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3.2 Development and Manufacturing

3.2.1 Development - Introduction

3.2.1.1 HNB (Heat Not Burn) Concept

THS operates on the principle of reducing exposure to HPHCs by electronically heating the tobacco to generate an aerosol rather than smoke. Smoke is the result of a combustion process.

Combustion is a physical-chemical process associated to a number of phenomena (heat and mass transfer) and side processes (pyrolysis and gasification).

The combustion process of solids involves the heating of the solid substrate to the point where chemical decomposition (pyrolysis or thermal degradation) starts. The chemical decomposition generates volatile compounds that leave the substrate in a gas phase, and a residual solid known as char.

Two indicators are required to unambiguously detect biomass and/or tobacco combustion:

1. Presence of relevant amounts of nitrogen oxides in the gaseous products, which are not formed from the decomposition of nitrates already present in the original biomass/tobacco substrate.
2. Clear evidence of an exothermic process.

Experiments have confirmed the absence of a combustion process in the electronically heated tobacco from THS (see Appendix A3.2.1-1). The electronically controlled elements only heat the tobacco plug to the point at which distillation of nicotine and tobacco flavors takes place.

3.2.1.1.1 Tobacco Stick Compared to a Conventional Cigarette

When a conventional cigarette is lit, the combination of paper, tobacco, heat and oxygen in the air generates a combustion process that consumes the tobacco.

During the smolder of a conventional cigarette, the in-between puffs temperatures range from 600°C to 800°C in the center of the burning cone, while, during a puff, the temperature increases to more than 900°C at the periphery of the lit end burning zone (see Figure 1).

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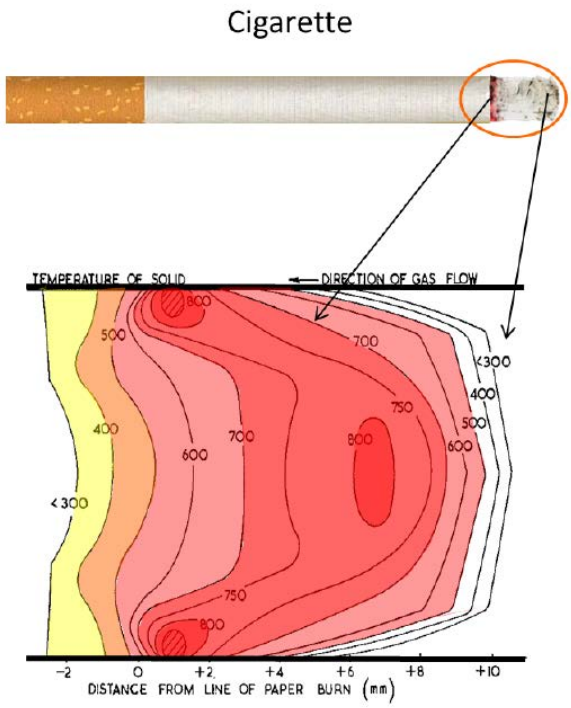


Figure 1 Tobacco Temperature in a Lit Conventional Cigarette

3.2.1.1.2 Temperature Profile of the Tobacco Stick in use

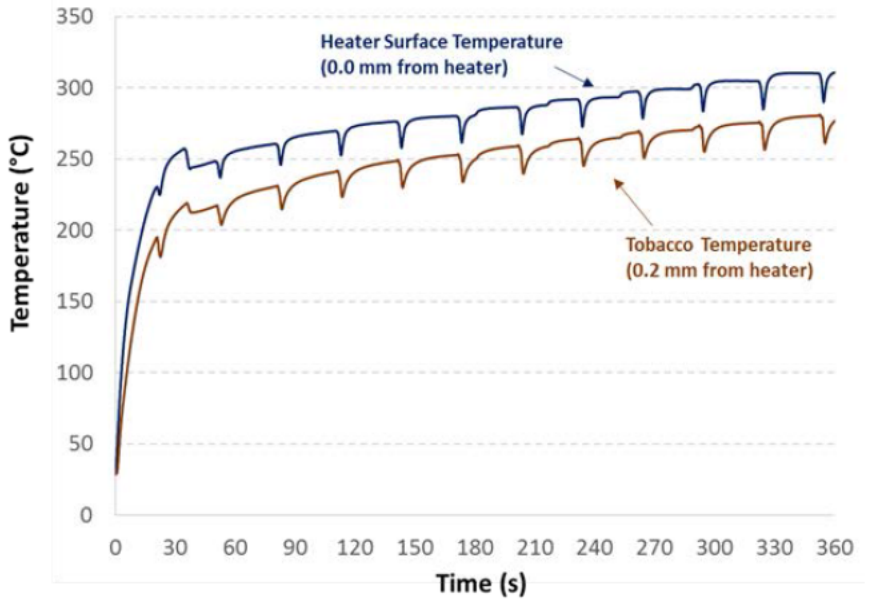
The heater starts heating the tobacco plug in a controlled and gradual manner, with the heater temperature set between 320°C and 350°C. The control mechanism is described in Section 3.1.

Heating the tobacco plug in a controlled manner and never allowing the temperature of the heater to exceed 350°C, prevents the combustion process from taking place. The temperature profiles in the tobacco plug at various distances from the heater are shown in Figure 2.

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(b) (4)



A B

Figure 2 Temperature Profile of the Heater (A) and Heater surface (B) (Blue) and in the Tobacco Plug (Brown)

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3.2.1.1.3 Aerosol Chemistry

The heated tobacco in THS generates a nicotine-containing aerosol with a chemical composition that differs substantially from conventional cigarette smoke. The levels of HPHCs are much lower, or not detectable, in the aerosol generated by THS when compared to those in conventional cigarette smoke, as shown in the report in Appendix A3.2.1-1).

The reduction of the HPHCs in the aerosol generated by the THS is achieved based on the following principles:

- By heating the tobacco plug at a lower, controlled temperature, combustion is eliminated, decreasing the level of thermal decomposition.
- The tobacco plug composition was specifically designed for use at the intended lower temperatures. In addition, the tobacco plug design consists of (b) (4) which act as (b) (4) .

3.2.1.2 Naming Convention

The naming conventions for THS are provided in Table 1.

Table 1 Product Naming

Submission Product		**THS (version 2.2)**
Device (DV)		THD (version 2.4)
DV codes (Holder/Charger)	Dark Slate	DV.000174/DAC.000027
	White Matte	DV.000180/DAC.000028
Tobacco Stick (TS)		C3.2
TS codes (R&D)	Menthol 1	CONS.02807.RD
	Menthol 2	CONS.02806.RD
	Regular	CONS.02873.RD
TS codes (Manufacturing)	Menthol 1	6AABC
	Menthol 2	6AAAL
	Regular	6AAFD

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3.2.1.3 Development Process

3.2.1.3.1 Product Development

When PMI started the development of THS, the Quality Management Systems (QMS) was evolving. Over the course of development of this product, different elements of the QMS were made effective.

The PMI design control process is described in Quality documents which are further described below. The relevant documents are listed in Table 2.

Hardware Development

Design and Development Planning

PMI is responsible for the design and development activities of THS. Different stages are followed during the design and development of a product:

- User Requirements
- Design Inputs
- Design Outputs
- Design Verification
- Design Validation

PMI has used the following support processes throughout the development stages:

- Design Reviews
- Risk Management
- Design Change Process

Once the design development was completed, the design was transferred to the manufacturing sites for scale-up and commercialization.

User Requirements

User Requirements were defined in the Target Product Profile (TPP). The acceptance criteria for the user requirements were defined in the Product Test Specification (PTS).

The TPP and the PTS were used as a basis for generating Design Input for the design control activities of THS.

Design Input

PMI has a process that describes how to create, approve and maintain Design Input requirements and to demonstrate through verification that the design meets all identified needs and intended use.

Initially, this document was called Functional Design Specification (FDS), which was later renamed into Design Input (DI) as it included functional, physical and performance requirements.

Design Output

The deliverables of the Design Output were created, reviewed and released following an established process for preclinical and clinical assessment, as well as commercialization.

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The examples of the available Design Output deliverables for THS are:

- Product and Module Specifications: Performance Specifications, Batch Release Specifications, Design Specifications and Incoming Material Inspection Specifications (see Section 3.2.2.2).
- Critical Quality Attributes (CQAs) and Critical Quality Material Attributes (CQMAs) with justification for their criticality.
- Other design documentation, e.g. drawings, schematics, layouts.

The Design Output was maintained in a controlled computerized system. Any change to the Design Output was recorded, assessed and approved according to the effective design change procedures.

Design Verification

Design Verification was performed at the module and functional (product) level. The results of the verification activities at the functional level were captured in the verification reports. The correlation between specification requirements and verification results are captured in a traceability matrix.

Design Validation

Aerosol characterization, panel reviews and consumer tests are used in order to validate the design. The following data are recorded for the activities:

- Validation results
- Identification of the design
- Validation methods
- Date(s) of validation
- Individual(s) performing the validation

This information summarizes how the evaluations ensure that the THS meets user needs and the intended use.

When finalized, the information is documented, and the risk management file is updated with the outcome of the validation activities (including software validation and any system integration testing).

Software Development

As stated, previously, software development was based on the FDS.

For the current version of the firmware, the following documents contain the relevant information:

- Software requirements including risk assessment
- Software design document
- Unit and integration tests reports (white box testing)
- Usability tests reports (black box testing)

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Table 2 Location of Development Documents

Product	Document	Appendix
System	TPP + PTS	Appendix A3.2.1-2
	Specifications (PS and BR)	Appendix A3.2.1-3
Device	FDS	Appendix A3.1-2
	Verification reports	Appendix A3.2.1-4
Tobacco Stick	Traceability matrix (FDS, FTS and FTR)	Appendix A3.2.1-5
	CQAs and CQMAs	Appendix A3.2.1-6
	Verification report	Appendix A3.2.1-7
Software	Software requirements	Appendix A3.2.1-8
	Software design document	Appendix A3.2.1-9

Note: In the development documentation, the Tobacco Sticks may also be referred to as HeatSticks.

Supporting Processes

Design Review

Formal design reviews were conducted at appropriate stages of the design and development process. The design reviews included:

- Project progress
- Readiness of the design for verification
- Proposed design changes

The outcome of these design reviews was documented.

Risk Management Activities

The risk management included:

- (b) (4)
- (b) (4) (see Appendix A3.2.1-10)
- (b) (4) see Section 3.2.1.3.2

Design Changes

Every change to a reference design starting from verification through preclinical and clinical studies and commercialization is recorded, assessed for impact and approved, according to severity, all design changes are documented.

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Scale-up and Commercialization

Design Transfer

During the design transfer process the following documents were provided to the manufacturing centers:

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

3.2.1.3.2 Process Development and Integration

Process Development (Scale-up)

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

Design Process

(b) (4)

Procurement/Development

(b) (4)
.

Characterization

Process characterization is the process by which an effective and appropriate process control strategy is defined and documented. An appropriate control strategy is based on knowledge and experience gained during the development phase.

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During this phase, the following documents are generated:

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

Optimization

Optimization can be supported by different processes, such as Process Performance Optimization and Process Efficiency Optimization. All improvements that are applied at this stage are assessed and documented.

Development Tools

The following tools are commonly used during process development and integration.

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

Process Integration (Technology Transfer)

Process Integration involves the integration of the manufacturing process to an appropriate, responsible and authorized party. It requires transferring documented knowledge and experience gained during development.

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The following are performed and documented in order to ensure a successful transfer:

- (b) (4)
- (b) (4)
- (b) (4) (see Table 3)
- (b) (4)

3.2.1.4 Design Optimization

3.2.1.4.1 Design Optimization: Process

PMI has a Change Management process overseen by a Change Management Board (CMB) to ensure that any changes implemented are assessed with regards to the product performance, meaning that the data generated on the proposed product prior to a change should be equally applicable to the product after the change. More information are given in Appendix A3.2.1-21.

The process oversees requested changes to the product, its manufacturing process and test methods, to ensure that they have no adverse impact on performance, quality attributes or safety for intended use.

The process entails procedures for the identification, documentation, validation, verification, review, and approval of changes before their implementation. This process is applicable to the product lifecycle from the start of the preclinical and clinical assessment, to product phase-out.

When a potential impact of a change on performance, quality attributes or safety for intended use of the product cannot be excluded, additional studies are conducted to assess product comparability.

3.2.1.4.2 Design Optimization: Comparability

A comparability assessment is initiated in order to generate additional evidence and finalize the assessment of the change.

Product Performance Comparability

Product Performance Comparability follows a (b) (4) approach. In the first stage, (b) (4)

Aerosol Chemical Composition

The chemical composition of the aerosol is assessed through measurements of chemical compounds on the PMI-58 list including 54 HPHCs (see Appendix A3.2.1-12 for the rationale on the PMI-58 list). (b) (4)

The purpose of the assessment is to compare the yields of each of the selected HPHCs of the post-change product, to predetermined acceptance criteria: (b) (4)

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(b) (4) is defined (b) (4)

(see Section 3.2.2.3) (b) (4)

(b) (4) .

(b) (4)

(b) (4)

Impact on Biological Endpoints

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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3.2.1.4.3 Design Optimization: Description of Major Design Steps

Table 3 Chronological Summary of the Major Changes for THS since (b) (4)

Change Item	Description	Applicable to	Comparable	Product Code Reference* Post Change Completion
2012/2013				
(b) (4)				

(table continues)

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Change Item	Description	Applicable to	Comparable	Product Code Reference* Post Change Completion
(b) (4)				
2014				
(b) (4)				

(table continues)

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Change Item	Description	Applicable to	Comparable	Product Code Reference* Post Change Completion
(b) (4)				
2015				
(b) (4)				

(table continues)

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Change Item	Description	Applicable to	Comparable	Product Code Reference* Post Change Completion
(b) (4)				
2016				
(b) (4)				

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All further improvements to THS (version 2.2) since the product performance lock, and a short summary of the pertinent design changes listed in Table 3 can be found described in Appendix A3.2.1-21.

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