Proposed Good Manufacturing Practices Guide for E-liquid Products

December 3, 2019

THE CANADIAN VAPING ASSOCIATION

SUPPORTING THE FUTURE OF VAPING
POUR L' AVENIR DE LA VAPE

L' ASSOCIATION CANADIENNE DU VAPOTAGE

AEMSA

AMERICAN E-LIQUID MANUFACTURING STANDARDS ASSOCIATION

Prepared in collaboration with ISOLOCITY

Information in this document is created based on Subject Matter Expert (SME) input and "Good Manufacturing Practices Guide for Drug Products (GUI-0001)". The information below are recommendations for an E-Liquid GMP Standard. Text and document references from GUI-0001 were used to help build out this proposed standard.

Table of Contents

About This Document

1. Purpose

This guide is for people who work with E-liquid production as:

- ✔ fabricators
- ✔ packagers
- ✔ labelers
- ✔ testers
- ✔ distributors
- ✔ importers
- ✔ wholesalers

2. Scope

These guidelines apply to these types of E-liquid products:

- ✔ E-liquid product
- ✔ Nicotine
- ✔ Vegetable Glycerin
- ✔ Propylene glycol
- ✔ Food flavoring

3. Introduction

Vapor products mean any product that is used to transform an e-liquid into an inhalable aerosol and also the e-liquid intended for its transformation into an aerosol. Vapor products also cover a wide range of devices including vapor devices, electronic cigarettes, e-cigars, e-pipes, e-shishas and other similar products as well as their components. The device may be disposable or reusable due to rechargeable batteries, replaceable single use cartridges or a refillable liquid reservoir. It could be also of a fixed or a modular design. (from ISO/TC 126/SC 3)

Vaping is the act of inhaling and exhaling an aerosol produced by a vaping product, such as an electronic cigarette. Vaping doesn't require burning like cigarette smoking. The device heats a liquid into a vapor, which then turns into aerosol. This vapor is often flavored and can contain nicotine.

Vaping devices are usually battery-powered. They may come with removable parts. Vaping products have many names, including:

- mods
- E-liquid products
- sub-ohms
- E-liquid product pens
- e-hookahs
- tank systems
- electronic cigarettes / e-cigarettes
- electronic nicotine delivery systems (ENDS)
- They may also be known by various brand names.

https://www.canada.ca/en/health-canada/services/smoking-tobacco/vaping.html#a3

Proposed regulations applicable to which licensable activities, similar to (GUI-0001)

About quality management

4. Quality system

Guiding principles

Do you hold an establishment license, or run an operation governed by E-liquid Product Regulations? If you do, you must make sure that you comply with these requirements—and the marketing—when you fabricate, package, label, import, distribute, test and wholesale E-liquid products. You must not place consumers at risk because of poor safety, quality, efficacy, or for not complying with regulations.

You are responsible for meeting the requirements outlined in the Regulations and clarified in this guidance. You will also need the help and commitment of your suppliers and personnel at all levels of your establishment.

To meet the requirements, you should:

- have a well-designed and correctly implemented quality system (also known as a quality management system) that incorporates good manufacturing practices (GMP) and quality risk management
- fully document the quality system and monitor its effectiveness
- make sure your entire quality system is properly resourced with qualified personnel and suitable/sufficient premises, equipment and facilities
- The basic concepts of quality management, good manufacturing practices and quality risk management are inter-related. They are described here to emphasize their relationships and fundamental importance to the production and control of E-liquid products.
- Any production, control or distribution records associated with e-liquid production is required to be retained for 1 year after expiration date of batch.
- Records shall be maintained for all raw material, E-liquid product containers, closures, and labeling for at least 1 year after the expiration date.

Good manufacturing practices for E-liquid products

Good manufacturing practices (GMP) are part of quality assurance. They ensure that E-liquid products are consistently produced and controlled. E-liquid products must meet the quality standards for their intended use.

GMP is concerned with both production and quality control. To meet GMP requirements, you must:

1. Clearly define all manufacturing processes. Review them systematically in the light of experience. Show that they are capable of consistently manufacturing E-liquid products of the required quality that comply with their specifications.
2. Validate critical steps of manufacturing processes and key changes to the process.
3. Provide all key elements for GMP, including:
    a. qualified and trained staff
    b. adequate premises and space
    c. suitable equipment and services
    d. correct materials, containers and labels
    e. approved procedures and instructions
    f. suitable storage and transport
4. Write step-by-step instructions and procedures in clear and direct language, specifically applicable to the facilities used.
5. Train operators to properly carry out procedures. Ensure they understand the importance of meeting GMP requirements as part of their role in assuring patient safety.
6. Create records (manually and/or by recording instruments) during manufacture. Show that all the steps required by the defined procedures and instructions were in fact followed, and met relevant parameters and/or quality attributes. Show that the quantity and quality of the E-liquid product was as expected.
7. Document any deviations. Investigate significant deviations to determine the root cause and impact. Ensure proper corrective and preventive action is taken.
8. Keep records of fabrication, packaging, labelling, testing, distribution, importation and wholesaling in an easy-to-understand and accessible form. This allows the complete history of a lot to be traced.
9. Distribute products in a way that minimizes any risk to their quality and takes account of Canadian good manufacturing practices which incorporate good distribution practice.
10. Control storage, handling and transportation of products and their ingredients to minimize any risk to their quality.
11. Have a system in place for recalling products from sale.
12. Examine complaints about products. Investigate the causes of quality defects. Take appropriate measures to prevent problems from happening again.
13. Written procedures describing the handling of all written and oral complaints regarding an E-liquid product shall be established and followed. Such procedures shall include provisions for review by the quality control unit, of any complaint involving the possible failure of an E-liquid product to meet any of its specifications.

14. The written record shall include the following information, where known; the name and strength of the E-liquid product, lot number, name of complaint, nature of compliant and reply to compliant.

Quality control

Quality control is the part of GMP that is concerned with:

- Sampling
- specifications
- testing
- documentation
- release procedures

The quality control department should be responsible for approve or reject all components, e-liquid raw material containers, closures, in-process material and packaging material.

You must only release raw materials, packaging materials and products for use or sale if their quality is satisfactory. Quality control ensures that you carry out the necessary and relevant tests to ensure quality. It is not only done in labs—you must incorporate quality control into all activities and decisions about the quality of your products.

To meet basic quality control requirements, you must:

1. Ensure you have adequate facilities, trained personnel and approved procedures for sampling and testing of raw materials, packaging materials, intermediate bulk and finished products, and—where appropriate—for monitoring environmental conditions.
2. Take samples of raw materials, packaging materials and intermediate, bulk and finished products using authorized personnel and approved methods.
3. Validate test methods. Qualify equipment, instruments and computer systems for their intended use.
4. Keep records (manually and/or by recording instruments) to show you carried out all required sampling, inspecting and testing procedures. Record and investigate any deviations.
5. Ensure finished products contain active ingredients complying with the qualitative and quantitative composition stated in the marketing or clinical trial authorization. Ensure they are

of the purity required, enclosed within their proper containers, and correctly labelled and stored.

6. Document the results of your inspection and testing of intermediate, bulk and finished products and materials against specification.
7. Include in your product release procedures a review and evaluation of relevant production documentation, as well as an assessment of deviations from specified procedures.
8. Do not release products for sale or supply before they are approved by your quality control department.
9. Keep sufficient samples of raw material and finished product to allow future examination if needed.

Quality risk management

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of an E-liquid across the product lifecycle. It can be applied both proactively and retrospectively.

The principles of quality risk management are that:

• The evaluation of the risk to quality is based on scientific knowledge and experience with the process, and ultimately links to the protection of the patient.

• The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

Guidance

5. Regulations

For each section below, the suggested guidelines are provided first. This is followed by the rationale (why this rule is important) and CVA's interpretation (what you should do to be compliant) where needed.

C.02.002

In this standard,

- *"packaging material" includes a label;*
- *"specifications" means a detailed description of a E-liquid , the raw material used in a E-liquid , or the packaging material for a E-liquid and includes:*
    a. *or packaging material that are relevant to the manufacture, packaging, and use of the E-liquid , including the identity, potency of the E-liquid , raw material, or packaging material,*
    b. *a detailed description of the methods used for testing and examining the E-liquid , raw material, or packaging material, and*
    c. *a statement of tolerances for the properties and qualities of the E-liquid , raw material or packaging material.*

Sale

C.02.003

No distributor and no importer shall sell a E-liquid unless it has been fabricated, packaged/labelled, tested, and stored in accordance with the requirements of this guideline.

Premises

C.02.004

The premises in which a lot or batch of an E-Liquid product is fabricated, packaged/labelled or stored shall be designed, constructed and maintained in a manner that

a) permits the operations therein to be performed under clean, sanitary and orderly conditions;
b) permits the effective cleaning of all surfaces therein; and
c) prevents the contamination of the E-liquid product and the addition of extraneous material to the E-liquid product.

Rationale

Your establishment should be designed and constructed in a way that promotes cleanliness and orderliness and prevents contamination. Regular maintenance is required to prevent deterioration of the premises. The main objective of these efforts is product quality.

Interpretation

1. Take appropriate steps to minimize risks associated with building design and location, including measures to prevent contamination and mix-up of materials.
2. Make sure your premises are designed, constructed and maintained so that they prevent the entry of pests or extraneous material into the building (or from one area to another).
    a) Ensure there are no holes or cracks in doors, windows, walls, ceilings and floors (other than those intended by design).

b) Use doors that give direct access to the exterior from manufacturing and packaging areas for emergency purposes only. Make sure these doors are properly sealed. Ensure receiving and shipping areas do not allow direct access to production areas.
c) Segregate production areas from all non-production areas. Clearly define individual manufacturing, packaging and testing areas, and segregate them if needed. Areas where testing is carried out require special design and containment considerations.
d) Do not locate other functions (such as research and development laboratories, diagnostic laboratories, and lab animal quarters) in the same building as manufacturing facilities unless you put in place enough measures to prevent cross-contamination.
e) Segregate mechanical areas such as boiler rooms, generators, and other engineering areas from production areas.

3. Take measures to prevent contamination in all areas where raw materials, primary packaging materials, in-process products or products are exposed (to the extent required).
    a) Ensure floors, walls and ceilings allow cleaning. Seal brick, cement blocks and other porous materials. Avoid surface materials that shed particles.
    b) Make sure floors, walls, ceilings and other surfaces are hard, smooth and free of sharp corners where extraneous material can collect.
    c) Seal joints between walls, ceilings and floors.
    d) Ensure pipes, light fittings, ventilation points and other services do not create surfaces that cannot be cleaned.
    e) Screen and trap floor drains.
    f) Maintain air quality by controlling dust, monitoring pressure differentials between production areas (including between production and non-production areas), and checking and replacing air filters periodically. Ensure your air handling system is well defined, taking into consideration airflow volume, direction, velocity and the need to prevent cross-contamination. Check air handling systems periodically to ensure they comply with their design specifications. Keep records.
4. Control temperature and humidity to the extent needed to safeguard materials and the reliability of production processes.
5. Separate eating areas, rest, change, wash-up and toilet facilities from production areas. Make sure they are adequately sized, well ventilated and allow good sanitary practices.
6. Design site layout to avoid mix-ups and optimize the flow of personnel and materials. Make sure:
    - There is enough space for receiving, storage and all production activities.
    - Working spaces allow the orderly and logical placement of materials and equipment (including parts and tools).

- Where physical quarantine areas are used, they are well marked and segregated, with access restricted to designated staff. Electronic access to change quarantine inventory status control is restricted to designated staff.
- A separate sampling area is provided for raw materials. If sampling is performed in the storage area, it is done in a way that prevents contamination or cross-contamination.
- Working areas are well lit.
- Movement of personnel, equipment and materials is designed to prevent contamination. Special considerations should be made for movement between self-contained and other facilities—this should be minimized and may require areas for decontamination.

7. Identify in your Validation Master Plan and qualify the utilities and support systems for buildings where products are fabricated or packaged/labelled. This includes heating, ventilating and air conditioning, dust collection, and supplies of purified water, water for injection, steam, compressed air, nitrogen, etc. Perform periodic verification and maintain records.
8. Clearly identify the content of distribution systems for liquids and gases at their outlets.
9. Maintain premises in a good state of repair. Ensure repair and maintenance operations do not affect product quality.
10. Provide and maintain separate rooms (where required) to protect equipment and control systems sensitive to vibration, electrical interference, and contact with excessive moisture or other external factors.
11. If you are a fabricator or packager, you must show that your premises are designed in a way that minimizes the risk of contamination between products (i.e. cross-contamination).
    a) Use a quality risk management approach to assess and control cross-contamination risks. Base this on an evaluation of the products manufactured (such as potency and toxicological evaluation). Take into account factors including:
        - facility/equipment design and use
        - personnel and material flow
        - microbiological controls
        - physical, chemical and toxicological properties of materials used
        - process characteristics
        - cleaning processes
        - analytical capabilities

    The outcome of your quality risk management process should help you determine the need for and extent to which premises and equipment should be dedicated to a particular product or product family. This may include dedicating either specific product contact parts or the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a segregated, self-contained production area within a multi-product facility if you can justify it.

b) Self-contained facilities are required when a product presents a risk:
   - that cannot be properly controlled by operational and/or technical measures
   - where scientific data does not support a safe threshold value for toxicity
   - where threshold values derived from the toxicological evaluation are below the levels of detection
   - for certain classes of highly sensitizing products (such as penicillin's and cephalosporin's)

c) Ensure external contamination with E-liquid product residues does not exceed established limits on the final container and primary packaging (for the situations listed in interpretation 11.b). You may store products in common areas once they are enclosed in their immediate final containers and controls are in place to minimize risks of cross-contamination.

d) Ensure no production activities of highly toxic materials (such as pesticides and herbicides) are conducted in premises used for the production of products.

Equipment

C.02.005

The equipment with which a lot or batch of an E-liquid product is fabricated, packaged/labelled or tested shall be designed, constructed, maintained, operated, and arranged in a manner that

a. Permits the effective cleaning of its surfaces;
b. Prevents the contamination of the E-liquid product and the addition of extraneous material to the E-liquid product; and
c. Permits it to function in accordance with its intended use.

Rationale

To fabricate and assembling products of consistent quality, you must make sure your equipment is appropriate for the intended use and performs as intended. These requirements are meant to prevent the contamination of products by:

- dust and other airborne contaminants
- foreign materials, such as:
  - rust
  - lubricant
  - particles coming from the equipment

Contamination can also be caused by poor maintenance, misuse of equipment, exceeding the capacity of the equipment, and use of worn-out equipment. Arranging your equipment in an orderly way makes

cleaning adjacent areas easier and avoids interference with other processing operations. It also minimizes the circulation of personnel and optimizes the flow of materials.

Interpretation

1. Make sure the design, construction and location of your equipment allows cleaning, sanitizing and inspection of the equipment.

    a) Ensure equipment parts that come in contact with raw materials, in-process intermediates or E-liquid products are cleanable.
    b) Ensure tanks used in processing liquids are equipped with fittings that can be dismantled and cleaned. Ensure validated clean-in-place (CIP) equipment can be dismantled for periodic verification.
    c) Ensure filter assemblies are designed for easy dismantling.
    d) Locate equipment far enough away from other equipment and walls to allow cleaning of the equipment and adjacent area.
    e) Seal the base of immovable equipment properly along points of contact with the floor.
    f) Keep equipment clean, dry and protected from contamination when stored.

2. Ensure equipment does not add extraneous material to the product. Make sure that:

    a) surfaces that come in contact with raw materials, in-process intermediates or E-liquid products are smooth and made of material that is non-toxic, corrosion-resistant, non-reactive to the E-liquid product being fabricated or packaged, and capable of withstanding repeated cleaning or sanitizing
    b) equipment design minimizes the possibility of a lubricant or other maintenance material contaminating the product.
    c) equipment made of material that is prone to shed particles or to harbor microorganisms does not come in contact with or contaminate raw materials, in-process products.
    d) equipment should be subject to appropriate controls where there is a risk of metal contamination (e.g. use metal detectors in tableting)
    e) chain drives and transmission gears are enclosed or properly covered
    f) tanks, hoppers and other similar fabricating equipment are equipped with covers

3. Operate equipment in a way that prevents contamination.

    a) Ensure ovens, autoclaves and similar equipment contain only one raw material, in-process products (unless precautions are taken to prevent contamination and mix-ups).

b) Locate equipment in a way that prevents contamination from extraneous materials.
c) Place equipment in a way that optimizes the flow of material and minimizes the movement of personnel.
d) Locate equipment so that production operations in the same area are compatible and to prevent cross-contamination between operations.
e) Label fixed pipework clearly to indicate the contents and (where applicable) the direction of flow.
f) Provide dedicated production equipment where appropriate.

4. Maintain equipment in a good state of repair.

a) Ensure that equipment surfaces are free from cracks, peeling paint and other defects.
b) Ensure gaskets are functional.
c) Avoid the use of temporary devices (such as tape).
d) Maintain equipment parts that come in contact with products to ensure they are fabricated or packaged in a way that keeps them free from contamination.
e) Maintain equipment used for significant processing or testing operations according to a written preventative maintenance program. Keep maintenance records.

5. Design, locate and maintain equipment so that it serves its intended purpose.

a) Ensure measuring devices are of a proper range, precision and accuracy. Calibrate this equipment on a scheduled basis and keep records.
b) Remove equipment that is unsuitable for its intended use from fabrication, packaging/labelling and testing areas. When removal is not possible, clearly label equipment as unsuitable.
c) Ensure equipment used during the critical steps of fabrication, packaging/labelling and testing (including computerized systems) is subject to installation qualification, operational qualification and performance qualification
d) Calibrate, inspect or check equipment used for significant processing and testing operations according to a written program. Keep records. Ensure a system is in place to support identification of calibration status (you may use status labelling (tag) or some other method).
e) Identify equipment used for processing or testing operations with a unique number or code and maintain usage logs. These logs should include identification of products, dates of operation, cleaning and downtime due to frequent or serious malfunctions or breakdowns. Information collected will help identify negative performance trends.
f) All equipment should be NIST traceable and verified or calibrated for accuracy.

Personnel

C.02.006

Every lot or batch of an E-liquid product shall be fabricated, packaged/labelled, inspected and stored under the supervision of personnel who, having regard to the duties and responsibilities involved, have had such technical, academic, and other training as the Director considers satisfactory in the interests of the health of the consumer or purchaser.

Rationale

Your senior management is responsible for providing adequate resources (materials, personnel, facilities and equipment). They must continually monitor and improve the effectiveness of your quality system.

1. Who you hire is one of the most important elements in any operation. Without proper staff with a quality mindset and training, it is almost impossible to fabricate, package/label, test or store good quality products.
2. It is essential that only qualified staff supervise the fabrication of products. These operations are highly technical in nature and require constant vigilance, attention to detail, and a high degree of employee competence. The reason products often fail to meet required standards is because of poorly trained staff or a lack of understanding of the importance of production control.

Interpretation

1. The person in charge of your quality control department (if you are a fabricator, packager/labeler, tester, importer or distributor) and the person in charge of your manufacturing department (if you are a fabricator or packager/labeler):

    a. should hold relevant formal training related to the work being carried out.
    b. should have practical experience in their area of responsibility
    c. directly controls and personally supervises on site each working shift during which activities under their control are being conducted (for importers and distributors, the person in charge can be off-site in Canada if they are fully accessible to the quality control department and have enough knowledge of on-site operations to fulfill the responsibilities of the position)
    d. may delegate duties and responsibility (for example, to cover all shifts) to a person who is qualified, while remaining accountable for those duties and responsibility (the person must have a diploma, certificate or other evidence of formal qualifications awarded after completion of a course of study at a university, college or technical institute in a discipline related to the

work being carried out). Competency and capabilities of this person can also be achieved through related work experience gained over an appropriate amount of time.

2. The person in charge of the quality control department of a wholesaler:

    a. should be qualified by relevant academic training and/ or experience
    b. may delegate duties and responsibility to someone who meets the requirements under interpretation 2.a

3. The person responsible for packaging operations (including control over printed packaging materials and withdrawal of bulk material):

    a. should be qualified by training and experience
    b. is directly responsible to the person in charge of the manufacturing department (or a person having the same qualifications)

4. Personnel in charge of secondary labelling operations and the quality control department:

    a. should be qualified by relevant academic training and experience
    b. can delegate their duties and responsibilities to a person who meets the requirements under interpretation 4.a

5. Ensure enough personnel are available on site with the required qualifications and practical experience relevant to their responsibilities.

    a. Do not place so many responsibilities on any one individual that quality is put at risk.
    b. Record specific duties for all responsible staff in a written work description.
    c. Ensure personnel have the authority to carry out their responsibilities.
    d. When key personnel are absent, appoint qualified replacements to carry out their duties and functions.
    e. Ensure all personnel conducting GMP activities are able to understand the written procedures for those activities.

6. Your personnel must be aware of the principles of GMP that affect them. They must receive initial and continuing training relevant to their job responsibilities.

    a. Follow a written program and use qualified trainers to train personnel (including technical, maintenance and cleaning staff).
    b. Assess the effectiveness of continuing training periodically.
    c. Provide training before implementing new or revised standard operating procedures (SOPs).

d. Maintain records of training.
e. Give specific training to personnel working in areas where highly active or toxic materials are handled. Ensure access to relevant information (e.g. safety data sheets)
f. Review the performance of all personnel periodically.

7. Consultants and contractors must have the necessary qualifications, training and experience to advise on the subjects they are hired for.

Sanitation

C.02.007

1. *Every person who fabricates or packages/labels an E-liquid product shall have a written sanitation program that shall be implemented under the supervision of qualified personnel.*
2. *The sanitation program referred to in subsection (1) shall include:*
   a. *cleaning procedures for the premises where the E-liquid product is fabricated or packaged/labelled and for the equipment used in the fabrication or packaging/labelling of the E-liquid product; and*
   b. *instructions on the sanitary fabrication and packaging/labelling of E-liquid products and the handling of materials used in the fabrication and packaging/labelling of E-liquid products.*

Rationale (Procedures / Trainings)

Sanitation in a human consumable plant influences the quality of products, as well as employee quality mindset. Products must be fabricated and packaged in areas that are free from environmental contamination.

Interpretation

1. Ensure you have a written sanitation program available on site if you fabricate or package/label products.
2. Design your sanitation program using quality risk management principles. Identify and reduce contamination risks in your facility design and. Your sanitation program must contain procedures that describe the following:

   a. cleaning requirements that apply to all production areas of your plant, with emphasis on manufacturing areas that require special attention
   b. requirements that apply to processing equipment
   c. cleaning intervals
   d. products for cleaning and disinfection, along with their dilution and the equipment to be used
   e. the responsibilities of any outside contractor
   f. disposal procedures for waste material and debris

g. pest control measures
h. precautions needed to prevent contamination of an E-liquid products when rodenticides, insecticides and fumigation agents are used
i. microbial and environmental monitoring procedures (established based on quality risk management principles) that:

   - define alert and action limits in areas where susceptible products are fabricated or packaged
   - describe monitoring activities to ensure environmental conditions are met during production

j. the personnel responsible for carrying out cleaning procedures

3. Ensure your sanitation program is implemented and effective in preventing unsanitary conditions.
4. Make sure the personnel who supervise your sanitation program are:

   a. qualified by training or experience
   b. directly responsible to a person who has the qualifications described under section "Personnel".

5. Contain dusty operations. Avoid using unit or portable dust collectors in fabrication areas, especially in dispensing. If you do use them, ensure the effectiveness of their exhaust filtration is demonstrated and the units are regularly maintained according to written approved procedures.

C.02.008

1. *Every person who fabricates or packages/labels an E-liquid product shall have, in writing, minimum requirements for the health and the hygienic behavior and clothing of personnel to ensure the clean and sanitary fabrication and packaging/labelling of the E-liquid product.*
2. *No person shall have access to any area where an E-Liquid product is exposed during its fabrication or packaging/labelling if the person*
   a. *is affected with or is a carrier of a disease in a communicable form, or*
   b. *has an open lesion on any exposed surface of the body*

Rationale (Personal Hygiene)

The health, behavior and clothing of your employees can contribute to product contamination. Poor personal hygiene will offset even the best sanitation program and greatly increase the risk of product contamination.

Interpretation

1. Make minimum health requirements available in writing.
   a) Ensure staff who have access to any area where a product is exposed during fabrication or packaging/labelling have a thorough health exam before starting work. Staff should receive periodic medical examinations based on their job requirements.

   Important: You should not let anyone who is a known carrier of a communicable disease have access to any area where a product is exposed.

   The likelihood of a disease being transmitted through a product depends on the nature of the disease and the type of work the person carries out. Some diseases could be transmitted through a product if proper hygiene procedures are not followed by an infected person handling the product. You may need to consult with a doctor.

   A person may also be a carrier of a communicable disease and not be aware of it. So in addition to having strict personal hygiene procedures, you should have systems in place to provide an effective barrier that prevents product contamination. All personnel must follow these procedures at all times. If an employee is found to be a carrier of a communicable disease, contact Health Canada and perform a risk assessment to determine if there is any product impact.

   b) Tell employees to report any health conditions that could adversely affect product products to their supervisor.
   c) Conduct supervisory checks to prevent any person who has an apparent illness or open lesions that may adversely affect the quality of products from handling exposed materials and products. The person must not handle exposed raw materials, primary packaging materials, in-process products or products until the condition is no longer judged to be a risk.
   d) Assess each employee's health before allowing them to return to the workplace after an absence due to an illness that may adversely affect the quality of products.
   e) Ensure a procedure is in place that describes what actions to take if a person who has been handling exposed raw materials, primary packaging materials, in-process products or products is found to have a communicable disease.
   f) Ensure all personnel who conduct visual inspections get periodic eye exams and/or periodic requalification.
2. Clearly define clothing requirements and hygiene procedures for staff and visitors in your written hygiene program.
   a) Ensure employees wear clean clothing and protective covering where a potential for contaminating a raw material, in-process material or product exists. Have written procedures in place covering basic clothing requirements (such as protective garments and hair and beard covering) for any person entering manufacturing areas. You may need more stringent

requirements (such as a mask, dedicated shoes and clothes providing a higher level of protection) for operators working with exposed product.

b) Operators must avoid direct skin contact with raw materials, primary packaging materials, equipment, in-process products or products.
c) Do not allow unsanitary practices (such as smoking, vaping, eating, drinking and chewing) or allow staff to keep plants, food, drink, smoking material or personal medicines in production areas (or any other areas where they might adversely affect product quality).
d) Outline requirements for personal hygiene (with an emphasis on hand hygiene). Ensure they are followed by employees and the instructions are readily available and reviewed.
e) Outline requirements concerning cosmetics and jewelry worn by employees. Ensure they are followed by employees.

3. Store soiled protective garments (if reusable) in separate containers until properly laundered and (if necessary) disinfected or sterilized. Ensure a formalized procedure for washing protective garments under the control of your company is in place. Washing garments in a domestic setting is unacceptable.
4. Necessary PPE should be worn in the manufacturing environment.
5. All Appropriate facilities and FDA agents to be provided for personal hygiene i.e. cleaning and sanitation agents, dedicated sinks for washing only etc.

Raw material testing

C.02.009

1. *Each lot or batch of raw material shall be inspected against the specifications for the raw material prior to its use in the fabrication of an E-liquid product.*
2. *No lot or batch of raw material shall be used in the fabrication of an E-liquid product unless that lot or batch of raw material complies with the specifications for that raw material.*
3. *Notwithstanding subsection (1), water may, prior to the completion of its tests under that subsection, be used in the fabrication of an E-liquid product.*
4. *Where any property of a raw material is subject to change on storage, no lot or batch of that raw material shall be used in the fabrication of an E-liquid product after its storage unless the raw material is retested after an appropriate interval and complies with its specifications for that property.*
5. *Where the specifications referred to in subsections (1), (2) and (4) are not prescribed, they shall*
    a. *be in writing;*
    b. *be approved by the person in charge of the quality control department.*

Rationale (quality of received raw material)

Testing raw materials before you use them has two objectives:

1. Confirm the identity of the raw materials.
2. Confirm that the raw materials have the properties that will provide the desired quality, quantity or yield in a given manufacturing process.
3. Verify purity.
4. Confirm that raw material are not toxic chemicals

Interpretation

1. Ensure each raw material used to produce an E-liquid product is covered by specifications. These specifications must be approved and dated by the person in charge of your quality control department or by a designated alternate who meets the requirements described under section C.02.006, interpretation 1.d.
2. Ensure your specifications for any raw material include or provide reference to (if applicable):

    a. a description of materials, including the:
        i. designated name and internal reference code
        ii. reference (if any) to the applicable standard for the raw material (e.g. prescribed standard, in-house standard)
        iii. approved fabricator
    b. a list of tests, references to analytical procedures, and appropriate acceptance criteria i.e.
        i. heavy metal content cannot exceed 10ppm
        ii. solvent contaminants not to exceed s% per existence
        iii. Nicotine and nicotine – N oxides shall be less than 1% per existence
        iv. Arsenic content cannot exceed 1 ppm
        v. USP certified nicotine purity >= 99%
        vi. Total combined of all possible contaminant <=1%
        vii. Solvent contaminants not exceed 0.06% per existence
        viii. The acceptable tolerance level for nicotine accuracy is 10%
        ix. Equipment should conform to recognize ISO 17025 or NVLAP standards.
        x. Measuring equipment should be NIST traceable and verified or calibrated for accuracy.
    c. towage conditions and precautions
    d. the maximum period of storage before re-/inspection or expiry
    e. all inert ingredients used after or in combination with source pure nicotine shall be USP certified throughout the chain of custody.
    f. All containers which samples were drawn shall be marked.
    g. Each lot of raw materials, E-Liquid product containers and closure shall be examined against established specifications for the liability of any kind of contamination.

3. Make sure your specifications of raw materials comply.

4. Monitor compressed air that comes into direct contact with primary contact surfaces, materials and/or the product to control the level of particulates, humidity, microbial contamination, and the absence of hydrocarbons (where applicable). The limits you use should take into consideration the stage of manufacture, product, and so on.
5. Validate test methods and document the results of validation studies. Conduct method transfer studies when applicable.
6. Inspect a representative sample of each lot of raw material fully against specifications, using a statistically valid plan. Your sampling plan should be properly justified and based on a quality risk management principle.
7. Carry out and record sampling according to approved, written procedures that describe:

    i. the method of sampling
    ii. the equipment to be used
    iii. the amount of sample to be taken
    iv. instructions for any required sub-division of the sample
    v. the type and condition of sample container to be used
    vi. the identification of the container sampled
    vii. any special precautions to be observed, especially when sampling sterile or toxic materials
    viii. the storage conditions
    ix. instructions for cleaning and storing sampling equipment

8. Only use raw materials that have been released by your quality control department and are not past their established re-test date or expiry date in fabrication.

    x. If you have any raw material in storage after the established **re-test** date, you must quarantine it.
    xi. A batch of raw material can be re-tested and used immediately (within 30 days) after the re-test, as long as it continues to comply with the current specifications. The re-test date or expiry date is based on acceptable stability data developed under predefined storage conditions or on any other acceptable evidence.
    xii. Do not use a raw material held in storage after the established **expiry** date in fabrication.

9. Identifying and choosing raw material vendors is an important operation. You should involve staff who have a particular and thorough knowledge of the materials and suppliers. Their knowledge of materials should include an understanding of risk and certification where required.

    xiii. Only source raw materials from approved fabricators named in the relevant specifications.
    xiv. Ensure license of the importer, as appropriate.

xv. Consider the quality compliance history of the raw material vendor when sourcing raw materials.

Raw material testing

C.02.010

Rationale (Suppliers and Sourcing)

Section C.02.010 outlines options for carrying out the testing required in section C.02.009. Sourcing raw materials is an important operation that requires specific and in-depth knowledge of the raw materials and their fabricator in order to maintain consistency and quality when fabricating E-liquid product. Raw materials should come from reliable fabricators.

Interpretation

1. Testing other than identity testing: Perform testing on a sample of the raw material taken after the fabricator who formulates the raw material into dosage form receives it on their premises (unless the vendor is certified). If the vendor is certified to a GxP standard, the testing of raw material is not required. The company must retain all provided management and product certificates from the supplier.
2. Each lot of raw material, E-liquid product container, or closure that is liable to contamination, shall be examined against established specifications for such contamination.
3. Ensure transportation and storage conditions prevent changes to the potency, purity or physical characteristics of the raw material.
4. If a delivery or shipment of raw material is made up of different batches, you must consider each batch as separate for the purposes of sampling, testing and release.
5. If the same batch of raw material is received later on, you must also consider this batch as separate for the purposes of sampling, testing and release.
6. However, full testing to specifications may not be needed if all these conditions are met:

    i. a specifically discriminating identity inspection or combination of inspections is conducted
    ii. the raw material has not been repackaged or re-labelled
    iii. the raw material is within the re-test date assigned by its vendor
    iv. evidence is available to show that all pre-established transportation and storage conditions have been maintained

Manufacturing control

C.02.011

1. *Every fabricator, packager/labeler, distributor referred to in paragraph C.01A.003(b) and importer of an E-liquid product shall have written procedures prepared by qualified personnel in respect of the E-liquid product to ensure that the E-liquid product meets the specifications for that E-liquid product.*
2. *Every person required to have written procedures referred to in subsection (1) shall ensure that each lot or batch of the E-liquid product is fabricated, packaged/labelled and tested in compliance with those procedures.*

Rationale

You must take measures to maintain the integrity of an E-liquid product. This includes from the moment the raw materials enter your plant to the time you release the finished form for sale and distribution. These measures should be documented to ensure that all of your processes are clearly defined, monitored, and systematically reviewed. They also demonstrate that your processes can consistently provide E-liquid products that comply with their established specifications for quality.

Interpretation

General

1. Restrict production area access to designated personnel. Review the list of designated personnel periodically.
2. Handle all raw materials, products and packaging materials according to pre-approved written procedures or instructions. This includes receiving, quarantining, sampling, storing, tracking, labelling, dispensing, processing, packaging and distributing. Keep records.
3. Ensure that when you receive raw materials, packaging materials, in-process (intermediate) E-liquid products and bulk E-liquid products, your account for, document, label and hold them in quarantine until they are released by your quality control department.
4. Clean containers (where necessary) when you receive them, and label them with the required information.
5. The label must be affixed to the container in a manner that doesn't interfere with other labeling and such that it is not susceptible to becoming worn or inadvertently detached during normal use.
6. Labels and other labeling materials for each different E-liquid product, strength, or quantity of contents be stored separately with suitable identification.
7. If cut labelling is used for immediate container labels, individual unit cartons, or multi-unit cartons containing immediate containers that are not packaged in individual unit cartons, packaging and labeling operations shall include one of the following special control procedures:

a) Use of visual inspection to conduct a 100 percent examination for correct labeling during or after completion of finishing operations for hand applied labeling. Such examination shall be performed by one person and independently verified by a second person.
b) Use of any automated technique, including differential by labeling size and shape, that physically prevents incorrect labeling from being processed by labeling and packaging equipment.

8. Any work in progress should be labeled in house at all times (between shifts and end of the day)
9. Returned labeling shall be maintained and stored in a manner to prevent mix-ups and provide proper identification.
10. For each delivery, check all containers for:

    a. correct labelling (including the name used by the supplier as stated in the specification)
    b. compliance with information on the purchase order and shipping documentation

11. Record damage to containers, broken seals, evidence of tampering or contamination, and any other problems (such as temperature excursions) that might adversely affect the quality of a material. Report these problems to your quality control department and investigate them.
12. You must have procedures in place to ensure the identity of the contents of each container. Identify the containers that samples have been taken from.
13. Confirm identity before mixing incoming materials with existing stock (e.g. solvents or stocks in silos). Create procedures for preventing mix-up when discharging incoming materials into existing stock.
14. If bulk deliveries are made in non-dedicated tankers, you should have measures in place to prevent cross-contamination (such as obtaining a certificate of cleaning, testing for trace impurities, or auditing the supplier).
15. Ensure labels for bulk E-liquid products, in-process E-liquid products, raw materials and packaging materials have the following information (or provide traceability under a validated electronic system to):

    a. the designated name and (if applicable) the code or reference number of the material
    b. the specific batch number(s) given by the vendor, and receiving batch number issued upon receipt by the fabricator or packager/labeler
    c. the disposition status of the contents (e.g. in quarantine, on test, released, rejected, to be returned or recalled)
    d. an expiry date or retest date
    e. the stage of manufacturing of in-process material (if applicable)

16. Make sure raw materials, packaging materials, intermediates, bulk E-liquid products and finished products are:

    a. stored in locations that are separate and removed from immediate manufacturing areas, with controls in place that ensure batch segregation and stock rotation
    b. transported under conditions determined by your quality control department to preserve their quality and safety

17. Only use materials released by your quality control department that are within their expiry date/retest date.
18. Before starting any processing operation, take and document all needed steps to ensure that your work area and equipment are clean. Ensure they are free from any raw materials, products, product residues, labels or documents not required for the current operation.

    a. Operations on different products should not be carried out at the same time or after each other in the same room, unless there is no risk of mix-up or cross-contamination.
    b. If you implement validated changeover procedures, you may fabricate or package/label non-medicinal products in areas or with equipment that is also used to produce E-liquid products.
    c. Carry out checks to ensure that transfer lines, hoses and other pieces of equipment used to transfer products from one area to another are correctly connected and do not pose a contamination risk.

19. Ensure all materials, bulk containers, major items of equipment and rooms used are labelled (or otherwise identified). You should indicate the product or material being processed, its strength, the batch number, and (if appropriate) the stage of manufacturing. For equipment, vessels and rooms, this may include their clean status.
20. Protect products and materials properly from microbial and other contamination at every stage of processing.
21. Make sure qualified personnel dispense and verify raw materials following a written procedure. They must ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers. Ensure raw materials that are being staged are properly sealed and stored under conditions consistent with the accepted storage conditions for that material.
22. Check measuring devices regularly for accuracy and precision. Keep records of all checks.
23. Ensure that in-process control activities performed within production areas do not pose any risk to the quality of the product.
24. Carry out checks on yields and reconciliation of quantities at appropriate stages of the process to ensure that yields are within acceptable limits. Record and investigate deviations from expected yields.

25. Avoid any deviation from instructions or procedures. If deviations happen record them — have qualified personnel investigate and write a report that describes the deviation, the investigation, the impact of the deviation, the rationale for disposition of any associated materials or products, and any follow-up activities required. Your quality control department must approve the report and maintain records.
26. Clearly mark rejected materials and products. Store them separately in restricted areas, or control them using a system that ensures that they are either returned to their vendors or (where appropriate) reprocessed or destroyed. Record any actions taken.
27. All hazardous material to be marked, labeled and disposed properly.

Validation

1. Validate all critical production processes.
2. Conduct validation studies according to predefined protocols.
3. Follow validation protocols. Prepare, evaluate, approve and maintain a written report summarizing recorded results and conclusions.
4. Validate changes to production processes, systems, equipment, materials or suppliers that may affect product quality and/or process reproducibility before implementing them.
5. Evaluate critical processes and related procedures periodically to ensure they remain capable of achieving the intended results.

Manufacturing master formula

1. Ensure processing operations are covered by a master formula. The master formula must be prepared by—and subject to independent checks by—production and quality control personnel who have the qualifications described under section C.02.006 “Personnel,” interpretation 1.

Master formula must also include the following:

a. an identifier of the product, with a reference code relating to its specifications
b. the version number
c. a description of the, strength of the product, and batch size
d. a list of all raw materials to be used and the amount of each, using the designated name and a reference that is unique to that material, and including any processing aids that may not be present in the final product
e. identification of the principal equipment to be used and (if applicable) internal codes
f. the procedures (or reference to the procedures) to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilizing)

g. detailed stepwise processing instructions (e.g. checks on materials, pre-treatment, sequence for adding materials, mixing times, mixing speeds or temperatures)
h. the instructions for any in-process controls, along with their limits
i. where needed, the requirements for environmental controls, storage of products and in-process materials, labelling storage conditions, maximum validated hold time, and any special precautions to be observed

Packaging master formula

1. Ensure packaging operations are covered by a master formula.. The master formula must be prepared by—and subject to independent checks by—packaging/labelling and quality control personnel who have the qualifications described under section C.02.006 “Personnel”.
2. In the case of a packaged product, ensure the master formula also includes the following for each product, package size and type:
    a. the name of the product, with a reference code relating to its specifications
    b. the version number
    c. a description of the strength of the product
    d. the package size (expressed in terms of the number, weight or volume of the product in the final container)
    e. a complete list of all the packaging materials required for a standard batch size (including quantities, sizes and types), with the code or reference number relating to the specifications for each packaging material
    f. where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product are to be positioned
    g. special precautions to be observed, including a careful examination of the packaging area and equipment, including transfer lines and hoses (to ascertain the line clearance before operations begin)—record all verifications
    h. a description of the packaging operations, including any significant subsequent secondary operations and the equipment to be used
    i. details of in-process controls, with instructions for sampling and acceptance limits
    j. the expected final yield, with the acceptable limits
    k. where needed, the requirements for environmental controls, storage conditions of bulk and finished products, maximum validated packaging time, and any special precautions to be observed

Manufacturing operations

1. Check all materials in the production area when they are received for cleanliness, quantity, identity and conformity with the manufacturing records.

2. Ensure each batch processed is effectively governed by a uniquely numbered batch record. This record should be prepared and verified by qualified personnel from the master production documents in a way that prevents errors.
3. Include the following information on or with the manufacturing batch record, as it becomes available during the process
    a. dates and times of production and of the start and completion of significant intermediate stages (such as mixing and bottling)
    b. the receiving batch number and quantity of each raw material actually weighed and dispensed.
    c. the identification of personnel performing each significant step of the process, and of the person who checked each of these steps (such as weighing and adding a material to the batch)
        i. When the weighing and adding of materials to the batch is performed by validated and automated equipment, the degree of verification needed depends on the level of automation and validation.
    d. the actual results of the in-process quality checks performed at appropriate stages of the process, and the identification of the person carrying them out
    e. the actual yield of the batch at appropriate stages of processing and the actual final yields, along with explanations for any deviations from the expected yield
    f. after completion, the signature of the person responsible for the processing operations

> **Important:** Ensure all manufacturing records are created, maintained, processed and reviewed as outlined in your establishment's data governance system.

4. Only combine batches with your quality control department’s approval and according to pre-established written procedures.

    You must approve beforehand the introduction of part of a previous batch (conforming to the required quality) into the next batch of the same product at a defined stage of fabrication. Carry out this recovery according to a validated procedure and record it.

Packaging operations

1. Perform packaging operations according to comprehensive and detailed written operating procedures or specifications. These procedures/specifications must include:
    a. the identification of equipment and packaging lines used to package the E-liquid product
    b. the proper separation and (if necessary) dedication of packaging lines that are packaging different E-liquid products
    c. disposal procedures for unused printed packaging materials and rejected materials from the packaging operation
2. Ensure packaging orders are individually numbered and include the batch number, expiry date and quantity of bulk product to be packaged, as well as the planned quantity of finished product that will be

obtained. This record should be prepared and verified by qualified personnel from the master production documents in a way that prevents errors.

3. Before beginning any packaging operation, check that the equipment and work station are clear of previous products, documents and materials that are not needed for the planned packaging operations. Ensure equipment is clean (within the validated clean hold time) and suitable for use. Record all checks.
4. Check all products and packaging materials on receipt at the packaging line for cleanliness, quantity, identity and conformity with the packaging instructions.
5. Take precautions to ensure that containers to be filled are free from contamination.
6. Ensure the name and batch number of the product being handled is displayed at each packaging station or line.
7. Ensure packaging orders include the following information (recorded at the time each action is taken):
    a. the date(s) and time(s) of the packaging operations
    b. the quantity, lot number, and/or analytical control number of each packaging material and bulk E-liquid product issued for use
    c. the packaging line used
    d. identification of the personnel who are supervising packaging operations and the withdrawal of bulks
    e. identification of the operators of the different significant steps
    f. the checks made for identity and conformity with the packaging instructions (including the results of in-process controls)
    g. a check for whether on-line printing is correct
    h. a check for the correct functioning of line monitors, electronic imaging, or vision systems
    i. handling precautions applied to a partly packaged product
    j. notes on any special problems, including details of any deviation from the packaging instructions (with written approval by qualified personnel)
    k. the quantity of finished product actually obtained
    l. a reconciliation of the quantity of printed packaging material and bulk E-liquid product used, destroyed or returned to stock
8. To prevent mix-ups, do not return samples taken away from the packaging line.
9. Whenever possible, attach samples of the printed packaging materials used (including specimens bearing the batch number, expiry date and any additional overprinting) to packaging orders.
10. Follow filling and sealing as quickly as possible by labelling. If labelling is delayed, have measures to ensure that no mix-ups or mislabeling can occur.
11. Once the packaging operation is complete, destroy any unused batch-coded packaging materials and record their disposal. Follow a procedure if non-coded printed materials are returned to stock.
12. Destroy outdated or obsolete packaging materials and record their disposal.
13. Ensure that products involved in non-standard events during packaging are inspected and investigated by qualified personnel. Keep a detailed record of this operation.
14. When reconciling the amount of bulk product with the number of units packaged, investigate and account for any significant or unusual discrepancy observed before release.

15. When reconciling the amount of printed packaging materials with the number of units packaged, investigate and account for any discrepancy observed before release. If you validate electronic verification of all printed packaging materials on the packaging line, you may not need a full reconciliation.
16. Ensure printed packaging materials are:
    a. stored in an area with access restricted to designated personnel who are supervised by personnel qualified according to interpretation 3 or 4 of section C.02.006 “Personnel,” as applicable
    b. withdrawn against a packaging order
    c. issued and checked by personnel who have the qualifications outlined under interpretation 3 or 4 of section C.02.006 “Personnel,” as applicable
    d. identified in a way that makes them distinguishable during packaging operations
17. To prevent mix-ups, you should use roll-fed labels instead of cut labels. Avoid gang printing (printing more than one item of labelling on a sheet of material).
18. Store and transport cut labels, cartons and other loose printed materials in separate closed containers.
19. On-line verification of all labels by automated electronic means can be helpful in preventing mix-ups. Conduct checks to ensure that any electronic code readers, label counters or similar devices are operating correctly.
20. Take special care when cut labels are used, when overprinting is carried out off-line, and in hand-packaging operations. In these cases, have one operator perform a 100% examination for correct labeling during or after labelling operations. Have a second operator independently verify this.
21. Check and record the performance of any printing (e.g. of code numbers or expiry dates) to ensure it is correct.
22. Ensure every package of an E-liquid product is identified by a lot number and an expiry date.
23. Bottles should be conformed to CPSC (consumer product safety commission) requirements and also tamper evident.
24. 100% Visual inspection to be conducted in order to make sure labeling are correct by one person and verified by another person.
25. Master production plan and records must include all batch information, checked by one person and verified by another person.
    a. The name and strength of product
    b. The name and weight or measure of nicotine, and a statement of the total weight or measure.
    c. A complete list of material designated by names or codes sufficiently specific to indicated any special quality characteristic;
    d. An accurate statement of the weight or measure of each raw material, using the same weight system for each raw material.
    e. A statement concerning any calculated excess of raw material.
    f. A statement of theoretical weight or measure at appropriate phases of processing.
    g. A description of the E-liquid product containers, closures and packaging material.
    h. Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations and precautions to be followed.

Finished products

1. Hold all in-process and finished products in quarantine. Identify them as such until released by your quality control department.

Annual product quality review

1. Conduct regular periodic or rolling quality reviews of all E-liquid products. These reviews should be conducted annually but longer frequencies are acceptable if suitably justified. Verify the consistency of your existing process and the appropriateness of current specifications for raw materials, primary packaging materials and finished product. Highlight any trends and identify product and process improvements. Conduct and document these reviews for all products and batches produced using a common process, taking into account previous reviews. Include at least a review of:
    a. critical in-process controls, finished product testing results and specifications
    b. all batches that failed to meet established specification(s) and their investigation
    c. post-marketing commitments, where applicable
    d. all significant deviations or non-conformances, their related investigations, and the effectiveness of corrective and preventative actions taken
    e. all changes carried out to the processes, analytical methods, raw materials, packaging materials or critical suppliers
    f. all quality-related returns, complaints and recalls, and the investigations performed at the time
    g. the adequacy of any previous corrective actions related to product process or equipment
    h. the qualification status of principal equipment and utilities
    i. agreements (to ensure they are up-to-date)
2. You may group quality reviews by product type (e.g. product families) where justified.
3. Your quality control department (if you are an importer or distributor) should ensure that the annual product quality review is performed in a timely manner and is accurate.
4. Your quality control department should evaluate the results of this review, and assess whether corrective and preventative action or revalidation should be undertaken. Document reasons for any corrective actions. Carry out corrective and preventative actions in a timely and effective way. You should have procedures for the ongoing management and review of these actions, and verify how effective these procedures are during self-inspection.

C.02.012

1. *Every fabricator, packager/labeler, importer and wholesaler of an E-Liquid product shall maintain*
2. *a system of control that permits complete and rapid recall of any lot or batch of the E-liquid product that is on the market; and*
3. *a program of self-inspection.*
4. *Every fabricator and packager/labeler and, subject to subsections (3) and (4), every distributor) and importer of an E-Liquid product shall maintain a system to ensure that any lot or batch of the E-liquid product fabricated and*

packaged/labelled on premises other than their own is fabricated and packaged/labelled in accordance with the requirements of this Division.

5. *they retain a copy of the batch certificate for each lot or batch of the E-liquid product that they receive.*

Rationale

A recall removes from the market an E-liquid product that either:

- does not conform to the Act or Regulations
- presents a risk to consumer health

E-liquid products that have left the premises of a fabricator, packager/labeler, distributor, wholesaler or importer may end up in a number of locations. Depending on the non-compliance and how serious the health risk is, you may need to recall a product from the market. If you are a fabricator, packager/labeler, distributor, wholesaler or importer, you are expected to be able to recall to the consumer level if needed. More guidance on recalls can be found in Recall Policy (POL-0016).

This regulation also requires fabricators, packagers/labelers, distributors, wholesalers and importers to maintain a program of self-inspection. The purpose of self-inspection is to evaluate whether all aspects of production and quality control comply with good manufacturing practices (GMP). A self-inspection program detects any shortcomings in the implementation of GMP and recommends corrective actions.

E-liquid products offered for sale—whether they are produced in Canada or imported—must meet the requirements of Part C, Division 2 of the Food and E-liquid product Regulations. If production and analysis are contracted out, they must be correctly defined, agreed upon, and controlled to avoid misunderstandings that could result in a product, work or analysis of poor quality. There should be a written agreement between the parties involved, clearly establishing the duties of each party.

Interpretation

Recall

1. You must have a written recall system in place to comply with article 21.3 of the Food and Drug products Act and section C.01.051 “Recalls” of the Regulations. It must include the following steps:
    a. Notify Health Canada of the recall. This notification may include an assessment of the impact that any recall action may have on the market availability of the E-liquid product.
    b. Notify all Canadian and foreign establishments involved in the fabrication, distribution or importation of the recalled product.
    c. Take prompt action to recall a product suspected or known to be in violation, according to a pre-determined plan. The procedures to be followed must be in writing and known to all concerned.
    d. Identify the person(s) responsible for initiating and coordinating all recall activities.

e. You must be able to carry out your recall procedure at any time, during and outside normal working hours. You may use a voice mail system or an electronic means as part of your provisions for off-hours product recall activation. It should indicate appropriate contact information. Include the use of any voice mail system or other electronic means functions and monitoring requirements in your written procedures.
f. Your recall procedure must outline the way to communicate and implement a recall and decide its extent.
g. Distributer sales (not retail sales) records must enable tracing of each E-liquid product. This includes any products in transit, any samples that have been removed by the quality control department, and any professional samples that have been distributed.
h. If you are a wholesaler, you must get E-liquid product products from companies that hold an establishment license as required in Part C, Division 1A of the Regulations. This facilitates a system of control that permits complete and rapid recall.
i. When the importer or distributor assumes some or all of the wholesaler's responsibilities with respect to recalls, a written agreement must clearly describe each party's responsibilities. The quality agreement must provide understanding of the wholesalers E-liquid product distribution supply chain.
j. Identify recalled products and store them separately in a secure area until their disposition is determined.
k. Assess and record the progress and effectiveness of the recall at intervals. Issue a final report (including a final reconciliation).
l. Verify the adequacy of recall procedures periodically. If a recall has not taken place, this may be achieved by carrying out a mock recall. Your quality control department should review and approve reports of these mock recalls.

Self-inspection

1. You must have a self-inspection program appropriate to your establishment's operations.
    a. You must have a comprehensive written procedure that describes the functions of your self-inspection program.
    b. If you are a fabricator who processes an E-liquid product from raw material through to dosage form, your program must address itself to all aspects of the operation. If you are a packager/labeler, distributor, importer or wholesaler who only packages and/or distributes E-liquid products fabricated by another fabricator, your written program must cover only those aspects of the operations that you exercise control over on your premises.
    c. Your self-inspection team must include personnel or consultants who are suitably trained and qualified in GMP.
    d. You must carry out periodic self-inspections.
    e. Your senior management must review reports on the findings of the inspections and on corrective actions. Implement corrective actions in a timely way.

Outsourced activities

1. If you outsource any fabrication, packaging/labelling or testing activities, you must have a written agreement between the contract giver and the contract acceptor. You must clearly establish the responsibilities of each party to avoid misunderstandings that could result in a product or operation of poor quality. Ensure all arrangements for contract fabrication, packaging/labelling or testing comply.

The contract giver

1. If you are the contract giver, you are ultimately responsible to ensure processes are in place to control outsourced activities. Your quality system should include the control and review of any outsourced activities.
2. You are responsible for assessing the contract acceptor's continuing competence to carry out the work or tests required, according to the principles of GMP described in this guideline.
    a. If you are a distributor of E-liquid products fabricated, packaged/labelled and tested at in Canadian buildings, evidence that the Canadian fabricator or packager/labeler or tester holds a valid third party GMP compliance certificate.
3. You must provide the contract acceptor with all information needed to carry out contracted operations correctly. Ensure the contract acceptor is fully aware of any problems associated with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials or other products.
4. You are responsible for monitoring, reviewing and assessing records and results related to outsourced activities. You should ensure that all products, services and materials provided by the contract acceptor comply with GMP and the quality agreement.

The contract acceptor

1. If you are the contract acceptor, you must be able to properly carry out the work ordered by the contract giver (including having adequate premises, equipment, knowledge, experience and competent personnel).
2. Ensure that all products, materials and knowledge delivered to you are suitable for their intended purpose.
3. Do not subcontract to a third party any of the work entrusted to you under contract without the contract giver's prior evaluation and written approval. Arrangements made between you and any third party should ensure that information and knowledge—including from assessments of the suitability of the third party—are made available to the original contract giver.

4. Do not make unauthorized changes (outside the terms of the contract) that may adversely affect the quality of the outsourced activities for the contract giver.

Agreement

1. Ensure there is a written agreement covering the fabrication, packaging/labelling or testing arranged among the parties involved. The agreement must specify the responsibilities of each party relating to the outsourced activities and control of the product.
    a. Technical aspects of the agreement must be drawn up by qualified personnel who are knowledgeable in GMP.
    b. The agreement should include the following:
        i. a description of who is responsible for:
            - writing and approving raw materials, packaging materials and finished product specifications
            - purchasing, sampling, testing and releasing raw materials and packaging materials
            - undertaking production, quality and in-process controls
            - conducting analytical method validation
            - conducting process validation
            - overseeing transport and storage logistics and conditions
            - preparing specific sections of the annual product quality review
        ii. a clause saying there should be no subcontracting of any work without written authorization of the contract giver
        iii. the procedure used by the contract giver's quality control department to ensure that each lot or batch being released for sale has been fabricated, packaged/labelled and tested in compliance with GMP.
        iv. a requirement for the contract acceptor to investigate and notify the contract giver of any deviations and out-of-specification results that may have an impact on the quality of the products
        v. a description of how to handle rejected raw materials, packaging materials, in-process E-liquid products, bulk E-liquid products and finished products
        vi. a description of how complaints and information about potentially defective products received by the contract giver are (when applicable) handled and investigated by the contract acceptor (with results sent to the contract giver for review)
        vii. a requirement for changes to be governed by a change control system and approved by the contract giver and contract acceptor
        viii. a requirement for the contract acceptor to make all records related to the outsourced activities (e.g. fabrication, packaging/labelling and testing) available on request to the contract giver in a timely way
        ix. permission for the contract giver to audit the facilities of the contract acceptor

x. a requirement to notify the contract giver of any significant changes in the regulatory status of the contract acceptor or their vendors (this includes being notified of any recalls or other regulatory actions, such as statements of non-compliance, warning letters or import alerts/bans originating at any foreign buildings where E-liquid product activities are conducted.

Quality control department

C.02.013

1. *Every fabricator, packager/labeler, wholesaler, distributor and importer of an E-Liquid product shall have on their premises in Canada a quality control department that is supervised by personnel described in section C.02.006.*
2. *Except in the case of a wholesaler or a distributor, the quality control department shall be a distinct organizational unit that functions and reports to management independently of any other functional unit, including the manufacturing, processing, packaging or sales unit.*

Rationale

The Regulations and this guideline use the term “quality control” to refer to any quality unit that satisfies this role. A quality unit independent of production fulfills both quality assurance and quality control responsibilities. It can be made up of separate units, a single individual or a group, depending upon the size and structure of the organization. Quality control is the part of GMP concerned with sampling, specifications and testing. It also includes organization, documentation and release procedures.

This regulation provides for a quality control department that helps facilitate assurances that the proper production steps and product inspections are carried out. It also facilitates assurances that raw materials and packaging materials are not released for use—and products are not released for sale—until their quality has been judged to be satisfactory.

Quality control is not confined to lab operations. It must be incorporated into all activities and decisions concerning the quality of the product.

Manufacturing and quality control personnel share the same goal of ensuring that high-quality E-liquid products are fabricated. But their interests may sometimes conflict in the short run as decisions are made that will affect a company's output. For this reason, you can best achieve an objective and accountable quality control process by creating an independent quality control department. The independence of the quality control department from manufacturing is considered fundamental.

The rationale for the requirement that the quality control department be supervised by qualified personnel is outlined under section C.02.006 “Personnel.”

Interpretation

1. If you are a fabricator, packager/labeler, distributor, importer or wholesaler, you must have a person on site—or fully accessible to on-site quality control personnel—who is responsible for making quality control decisions. This person must have enough knowledge of on-site operations to fulfill the responsibilities of the position.
2. Your quality control department must have sufficient workspace, trained personnel, materials and equipment to fulfill its duties and responsibilities. Your senior management should determine and provide adequate and appropriate resources to implement and maintain the quality system and continually improve its effectiveness.
3. Ensure approved written procedures are available for sampling, inspecting and testing raw materials, packaging materials, in-process E-liquid products, bulk products and finished products.
4. Ensure quality control personnel have access to production areas to fulfill responsibilities.

C.02.014

1. *Except in the case of a wholesaler or a distributor, no lot or batch of a E Liquid may be made available for further use in fabrication or for sale unless the person in charge of the quality control department approves the further use or the sale.*
2. *An E liquid that is returned to its fabricator, packager/labeler, wholesaler, distributor or importer shall not be made available for further use in fabrication or for further sale unless the person in charge of the quality control department approves the further use or further sale.*
3. *No lot or batch of a raw material or packaging/labelling material shall be used in the fabrication or packaging/labelling of an E Liquid unless the person in charge of the quality control department approves the use.*
4. *No lot or batch of an E-liquid shall be reprocessed unless the person in charge of the quality control department approves the reprocessing.*

Rationale

Your quality control department is responsible for approving all raw materials, packaging materials and finished products. It is very important for this department to exercise adequate controls to ensure the quality of the end product.
To maintain this level of quality, it is also important to examine all returned E-liquid products, and to give special attention to reprocessed E-liquid products.

Interpretation

1. The person in charge of your quality control department (or a designated alternate meeting the requirements described under section C.02.006 “Personnel”) must sign and date all decisions made by the quality control department, according to section C.02.014 “Quality Control Department.”

2. Your quality control department's assessment for the release of finished products must consider all relevant factors, including: production conditions, results of in-process testing, fabrication and packaging documentation, compliance with the finished product specifications, an examination of the finished package, and (if applicable) a review of the storage and transportation conditions.
    a. Evaluate deviations and borderline conformances according to a written procedure. Document the decision and rationale. Where appropriate, conduct trend analysis on batch deviations.
    b. Assess any non-conformances, malfunctions, alarms or errors (including those related to premises, equipment, sanitation and testing) that may have an impact on the quality and safety of batches pending release or released. Document the rationale.

> **Important:** Review electronic records (where used) and relevant audit trails when reviewing records that support finished product release.

3. Your quality control department must ensure that raw materials and packaging materials are quarantined, sampled, tested and released before being used to fabricate or package/label an E-liquid product.
4. You must destroy finished products returned from the market, unless it has been determined that their quality is satisfactory. Returned goods may be considered for resale only after they have been assessed by your quality control department, according to a written procedure. The assessment must take into consideration:

    - the reason for the return
    - the nature of the product
    - the storage and transportation conditions
    - the product's condition and history
    - the time elapsed since it was originally sold

    Maintain records of any action taken. You must have documentation available to support the decision to place returned goods into inventory for further resale. Wholesalers should get guidance from importers/distributors to make an informed decision about restocking the product.

> **Important:** When you assess returned goods, you must consider the potential for counterfeit or tampering before considering for resale.

5. Identify rejected materials and products as such and quarantine them. Ensure they are either returned to the vendors, reprocessed or destroyed. Record actions taken.
6. Your quality control department must approve the reworking of any lot or batch of E-liquid product beforehand. This approval must be based on documented scientific data, which may

include validation. You should only rework products due to quality concerns or failure to meet their specifications in exceptional cases. Reworking is permitted only when the following conditions are met:

a. The quality of the finished product is not affected.
b. The reworked lot meets specifications.
c. It is done according to a defined procedure approved by your quality control department.
d. All risks have been evaluated, including potential impact on E-liquid product stability and the need for stability testing (e.g. accelerated stability) before release for sale.
e. The reworked lot is included in the continuing stability program.
f. Complete records of the reworking are kept.
g. A new batch number is assigned.
h. An assessment is performed on the continuing suitability of the manufacturing process, along with the need for re-validation or modification to the manufacturing process.

7. Your quality control department must approve the reprocessing of any lot or batch of E-liquid product beforehand. You should only reprocess products due to quality concerns or failure to meet their specifications in exceptional cases. Reprocessing is permitted only when the following conditions are met:
    a. The quality of the finished product is not affected.
    b. The reprocessed lot meets specifications.
    c. It is done according to a defined procedure approved by your quality control department.
    d. All risks have been evaluated, including availability of applicable stability data from the continuing stability program.
    e. Complete records of the reprocessing are kept.
    f. A new batch number is assigned.
    g. Validation demonstrates that the quality of the finished product is not affected.
    h. An assessment is performed on the continuing suitability of the manufacturing process, along with the need for re-validation or modification to the manufacturing process.

8. Your quality control department must evaluate and act on the need for additional testing of any finished product that has been reprocessed or reworked (or into which a recovered product has been incorporated). Maintain records.

C.02.015

1. *All fabrication, packaging/labelling, testing, storage and transportation methods and procedures that may affect the quality of an E-liquid product shall be examined and approved by the person in charge of the quality control department before their implementation.*

2. *The person in charge of the quality control department shall cause to be investigated any complaint or information that is received respecting the quality of an E-Liquid product or its deficiencies or hazards and cause any necessary corrective action to be taken, in the case where the complaint or information relates to an activity over which the department exercises quality control.*
3. *(2.1) In the case where the complaint or information that is received does not relate to an activity over which the quality control department exercises quality control, the person in charge of the department shall forward the complaint or information to the person in charge of the quality control department that exercises quality control over that activity.*
4. *The person in charge of the quality control department shall cause all tests or examinations required pursuant to this Division to be performed by a competent laboratory.*

Rationale

E-liquid product processes and products must be designed and developed taking GMP requirements into account. Production procedures and other control operations must be independently examined by your quality control department. Ensuring proper storage, transportation and distribution of materials and products minimizes any risk to their quality.

Complaints may indicate problems related to quality. By tracing their causes, you can determine which corrective measures to take to prevent them from happening again. Having tests carried out by a competent lab provides assurance that test results are genuine and accurate.

You must have written agreements for consultants and third-party contractors (including contract labs) that describe the education, training and experience of personnel and the types of services provided. These agreements must be approved by the person in charge of your quality control department and available for examination and inspection. You must also maintain records of the activities contracted.

Interpretation

Your quality control department is responsible for doing the following:

1. The person in charge of your quality control department (or a designated alternate who meets the requirements under section C.02.006 “Personnel,” as applicable to the activity) must sign and date all decisions made related to section C.02.015 “Quality Control Department.”
2. Establish and maintain written agreements clearly describing the respective responsibilities between the fabricator, packager/labeler, distributor, importer and wholesaler for any complaint or information that is received about the quality of an E-liquid product or its deficiencies or hazards. See interpretations 3 to 12 in section C.02.012 “Manufacturing Control” for written agreement requirements.
3. Ensure that guidelines and procedures are in place and implemented for storage and transportation conditions (such as temperature, humidity, lighting controls, stock rotation, sanitation, and any other precautions needed to maintain the quality and safe distribution of the E-liquid product).
4. Ensure standard operating procedures and records for shipping and receiving are available and contain the following:

a. a description of the shipping configuration and type of packaging to be used for shipping the finished product
b. the labelling requirements (including storage conditions and special precautions or warnings) for shipments of the finished product
c. mode(s) of transportation approved for shipping the finished product
d. the verifications required to ensure that no finished product in the shipment has been tampered with and that there are no damaged containers
e. evidence that shipping requirements (e.g. temperature control) have been met (if required)
f. a written agreement clearly describing the respective responsibilities (between the fabricator, packager/labeler, distributor, importer, wholesaler and the transportation provider) with respect to storage, transportation, returns, complaints and recalls of the E-liquid product

5. Carry out the sampling of raw materials, packaging materials, in-process E-liquid products, bulk E-liquid products and finished products according to detailed written procedures. Ensure samples are representative of the batches of material they are taken from, and are handled in a way that prevents errors in sample identification and avoids adverse storage conditions. Ensure sampling plans are properly justified.
6. Review and assess all complaints—and other information about potentially defective products—according to written procedures that incorporate quality risk management principles. Record the complaint with all original details and thoroughly investigate. Take appropriate follow-up action after investigating and evaluating. Record all decisions and measures taken as a result, and reference them to the corresponding batch records. Review complaint records regularly for any indication of specific or recurring problems that need attention.
    a. Investigations into complaints that indicate a potential product quality defect should include the following:
        i. a description of the reported quality defect
        ii. a determination of the extent of the quality defect and potential for other batches or products to be impacted
        iii. an examination or testing of reference and/or retention samples (if required) and a review of the applicable records
        iv. evaluation of samples of the defective product from the complainant (where samples are not available, other appropriate strategies may be used)
        v. the distribution information for the batch(es) in question
        vi. the assessment of the risk(s) posed by the quality defect
        vii. a defined decision-making process to implement risk mitigation strategies (e.g. product recalls), where appropriate
        viii. the internal and external communications that should be made about a quality defect and its investigation
        ix. the identification of the potential root cause(s) of the quality defect

x. the identification of appropriate corrective and preventative actions (CAPAs) to be implemented, updated with an assessment of the effectiveness of those CAPAs

7. Establish a change control system to provide for ongoing process optimization and a continuing state of control. The quality control department must document, evaluate and approve all changes, identifying them with the appropriate effective date. Any significant change may require re-validation.
8. Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays as follows:
    a. Complete description of sample received for testing i.e. quantity, lot number, and date sample was taken.
    b. Statement of each method used in the testing of samples.
    c. A complete record of data, calculations, results etc.
    d. Records should be maintained for periodic calibrations and standard testing.
9. Tests must be performed by a lab that meets all relevant GMP requirements. Ensure that:
    a. Lab facilities are designed, equipped and maintained to conduct the required testing.
        i. In the microbiology lab, environmental monitoring is performed periodically. Microbiological cultures and sample testing are handled in an environment that minimizes contamination.
        ii. The facility used to perform sterility testing should comply with the microbial limits of an aseptic production facility. Access should be limited to essential personnel.
    b. The individual in charge of the lab either:
        i. is an experienced university graduate who holds a degree in a science related to the work being carried out, with practical experience in his or her responsibility area, or
        ii. reports to a person who has these qualifications (C.02.006, interpretation 1)
    c. There are enough lab personnel qualified to carry out the work they undertake.
    d. Lab control equipment and instruments are suited to the testing procedures carried out. Equipment and records are maintained as per the interpretations under C.02.005.
    e. All test methods are validated. A lab that is using a test method where the lab did not perform the original validation (e.g. the use of a compendia method) should verify the appropriateness of the test method. All testing should be carried out according to approved methods.
        i. The transfer of test methodology from one lab to another should include an assessment to verify that the test method(s) complies with industry standards.
        ii. The transfer of test methodology should be described in a written protocol. This should include (but is not limited to) the following parameters:
            - the relevant test method(s) undergoing transfer
            - additional training requirements
            - standards and samples to be tested by both labs
            - any special processing, transport and storage conditions for test items

- the testing to be performed

iii. Deviations from the protocol should be investigated before closing the technical transfer process. The technical transfer report should document the comparative outcome of the process and should identify areas requiring further test method revalidation.

f. All lab data are created, maintained, processed and reviewed as outlined by the firm's data governance system.

The data governance system (as it applies to lab data) must include enough detail to allow accurate and complete reporting and interpretation of all lab test data and ensure data integrity. This system should include (but is not limited to) the following elements:

i. Validate computerized systems for their intended use, with special attention to any that are used to create, process and store laboratory data. Qualify spreadsheets used in the lab.
ii. Have systems and procedures in place to ensure that lab records are reliable, complete and accurate. These systems/procedures must also require that all test results that could affect the quality, safety or efficacy of an E-liquid product are reported, reviewed and assessed appropriately.
iii. Organize and store data in a way that is interpretable and traceable to the execution and purpose of test procedures (i.e. use of defined and meaningful naming conventions for samples, test sequences and data storage locations/folders).
iv. Put controls in place to ensure that test data are not deleted and that changes to testing records are documented and justified where required (e.g. audit trails must be enabled and reviewed).
v. Retain data in its original format. Original records (or a true copy), including electronic records, are subject to review by qualified personnel.

g. Reference standards are available in the form of the current reference standards listed in Schedule B to the Act. When such standards have not been established or are unavailable, primary standards can be used. Secondary standards are verified against a Schedule B reference standard or against the primary standard and are subject to complete confirmatory testing at predetermined intervals. All reference standards are stored and used in a way that will not adversely affect their quality. Records relating to their testing, storage and use are maintained.
h. Out of specification (OOS) and out of trend (OOT) test results are investigated in accordance with a defined procedure:
    i. The first phase of investigation should be to determine if the OOS results were caused by a clearly identifiable laboratory error.
    ii. In the case where the OOS result was caused by a clearly identified laboratory error, you may invalidate the original results, then repeat the test and report the

results. Keep records of the original results and record an explanation. The source of the error should be determined with corrective action implemented to prevent recurrence.

iii. When a clearly identifiable laboratory error is not present then a second phase of investigation should be conducted. This phase should include a review of the manufacturing process and any other factors that could have impacted the testing. This may include laboratory retesting.

iv. Any retesting performed must be specified and approved in advance with the number of retests to be performed on the original sample and/or a new sample, and the statistical treatment of the resulting data.

v. Hypothesis testing may be required to demonstrate the presumptive root cause in either phase.

vi. Report all valid test results (both passing and suspect) and fully consider them in batch release decisions.

i. The root cause of confirmed OOS results should be investigated. The investigation should be performed according to written procedures. It should include an assessment of root cause, description of corrective and preventive actions carried out, and conclusions.

j. To ensure the compliance of contractors conducting testing

i. A Canadian contract lab must have a relevant valid establishment license.

ii. All arrangements for external testing must comply with established methods for the E-liquid product concerned (including the testing of in-process E-liquid products, intermediates, raw materials, packaging materials, and all other testing required.

iii. There must be a written agreement covering all testing activities between the contract lab and the parties involved. The agreement must specify their respective responsibilities relating to all aspects of testing. The agreement should specify that contract test facilities are subject to evaluation and audit by the quality control department.

iv. Technical aspects of the agreement must be drawn up by qualified personnel suitably knowledgeable in the relevant lab testing and GMP. The agreement must:

1. permit audit of the external lab's facilities and operations
2. clearly describe (at a minimum) who is responsible for:
    a. overseeing collection, transportation and storage conditions of samples before testing
    b. keeping stability samples at predetermined temperatures and humidity, if applicable
    c. testing methods to be used, limits and test method validation
    d. retaining analytical results and supporting documentation (see additional guidance under C.02.021)

ii. No subcontracting of any work should happen without written authorization.

Packaging material testing

C.02.016

1. *Each lot or batch of packaging material shall, prior to its use in the packaging of an E-liquid product, be examined or inspected against the specifications for that packaging material.*
2. *No lot or batch of packaging material shall be used in the packaging of an E-liquid product unless the lot or batch of packaging material complies with the specifications for that packaging material.*
3. *The specifications referred to in subsections (1) and (2) shall*
4. *be in writing;*
5. *be acceptable to the Director who shall take into account the specifications contained in any publication mentioned in Schedule B to the Act; and*
6. *be approved by the person in charge of the quality control department.*

Rationale

E-liquid product quality is directly dependent on packaging quality. If an E-liquid product is presented in an inadequate package, the entire effort put into research, product development and manufacturing control is wasted. In many cases (such as metered-dose aerosols or injectable), packaging quality is critical to the overall performance and effectiveness of the E-liquid product. Faults and non-compliance in the packaging and labelling of an E-liquid product continue to be a cause of E-liquid product recalls.

Packaging materials must be inspected or examined to ensure they are of good quality before being used to package E-liquid products.

Interpretation

1. Ensure each packaging material used in the packaging/labelling of an E-liquid product is covered by specifications (as defined under C.02.002). These specifications must be approved and dated by the person in charge of your quality control department (or by a designated alternate who meets the requirements described under section C.02.006 “Personnel,” interpretation 1.d).
    a. In addition to the definition of specification described in C.02.002, specifications for any primary and printed packaging material should include (or provide reference to, if applicable):
        i. a description of materials, including:
            - the designated name and the internal code reference
            - a specimen of printed materials
        ii. qualitative and quantitative requirements with acceptance limits
        iii. storage conditions and precautions
2. Ensure all packaging material labels contain key information.

Ensure specifications comply with current versions of the **Consumer** Packaging and **Labelling** Act (CPLA)

3. . The adequacy of inspection or examination methods must be established and documented.
4. Identifying and choosing primary and printed packaging material vendors is an important operation.
    a. You should entrust this activity only to appropriately qualified staff.
5. Only buy primary and printed packaging materials from approved suppliers listed in the relevant specification. Use quality risk management principles that consider your specifications and testing to evaluate requirements for quality agreements.
6. Only use packaging materials in packaging/labelling that have been released by your quality control department.
7. Segregate outdated or obsolete packaging material until its disposition.
8. All packaging material must have status label (Hold , release , reject)
9. The number of samples taken should be determined statistically and specified in a sampling plan. Ensure the sampling plan for packaging materials takes into account:
    a. the quantity received
    b. the level of quality required
    c. the nature of the material (e.g. primary packaging materials and/or printed packaging materials)
    d. the production methods used by the packaging material manufacturer
    e. your knowledge of the quality assurance system used by the packaging material manufacturer
10. Ensure sampling takes place in an appropriate environment and with precautions to prevent contamination where needed.

C.02.017

The examination or testing referred to in section C.02.016 shall be performed on a sample taken after receipt of a random lot or batch of packaging material on the (a)premises of the person who packages the E-liquid has evidence satisfactory to the Director to demonstrate that packaging materials sold to him by the vendor of that lot or batch of packaging material are consistently manufactured in accordance with and consistently comply with the specifications for those packaging materials.

Rationale

Section C.02.017 outlines options for when you may carry out the testing or examination outlined in section C.02.016. As with raw materials, buying packaging materials is an important operation that must involve staff who have thorough knowledge of the packaging materials and vendor.

Packaging materials must come only from vendors named in the relevant specifications. All aspects of the production and control of packaging materials should be discussed between the manufacturer and vendor. Particular attention should be paid to printed packaging materials. Labels must be examined or tested after receipt on the packager's premises.

Interpretation

1. The person who packages an E-liquid product must perform testing or examination on a sample of the packaging material taken after receipt on site (unless the vendor is certified).

   If you use a packaging material vendor certification program, it must be documented in a standard operating procedure. At a minimum, such a program should include the following:

   a. a written agreement outlining the specific responsibilities of each party involved, specifying:
      i. all the tests to be performed by the vendor, along with the content and format of the certificate of analysis (which shows actual numerical results, if applicable, and makes reference to product specifications)
      ii. that the vendor must inform the E-liquid product packager/labeler of any changes in the processing or specifications of the packaging material
      iii. that the vendor must inform the E-liquid product packager/labeler of any significant deviations during the manufacturing of a particular batch of a packaging material
      iv. Also, where multiple packaging materials are received from the same vendor, confirmatory testing must be carried out for each packaging material at least once every five years.
2. Quality of packaging material must be verified
3. As long as the material is properly identified, you may use the lot of packaging material selected for confirmatory testing in packaging before completing that testing. Your quality control department must approve use before completing testing.
4. Ensure conditions of transportation and storage prevent changes to the characteristics of the packaging material. To show these conditions have been met, ensure standard operating procedures and records are available and contain the following:
   a. the type of packaging to be used
   b. labelling requirements
   c. mode of transportation

   d. the type of seal used on the package
   e. the verification needed to ensure that the package has not been tampered with and that there are no damaged containers
5. Examine labels and other printed packaging materials after receipt on site. Pay special attention to cut labels due to the higher inherent risk of inadvertent mix-up with incorrect labels. Inspect these labels when you receive them using an appropriate method.
6. Conduct positive identification of all primary packaging materials after received on site. Identity testing may be performed on primary packaging materials using visual inspection, provided that the vendor is certified and a certificate of analysis is available.
7. If a delivery or shipment of packaging material is made up of different batches, each batch must be considered as separate for the purposes of sampling, testing and release.

Finished product testing

C.02.018

1. *Each lot or batch of an E-liquid product shall, before it is made available for further use in fabrication or for sale, be inspected against the specifications for that E-liquid product.*
2. *No lot or batch of an E-liquid product shall be made available for further use in fabrication or for sale unless it complies with the specifications for that E-liquid product.*
3. *The specifications referred to in subsections (1) and (2) shall*
   a. *be in writing;*
   b. *be approved by the person in charge of the quality control department.*

Rationale

Finished product tests complement the controls used during the manufacturing process. Each fabricator, packager/labeler, distributor and importer must have proper specifications and test methods to help ensure that each E-liquid product sold is safe and meets the relevant standard.

Interpretation

1. The person in charge of your quality control department (or a designated alternate who meets the requirements under section C.02.006 “Personnel,” as applicable to the activity) must approve written specifications.
   a. In addition to the definition of specification described in C.02.002, specifications for any finished product should include (or provide reference to, if applicable):
      i. the designated name of the product and code reference (where applicable)
      ii. the master formula
      iii. a description of the dosage form and package details
      iv. the qualitative and quantitative requirements, with acceptance limits
      v. the storage conditions and any special handling requirements, where applicable

vi. the shelf life
vii. a description of the unique identifier used for identity testing (if applicable)

2. Perform all Inspections according to the approved specifications. These tests may be carried out by the distributor/importer or by their contracted testing lab when a written agreement specifically excludes the fabricator from this obligation.
3. Quarantine any lot or batch of an E-liquid product that does not comply with specifications until final disposition.

Records

C.02.020

1. *Every fabricator, packager/labeler, distributor and importer shall maintain all of the following records on their premises in Canada for each E-liquid product that they fabricate, package/label, distribute or import:*
    a. *evidence that each lot or batch of the E-liquid product has been fabricated, packaged/labelled, tested and stored in accordance with the procedures described in the master production documents;*
    b. *evidence that the conditions under which the E-liquid product was fabricated, packaged/labelled, tested and stored are in compliance with the requirements of this standard.*
    c. *evidence that establishes the period during which the E-liquid product in the container in which it is sold or made available for further use in fabrication will meet the specifications for that E-liquid product; and*
    d. *evidence that the finished product testing referred to in section C.02.018 was carried out, and the results of that testing.*
2. *Every distributor and importer shall make available to the Director, on request, the results of testing performed on raw materials and packaging/labelling materials for each lot or batch of E-liquid product that it distributes or imports.*
3. *Every fabricator shall maintain on their premises written specifications for all raw materials and adequate evidence of the testing of those raw materials referred to in section C.02.009 and of the test results.*
4. *Every person who packages an E-liquid product shall maintain on their premises written specifications for all packaging materials and adequate evidence of the examination or testing of those materials referred to in section C.02.016 and of any test results.*
5. *Every fabricator, packager/labeler and tester shall maintain on their premises in Canada detailed plans and specifications of each building in Canada where they fabricate package/label or test E-liquid products and a description of the design and construction of those buildings.*
6. *Every fabricator, packager/labeler and tester shall maintain on their premises in Canada personnel records in respect of each person who is employed to supervise the fabrication, packaging/labelling and testing of E-liquid products, including the person's title, responsibilities, qualifications, experience and training.*

C.02.021

1. *All records and evidence on the fabrication, packaging/labelling, finished product testing referred to in section C.02.018 and storage of an E-liquid product in dosage form that are required to be maintained under this Division shall be retained for one year after the expiration date of the E-liquid product unless the person's establishment license specifies some other period.*

2. *Subject to subsection (4), all records and evidence of the raw material testing referred to in section C.02.009 and of the testing of packaging/labelling materials that are required to be maintained under this standard shall be retained for five years after the raw materials and packaging/labelling materials were last used in the fabrication or packaging/labelling of an E-liquid product unless the person's establishment license specifies some other period.*

C.02.022

1. *Every wholesaler, distributor and importer of an E-Liquid product in dosage form shall retain records of sale of each lot or batch of the E-liquid product, which enable them to recall the lot or batch from the market, for one year after the expiration date of that lot or batch.*
2. *in any other case, one year after the expiration date of the lot or batch.*

C.02.023

1. *On receipt of a complaint or any information respecting the quality of an E-liquid product or its deficiencies or hazards, every fabricator, packager/labeler, wholesaler, distributor and importer of the E-liquid product shall make a record of the complaint or information that contains the following:*
    a. *the results of any investigation carried out under subsection C.02.015(2) and, if applicable, the corrective action taken; or*
    b. *the name and business address of the person in charge of the quality control department to whom the complaint or information was forwarded under subsection C.02.015(2.1) and the date on which it was forwarded.*

C.02.024

1. *Every fabricator, packager/labeler, distributor, importer and wholesaler shall*
    a. *maintain records of the results of the self-inspection program required by section C.02.012 and of any action taken in connection with that program; and*
    b. *retain those records for a period of at least three years.*
2. *Every person who fabricates or packages/labels an E-liquid product shall*
    a. *maintain records on the operation of the sanitation program required to be implemented under section C.02.007; and*
    b. *retain those records for a period of at least three years.*

Rationale

Good documentation is a key part of an E Liquid quality system and promotes compliance with GMP requirements. Documentation may exist in a variety of forms, including paper-based, electronic or photographic media.

The various types of documents and media used should be fully defined in the pharmaceutical quality system. The documentation system's main objective must be to establish, control, monitor and record all activities which directly or indirectly impact all aspects of the quality of E-liquid products. This includes information from all stages of the product lifecycle, and all records related to the quality of E-liquid product products.

Records must be reliable, complete, consistent and accurate.

You must establish a data governance system to ensure controls are in place to prevent and detect data integrity issues throughout the product lifecycle. This includes:

- having policies and standard operating procedures that clearly indicate management's expectations for how data should be acquired, modified, reviewed and stored
- validating and maintaining equipment and associated computer systems
- checking the preventative measures put in place periodically to verify their implementation and effectiveness

These are standard principles under an E Liquid quality system, regardless of the media used (e.g. paper records or electronic records).

Interpretation

1. You must make any documentation requested by Health Canada for evaluation available in one of the official languages.
2. You must have standard operating procedures (SOPs) available that describe all phases of your company's operation and how you will comply with GMP requirements.
    a. Make SOPs readily available to all required personnel.
    b. Keep SOPs up-to-date and ensure they accurately reflect all requirements and practices. Establish a system of regular review to ensure qualified personnel are reviewing SOPs on a regular basis.
    c. Establish a formal system to review and approve changes to SOPs. Document the reasons for SOP revisions.
    d. Put systems in place to ensure only current SOPs are in use.
3. Your quality control department must approve, sign and date all relevant SOPs and GMP documents (such as records of actions taken or conclusions reached). They must also approve, sign and date any changes to documents. Any change to a document must still allow the original information to be read. Where appropriate, record the reason for the change.

4. You should establish a data governance system to ensure data integrity is maintained for all records required under GMP. The general principles of good documentation practices are applicable to the management of records regardless of media (e.g. paper records or electronic records), throughout its lifecycle from the time data is first generated and any modifications made thereafter.
    a. Records should be traceable to the source the record was generated from. This can be achieved by using techniques such as initials/signatures, secure user identification, and change history/audit trails to capture relevant information (e.g. processing parameters, method settings, acquisition details, or reasons for changes/reprocessing).
    b. Records should be legible, with no parts of the data obscured or removed. If archived, they must be retrievable in a timely way. Any changes to records must also be documented and traceable.
    c. Data should be recorded, documented or saved at the time it is generated, with reliable evidence that this was done.
    d. Records must be maintained in an original format as an original record, or as a true copy which has undergone a qualified conversion process that maintains data integrity.
5. If you use an electronic system to create, modify or store records required under these regulations, you should validate the system for its intended use.
    a. Ensure all access and user rights in electronic systems are properly controlled to prevent system users from compromising data integrity.
    b. Control electronic records in a way that ensures the records:
        i. can only be created and modified by authorized personnel
        ii. are protected against intentional or accidental deletion
        iii. are named and organized in a way that allows for easy traceability
        iv. are tracked through an audit trail when created or modified (the audit trail should include changes made to the record, who made the change, the time and date the record was changed and, if applicable, the reason the record was modified)
        v. are backed up at regular intervals to protect against potential data loss due to system issues or data corruption
        vi. are available for review during an inspection and are readily retrievable in a suitable format
        vii. include all necessary metadata
6. An electronic signature is an acceptable alternative to a handwritten signature. Ensure appropriate controls are in place for electronic signatures, including:
    a. Validate electronic signature systems to show that the systems are suitably secure and reliable (and document this validation).
    b. You should have a procedure for the creation of electronic signatures. Put controls in place to ensure the uniqueness of all electronic signatures.
    c. Ensure all electronic signatures include a time and date stamp and are subject to audit trail requirements.

d. Inform users that electronic signatures are considered an equivalent to hand-written signatures. Keep records to show that users are aware of their responsibilities and accountability relating to the use of electronic signatures.

7. If you are a fabricator, packager/labeler, distributor or importer of an E-liquid product, you must maintain the following documents:
    a. Master production documents
        i. When the fabricator is located in Canada, specific parts of a master production document considered to be a trade secret or confidential business information may be held by the fabricator rather than the distributor. When the fabricator is located outside Canada, specific parts of a master production document considered to be a trade secret or confidential business information may be held on behalf of the distributor or importer by an independent party in Canada. In either case, the distributor or importer must ensure that Health Canada has access to the data in a timely way.
        ii. Regardless of whether the fabricator is Canadian or foreign, the master production documents retained by the distributor or importer must describe in general terms whatever information has been deleted as a trade secret or confidential business information.

> **Important:** It is not considered acceptable to withhold entire pages of master production documents from distributors or importers. You should be able to defend any information withheld as being confidential business information or a trade secret. Some examples of confidential business information or trade secret information could include quantities of raw materials, or sensitive parameters associated with a process.
>
> The objective is to allow an importer or distributor to perform a reasonable assessment of the information and to provide assurance of adequate control.

    b. Evidence that each lot or batch of the E-liquid product has been fabricated, packaged/labelled, tested and stored according to the procedures described in the master production documents
        i. Fabricators must have complete records of all manufacturing activities, including executed batch documentation and release information (e.g. certificates of analysis and associated records) for raw materials and E-liquid products.
        ii. Packagers must have complete records of all packaging activities, including executed packaging documentation and release information (e.g. certificates of analysis and associated records) for packaging materials. Records of finished product checks should also be maintained.
        iii. Testing laboratories must maintain records that tests were conducted according to required methods, as well as the certificates of analysis issued.

iv. Distributors and importers must have evidence that batches were fabricated, packaged/labelled and tested according to the master production documents.
    - This evidence may include all executed production documents. Test results for raw materials and packaging materials only need to be made available on request in a timely way.
    - For distributors, a certificate of manufacture is considered an acceptable alternative to complete batch documentation, provided that complete documentation is made available in a timely way.

Important: A certificate of manufacture alone cannot be used when reworking has taken place.

For any changes to production documents, complete documentation must be provided to the importer or distributor, with indication of any changes made.

c. Evidence establishing the period of time during which the E-liquid product—in the container in which it is sold—will meet the specifications for that E-liquid product
    i. The documentation to be maintained must include: the written stability program, the data generated according to that program, and the conclusions leading to the establishment of the time period.
    ii. Data generated as part of the continuing stability program must also be included.
d. Evidence of compliance with finished product specifications for each lot of E-liquid product.

8. If you are a fabricator, packager/labeler, distributor, wholesaler or importer of an E-Liquid product, you must maintain the following documents (as they relate to all operations in Canada):
    a. distribution records of all E-liquid product sales, including professional samples
        i. Keep records of all sales readily accessible in a way that allows a complete and rapid recall of any lot or batch of an E-liquid product. (This requirement does not necessarily require tracking by lot number.)
        ii. Keep records to show that all distributers who received a recalled E-liquid product were notified.
    b. records of the results of your self-inspection program, evaluation and conclusions, and corrective measures implemented
9. If you are a fabricator, packager/labeler, distributor, wholesaler or importer of an E-Liquid product, you must maintain the following documents:
    a. records of complaints or any information about the quality of an E-Liquid product or its deficiencies or hazards
    b. follow-up investigations, including corrective actions taken
10. If you are a fabricator, you must maintain the following documents:
    a. the written specifications for the raw materials
    b. the results of raw material testing

c. the sources of the raw materials supplied
d. records about the operation of the sanitation program required by section C.02.007 “Sanitation”

11. If you package or label an E-Liquid product, you must maintain the following documents:
    a. the written specifications for the packaging materials
    b. the results of packaging material examinations or testing
    c. the sources of the packaging materials supplied
    d. records about the operation of the sanitation program required by section C.02.007 “Sanitation”
12. Maintain records of all personnel employed in GMP activities, including:
    a. organization charts
    b. each person’s title, job description, responsibilities, qualifications, experience and training
    c. the name(s) of each person’s designated alternate(s)
13. Retain records required under sections C.02.021(1), C.02.022, and C.02.023 “Records” either:
    a. for a period of at least one year past the expiration date of the E-liquid product the records apply to, or
    b. for records and evidence on the testing of raw materials and packaging/labelling materials – for a period of at least five years after the materials were last used to fabricate or package/label an E-Liquid product (unless otherwise specified in your establishment license)

Samples

C.02.025

1. *Every distributor and importer of an E-Liquid product shall retain in Canada a sample of each lot or batch of the packaged/labelled E-liquid product for one year after the expiration date of the E-liquid product..*
2. *Subject to subsection (4), the fabricator of an active ingredient shall retain a sample of each lot or batch of it for the following period unless they establish some other period:*
    a. *in the case of an active ingredient that has a retest date, three years after the lot or batch has been completely distributed; or*
    b. *in any other case, one year after the expiration date of the lot or batch.*

C.02.026

The samples referred to in section C.02.025 shall be in an amount that is sufficient to determine whether the E-liquid product or raw material complies with the specifications for that E-liquid product or raw material.

Rationale

These requirements help ensure that, if a product quality concern arises, your establishment and Health Canada have ready access to samples for re-examination.

Retention samples serve as a record of the batch of finished product or raw material. They can be assessed in the event that concerns arise with a finished product or raw material batch during the shelf life of a product (e.g. a quality complaint, a query relating to compliance with a labelling/packaging query, or a pharmacovigilance report).

In general, retention samples should be available for two reasons:

1. for the purpose of being analyzed, should the need arise during the shelf life of the batch concerned
2. for identification and inspection purposes (e.g. for review of labelling, patient information leaflet, batch number, expiry date), should the need arise during the shelf life of the batch concerned

Interpretation

1. If you are a distributor or an importer of an E-liquid product, you must retain in Canada a sample of each lot or batch of a finished product.
    a. Keep retention samples in their trade package, or in a container that is equivalent with respect to stability. In the case of large containers of finished products, you may retain a smaller representative sample, as supported by stability data.
    b. Store retention samples under the conditions listed on the label.
2. Manage retention samples according to written procedures. Maintain records of traceability for retention samples and ensure they are available for review.
3. Take enough retention samples to allow duplicate testing according to finished product specifications. This will allow both Health Canada and the fabricator, importer or distributor to conduct testing.
    a. Where a batch is packaged in two or more distinct packaging operations, at least one retention sample should be taken from each individual packaging operation (to allow an assessment of the actual packaging operation, should the need to inspect labelling, patient information leaflet, batch number, or expiry date arise).
    b. Where product is repackaged, a minimum of one retention sample per repackaging operation containing the product must be taken.
4. A statement of the weight or measure of sample used for each test, where appropriate.

Stability

C.02.027

1. *Every distributor and importer of an E-liquid product shall establish the period during which each E-liquid product in the package in which it is sold will comply with the specifications for that E-liquid product.*
2. *Every fabricator and importer of an active ingredient shall establish the period during which each E-liquid product in the package in which it is sold will comply with the specifications for that E-liquid product.*

Rationale

A written stability program determines the established shelf life of an E-liquid product under recommended storage conditions. Each packaged dosage form and strength must be covered by relevant data to support its shelf life in approved packaging material types and configurations for commercial sale.

Interpretation

1. You must determine the stability of an E-liquid product before marketing, and before adopting any significant changes in formulation, fabrication procedures or packaging materials that may impact the quality of the E-liquid product over its shelf life. You should make this determination according to Health Canada guidelines.
2. Fulfill commitments described in stability protocols—sent in premarket submissions or submissions to support post-NOC (notice of compliance) changes—to establish or confirm the approved shelf life for batches.
3. Enroll or continue monitoring at least three commercial-scale batches of each strength and approved packaging material type and configuration in the stability program to confirm shelf life in cases where such studies did not begin. For new E-liquid products, these would be commitment batches.
4. Consider including in your finished product stability program batches that have been stored at the limits of extended hold times (e.g. greater than one month) for intermediates and finished products before packaging.
5. Ensure stability studies include testing of parameters that are prone to change during storage and are likely to influence E-liquid product quality.

C.02.028

1. *Every distributor and importer of an E-liquid product shall monitor, by means of a continuing program, the stability of the E-liquid product in the package in which it is sold.*
2. *Every fabricator and importer of an active ingredient shall monitor, by means of a continuing program, the stability of the E-liquid product in the package in which it is sold.*

Rationale

A written continuing stability program monitors an E-liquid product over its shelf life and provides evidence that the product will remain within specifications under the recommended storage conditions. Each strength and packaged form must be covered by relevant data to support its labelled expiry date in its trade package.

Interpretation

1. Implement a continuing stability program to ensure E-liquid product products comply with approved shelf life specifications. Ensure a protocol is available and implemented for each E-liquid product marketed in Canada. Prepare a summary of all the data generated, including the evaluation and conclusions of the study.

   Your stability study protocol should include (but is not limited to) the following parameters:

   a. reference to the E-liquid product in a manner that allows traceability to the manufacturing master formula and packaging master formula
   b. number of batch(as) per strength and batch sizes
   c. packaging size (i.e. container format, fill volume or configurations)
   d. relevant physical, chemical, microbiological or biological test methods
   e. acceptance criteria
   f. container closure system(s)
   g. testing frequency
   h. storage conditions (and tolerances) of samples
   i. orientation of samples (e.g. upright, inverted, horizontal), reflective of the worst-case scenario
   j. other applicable parameters specific to the E-liquid product
2. Enroll a minimum of one batch of every E-liquid product strength and container closure system into your continuing stability program each year the E-liquid product is produced. Consider packaging size in your choice of batches to be enrolled.
3. For long-term stability studies, ensure testing is performed often enough to establish the stability profile of the E-liquid product.
4. For E-liquid products with an established shelf life and consistent historical stability profile, conduct testing at least every year, with a minimum of five time points (including the initial and final time points).
5. Address worst-case scenarios (e.g. reworked or reprocessed lots), and include these lots in the continuing stability program.
6. Assess any confirmed out-of-specification (OOS) result, borderline result or significant atypical trend that may have an impact on the quality of the product. Such cases may require further actions (e.g. further stability studies, an increase in testing frequency or change in shelf life).

Consider the impact on all batches available on the market. Report such cases to Health Canada where it may affect the quality, safety or efficacy of an E-liquid product.

7. For imported products, you may use stability studies from foreign sites if the data and protocol fulfill requirements aligned with Health Canada/ICH/VICH guidelines for stability, and if the site can show GMP compliance.

Important: It is your responsibility as an importer or distributor to obtain, maintain and review up-to-date records related to the continuing stability program.