitivity to detect DNA damage vs. in vitro system tested.
- The genotoxicity study indicates that total aerosol collected matter (ACM) and gas vapor phase (GVP) from all new products, under the conditions of the study, had no mutagenic potential in vitro in a bacterial reverse mutation assay (Ames test) at any concentration tested, either with or without metabolic activation. In contrast, total particulate matter (TPM) from 3R4F reference cigarette and CC Pall Mall Red Kings smoke produced a positive result in five strains of bacteria used in the Ames test after metabolic activation. In addition, for all new products, no evidence of mutagenic toxicity was observed in in vitro and in vivo micronucleus assays; and there was no evidence of cytotoxicity in neutral red uptake (NRU) assay under the conditions of these studies.
- In general, exposure of CC mainstream smoke tested at all the concentrations (low, mid, and high) produced toxic effects that were more severe than those produced by the new products.
- The ingredients and structural materials for the new products are in the TPMF, and the provided information is acceptable from a toxicological perspective.
- There are some caveats in comparing ENDS to combusted tobacco products: 1) these two types of tobacco products are greatly different (e.g., constituents and the ways they are used); 2) different consumer topographies and different testing regimens are used to compare them. Due to the differences, not all HPHCs reported for the new products were reported for the CC and vice versa.
- Chromium was detected in the aerosols of the new products and the comparison ENDS, but was not present at sufficient levels for quantification in the CC mainstream smoke. High levels of heavy metals are known to be involved in respiratory and gastroenterology pathology, and are carcinogenic. However, overall HPHCs are lower in all new products' aerosols compared to a CC, Pall Mall Red Kings. On per TPM weight basis, HPHC levels were lower in new products' aerosols by 70%-100% compared to the CC. These HPHC levels for the new products were also lower (83%-100%) when compared to the CC levels on per nicotine yield basis.
- The applicant submitted a risk assessment for the identified, partially identified, and unknown simulated leachable compounds in the new products. The applicant concluded that the potential risks to consumers from identified and partially identified leachable compounds are acceptable but risk for the unknown leachable compound was above the benchmark value of 1.0 which indicates potential risks of concern. Although the simulated leachable compounds for all new products can be hazardous, at the low levels present, if there is any contribution towards cancer hazard, these risks are outweighed by decreases in HPHCs by 83-99% in all new products.

3.5.1.2. Biomarkers of exposure

Per the BCP review:

- Exposure to ENDS increased during the course of the 60-day clinical studies (LP004, LP005), evidenced by the significant increase in urinary PG concentration in all new product cohorts.
- In LP004 and LP005, total nicotine equivalents (TNeq) were not different between any Logic Power or Pro Tobacco product and usual brand CC cohorts. TNEq was significantly lower in the Logic Vapeleaf Regular product cohort compared to usual brand CC cohorts, indicative of the low nicotine delivery associated with the Logic Vapeleaf Regular product.
- The applicant-submitted clinical studies (LP004, LP005) showed that BOEs (e.g., TSNAs, VOCs, s-phenylmercapturic acid [S-PMA], and carboxyhemoglobin [COHb]) are generally lower in CC smokers who used the new products compared to CC smoking cohorts. NNN, however, was not significantly lower in any of the Logic product cohorts on day 59, compared to CC cohorts; however, the NNN $t_{1/2}$ (half-life; the time it takes for a drug to reach half of its initial concentration in the body) in humans is unknown.
- Although complete switching from usual brand CC to the new products is low, the literature and applicant-sponsored clinical studies (LP004, LP005) demonstrate that CC smokers who initiate ENDS use and significantly decrease CPD (i.e., dual users) are generally exposed to lower levels of multiple BOEs.

Per the epidemiology review:

- Biomarker data from observational studies generally show that ENDS users have higher exposure to nicotine, some VOCs, and TSNAs than do non-tobacco users (Goniewicz et al., 2018; Rubinstein, Delucchi, Benowitz, & Ramo, 2018). Some biomarker data from observational studies have also found that dual users can have higher levels of certain BOE than exclusive CC smokers (Goniewicz et al., 2018; Rostron et al., 2019).

3.5.2. Synthesis

I agree with the toxicology review that the in vitro toxicology data suggest aerosols from the new products are less mutagenic, genotoxic, and cytotoxic compared to smoke from CC under the conditions tested. In addition, the effects of in vivo exposure to the new products were typically reversible and less severe compared to the effects of exposure to mainstream CC smoke, which produced toxic effects that were more severe and often irreversible. In lieu of long-term health data (see Section 3.6.1.4.), these in vitro toxicology data may suggest that the new products are associated with fewer (or less severe) long-term health risks than continued CC smoking. However, these in vivo data did not evaluate the impact of dual use of the new products and CC, which is the most likely use behavior associated with the new products (see Section 3.4.2.1.1.).

I also agree that most HPHCs and other constituents are lower in aerosol yields (from all regimens tested) from the new products compared to CC smoke yields (see Section 3.2.1.4.). Chromium levels are significantly higher in new product aerosols compared to CC smoke, but the chemistry discipline review noted that the levels are analytically equivalent to the representative ENDS, suggesting that their presence is due to the metal components in ENDS. Furthermore, the higher chromium levels in the new products, compared to CC, are outweighed by the decreases in HPHCs associated with the new products. Nevertheless, the

impact of metal exposure from ENDS has not been evaluated in the long-term health risk literature. These results are reflected in the BOE evaluated in the clinical 60-day switching studies that showed the new products are associated with lower levels of many BOE compared to CC smoking cohorts. The BCP review concluded that these lower BOE are evident even upon dual use of the new products and CC, when CC smoking decreased; indeed, the peer-reviewed literature suggests that reductions in BOE are dependent upon decreased CPD. Although the likelihood of exclusive new product use is low given the new products' relative low abuse liability (see Section 3.3.), it is likely that exclusive new product users who switch from CC would experience greater reductions in many BOE.

3.6. HEALTH EFFECTS

The toxicology discipline evaluated results from 90-day nose-only repeated inhalation non-clinical studies (95019D, 95019B, 95019F) that were conducted with adult male and female rats to evaluate toxicity endpoints, including survival, body weight, respiratory physiology, and gross observations. All new product aerosols were tested at various concentrations and compared to Pall Mall Red Kings CC smoke.

The short-term health effects of new products were evaluated through the applicant-submitted clinical studies and literature review. The BCP discipline evaluated nicotine and non-nicotine BOE in LP004 and LP005. The medical discipline evaluated adverse experience (AE) data in all applicant-submitted clinical studies, and evaluated physiological effects and BOPH associated with the new products compared to CC smoking and cessation cohorts in the clinical 60-day switching studies (LP004, LP005). In addition, they evaluated FDA's internal databases of voluntary reports related to Logic ENDS in general. Furthermore, the medical discipline evaluated the applicant-submitted literature search about ENDS and their associated health effects.

3.6.1. Discipline key findings

The following discussion is based on key findings provided in the discipline reviews:

3.6.1.1. Toxicology

Per the toxicology review:

- Studies submitted by the applicant indicate that 90 days of non-clinical, repeated inhalation exposure to all new products' aerosols is associated with concentration-dependent exposure to biomarkers such as nicotine and cotinine when compared to control, demonstrating systemic exposure to nicotine. There was no accumulation or sex dependent differences observed in the non-clinical studies (95019D, 95019B, 95019F) submitted by the applicant.
- Data submitted by the applicant from 90-day inhalation studies with rats indicates that repeated exposure to the Pall Mall Red Kings CC smoke affected body weight, increased presence of proinflammatory markers in the lungs, produced some evidence of liver toxicity, affected differential blood counts, and altered lung physiology. These changes were either not observed, or were significantly less severe, in male and female rats repeatedly exposed to all new products' aerosols. Similarly, while rats exposed to all new products' aerosols exhibited histopathological changes like hyperplasia, metaplasia, and tissue degeneration,

those changes were generally less severe than those observed in rats exposed to CC smoke.

- Seizures were observed in female rats exposed to high concentrations of Logic Pro Tobacco (PM0000535.PD1) aerosol (up to 20% incidence). The reasons for the seizures are unknown. Due to the recent clinical surveillance reports of cases of seizures associated with ENDS use (Faulcon, Rudy, Limpert, Wang, & Murphy, 2020) which suggest an association between ENDS use and seizures, the current experimental results are relevant and of concern. The applicant provided a response to FDA Deficiency letter dated June 26, 2020, in regard to seizure occurrence in Logic Pro Tobacco (PM0000535.PD1) products in Sprague Dawley female rats with rationale from the scientific literature. However, the applicant did not provide rationale for why scientific literature (Gauvin, Zimmermann, Yoder, & Baird, 2018) can be bridged to the tobacco regulatory environment and is solely used to determine test-article related seizures. The applicant also did not provide information to determine if other physiological factors (i.e., blood glucose, oxygen saturation, body temperature), external stimuli (i.e., handling, light stimulation), sex differences, or constituents other than nicotine influenced seizure occurrence. The scientific evidence provided by the applicant also lacks information or a discussion regarding ENDS use in the central nervous system and there is no neurotoxicity test data related to the new product. In addition, much of the ENDS literature does not discriminate between different types or brands of ENDS. Moreover, the literature is not sufficient to clarify relative health effects among different ENDS. In conclusion, any association that may exist between the usage of the new product and seizure occurrence has not been fully characterized. Therefore, the toxicology discipline recommends monitoring post-market AE reports for seizures and/or neurological symptoms.
- There are several limitations to these non-clinical studies (95019D, 95019B, 95019F). No biomarkers such as reactive oxygen species (i.e., oxidative stress) or cardiovascular parameters were measured or discussed. In fact, published data suggest that user exposure to ENDS is a potential concern for cardiovascular toxicities (Buchanan et al., 2020). The applicant provided absolute and relative heart weights and gross and histopathological findings for heart and aorta. Although the applicant did not provide enough details regarding a statistical analysis plan (including the statistical power analysis) for absolute and relative heart weights in male and female Sprague Dawley rats, it follows the OECD guidelines (No. 413) of utilizing 10 male and 10 female rats in the 90-day sub-chronic study. The statistical analyses from both the applicant and a CTP statistical consult did not find significant differences in heart weight between the study groups. In addition, there were no gross or histopathological findings in the heart or aorta of the core and recovery groups exposed to any new products' aerosol. Therefore, the toxicological evaluation determined that the applicant has adequately addressed the concerns from the toxicology perspective. Repeated exposure to the new products and the CC resulted in increased plasma nicotine and cotinine in a dose-dependent manner. There are no apparent sex differences or accumulation in the systemic exposure of nicotine and cotinine. Differences in time of exposure to all new products correlated with T_{max}. The nicotine concentrations (AUCs) measured at the no observable effect level (NOEL) from exposure to all new products were approximately 2-fold higher

than that of the CC at the lowest concentrations tested; however, HPHCs were lower for all new products when compared to the HPHCs from the CC.

- The applicant provided supporting data from ENDS published literature on cancer risk, cardiovascular effects, and other health effects (respiratory). The new products deliver similar nicotine (or less for the Logic Vapeleaf Regular [PM0000529.PD1] product) than Pall Mall Red Kings, and generally have lower or non-measurable levels of unwanted HPHCs, than Pall Mall Red Kings CC.
- The evaluation of the health risks of the new products is based on a comparison to CC. However, there are some caveats in comparing ENDS to combusted tobacco products: 1) these two types of tobacco products are greatly different (e.g., constituents and the ways they are used); 2) different consumer topographies and different testing regimens are used to compare them. Due to the differences, not all HPHCs reported for the new products were reported for the CC and vice versa.

3.6.1.2. BIMO inspection findings

FDA conducted BIMO inspections for two of the five applicant-submitted clinical studies (LP004, LP005). The first site was involved in LP004 and LP005: George S. Stoica, MD at Bioclinical Research. The second site was involved in LP005: Charles S. Tomek, MD at Celerion Inc. OCE concluded there were no human subjects concerns at either site. However, OCE classified Dr. Stoica's site as Voluntary Action Indicated due to investigational findings, including missing data and inadequate documentation of blood and urine storage, that may affect data reliability. Such findings likely do not have a major impact on the overall conclusions drawn in LP004 and LP005 because the conclusions from these studies are supported by other applicant-submitted data. Dr. Tomek's site was classified as NAI and there were no data integrity concerns. These findings were considered in disciplines' assessments of the data and outcomes.

No BIMO inspections were recommended or conducted during 2nd cycle scientific review.

3.6.1.3. Addiction as a health endpoint

Per the BCP review:

- The abuse liability of all new products is lower than that of CC. Current CC smokers (i.e., the applicant's stated intended user population for the new products) largely dual-use the new products with CC but reduce their CPD upon initiating use of the new products. In the actual use clinical studies, TNeq was not different between CC smoking and the Logic Pro Tobacco and Logic Power Tobacco cohorts upon dual use. Therefore, current CC smokers are likely to maintain their nicotine addiction severity via dual use of Logic Pro Tobacco and Logic Power Tobacco products and CC. TNeq was significantly lower in the Logic Vapeleaf Regular (PM0000529) cohort upon dual use compared to CC smoking cohorts, suggesting that current CC smokers may decrease their nicotine addiction severity via dual use of Logic Vapeleaf Regular products and CC.
- The risks of addiction associated with the new products are similar to risks associated with using other ENDS.

3.6.1.4. Short and long-term health effects (clinical and observational)

Per the medical review:

- Applicant-submitted clinical studies (LP004, LP005) assessed physiological effects following a 5-day, 30-day, and 60-day switch to all new products, compared to continued CC smoking. Physiological endpoints included blood pressure, pulse rate, and lung function. For all new products, there were no distinct, clear, or consistent trends in systolic or diastolic blood pressure or pulse rate that emerged from study data over the 60-day study period after switching to the new products. Lung function measurements were largely unchanged after switching to the new products. Statistically higher forced expiratory flow 25-75% values were observed in the Logic Pro Tobacco product cohort after 60 days, compared to continued use of usual brand CC, which may be indicative of improved lung function. However, the long-term clinical implications of these changes have not been determined. Other lung parameters generally did not show significant differences.
- Elevated transaminases were noted among study participants using all new products in the 60-day clinical studies (LP004, LP005). The clinical significance of these abnormal liver enzymes is unclear. The applicant performed a liver safety assessment to address these observations which indicated the incidence was below what could be expected in a true signal of liver toxicity. Although this conclusion was based on the criteria used for new medical drugs, no similar criteria has been established for tobacco products. This evaluation also did not consider the limited exposure participants had to the new products. The effect(s) of using these new products for more than 60 days cannot currently be determined. It may be possible for a signal to emerge with use in the broader population. The medical discipline recommends monitoring post-market reports for events related to liver toxicity.
- The differences in BOPH between the Logic Power Tobacco product, CC, and tobacco cessation cohorts were typically small and not statistically significant. There are currently no known definitive markers of health effects for ENDS and it remains unclear how the changes in BOPH associated with ENDS use impact long-term human health. Thus, the selected BOPH are inadequate for predicting short-term or long-term disease risk.
- The 60-day clinical studies (LP004, LP005) had extensive dual use with CC and were not powered to detect any patterns of AEs or examine long-term health consequences, and are unlikely generalizable to other populations. However, it is possible that within a larger population, there could be differences among flavors for the prevalence of users affected by AEs, or the potential for abuse liability. Overall, there was not a clear, strong, and consistent pattern within the context of the applicant-submitted clinical studies (LP004, LP005) to suggest that the new products are particularly likely to directly contribute to tobacco-related disease. In addition, the likelihood of partially or completely switching to the new products, as compared to continuing to use CC, leading to reduced incidence of chronic tobacco-related diseases such as pulmonary disease, cardiovascular disease, or cancer in CC smokers has not been established.

Per the epidemiology review:

- The applicant did not provide conclusions or final assessments of their findings from the submitted studies or the peer-reviewed literature on the long-term health risks associated with use of the new products or for ENDS as a product class.

- The applicant relied on short-term health effect findings from two clinical studies (LP004, LP005) to describe health effects and outcomes related to use; however, the applicant did not provide justification for how short-term health effect information can be bridged to long-term outcomes.
- Some published literature suggests that ENDS use compared to never tobacco use may be associated with a higher likelihood of some health outcomes such as cardiovascular disease, respiratory disease, and oral health (although temporality may be an issue with some of these studies) (Giovanni, Keller, Bryant, Weiss, & Littman, 2020; Osei et al., 2020; Osei et al., 2019).
- A meta-analysis found that compared to heavy CC smokers, those who reduce their CPD by at least 50% had a significant reduction in lung cancer risk (Chang, Anic, Rostron, Tanwar, & Chang, 2021). However, reductions in CC smoking have not been found to lower the risk of all-cause mortality, all-cancer risk, or other smoking/tobacco related cancers (Chang et al., 2021).
- Switching and CC smoking reduction likely reduce exposure to tobacco related toxicants (Goniewicz et al., 2017; Rostron, Corey, et al., 2020).

3.6.1.5. Likelihood and effects of product misuse

Per the medical review:

- There were no AEs reported in the applicant-submitted clinical studies (LP001-LP005) suggesting accidental exposure. It is possible that some of the AEs such as burns may represent product misuse.
- There were no AEs reported in the submitted clinical studies related to secondary exposure to the new products.
- The package insert for Logic Vapeleaf Regular products includes a warning that there is a possibility that the battery may burst. However, Logic Power Tobacco and Logic Pro Tobacco products do not include this warning on the packaging or leaflet insert. In addition, the new products are not UL8139 certified. In general, ENDS can explode and cause projectile injuries and burns to human users and nonusers.

Per the BCP review:

- The likelihood of misuse (using the product in ways other than intended such as product modifications, dripping, and stealth use) among all new products is low. The new products are all closed ENDS with replaceable cartridges or capsules. The applicant stated that all AEs in the new product cohorts throughout the applicant-submitted clinical studies were due to product misfunction and not misuse. There are no published reports that describe misuse of the new products in the literature.

3.6.1.6. Adverse experiences

Per the medical review:

- The TPST Safety Reporting Portal search for AEs reported by the public showed six unique entries for Logic ENDS for reports submitted prior to May 18, 2021. Of the six entries, three described a health problem – one a cough, one of gingival bleeding, and one of hypoxia requiring intubation. Reviewer assessment of these problems determined that these reports were possibly related to product use. It is unknown whether the most significant health problem – hypoxia requiring intubation - is associated with the patient's reported use of a Logic ENDS. Two of

the other entries were notable for the potential to be associated with an adverse health experience – one was a product problem of a fire, and the other an environmental issue where a discarded part caused a flat tire while driving.

- An updated TPST search was conducted on February 02, 2022 to identify potential AEs reported by the public since the last search. No unique entries were for Logic ENDS were found.

- FDA is aware of several health issues regarding the use of ENDS, specifically e-cigarette or vaping product use-associated lung injury (EVALI), seizures, and thermal burns:
    - EVALI is a potential respiratory health effect that could occur in individuals who use vaping products. There were no reports of EVALI in the applicant-submitted clinical studies and there did not appear to be any subjects who experienced the constellation of symptoms indicative of EVALI as an AE that required hospitalization. However, since EVALI is associated with use of vaping products, CTP is interested in evaluating any additional information related to respiratory illness in association with ENDS and specifically the new products.
    - Participants in the applicant-submitted clinical studies (LP004, LP005) reported some neurological AEs, but seizures were not reported. While this data is insufficient to fully evaluate the potential association of the new products with seizures, CTP is interested in monitoring an on-going evaluation of this potential health consequence of ENDS use.
    - A few participants reported thermal burns during use; data were not provided to determine whether these were due to a product problem, product misuse, or other cause. However, the risk is still an issue regarding ENDS use overall.

  Therefore, to further monitor and evaluate potential ENDS health effects such as EVALI and seizures, the medical discipline recommends that post-market reporting include a specific plan to monitor respiratory-related illnesses, neurological symptoms, and AEs related to thermal burns associated with the new products.
- Across all new products, data showed elevated transaminases, indicative of possible hepatocellular injury in some study participants after use of the new products. If marketed, we recommend monitoring periodic reports for events related to liver toxicity.
- There were no AEs reported in the submitted clinical studies related to secondary exposure to the new products.
- In the applicant-submitted clinical studies (LP004, LP005), for all new products, the majority of product emergent AEs were non-serious and reported to be either mild or moderate in severity. Almost all had improved or resolved by the study end.

3.6.2. Synthesis

As TPL, I agree with the toxicology discipline conclusions that the non-clinical data suggest that the overall toxicological risks of the new products are likely significantly lower compared to CC smoking for individual users because, in part, responses to the non-clinical inhalation studies were milder and less severe than responses from CC exposure. However, the incidence of elevated liver enzymes (see below) and seizures in PM0000535.PD1 merits

further monitoring, if marketed, particularly given their prevalence in the LP004 and LP005 clinical studies and the ENDS literature, respectively (see Section 3.6.1.4. and below).

As TPL, I agree with the BCP review that when CC smokers partially switch to the new products, and reduce CPD, total nicotine exposure stays the same (Logic Pro Tobacco and Logic Power Tobacco products; PM0000535.PD1, PM0000540.PD1) or is lower (Logic Vapeleaf Regular product; PM0000529.PD1) than CC cohorts. Thus, the risk for addiction is mostly maintained upon dual use with the new products, although the addiction risk may be reduced in Logic Vapeleaf Regular product users.

The medical review concluded that most reported AEs in the applicant-submitted clinical studies were mild and expected. Furthermore, no new product-specific AEs were identified in the TPST searches. Limited data are available related to the short-term health effects of all new products. For example, although participants in the new product cohorts had elevated liver enzymes, their clinical significance and associations with the new products are unclear. One reason that the significance of elevated liver enzymes with new product use is unclear is that elevated liver enzymes were also observed in the CC cohort. It seems likely that there is a concomitant condition that leads to elevated liver enzymes. Elevated liver enzymes were also present in some non-clinical 90 day inhalation studies (95019D, 95019B, 95019F); because the effects were partly reversed upon exposure removal, the applicant determined them to be not toxicologically relevant. In light of the severity of the elevated liver enzymes being low, I do not find that this clinical observation should impede a conclusion that marketing of the new products is appropriate for the protection of the public health.

Additionally, the applicant-submitted non-clinical studies (95019D, 95019B, 95019F) showed evidence of seizures in PM0000535.PD1, and although no related symptoms were reported in the applicant-submitted clinical studies (LP004, LP005), the peer-reviewed literature suggests that seizures may be related to ENDS use. The medical review also noted that, although not reported in the applicant-submitted clinical studies, EVALI is a serious concern related to vaping product use. Therefore, I recommend monitoring periodic reports for events related to liver safety, seizures or other neurological symptoms, and respiratory symptoms characteristic of EVALI, thermal burns given their prevalence in the applicant-submitted studies, non-clinical studies, or the general ENDS literature.

Furthermore, the submitted BOPH data from the applicant-submitted 60-day clinical studies (LP004, LP005) are limited in their ability to assess the impact of the new products on human disease risk; yet it is unclear whether any currently available BOPH are appropriate to assess health risks associated with ENDS use. Furthermore, there is no data about the long-term effects of the new products and limited data about the long-term effects of ENDS, in general.

However, I also recognize that some short-term health outcomes (e.g., lung function) associated with ENDS use are significantly better than CC smoking for individual users. Furthermore, although the long-term impacts of lower BOE or BOPH associated with ENDS is unclear (particularly with dual use), it is unlikely that these reduced exposures pose a greater health risk than continued CC smoking to individuals. While the long-term health effects of dual use were not assessed, significant reductions in systemic exposures after

short-term switching and the available evidence suggest that daily use of the new products with concomitant reduction in CPD may reduce an individual's exposure to HPHCs relative to continued CC smoking alone. Furthermore, there is no information to suggest that the expected AEs or short- or long-term health risks associated with the new products differ in incidence or severity compared to other representative ENDS.

Adults who initiate the new products are likely to use them with CC (see Section 3.4.1.2.); the literature on health outcomes for CC smokers who dual use and reduce CPD is mixed. The epidemiology review noted that some dual users who drastically decrease CPD may see some health benefits, particularly for those whose long-term goal is cessation. However, use of the new products may still pose significant long-term health risks to non-tobacco users. Past Surgeon Generals' reports have suggested that reductions in smoking may lead to long-term health benefits (U.S. Department of Health and Human Services & National Center for Chronic Disease Prevention and Health Promotion, 2014); however, the benefits associated with complete switching from CC to ENDS are much more substantial (U.S. Department of Health and Human Services, National Center for Chronic Disease Prevention and Health Promotion, & Office on Smoking Health, 2020). Thus, the peer-reviewed literature suggests that individual CC smokers will receive a greater health benefit when switching to exclusive ENDS use compared to dual use, but given the lower BOE (see Section 3.5.1.3) and short-term effects (see Section 3.6.1.4.) associated with the new products, I conclude that dual use (as is likely to occur with these new products) associated with significantly reduced CPD (as evidenced in LP004 and LP005) will support lower health risks and provide health benefits by reducing HPHC exposures to CC smokers who initiate use of the new products and decrease their CPD. Because the Consumer Perception Studies indicated that intention to use among adult never tobacco users was low (see Section 3.4.1.3.), the increased health risks associated with ENDS use compared to no tobacco use among adults are outweighed by the decreased health risks among current adult CC smokers.

Lastly, no significant issues of misuse were identified, and given that the new products are closed e-liquids, the potential for tampering with the new products and associated risks of accidental exposure are minimal. Furthermore, the risk of accidental exposures among children is also minimal given the child-protective packaging and adequate testing (in nicotine-containing products). The applicant also provided adequate instructions about how the new products should be used and warnings against misuse in the products' leaflets.

3.7. POPULATION AND PUBLIC HEALTH

3.7.1. Discipline key findings

The following discussion is based on the key findings provided in the epidemiology review:

3.7.1.1. Population health impact (PHI) model

- The population model submitted by the applicant used appropriate U.S. data sources for inputs, conducted data analyses using PATH data, and generally used reasonable assumptions (with some exceptions). However, it is likely that the model may have overestimated the benefits of the new products; while the applicant refers to the new products, it appears that they modeled use of all ENDS and not just the new products. The potential overestimation of the population health

benefit limits the utility of the model. The population model also does not characterize the potential public health benefit for any specific new product.

3.7.2. Synthesis

As TPL, I agree with the limitations of the applicant-submitted population model as described in the epidemiology review: the model did not characterize the potential public health benefit for the new products. Thus, the model is not particularly informative in the evaluation of whether the new products are appropriate for the protection of the public health.

Although the applicant's population health model may have overestimated the anticipated health benefits associated with the new products' marketing, these new products are likely to be associated with a population health benefit if CC smokers completely switch to them. However, population harm would likely occur when non-tobacco users, including youth, who otherwise would not have used tobacco products initiate with them (particularly when they then transition to CC smoking) and when CC smokers who would have otherwise quit all tobacco use switch to them instead.

The applicant-submitted data do not suggest that CC smokers will completely switch to the new products and indicate instead that dual use is the most likely use behavior. Because the greatest potential health benefit to CC smokers is associated with cessation, the population health model may overestimate the impact actual use of these products has on population health.

The available evidence suggests that current CC smokers may use the new products to decrease CC consumption (and aid in CC quit attempts and subsequent successful CC cessation) and that adult non-tobacco users are unlikely to progress to regular use with them. Dual use associated with significantly reduced CPD also decreases exposure to many BOE. Although short- and long-term health implications of these decreases and general product use are unknown, it is unlikely that these reduced exposures pose a greater health risk than continued CC smoking. Additionally, because the tobacco-flavored new products are unlikely to have high youth appeal and currently have low market share among youth, the applicant's mitigation strategies to alleviate youth use of the new products appear adequate. Thus, I believe that the evidence suggests that marketing of these new products with a tobacco characterizing flavor will promote public health. Furthermore, potential risks to youth posed by marketing of the new products will likely be decreased provided that the applicant follows post-marketing requirements and implements marketing restrictions to further reduce youth exposure to marketing of the new products and youth access to the new products.

3.8. STATUTORY REQUIREMENTS

3.8.1. Public health conclusion

Based on the findings and evaluations discussed in Sections 3.1-3.7, I find that permitting the marketing of the new products in accordance with the requirements in the marketing granted orders is APPH.

3.8.2. Tobacco product manufacturing practices[12]

The PMTAs contain sufficient information to characterize the products' design and adequate processes and controls to help ensure that the new products meet the manufacturer's specifications. The methods used in, and the facilities or controls used for, the manufacture, processing, and packing of these products do not fail to conform to the requirements in Section 906(e) of the FD&C Act.

3.8.3. Labeling

For all PMTAs, the applicant provided proposed labeling. Based on the information presented at this time, we have not concluded that the proposed labeling is false or misleading in any particular.

3.8.4. Product standards

There are no applicable product standards for these PMTAs.

4. ENVIRONMENTAL DECISION

4.1. DISCIPLINE FINDINGS

Environmental science concluded that the environmental assessments for all PMTAs contain sufficient information to determine whether the proposed actions may significantly affect the quality of the human environment. As TPL, I agree with this conclusion.

4.2. ENVIRONMENTAL CONCLUSION

For all new products, a finding of no significant impact (FONSI) was signed by Hans Rosenfeldt on behalf of Luis Valerio, Jr. on March 18, 2022. The FONSI was supported by an environmental assessment prepared by the applicant on December 8, 2020.

5. CONCLUSION AND RECOMMENDATION

Section 910 of the FD&C Act requires that, for a product to receive a PMTA marketing authorization, FDA must conclude, among other things, that permitting the product to be marketed would be APPH. Section 910(c)(2)(A). The statute specifies that, in assessing APPH, FDA must consider the risks and benefits to the population as a whole, including both tobacco users and nonusers, taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products and the increased or decreased likelihood that those who do not use tobacco products will start using such products. Section 910(c)(4). FDA interprets the APPH standard to require a showing that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole, which includes youth, young adults, and other vulnerable populations. In determining whether permitting the marketing of a new tobacco product would result in a net benefit to public health, FDA weighs the potential negative public health impacts (e.g., harm from initiation and use among nonusers, particularly youth) against the potential positive public health impacts (e.g., benefit from adult users of more harmful tobacco products completely switching).

Based on its evaluation of these PMTAs, FDA determined that these PMTAs contain sufficient information to characterize the product designs and that there are adequate process controls and

[12] FDA has not promulgated a tobacco product manufacturing practices (TPMF) rule.

quality assurance procedures to help ensure both the device and e-liquids are manufactured consistently. Based on the information provided in the PMTAs, the abuse liability of the new products is lower than CC and is similar to, or lower than, that of other ENDS. The overall toxicological risk to the users of the new products is lower compared to cigarettes due to significant reductions in aerosol HPHCs of the new products' compared to CC and as evidenced by results of nonclinical studies. In vitro toxicology data suggest aerosols from the new products are less mutagenic, genotoxic, and cytotoxic compared to smoke from CC under the conditions tested. In addition, the effects of in vivo exposure to all new products were typically both reversible and less severe compared to the effects of exposure to mainstream CC smoke, which produced toxic effects that were more severe and often irreversible. In the clinical studies, most participants (in new product cohorts) substantially decreased CPD from an average of 13-16 CPD at screening to 1-2 CPD by Day 59 (greater than 80% reduction). (Study enrollees were current CC smokers, not dual users.) Such dual use was sufficient to decrease most biomarkers of exposure (e.g., VOCs, TSNAs, and PAHs) in CC smokers who used the new products compared to CC smoking cohorts.

In the Consumer Perception Studies, during which the adult participants were exposed to pictures but did not use the new products, adult current dual users reported the greatest interest in purchase, trial, and use of all Logic Vapeleaf, Pro, and Power products, followed by current tobacco users, and then former and never users, suggesting the highest likelihood of uptake by dual users of ENDS and other tobacco products. Therefore, the applicant has demonstrated that current CC smokers will likely use the new products to significantly decrease CC consumption and that non-tobacco users are unlikely to initiate and progress to regular use with the tobacco-flavored new products. These new products have the potential to benefit CC users who reduce CC use through either dual use or exclusive use of the new products. For example, the reduction in CPD associated with the use of the new products may help promote CC quit attempts and lead to successful CC cessation among CC smokers who are interested in quitting; however, these outcomes are not assessed in the current PMTAs.

In terms of the risks to nonusers, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood and thus youth are at particular risk of tobacco initiation. Existing evidence consistently indicates that use of tobacco-flavored ENDS is less common than non-tobacco-flavored ENDS among youth. The current data suggest that few youth are using Logic ENDS. In 2021 NYTS data, Logic products were not among the top five brands reported for use among youth (despite being one of the options available for selection). The applicant-submitted Consumer Perception Studies concluded that intent to use among former and never users was low. In addition, due to the relatively low abuse liability associated with these tobacco-flavored ENDS as compared to CC, former and non-tobacco users (including youth) who initiate use of the new products are less likely to progress to regular use of the new products. Nonetheless, given the strong evidence regarding the impact of youth exposure to marketing on youth appeal and initiation of tobacco use, a marketing authorization should include marketing restrictions and postmarket requirements to help ensure that youth exposure to tobacco marketing is limited. Together, based on the information provided in the PMTAs and the available evidence, the potential to benefit smokers who switch completely or significantly reduce their cigarette use would outweigh the risk to youth, provided the applicant follows post-marketing requirements aimed at reducing youth exposure and access to the products.

The applicant provided complete shelf life data sets for all finished new products and the intermediate bulk e-liquids for PM0000530.PD1, PM0000535.PD1, and PM0000540.PD1 under long-term (25°C, 60% relative humidity; 24 months for bulk e-liquids, 18 months for finished products) and accelerated conditions (40°C, 75% relative humidity, 6 months for all bulk and finished products). This data is sufficient to demonstrate satisfactory microbial and chemical stability and engineering functionality/safety of the new products over the applicant-proposed shelf lives.

Based on my review of the PMTAs and the available evidence, I find that permitting the marketing of the new products, as described in the applications and specified in Appendix A is appropriate for the protection of the public health. The potential of the new products to benefit smokers who significantly reduce CC use or who experience CC cessation outweighs the risk to youth. Furthermore, potential risks to youth posed by marketing of the new products will likely be decreased provided that the applicant follows post-marketing requirements and implements marketing restrictions to further reduce youth exposure to marketing of the new products and youth access to the new products. The issuance of these marketing granted orders confirms that the applicant has met the requirements of section 910(c) of the FD&C Act and authorizes marketing of the new products. Under the provisions of section 910, the applicant may introduce or deliver for introduction into interstate commerce the products, in accordance with the marketing order requirements outlined in marketing granted orders.

FDA has examined the environmental effects of finding the new products APPH and made a Finding of No Significant Impact (FONSI).

Marketing granted orders should be issued for the new products subject to this review, as identified on the cover page of this review.

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7. APPENDICES

Appendix A. New tobacco products subject to Granted Orders[13]

Common Attributes of PMTAs	
Submission date	August 19, 2019
Receipt date	August 19, 2019
Applicant	Logic Technology Development LLC
Product manufacturer	Logic Technology Development LLC
Product category	ENDS (VAPES)
Attributes	**New Tobacco Product**
STN	**PM0000529.PD1**
Product name	Logic Vapeleaf Regular Cartridge/Capsule Package[14]
Product subcategory	ENDS Other
Package type	Blister Pack
Package quantity	5 Capsules
Characterizing flavor	None
Additional properties	Mass of flavored tobacco granules per capsule: 310 mg Nicotine Content: < 39.8 mg-dry base/g
STN	**PM0000530.PD1**
Product name	Logic Vapeleaf Cartridge/Capsule Package[14]
Product subcategory	Closed E-Liquid
Package type	Cartridge
Package quantity	1 Cartridge[14]
Characterizing flavor	None
Nicotine concentration	0 mg/mL
E-liquid volume	1.125 mL
PG/VG ratio	50/50
Additional properties	Contains an atomizer
STN	**PM0000531.PD1**
Product name	Logic Vapeleaf Tobacco Vapor System[14]
Product subcategory	Closed E-Cigarette
Package type	Box
Package quantity	1 Battery Unit
Characterizing flavor	Not Provided
Additional properties	Diameter: 9.2 mm, Length: 69.4 mm, Battery Capacity: >210 milliAmpere hours (mAh), Wattage: Ranges from 3.5 to 3.0 watts over the course of approximately 300 puffs, Universal Serial Bus (USB) Charger

[13] Brand/sub-brand or other commercial name used in commercial distribution.
[14] This product contains properties of ENDS and Heated Tobacco Products (HTPs). As such, it may be considered an HTP in the future.
[15] Contains U-Plugs on either end of cartridge.

STN	PM0000535.PD1
Product name	Logic Pro Tobacco e-Liquid Package
Product subcategory	Closed E-Liquid
Package type	Blister Pack
Package quantity	2 Cartridges
Characterizing flavor	Tobacco
Nicotine concentration	20.0 mg/mL
E-liquid volume	1.5 mL
PG/VG ratio	69/25
STN	**PM0000536.PD1**
Product name	Logic Pro Capsule Tank System
Product subcategory	ENDS Other
Package type	Box
Package quantity	1 Capsule Case
Characterizing flavor	Not Provided
Additional properties	Diameter: 14.1 mm, Length: 65.5 mm
STN	**PM0000537.PD1**
Product name	Logic Pro Capsule Tank System
Product subcategory	Closed E-Cigarette
Package type	Box
Package quantity	1 Battery Unit
Characterizing flavor	Not Provided
Additional properties	Diameter: 14.1 mm, Length: 78.2 mm, Battery Capacity: 650 mAh, Wattage: Ranges from 5 to 4.5 watts over the course of approximately 520 puffs, USB Charger
STN	**PM0000540.PD1**
Product name	Logic Power Tobacco e-Liquid Package
Product subcategory	Closed E-Liquid
Package type	Blister Pack
Package quantity	2 Cartridges
Characterizing flavor	Tobacco
Nicotine concentration	27.0 mg/mL
E-liquid volume	1.2 mL
PG/VG ratio	68/25
STN	**PM0000541.PD1**
Product name	Logic Power Rechargeable Kit
Product subcategory	Closed E-Cigarette
Package type	Box
Package quantity	1 Battery Unit
Characterizing flavor	Not Provided
Additional properties	Diameter: 9.2 mm, Length: 82.6 mm, Battery Capacity: 340 mAh, Wattage: Ranges from 5.25 to 4 watts over the course of approximately 300 puffs, USB Charger

Appendix B. Amendments received

Submission Date	Receipt Date	Amendment	Applications being amended	Reviewed	Brief Description
9/25/2019	9/25/2019	PM0000545	PM0000529.PD1-PM0000531.PD1	Yes	Response to FDA's September 18, 2019 information request
9/25/2019	9/25/2019	PM0000546	PM0000540.PD1-PM0000541.PD1	Yes	
9/25/2019	9/25/2019	PM0000547	PM0000535.PD1-PM0000537.PD1	Yes	
10/22/2019	10/22/2019	PM0000569	PM0000529.PD1-PM0000531.PD1	Yes	Response to FDA's October 15, 2019 information request
10/22/2019	10/22/2019	PM0000570	PM0000535.PD1-PM0000537.PD1	Yes	
10/22/2019	10/22/2019	PM0000571	PM0000540.PD1-PM0000541.PD1	Yes	
11/1/2019	11/1/2019	PM0000574	All	Yes	Response to FDA's October 24, 2019 information request
11/1/2019	11/1/2019	PM0000575	All	Yes	
11/1/2019	11/1/2019	PM0000576	All	Yes	
11/18/2019	11/18/2019	PM0000578	All	Yes	Final Site Inspection Agenda
12/20/2019	12/20/2019	PM0000581	All	Yes	Final Site Inspection Logistics
2/27/2020	2/27/2020	PM0000625	PM0000535.PD1-PM0000537.PD1 and PM0000540.PD1-PM0000541.PD1	Yes	New product label information
7/9/2020	7/9/2020	PM0000825	All	Yes	Request for extension to June 26, 2020 Deficiency letter.
12/17/2020	12/20/2020	PM0004435	All	Yes	Response to June 26, 2020 Deficiency letter