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Given the above, you should not use this document as a tool, guide, or manual for the preparation of applications or submissions to FDA. Instead, all interested persons should refer to the Federal Food, Drug, and Cosmetic Act, and its implementing regulations, as well as guidance documents prepared by FDA, for information on FDA's tobacco authorities and regulatory framework. FDA also regularly posts additional resources for applicants, such as webinars and application tips, on CTP's website and social media.

U.S. FOOD & DRUG ADMINISTRATION

Memorandum

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Subject: E-liquid Manufacturing Evaluation Responsibilities of Chemistry in the PMTA and MRTPA Review Program

Table of Contents

1. Background

As part of the requirements of Premarket Tobacco Product (PMTA) and Modified Risk Tobacco Product (MRTPA) Applications, applicants must demonstrate that submitted products meet the relevant public health standards.[1] To demonstrate this, applicants generally must provide engineering, chemical, and microbiological data, including stability data, product design characteristics, manufacturing, and harmful or potentially harmful constituents (HPHCs) for the new tobacco products.

Office of Science Leadership, Science Policy Branch, and chemistry reviewers from the Division of Product Science (DPS) have identified some discrepancies related to the information submitted by applicants and reviewed by FDA, such as the evaluation of the manufacturing processes and controls, and acceptance criteria in the new tobacco products and the appropriateness for the protection of public health. As such, in the interest of clarity and efficiency in completing a substantive scientific review assessment, this memorandum serves as a resource for chemistry reviewers when evaluating e-liquid manufacturing information in electronic nicotine delivery systems (ENDS)[2] tobacco product applications.

2. Manufacturing Process

The evaluation of the manufacturing process can provide insight as to whether the products are manufactured consistently and the quality of the resulting finished products.[3,4] This evaluation consists of an assessment of all steps and controls, starting with receipt of raw materials to the storage conditions of the finished products.

[1] Under section 910(c)(4), a PMTA must enable FDA to find whether there is a showing that permitting the marketing of the new tobacco product would be appropriate for the protection of the public health with respect to the risks and benefits to the population as whole. An MRTPA must contain sufficient information for FDA to determine whether it should issue a modified risk granted order for the product under 911(g)(1) or (2) of the FD&C Act. Under 911(g)(1), the applicant must demonstrate that the product, as it is actually used by consumers, will: (a) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (b) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products. Under 911(g)(2), the applicant must demonstrate, among other things, that such an order would be appropriate to promote the public health and that issuance of the exposure modification order is expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

[2] OS references to ENDS products as VAPES as of November 4, 2021 when the final SE and PMTA rules went into effect.

[3] Under section 910(b)(1)(C), the applicant is required to disclose a description of the methods and controls used during the manufacturing process.

[4] See: Premarket Tobacco Product Applications and Recordkeeping Requirements. 86 FR 55300. https://www.federalregister.gov/documents/2021/10/05/2021-21011/premarket-tobacco-product-applications-and-recordkeeping-requirements

This memorandum outlines the important items to examine during the evaluation of the manufacturing process of ENDS products. Generally, this evaluation is performed in three major sections that are outlined in Sections 2.1, 2.2, and 2.3 of this memorandum.

2.1. Purchased ingredients steps and controls

Chemistry will not evaluate detailed manufacturing process of complex flavoring ingredients (CFIs) or complex purchased ingredients (CPIs) that are typically present in low quantities. However, the applicant needs to provide information on the selection process of raw material suppliers. This includes criteria for selecting a supplier; quality control of selected suppliers (e.g., maintaining records and accreditation, periodic audit, and product monitoring); and action plans when a supplier fails manufacturing compliance, falsifies information, is sanctioned by public health authorities (e.g., local and state health departments, FDA, Environmental Protection Agency, or Drug Enforcement Administration), or supplies non-conforming raw materials. The applicant also needs to provide detailed information on how incoming raw materials are inspected. This includes inspecting the bill of materials (BOM), expiration date (including acceptable stability period), certificate of analysis (COA), and integrity of tamper seal of received raw material. Additionally, the applicant needs to provide action plans for receipt of non-conforming batches of raw materials.

Chemistry will evaluate, at a minimum, manufacturing information for ingredients that are present in large quantities. In particular, the following manufacturing information for propylene glycol (PG), vegetable glycerin (VG), nicotine source, and pH modifier (e.g., benzoic acid or lactic acid) must be fully evaluated. Chemistry reviewers can follow the most recent version of the PMTA discipline review template posted on the Reviewer Resource Site[5] as references on how and where to evaluate these ingredients. The applicant needs to provide manufacturer name and purity or grade (e.g., United States Pharmacopeia (USP), European Pharmacopeia (Ph. Eur.), pharmaceutical, or food grade) of ingredients used in the new products, supported by proper documentation (e.g., certificate of analysis and manufacturing data sheet specification (MDSS)). Additionally, chemistry will evaluate data submitted for the following compounds in the supporting documents:

- Nicotine
    - Nicotine related compounds
        - Anatabine
        - Nicotyrine
        - Cotinine
        - Myosmine
        - Nicotine N-oxide
        - Nornicotine
        - Anabasine
    - Tobacco-specific nitrosamines (TSNA)
        - N-nitrosonornicotine (NNN), N-nitrosoanatabine (NAT), N-nitrosoanabasine (NAB), and N-Nitrosonornicotine ketone (NNK)
    - Pesticide - organochlorine and organophosphorus
    - Residual solvent - benzene, cyclohexane, and alcohol
- Vegetable glycerin
    - diethylene glycol and ethylene glycol

[5] http://sharepoint.fda.gov/orgs/CTP-OS/scientific-reviews/SitePages/Home.aspx

The supporting document needs to contain analytical testing methods, including the title of the methods and designations (e.g., USP, Ph. Eur., or in-house developed method), target and measured values with appropriate unit, and acceptance criteria. The applicant needs to provide storage requirements, stability period, and expiration dates for sealed and opened purchased ingredients. The PMTA applicant also needs to provide information for the selected manufacturers and suppliers and inspection of purchased PG, VG, nicotine, and pH modifiers.

Manufacturing control information for the purchased ingredients can be submitted in the PMTA submission, tobacco product master file (TPMF), or modified risk tobacco product application (MRTPA), which the applicant can use in support of their PMTA submissions. Appropriate reference is also necessary to reference the TPMF or MRTPA for chemistry to evaluate this information, e.g., letter of authorization (LOA) for TPMF and submission tracking number (STN) for MRTPA.

The following information needs to be included in the raw materials/ingredients evaluation:

- Supplier selection criteria
- Incoming shipment inspection and acceptance criteria (e.g., identification, COAs, expiration date/shelf-life)
- Single chemical constituent breakdowns (provide in submission, TPMF, or pending MRTPA (requires LOAs or STN reference))
- Purity, quality control, acceptance criteria, and testing methods for PG, VG, nicotine, and pH modifier (LOAs and TPMF if carried out by 3rd party))
- Specific impurity compounds that may be present in nicotine PG and VG
- Storage conditions and re-testing (if applicable) for non-confirming/expiring raw materials

2.2. New product manufacturing steps and controls

The chemistry review should include a list of all the manufacturing *controls* for each step or process. The evaluation may include the temperature and air quality of the rooms where manufacturing occurs. In addition, a list of components and subcomponents (individual ingredients in CFI and CPI) of incoming raw materials used to manufacture the new products need be provided by the applicant. Raw materials purchased by the applicant may be used directly in the final product assembly or tested by the applicant before use in the final product assembly. However, testing is not required for the raw materials since HPHC testing data is sufficient for the evaluation of the new products. The chemistry review may also discuss whether any pre-manufacturing control, such as weighing scale and volume dispenser calibration, ingredients verification, and batch formulation verification is performed.

The following information needs to be included in the manufacturing control evaluation:

- Name, address, FEI (FDA Establishment Identification) number, contact name and phone number for a representative from each manufacturing facility.
- Manufacturing process performed at each facility
- Managerial oversight and employee training related to the manufacture, processing, packing, and installation of the tobacco product, as applicable
- Manufacturing certification and compliance
- Temperature, humidity, and air flow requirements for the production room
- Manufacturing documentation and safekeeping
- Volume dispenser and weighing scale calibration (e.g., frequency, documentation, and party)

- Quality control/testing of in-process and finished products; acceptance criteria and analytical methods, LOAs if necessary.
- Steps for non-conforming finished products
- New product COA and batch record
- Storage requirement for the intermediate/finished products (e.g., temperature, humidity, and UV exposure) (during warehouse storage and transit to distributors)

The chemistry review should include a high-level summary of each manufacturing *step* with a reference to the document provided by the applicant. Additionally, it is noteworthy to mention whether the provided information is sufficient to show that the new tobacco products can be consistently manufactured. This can be accomplished by verification of the provided standard operating procedures (SOPs) or work instructions (WIs) for each manufacturing process and step for each component or subcomponent. If the submission lacks sufficient information to determine whether the new products are manufactured in a consistent manner, a deficiency should be issued to the applicant. However, if the missing information is not significant to determine whether the new products are appropriate for the protection of public health, it can be noted as a limitation of the manufacturing in the new products. Furthermore, the applicant needs to provide documentation, including stability data for intermediates and finished products as well as the acceptance criteria for the chosen expiration dates and re-testing protocols (if applicable) for expiring products. Storage conditions (e.g., inert gas blanket, seal, temperature, humidity, and UV exposure) for the intermediates and finished products also need to be provided by the applicant.

The chemistry review could include a discussion of any new tobacco product manufacturing and product quality issues identified by the applicant and whether these issues were appropriately mitigated. If not adequately mitigated, discuss how these issues may impact manufacturing and product quality consistency.

The following information needs to be included in the manufacturing steps evaluation:

- Bulk e-liquid manufacturing process
    a. Bulk flavor mixing
    b. Nicotine salt mixing (if applicable)
    c. Prefill e-liquid mixing (mixing flavors and base formulation)
- Device manufacturing process (If applicable)
- Finished product storage and distribution

The applicant needs to establish and maintain a quality management system (QMS). A QMS is a system or collection of processes that ensures products are manufactured consistently to meet customer and applicable statutory and regulatory requirements.[6] A proof of accreditation (e.g., ISO 9001:2015) should be provided by the applicant. Good manufacturing practices (GMP) and cGMP are not enforced by FDA for tobacco at this time, thus not required for tobacco product manufacturing.

[6] Quality System Regulation. 21 C.F.R. § 444.1 (1996).

2.3. Product specification

The applicant should provide COAs and batch record from at least three to five most recent finished batches of the new products. The applicant should provide samples of COAs and batch record in the submission for chemistry to evaluate.

The chemistry review should discuss the sample extraction method (e.g., samples are extracted from top, middle, and bottom of the mixing vessel to check for consistency) and quality control testing that the applicant carries out to ensure the finished product conforms to product formulation and is manufactured consistently. This can be completed by evaluating the methods used by the applicant to evaluate the finished products including, but not limited to, clarity (e-liquid homogeneity), color, refractive index, specific gravity, pH, and nicotine content. Alternatively, batch release specifications of the finished products such as nicotine, pH, and assay uniformity of dosage can also be evaluated. The chemistry review could discuss whether the justification for the acceptance criteria is suitable and how this analysis was performed, procedures, instrumentations, and whether the methods used reflect national or international standards and were validated for use of the intended purpose. The applicant also should have an action plan or process map for non-conforming finished products. This includes any re-work and re-test processes, re-worked batch release steps and criteria, and disposal protocol that adheres to local and state hazardous waste regulations. If this information is missing or ambiguous, a deficiency should be issued.

The following information should be included in the product specification evaluation:

- Verification of materials and batch testing
- Quality control and verification of formulation
- Finished product batch testing

2.4. Inspection findings

During the cycle 1 review process, the scientific review team works with the Office of Compliance and Enforcement (OCE) to determine whether inspections should be recommended. During this process, it is important to consider the manufacturing information submitted in the application and any information provided by OCE, such as inspection history and previous concerns, to be able to provide concurrence with OCE inspection recommendations and justifications for non-concurrence. A job aid that outlines the role of the DPS reviewers in OCE inspections is available for guidance.[7]

If inspection is conducted before or during the cycle 2 review, this section should include key findings from the final Establishment Inspection Report(s) (EIR(s)). If the chemistry reviewer provided action items to be addressed by the applicant during the manufacturing inspection, the findings should be summarized in the Inspection Findings Section of the review. Additional findings from the manufacturing inspections that would impact chemistry review, such as adherence to manufacturing controls, should also be discussed in the inspection findings section of the review.

[7] DPS Reviewer's Role in OCE Inspections Job Aid (June 18, 2021)

3. Summary

Manufacturing evaluation should be limited to a high-level summary of the manufacturing documents. However, the documents should be thoroughly inspected and referenced in the chemistry review. It is important for chemistry reviewers to verify that all pertinent documents are provided by the applicant to ensure that the new products are manufactured in a consistent manner.

4. Resources

PMTA final rule
PMTA Scientific Review Job Aid
TPMF Job Aid
PMTA Discipline Review Template