APPENDIX A3.2.1-4

STABILITY SPECIFICATIONS

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P1 PRODUCT SPECIFICATIONSFOR SHELF LIFE

PROGRAM NAME	P1
PROJECT NAME	P1 Product Specifications for Shelf Life
EXPERIMENTAL WORK TYPE	Exploratory ☐ Developmental X Regulatory submission ☐

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1 Abstract

The historical stability study performed on the Dorado II (Regular Tobacco Sticks) and Dorado I High Menthol (Menthol 2 Tobacco Sticks) demonstrated that (b) (4) (b) (4) .

(b) (4) . As stated in ICH Q6A, it is possible to have broader criteria for shelf life than for release, as long as the quality and safety of the product is ensured.

(b) (4) and the proposed product specifications for shelf life are based on (b) (4) (b) (4) .

For Menthol in aerosol the maximum expected level based on the obtained stability data is (b) (4) (b) (4) , and the proposed product specifications for shelf life is (b) (4) .

2 Introduction

The quality of P1 is determined by its design, development, in-process controls, batch controls, process validation, and by specifications applied to them throughout development and manufacture.

Product specifications for shelf life are a set of chemical, physical, sensorial, and visual attributes for which the P1 product must remain within pre-determined limits over the entire shelf life of the product so that its quality is not affected (*Figure 1*).

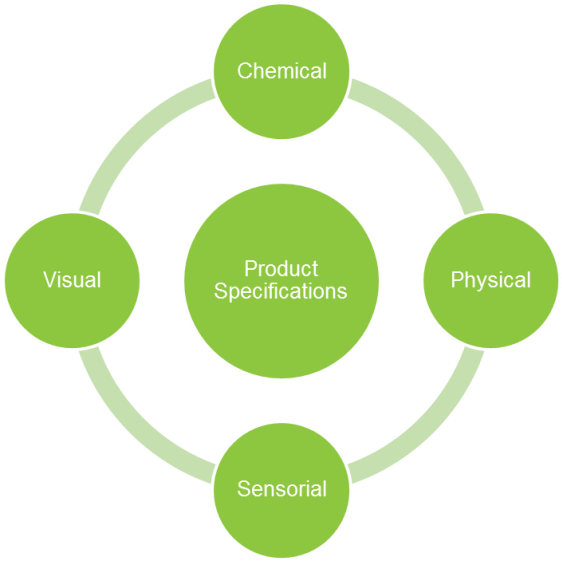


Figure 1: Product Specifications for Shelf Life

(b) (4) .

In this report the product evolution over time is evaluated for (b) (4) (b) (4) (*Figure 2*).

(b) (4)

Figure 2: Relation between Specification and Product Lifecycle

3 Research Question / Approach

- Which of the stability attributes of P1 are sensitive to the storage conditions?
- What are the product specifications for shelf life for P1 Dorado II (Regular Tobacco Sticks) and Dorado I 1.2M High Menthol (Menthol 2 Tobacco Sticks)?

4 Experimental Plan and Results

The stability protocol for the Dorado Blends was used to generate the stability data post-analysed in this report.

4.1 Data Evaluation

Data evaluation for quantitative P1 stability attributes amenable for statistical analysis was performed according to 4.1.1 and 4.1.2.

4.1.1 Identification of P1 Attributes Sensitive to Storage Conditions

The identification of the tested stability P1 attributes sensitive to the storage conditions was performed by calculating the relation between the attribute and time. (b) (4) If the attribute has only an upper limit and the trend indicates a decrease with time, then the parameter is not considered to be sensitive.

(b) (4)

(b) (4)

4.1.2 Calculation of the Degradation Rate

$$Degradation\ rate = \left(\frac{Slope}{Intercept}\right) * 100$$

Equation 2

The calculation of the degradation rate and R^2 was performed using the Microsoft Excel standard functions: CORREL, INTERCEPT and SLOPE.

The change after 12 Months is obtained by multiplying the slope by 12.

4.2 Results Dorado II

Tables 1 to 3 summarize the results of the stability study per storage condition for Dorado II.

Table 1: Result of the Stability for Dorado II at (b) (4)

(b) (4) - Dorado II			
Test	**Degradation rate**	**R^2**	**Change after 12 Months**
(b) (4)			

Table 2: Result of the Stability for Dorado II at (b) (4)

(b) (4) - Dorado II			
Test	**Degradation rate**	**R^2**	**Change after 12 Months**
(b) (4)			

Table 3: Result of the Stability for Dorado II at (b) (4)

(b) (4) **- Dorado II**			
Test	**Degradation rate**	**R^2**	**Change after 12 Months**
(b) (4)			

4.3 Results Dorado I

Tables 4 to 6 summarize the results of the stability study per storage condition for Dorado I.

Table 4: Result of the Stability for Dorado I at (b) (4)

(b) (4) - Dorado I			
Test	**Degradation rate**	**R^2**	**Change after 12 Months**
(b) (4)			

Table 5: Result of the Stability for Dorado I at (b) (4)

(b) (4) - Dorado I			
Test	**Degradation rate**	**R^2**	**Change after 12 Months**
(b) (4)			

Table 6: Result of the Stability for Dorado I at (b) (4)

(b) (4) **- Dorado I**			
Test	**Degradation rate**	**R^2**	**Change after 12 Months**
(b) (4)			

4.4 Stability Attributes Sensitive to the Storage Conditions and Change after 12 Months

The stability attributes sensitive to the storage conditions and change after 12 months are listed in *Table 7*.

Table 7: Dorado II Stability Attributes Sensitive to the Storage Conditions and Change after 12 Months

Attribute	Average Change after 12 Months
(b) (4)	

* (b) (4) (*Figure 3*)

(b) (4)
(b) (4) (4)

Figure 3: (b) (4)

The stability attributes sensitive to the storage conditions and change after 12 months are listed in *Table 8*.

Table 8: Dorado I Stability Attributes Sensitive to the Storage Conditions and Change after 12 Months

Attribute	Average Change after 12 Months
(b) (4)	

(b) (4) (*Figure 5*)

(b) (4) *Figure 4*)

(b) (4)

(b) (4)

(4)

X

Figure 4: (b) (4)



Figure 5: Evolution of Menthol for Dorado I High

5 Conclusions

- The P1 chemical stability attributes sensitive to the storage conditions (b) (4) (b) (4) The P1 physical stability attribute sensitive to the storage conditions (b) (4) (b) (4) The product specifications for shelf life are listed in *Table 9*.
- (b) (4)
- (b) (4)
- (b) (4)

Table 9: P1 Product Specifications for Shelf Life

Attribute	Product Specifications for Shelf Life	Justification
(b) (4)		

6 References

- ICH: Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

7 Revision History

Version N°	Author	Description of change (including reason for change)	Type of change
1.0	Campelos, Pedro	Original issue	1
1.0 SV	Campelos, Pedro	Submission version (hyperlinks and internal references removed)	2

(1. Major change/new version; 2. Minor change; 3 Review without change)

8 Review and approval

This document has been reviewed and approved by:

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