APPENDIX A3.3-3

P1 THS 2.2 STABILITY STUDY PROTOCOL DORADO II RON

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Introduction

This document describes the conditions for the THS 2.2 Regular (Dorado II Ron) version (Platform 1) stability study and the tests planned for each time point, with the objective to demonstrate that the commercial product THS 2.2 produced at Philip Morris Manufacturing & Technology Bologna (PMMTB) remains within specifications, over the required period of (b) (4).

(b) (4)

(b) (4)

Batches

The batches were produced in PMMTB.

Table 1: Identification of THS 2.2 Dorado II Ron

Product/ Test Item	Consumable Batch Number	Finished Product Code	Manufacturing Date	Batch Size (sticks)
THS 2.2 Dorado II Ron	B-25904 / 41-2397948	ME000004.02	18.01.2016	(b) (4)
	B-25905 / 41-2397950	ME000004.02	18.01.2016	
	B-25906 / 41-2382704	ME000004.02	14.01.2016	

1.1 Samples Management

The samples required for the Stability study were delivered by the manufacturing site to the QC Unit after manufacturing and were placed in the climatic chambers in Philip Morris International, Neuchatel, R&D testing laboratories.

The samples are stored in the climatic chambers in packs. The packs are polypropylene wrapped packs consisted of two collations, each collation containing 10 Tobacco Sticks.

At each time point, the dedicated number of samples will be removed from the climatic chambers for chemical, physical, sensorial evaluations and visual inspection.

Storage Conditions

Table 2 – Stability Storage Conditions

(b) (4)

(b) (4)

(b) (4)

Table 3 – WHO Climatic Zones

Climatic Zone	Definition	Long Term Testing Conditions
I	Temperate climate	21°C / 45% RH
II	Subtropical and Mediterranean Climate	25°C / 60% RH
III	Hot and dry climate	30°C / 35% RH
IVA	Hot and humid climate	30°C / 65% RH
IVB	Hot and very humid climate	30°C / 75% RH

Selection of Stability Parameters

1.2 Chemical and Physical Characterization

The chemical mainstream aerosol and physical parameters that will be followed during the stability study are listed in Table 4 to Table **6**.

Table 4 - List of Parameters Measured in the Mainstream Aerosol for the THS 2.2 Dorado Stability Study

Parameter	Units
(b) (4)	

Table 5 - List of Physical Parameter Measured for the THS 2.2 Dorado Stability Study

Parameter	Unit
(b) (4)	

Table 6 – Visual Inspection for the THS 2.2 Dorado Stability Study

Parameter	Unit
(b) (4)	

* NA = Not Applicable

1.3 Sensorial Analysis

Quantitative Descriptive Profile (QDP) will be performed by a trained panel in blind booths at the Sensory Evaluation Center (SEC). The results of this analyses are considered as stability indicator and will be used for shelf-life assessment.

Table 7 – Sensorial Analysis for the THS 2.2 Dorado Stability Study

Parameter	Unit
Quantitative Descriptive Profile	NA

Tests Methods and Specifications

(b) (4)

Generation of the aerosol will be performed using the Health Canada Intense (HCI) smoking regime:

- Laboratory temperature: 22 ± 2°C
- Laboratory relative humidity: 60 ± 5%
- Puff volume: 55 mL
- Puff duration: 2.0 s
- Puff interval: 30 s
- Number of puffs: 12

All the instruments and material are listed in the relevant current work instructions in Table 8.

Device DV.000174 is used to generate aerosol, (b) (4) (b) (4) The following test are performed by the testing laboratories.

Table 8 – Tests, Methods and Specifications

Parameter	Method Name	Specifications
(b) (4)		

Parameter	Method Name	Specifications
(b) (4)		

(*) Comments about the specifications:

(b) (4)

(b) (4)

Testing Frequency

The samples are stored in climatic chambers in R&D Neuchâtel Product testing laboratories by the Test Item Management team.

The chemical and physical analyses are performed in R&D Neuchâtel Product testing laboratories.

(b) (4) .

The visual inspection is performed in PMP QA laboratories.

Table 9 - Testing Matrix Regular Product

(b) (4)

(b) (4) according to Table 9, (b) (4).

The number of replicates performed per analyses will be as follows:

(b) (4)

Data Evaluation

The statistical analysis performed on stability data according to current procedures, following ICH Q1E and is performed by modelling the degradation profile of each test parameter by using regression models.

The regression analysis is performed to prove that a batch is capable of performing within the specification limits until the expiry date, at a certain confidence level.

The regression analysis defines the trend of a quantitative stability test parameter for each batch over time on the predetermined stress conditions.

Data Presentation

The results will be presented in a tabular form at the end of each time point. An intermediate report will be also written at T6. The raw data will be archived and can be audited upon request.

The analysis of the stability results will be performed at each time point and a final report will be issued at the end of the stability study.

Responsibilities

It is the responsibility of the Stability studies coordinator to ensure that the stability protocol is followed under the defined rules. It is also his (her) responsibility to schedule the analysis at each time point with the Test Item Management team and testing representatives as well as preparing at each time point the stability results tables.

It is the responsibility of the Test Item Management team to distribute the samples in the climatic chambers according to the defined protocol and make sure that the stability conditions in the stability chambers are being met.

The elaboration of the stability report(s) is performed by the Statistician.

References

WHO Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products

ISO 3402:1999 Tobacco and Tobacco Products -- Atmosphere for Conditioning and Testing

International Conference for Harmonization ICH Q1E: Q1E Evaluation for Stability Data

International Conference for Harmonization ICH Q1A R2: Q1A(R2) Stability Testing of New Drug Substances and Products

P1 Product Specifications – appendix A3.2.1-3

Revision History for Stability Protocol

Version Nr	Description of change (including reason for change)	Justification
2.0	1. [redacted] (b) (4) [redacted] 2. (b) (4) [redacted] 3. (b) (4) [redacted] 4. (b) [redacted] 5. Added reference for P1 Product Specification report 6. Added Revision History for Stability Protocol	Update of protocol.
3.0	(b) (4) [redacted] 2. Added Stability study number in the header 3. Replaced Class of the parameters with units in Table 4 to 7 4. Updated Signature list and added roles	
3.0 SV	1. General revision for submission purposes.	Update of protocol.

Signatures

Prepared by: Pedro Campelos Quality Control unit statistician		Date: 07 Jul. 2016
Prepared by: Rita Hajdu Schenk Quality Control unit coordinator		Date: 07 July 2016
Approved by: Cyril Jeannet Head of Quality Control unit		Date: 07-Jul-2016
Reviewed by: Shelley Moores Quality Assurance		Date: 07-July-2016