Cooperation Centre for Scientific Research Relative to Tobacco

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Technical Guide for Designing E-Vapour Product Stability Studies

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1. Introduction

With the global development of electronic cigarettes, knowledge of stability and storage conditions for marketed products becomes increasingly important for product shelf life determination. This document provides guidance on how to conduct a study.

In June 2019, the U.S. Food and Drug Administration (FDA) published a guidance for industry entitled the Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems[1], it states:

- "Stability information for the new tobacco product. This information should include the established shelf life of the product and changes in pH and constituents (including HPHCs and other toxic chemicals) over the lifespan of the product, such as the factors that determine the shelf life (e.g., volume of e-liquid, power supply, atomizer, coil); how stability is affected by the storage conditions, such as moisture and temperature; full reports of all stability testing; and how the product's performance may significantly decline (e.g., decrease in aerosol flow rate or change in aerosol constituents) over the product's lifetime."

It is likely that regulators will be interested in evaluating e-vapour products by reviewing each product's stability study and shelf life information. As such, CORESTA has prepared the following guidance on designing e-vapour product stability studies.

2. Purpose and Scope

2.1 Purpose

The purpose of this document is to provide guidance in designing stability studies for e-vapour products.

In this guidance, the general term e-vapour products, can also be applied to include the following aerosol generating products as mentioned in several regulatory documents and voluntary guidances[1,2,3]:

- e-cigarettes, packaged in a kit (a marketed product containing one or more cartridges containing e-liquids and an aerosolizing apparatus packaged together)
- open tank systems
- refill cartridges (cartridges containing e-liquids)
- refill bottles containing e-liquids

2.2 Scope

The purpose of a stability study is to examine how the manufacturer's determined critical quality attributes associated with each product vary with time under different environmental factors. Once product stability and the associated conditions that limit product stability have been determined, a product shelf life can be assigned. The stability of an e-vapour product will depend upon each manufacturer's product profile and characteristics associated with each product. Stability testing can be used to establish a shelf life and recommended storage conditions for the e-vapour product.

Formal stability testing should address physical and chemical attributes and most critically, any e-vapour product attributes that are susceptible to change during storage and are likely to influence quality and safety of the e-vapour product. The stability studies should be done in

the marketed, finished packaging material for the e-vapour product. Formal stability studies should be performed on each individual commercial variant of the e-vapour product unless a bracketing approach is applied. For designing stability studies using bracketing, ICH Q1D[4] gives an example of this approach. Formal stability studies that produce information for a regulatory submission may require the testing of more analytes and attributes. References to CORESTA analytical methods for e-liquid components are provided in this guidance. It is recommended that a stability study protocol be written for any formal regulatory stability study and each manufacturer can detail the rationale for the key quality attributes selected for assessment.

From a non-regulatory viewpoint, e-vapour product sensory attributes, such as color, odor, taste, flavor attributes, harshness and nicotine delivery are viewed as being critical to defining a product's shelf life. Consequently, e-vapour product stability studies may include some aspect of sensory testing to provide shelf life information.

There is no comprehensive technical guidance for designing e-vapour product stability studies. This guidance leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated.

3. Designing Stability Studies

3.1 Test Articles

The test articles include e-vapour products manufactured in a variety of configurations and nicotine strengths and flavors, open tank systems, refill cartridges and refill bottles containing e-liquids, preferably all packaged in the commercial packaging material.

3.2 Critical Quality Attributes

Before beginning stability studies, the manufacturer should define the e-vapour product's critical quality attributes that are important for the shelf life of the product. Such attributes can include product appearance, color, clarity, refractive index, level of nicotine, nicotine impurities and degradation products, levels of base ingredients (propylene glycol, glycerol), water, pH, flavor compounds such as menthol, product leakage and any other attributes such as e-liquid volume, density and viscosity that may affect product quality and safety. Leachables, as determined by extraction studies, that may result from the interaction of e-liquids with e-vapour product components or product packaging may need to be monitored in the stability study.

3.3 Stability Study Storage Conditions

Formal stability studies should address the e-vapour product's thermal and chemical stability and sensitivity to relevant factors such as moisture, light and oxygen. The storage conditions and study duration should be sufficient to cover storage, shipment and subsequent use.

Long term stability study conditions are determined by the climate condition under which the e-vapour product is intended to be stored. One should consider the climate conditions for the intended market and select the appropriate environmental chambers to conduct the study.

Examples of different climatic zones are available in WHO guidelines[5] as shown in Table 1.

Table 1. Climatic Zones and Suggested Long-Term Testing Conditions.

Zone	Climate	Example	Criteria (Mean Annual Temperature in Open Air/Mean Annual Partial Water Vapour Pressure (atm))	Long-Term Testing Conditions (Temp/RH)
I	Temperate	Northern Europe	≤ 15 °C / 0.011 atm	21 °C / 45 % RH
II	Subtropical and Mediterranean	Southern Europe	15-22 °C / > 0.011-0.018 atm	25 °C / 60 % RH
III	Hot and dry	Iraq	> 22 °C / ≤ 0.015 atm	30 °C / 35 % RH
IVa	Hot and humid/tropical	Yemen	> 22 °C / > 0.015-0.026 atm	30 °C / 65 % RH
IVb	Hot and very humid	Brazil, ASEAN*	> 22 °C / > 0.026 atm	30 °C / 75 % RH

*ASEAN is the region represented by the Association of Southeast Asian Nations and includes Indonesia, Malaysia, the Philippines, Singapore, Thailand, Brunei, Vietnam, Cambodia, Laos and Myanmar.

Various guidelines for stability storage conditions in different climate zones are published. ICH Q1A(R2) on Stability testing of new drug substances and products[6] deals with Climatic Zones I and II. Climatic Zones III and IV are currently defined by the respective regions and WHO member states. Annex 2 of the WHO Technical Report Series, No. 953 Stability testing of active pharmaceutical ingredients and finished pharmaceutical products 2009, addresses Climatic Zones IVa and IVb[7]. Depending upon the climatic zones, different long term testing conditions are defined by the WHO and ICH as shown in Table 2 below. To reduce the amount of stability testing, the number of different long term testing conditions may be streamlined as summarized in the column, "Long Term Stability Testing Which Could be Realized in Order to Cover All Climatic Zones (Temp/RH)", in Table 2 below. Conducting stability testing at these conditions, 25 °C/60 % RH, 30 °C/65 % RH and 30 °C/75 % RH could cover stability requirements for all climatic zones.

Table 2. Sum of the Required Storage Conditions According to WHO and ICH Guidelines.

Long Term Testing Conditions (Temp/RH)	Testing Conditions	Climatic Zones	Long Term Stability Testing Which Could be Realized in Order to Cover All Climatic Zones (Temp/RH)	Minimum Duration
21 °C ± 2 °C/ 45% RH ± 5 % RH	Long-term	I	25 °C/60 % RH	12 Months
25 °C ± 2 °C/ 60% RH ± 5 % RH	Long-term	I and II		
30 °C ± 2 °C/ 35 % RH ± 5 % RH	Long-term	III	30 °C/65 % RH	12 Months
30 °C ± 2 °C/ 65 % RH ± 5 % RH	Intermediate Long-term	I and II / IVa		
30 °C ± 2 °C/ 75 % RH ± 5 % RH	Long-term	IVb	30 °C/75 % RH	12 Months

In general, this is in agreement with the general case for storage conditions as outlined in ICH Q1A(R2) Guideline as shown in Table 3 below.

Table 3. General Case for Product Storage Conditions Per ICH Q1A(R2).***

Study	Storage Condition	Minimum Duration
Long term*	25 °C ± 2 °C/60 % RH ± 5 % RH or 30 °C ± 2 °C/65 % RH ± 5 % RH	12 Months
Intermediate**	30 °C ± 2 °C/65 % RH ± 5 % RH	6 Months
Accelerated	40 °C/75 % RH	6 Months

* It is up to the manufacturer to decide if long term stability studies are performed at 25 °C ± 2°C/60 % RH ± 5 % RH or at 30 °C ± 2 °C/65 % RH ± 5 % RH.

** If 30 °C ± 2 °C/65 % RH ± 5 % RH is the long term storage condition, there is no intermediate condition.

*** For stability studies for products intended for storage in a refrigerator (5 °C) or freezer (-20 °C) conditions, please refer to ICH Q1A(R2).

A similar approach could be applied to e-liquids but it may need to be modified to take into account the required shelf life of the products. ICH Q1A(R2) may help to give some guidance on stability conditions to use, but ultimately it is up to the product manufacturer to decide what is appropriate.

Data from formal e-vapour stability studies may ultimately be filed in regulatory submissions. In those cases, it is highly recommended that environmental chambers be qualified, including chamber calibration and mapping[8]. For formal stability studies, the environmental chambers should be monitored with the recording of temperature and relative humidity over the course of the studies. Temperature and relative humidity excursions for over 24 hours should be assessed with regard to the impact to the product and the stability study[6]. In the case of environmental chamber failure, a backup storage location with environmental chambers for continuing the study should always be considered.

3.4 Analytes

Conducting a formal stability study involves the monitoring of a selective number of analytes in e-liquids and aerosols over the duration of the study by applying suitable analytical methods. The selection of the analytes will depend upon the critical quality attributes of the e-vapour product as determined by the manufacturer. Analyte selection will also depend upon the regulatory authorities in the location where the e-vapour product will be marketed. The following are possible analytes and attributes that could be monitored during a stability study: Nicotine, nicotine degradation products, carbonyls, heavy metals, tobacco specific nitrosamines (TSNAs), harmful and potentially harmful constituents (HPHCs)[9], water, pH and leachables deemed to be of toxicological significance from extraction studies or other analytes or attributes that could change over time. Suggested analytes can be found in the May 2016 PMTA draft guidance, lines 1026 – 1061[1] and the WHO Technical Report Series 945[8]. In addition, manufacturers should also measure "other toxic chemicals contained within the product or delivered by the product, such as a reaction product from leaching or aging and aerosol generated through the heating of the product," per lines 1004 – 1007[1]. Microbial testing is recommended to ensure the absence of yeast, mold and bacterial growth[10,11] if the water activity of the e-liquid solution exceeds 0.8. The frequency of testing for specific analytes, such as selected HPHCs or heavy metals, can be altered by the manufacturer who has product knowledge and thereby can reduce the analytical testing burden.

3.5 Analytical Methods

Analytical methods that are used to support formal regulatory stability studies of e-vapour products must be suitably validated. One guideline for validation is ICH Q2(R1)[12].

Analytical methods must be analyte specific.

For analytical methods for glycerin, propylene glycol, water and nicotine, please refer to CORESTA Method No. 84[13].

For e-liquid extraction and aerosol collection procedures, please refer to CORESTA Guide No. 18[14].

For requirements found to be necessary for the generation and collection of e-vapour product aerosol for analytical testing purposes, please refer to CORESTA, 2015, Method No. 81[15].

For guidance on conducting photostability testing, please refer to ICH Q1B Guideline[16].

For guidance on conducting microbial testing, please refer to ICH Q6A[10] and the Pharmaceutical Microbial Manual[11].

As new CORESTA recommended analytical methods are developed, these methods will be added in updated versions of this guidance.

3.6 Testing Frequency and Stability Study Duration

The testing frequency and duration for long term stability studies will depend upon the manufacturer's needs and requirements. As a suggestion, formal stability studies could follow the ICH Q1A(R2) guidance for drug substances[6], which indicates that for long term storage, testing should be done every 3 months over the first year and every 6 months for the second year and annually thereafter as shown in Table 4. At the accelerated storage condition, a minimum of 3 time points is recommended including 0, 3 and 6 months. Accelerated conditions are generally used to predict shelf life and the predictions are later supported by long term studies. The required shelf life of the product needs to be taken into account, and thus a different testing schedule than detailed in Table 4 may be required. This should be defined by the product manufacturer.

Table 4. Stability Study Storage Conditions and Testing Frequency.

Storage Condition	0	3	6	12	24	36
(25 ± 2) °C, (60 ± 5) % RH	x	x	x	x	x	x
(40 ± 2) °C, (75 ± 5) % RH		x	x			

3.7 Power Units, Batteries, Atomizers and Software

Many different aspects of batteries can cause health risks, such as leaching of battery materials into the product, battery explosion, or other defects. In addition, the properties of atomizers and software are requested per the PMTA lines 1669 – 1741[1]. For e-vapour product stability studies, it is recommended that the quality of power units, batteries, atomizers and software be monitored over the course of the stability study.

When collecting aerosol from e-vapour products, it is recommended that power units and batteries be fully charged before beginning the collection of aerosol.

When the stability testing of refill cartridges (cartridges containing e-liquids) is done, the same assets (fully charged power units/batteries) should be used at the initial and at subsequent stability testing time points in the e-vapour product study.

When the stability testing of e-vapour products packaged in a kit (a marketed product containing one or more cartridges containing e-liquids and an aerosolizing apparatus packaged together) is done, the same components (fully charged power units/batteries) found in the kit should be used at the initial and subsequent stability testing time points in the study. Also, separate stability studies can be conducted for each of the components in the kit to obtain information on single components.

3.8 Sensory Testing

Sensory testing is certainly product specific and will depend upon the objectives of each e-vapour products manufacturer. Sensory attributes may be tested to the schedule given in Section 3.6.

4. Summary

The purpose of this guidance is to provide guidance to the industry in designing stability studies for e-vapour products. Stability studies are done to examine how the critical quality attributes of a product vary with time under different environmental conditions such as temperature, humidity and light. It is important that stability studies should be done in the actual marketed, finished packaging material for the e-vapour product.

Stability testing should cover physical and chemical attributes and any e-vapour attributes that are susceptible to change during storage and are likely to influence quality, and safety of the e-vapour product. Formal stability studies can be performed on each individual level of nicotine for the e-vapour product but a bracketing approach may be applied. Analytical methods for each analyte must be validated.

This guidance provides direction for designing formal stability studies for regulatory purposes and also provides direction for designing e-vapour product stability studies for sensory attributes. From that perspective, less formal and less rigorous stability studies may suffice to define product shelf life. From the customer viewpoint, e-vapour product sensory attributes, such as appearance, color, odor, taste, flavor attributes and harshness are viewed as being critical to defining a product's shelf life. Therefore, e-vapour product stability studies may include some aspect of sensory testing to provide product shelf life information.

5. References

[1] FDA Guidance for Industry: Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products. June 2019.

[2] Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014, Title I, Article 2, 2014.

[3] AFNOR, XP D 90-300-3 (E) Electronic cigarettes and e-liquids: Part 3: Requirements and test methods for emissions, July 2016 and preceding Parts 1 and 2.

[4] ICH Harmonised Tripartite Guideline. Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products Q1D. Current Step 4 version, dated 7 February 2002.

[5] Annex 2 of the WHO Technical Report Series, No. 953, 2009. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. 2009.

[6] ICH Harmonised Tripartite Guideline. Stability Testing of New Drug Substances and Drug Products Q1A(R2). Current Step 4 version, dated 6 February 2003.

[7] Qualification of Temperature-Controlled Storage Areas. Technical Supplement to WHO Technical Report Series, No. 961, 2011. QAS/14.598 Supplement 7. Annex 9: Model Guidance for the Storage and Transport of Time and Temperature-Sensitive Pharmaceutical Products. August 2014.

[8] WHO Technical Report Series 945, The Scientific Basis of Tobacco Product Regulation, Chapter 5, Setting maximum limits for toxic constituents in cigarette smoke. 2007.

[9] Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List, Federal Register, A Notice by the Food and Drug Administration on April 3, 2012.

[10] ICH Harmonised Tripartite Guideline. Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances Q6A, Current Step 4 version, dated 6 October 1999.

[11] Pharmaceutical Microbiology Manual (PMM) 2014. ORA.007 Version 1.2, US FDA, Office of Regulatory Affairs, Office of Regulatory Science, Medical Products and Tobacco Scientific Staff, dated 30 March 2015.

[12] ICH Harmonised Tripartite Guideline. Validation of Analytical Procedures: Text and Methodology Q2(R1). Current Step 4 version Parent Guideline dated 27 October 1994.

[13] CORESTA, 2017. Recommended Method No. 84: Determination of Glycerin, Propylene Glycol, Water and Nicotine in the Aerosol of E-Cigarettes by Gas Chromatographic Analysis. 2017.

[14] CORESTA, 2016. Guide No. 18: Technical Guide for Sample Handling and Sample Collection of E-Cigarettes and E-Vapour Generating Products. 2016.

[15] CORESTA, 2015. Recommended Method No. 81: Routine Analytical Machine for E-Cigarette Aerosol Generation and Collection – Definitions and Standard Conditions. 2015.

[16] ICH Harmonised Tripartite Guideline. Stability Testing: Photostability Testing of New Drug Substances and Products Q1B, Current Step 4 version, dated 6 November 1996.