**FDA CIRCULAR**

No. _____

TO : **ALL MANUFACTURERS/ TRADERS/ IMPORTERS OF HEATED TOBACCO PRODUCTS.**

SUBJECT : **PROCEDURE FOR PRE-APPLICATION DOCUMENTARY EVALUATION (PADE) FOR HEATED TOBACCO PRODUCTS SEEKING ELECTRONIC REGISTRATION NUMBERS (FERNs) UNDER THE FOOD AND DRUG ADMINISTRATION**

## I. BACKGROUND

Pursuant to Republic Act No. 11467, Republic Act 9711, and Executive Order No. 106, the Food and Drug Administration (FDA) is mandated to regulate Heated Tobacco Products (HTPs) consistent with evolving medical, public health, and scientific evidence. To this end, the FDA hereby implements this Circular applicable to all HTP refills, cartridges and electronic delivery devices.

## II. OBJECTIVE

This Circular is being issued to provide the supplemental procedures and guidelines for the issuance of a Pre-application Documentary Evaluation (PADE) certificate as part of the requirements of HTP registration for the issuance of an FDA Electronic Registration Number (FERN) certificate.

## III. SCOPE AND COVERAGE

This Circular shall cover all manufacturers, traders, and importers that seek to apply for a FERN certification of their HTPs.

## IV. GENERAL PROCEDURE

**1.** Manufacturers, traders, and importers of HTPs who intend to apply for FERN, shall submit an application for PADE at least one hundred twenty (120) calendar days as

part of the documentary requirements for HTP FERN certification under the Center for Cosmetics Regulation and Research (CCRR).

**2.** Submission of PADE shall be done electronically, through FDA's current e-portal system for HTPs.

**3.** The FDA shall automatically disapprove applications with incomplete or incorrect submissions.

**4.** The CCRR may request for additional information and documents from the applicant should there be any clarification on the submitted documents.

**5.** The final disposition on the evaluations shall lie solely with the Director General of the FDA upon the recommendation of the Director IV of the CCRR.

**6.** Under no circumstances shall evaluations with favorable dispositions be deemed as an imprimatur of FDA approval nor shall nor shall it mean the approval of a product claim. Any industry promotion, advertisement, or communication, explicit or implicit, contrary to this provision shall be grounds for immediate and final denial of active HTP applications on the said product.

## V. SPECIFIC GUIDELINES

**1.** The Pre-Application Documentary Evaluation shall contain the following documents:

**1.1.** Administrative Data if MAH

**1.1.1.** Complete company information, including:

**1.1.1.1.** Company name

**1.1.1.2.** Organizational chart

**1.1.1.3.** Business addresses and other contact details

**1.1.1.4.** Notarized authorized responsible person to apply in behalf of the manufacturer, in case the applicant is a distributor or importer.

**1.1.2.** Authorization for the FDA to use, copy, store, and distribute digital and physical copies of all documents submitted to FDA for the purposes of (1) review and evaluation of the application; (2) enforcement; and (3) conduct of research for the development of regulatory standards and public health policies. All information and documents submitted to the FDA shall be deemed as Confidential Information and shall be protected in accordance with the Data Privacy Act with respect to personal data, the Department of Health's Freedom of Information Manual, and also in accordance with other applicable laws, rules and

regulations, and existing jurisprudence protecting Confidential information.

Confidential Information for purposes of this Circular shall include personal data, trade secrets, intellectual property, business, commercial, financial, or proprietary information, or any other information or date that by its nature should be kept confidential.

**1.1.3.** An attestation from the manufacturer, trader, or importer that the information contained in the bundle is complete, accurate, and unredacted, under the penalties of all relevant legislation.

**1.2. Data on Raw Materials**

**1.2.1.** Administrative Data and Information

**1.2.1.1.** Name and address of the manufacturer

**1.2.1.2.** Name and address of the supplier

**1.2.2.** Chemistry, Manufacturing and Controls

**1.2.2.1.** General properties

**1.2.2.2.** Schematic flow diagram and sequential procedural narrative of the manufacturing process

**1.2.2.3.** Materials used in the manufacture of the components

**1.2.2.4.** Technical specifications

**1.2.2.5.** Analytical Procedures

**1.3. Data on Finished Product**

**1.3.1.** Administrative Data and Information

**1.3.1.1.** Name and address of the manufacturer

**1.3.1.1.1.** LTO number (for local manufacturers)

**1.3.1.2.** Name and address of the supplier (for imported products)

**1.3.2.** Chemistry, Manufacturing and Control

**1.3.2.1.** Qualitative and quantitative composition of the product

**1.3.2.2.** Compatibility of the ingredients/components

**1.3.2.3.** Master Formula per batch size

**1.3.2.4.** Schematic flow diagram and sequential procedural narrative of the manufacturing process

**1.3.2.5.** Complete list of equipment used during the manufacturing process

**1.3.2.6.** Process validation

**1.3.2.7.** Technical specifications

**1.3.2.8.** Analytical procedures

**1.3.2.9.** Validation of analytical procedures

**1.3.2.10.** Batch analyses

**1.3.2.11.** Characterization of impurities

**1.3.2.12.** Container closure system

**1.3.2.13.** Stability

## 1.4. Toxicological Risk Assessment

**1.4.1.** Certificates of Analysis for the panel of Harmful and Potentially Harmful Chemicals (HPHC) in Tobacco Products as listed in the United States Food and Drug Administration panel, as tested under conditions outlined by the World Health Organization (WHO) Tobacco Laboratory Network (TobLabNet) or Health Canada, relative to typical emissions of the University of Kentucky reference cigarette 3R4F, and as obtained under the Health Canada intense smoking protocol (55mL puff volume every 30 seconds, with 100% of ventilation mechanisms occluded, until exhaustion or complete consumption of the Heated Tobacco Product cartridge), for mainstream and sidestream emissions, as determined by an ISO-certified government or independent laboratory that is not owned, partly owned, or otherwise controlled by the tobacco industry and their agents and/or representatives.

**1.4.2.** Results of the following in vitro tests on product emissions, as determined by ISO-certified government or independent laboratories not owned, partly owned, or otherwise controlled by the tobacco industry and their agents and/or representatives:

**1.4.2.1.** Salmonella/microsome fluctuation (Ames) Test following the OECD 471 protocol

**1.4.2.2.** In vitro dosimetric and cytotoxic assessment by neutral red uptake

**1.4.2.3.** Mouse Lymphoma Assay, in accordance with the OECD 490 protocol

**1.4.3.** Results of the following in vivo tests on product emissions, as determined by ISO-certified government or independent laboratories not owned, partly owned, or otherwise controlled by the tobacco industry and their agents and/or representatives:

**1.4.3.1.** 90-day Nose-only Inhalation Studies

**1.4.3.2.** 18-month Carcinogenicity Study with A/J mice

**1.4.3.3.** Nicotine Pharmacokinetic (PK) Study with Rats

**1.4.4.** Results of the following systems toxicology studies on product emissions, as determined by ISO-certified government or independent laboratories not owned, partly owned, or otherwise controlled by the tobacco industry and their agents and/or representatives:

**1.4.4.1.** Acute and Repeated Exposure Studies with Human Bronchial Epithelial Cells

**1.4.4.2.** ApoE-/- Mouse Switching Study

**1.5. Clinical Behavioral Pharmacology**

**1.5.1.1.** Pharmacokinetic/Pharmacodynamic (PK/PD) Studies

**1.5.1.2.** Intrinsic and Extrinsic Factors Affecting Nicotine Pharmacokinetic Data

**1.5.1.3.** Nicotine Equivalents (NEQ) in Urine

**1.5.1.4.** Use Behavior and Topography

**1.5.1.5.** Product Use/Consumption

**1.5.1.6.** Product Acceptability

**1.5.1.7.** Product Abuse Potential

**1.6. Laboratory Competency**

**1.6.1.** A complete list of relevant certifications held by the laboratory conducting the in vitro, in vivo, and systems toxicology studies.

**1.6.2.** An attestation from the said laboratory of the exact make, model, and brand of the smoking robot used in the conduct of the in vitro studies.

**1.6.3.** A complete declaration of interest of all researchers conducting the clinical and behavioral pharmacology evaluation and their relevant qualifications and affiliations.

## VI. APPROVAL

Approval of the PADE shall mean that the Marketing Authorization Holder may already apply for FERN under for the specific HTP product combination.

## VII. FEES

Per submission shall have a fee of Php 50,000.00 plus a legal research fee of 1%.

## VIII. PENALTIES

Violation to any provisions of this Circular shall be subject to the penalties/sanctions provided under Book III, Article XI of the Rules and Regulations Implementing Republic Act No. 9711, Republic Act No. 11467, Executive Order No. 106 and other penalties provided by other applicable laws.

## IX. SEPARABILITY CLAUSE

If any provision in this Circular, or application of such provision to any circumstances, is held invalid, the remainder of the provisions in this Circular shall not be affected.

## X. EFFECTIVITY

This Circular shall take effect 15 days after publication in a newspaper of general circulation and the Office of National Administrative Register of the UP Law Center.