APPENDIX A3.2.1-14

THS2 COMPARABILITY SUMMARY(b) (4) -IDC

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Contents

APPENDIX A3.2.1-14 1
1 INTRODUCTION 3
2 RESEARCH QUESTION, SCOPE AND APPROACH 3
2.1 Primary end-points 3
2.1.1 Equivalent and non-inferior attributes 4
2.2 Secondary end-points 7
2.3 Samples 8
2.4 Data Processing and Reporting 8
2.4.1 Historical Data 9
2.4.2 Determination of Tolerance Limits – Primary End Points 9
2.4.3 Determination of Tolerance Limits – Secondary End Points 9
2.5 Statistical Analysis 9
2.5.1 Equivalence 10
2.5.2 Non-inferiority 10
2.6 Acceptance Criteria. 10
2.7 Results 10
2.8 Conclusion 17
2.9 Revision History 17
2.10 Approvals 17

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

1 INTRODUCTION

For the development of PMI's MRTPs, which use distillation as main operating principle (so called "heated product platforms"), a specific tobacco based material has been developed, the tobacco substrate. The manufacturing process of the tobacco substrate is based on the cast leaf tobacco reconstitution process principles.

(b) (4)

(b) (4)

2 RESEARCH QUESTION, SCOPE AND APPROACH

(b) (4)

2.1 Primary end-points

(b) (4) .

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 1: (b) (4)

(b) (4)

2.1.1 (b) (4)

(b) (4)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 2: (b) (4)

(b) (4)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(b) (4)



Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

2.2 (b) (4)

(b) (4)

in Table 3.

Table 3 (b) (4)

(b) (4)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(b) (4)

[redacted]

2.3 **Samples**

(b) (4)

[redacted]

2.4 **Data Processing and Reporting**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

2.4.1 Historical Data

The majority of the reference data are historical data generated on the control product. Therefore the data of previously performed studies studies at the time have been consolidated. Where there were insufficient data points available on the control product to determine the tolerance limits further analyses were requested prior to the execution of the comparability protocol.

2.4.2 (b) (4)

(b) (4)

2.4.3 (b) (4)

(b) (4)

2.5 **Statistical Analysis**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

2.5.1 Equivalence

(b) (4)

2.5.2 Non-inferiority

(b) (4)

2.6 **Acceptance Criteria.**

(b) (4)

2.7 **Results**

Figure 1 - Figure 4 show, (b) (4)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(b) (4)

Figure 1: (b) (4)
s.

Figure 2: (b) (4)
.

(b) (4)

Figure 3: (b) (4)
.

Figure 4: (b) (4)
.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(b) (4)

[redacted]

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 4: (b) (4)

(b) (4)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 5: (b) (4)

(b) (4)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(b) (4)

Table 6: (b) (4)

(b) (4)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(b) (4)

(b) (4)

Table (b) (4)

(b) (4)

ion 2.5, to (b) (4)

(b) (4)

[1] (b) (4)

[a]

(b) (4)

in section 2.5 are also met.

(b) (4)

[i]

[j]

[k]

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(b) (4)
d
(b) (4)
in section 2.5 are also met.

2.8 **Conclusion**

A(b) (4)
.
(b) (4)
.

2.9 **Revision History**

Version N°	Author	Description of change (including reason for change)	Type of change
1.0	Pijnenburg, Johannes	Extract of Original protocol and report	N/A

2.10 **Approvals**

	Name	Role	Signature	Date
Author	Johannes Pijnenburg	Manager HTP Substrate Developemnt		08.07.2016
Owner	Marco Esposito	Director Product Stewardship		07.07.2016

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

QA Review	Shelley Moores	Manager QA	S. Moores	07-Jul-2016

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.