APPENDIX 2: INDEPENDENT EXPERT RISK BENEFIT ASSESSMENT BY AUTHOR

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2.1.1 Background

Tobacco products are currently regulated by *Directive 2014/40/EU* of the European Parliament and of the Council

- Art. 19 sets forth provision for novel tobacco products. Placing these products on a national market of a Member State will be subject to submission of a Notification or Authorization to the competent authority of a Member State. The manufacturers and importers submitting notification or application for authorization of novel tobacco products in accordance with Art.19.1(c) shall also provide the competent authorities with a risk/benefit analysis of the product and its expected effects on cessation/initiation of tobacco consumption and predicted consumer perception.

This risk/benefit analysis was conducted independently upon request from Philip Morris Products SA.

2.1.2 Tobacco Heating System

The Tobacco Heating System (THS) is a product, which consists of a device electrically heating specifically-designed Tobacco Sticks to produce an aerosol which contains nicotine at levels similar to a conventional Combustible Cigarette (CC), but with Harmful and Potentially Harmful Constituent (HPHC) levels which are substantially reduced compared to CC. This is facilitated by the lower temperatures used for heating tobacco in the THS rather than higher ones used for burning tobacco in CC.

THS has three distinct components that perform different functions: (i) an electrically heated tobacco product (the HeatStick) -- a novel (patent pending) tobacco product with specially processed tobacco made from tobacco powder, (ii) a Holder into which the HeatStick is inserted and which heats the tobacco material by means of an electronically controlled heater, and (iii) a Charger that is used to recharge the Holder after each use (see Section 4.1 in Philip Morris International (PMI) Technical and Scientific Dossier for THS, v 1.0).

Many HPHCs are formed expressly during the burning of tobacco at high temperature in a CC, and the principle of the THS is to reduce the formation of and exposure to HPHCs by controlled heating of tobacco at lower temperatures (compared to CC) - that do not cause combustion of tobacco - to generate an aerosol that is acceptable to adult smokers.

Philip Morris Products S.A. has provided the following documentation for the risk/benefit analysis. This documentation (PMI Technical and Scientific Dossier for THS, v 1.0) includes:

- detailed description of the THS
- its manufacturing and manufacturing controls
- substances in the inhaled aerosol from THSand compared to CC
- indoor air quality before and after use of THS
- non-clinical assessment of the aerosol generated by THS, and clinical study assessment results – as compared to standard cigarettes. *Data from epidemiological studies are not (yet) available*

2.1.3 **Risk/benefit analysis summary**

- The results of the extensive **non-clinical assessments** performed on the THS (with or without menthol) demonstrate that the reduced formation of harmful and potentially harmful constituents, when compared to combustible cigarettes, translates into reduced toxicity in both in vitro and in vivo models of exposure (see Section 5.4 in PMI Technical and Scientific Dossier for THS, v 1.0).

- The **pharmacokinetic and pharmacodynamic** clinical studies demonstrate that the THS delivers nicotine in a predictable and controlled manner at levels and kinetics similar to conventional cigarettes. Pharmacokinetic and pharmacodynamic behavior of nicotine released by using the THS are important indicators of potential product acceptance by adult current smokers willing to switch from CC to THS (see Appendices 7, 8, 11 and 12 of the PMI Technical and Scientific Dossier for THS, v 1.0).

- Whereas nicotine uptake into the body resembles that of smoking conventional cigarettes, data from **clinical studies** in which subjects were allowed to use the product ad libitum, demonstrated that levels of various relevant **biomarkers** of exposure are substantially reduced when compared to CC, and may even approach the levels measured after smoking cessation. These results demonstrate that the reduced formation of HPHCs in the THS results in reduced exposure to HPHCs in product users. This should lead to lower toxicological effects from the THS use as compared to CC, but a longer term clinical study on clinical risk markers is still in progress. *Also, in a pre-market phase long-term epidemiological studies/data cannot yet be provided* (see see Appendices 9, 10, 13 and 14 of the PMI Technical and Scientific Dossier for THS, v 1.0.)

  Based on **human clinical safety data** (monitoring and observation of adverse events) there were no safety signals suggesting any new or increased risk associated with the THS use by adult smokers compared to CC (See Section 5.5.2 in PMI Technical and Scientific Dossier for THS, v 1.0 for the Clinical Assessment overview).

In this report, the **risk associated with use of the THS** is described in relation to current smokers continuing to smoke, those that stop smoking and non-smokers– i.e. whether being

lower, higher or comparable. **Benefit** is described in relation to the risk from smoking CC, i.e. whether this risk would be lower when switching to THS.

Novel tobacco products by law, must show *reduced risk* per se (encompassing hazard, exposure, the characterized risk, and its analysis and comparative assessment), and *benefit* (from risk being lower than that from smoking conventional cigarettes) (*caveat*: the suggestive false use of terms that are applied here is caused by criteria and definitions having been set elsewhere already - *BfR (2010)*: whereas for lay people risk comes from smoking, and benefit comes from non-smoking and cessation of smoking, respectively, we have to refine this simplification as described in the following points:

- Comparisons between switching from smoking CC to using Tobacco Heating System and to smoking cessation: When using the THS in comparison to smoking cessation, the use of THS partially approaches and partially reaches levels of smoking cessation. *Smoking cessation would be considered the benchmark for maximum risk reduction after having smoked.* Similarity of risk may be achievable when comparing switching to THS and smoking cessation (such may be ascertained by long-term studies): **Currently no differentiation possible, neither for Risk nor for Benefit.**
- Comparison between using the THS and never smoking: the use of Tobacco Heating System has to be expected to exhibit higher risk compared to never smoking. Differentiation has to be made between those who chose THS over CC when starting smoking, and those who would not have started on CC, but found THS attractive. *Never having smoked would be considered the benchmark for lowest possible risk from smoking (through passive exposure):* **Potentially somewhat higher Risk at No Proven Benefit.** It should be kept in mind that switching from non-smoking to THS is not intended, and the potential risk thus remains theoretical.
- Comparison between switching to THS and continuation of smoking: compared to continuation of CC smoking, the use of THS - from the physical/analytical/non-clinical and clinical data provided - can be assumed to lower the risk (depending on the comparator chosen and detection limit). *Continuation of smoking CC would be considered the benchmark for highest possible risk from smoking:* **Proven increased benefit and proven lower risk after switching to THS**. This is most important, and will be discussed in detail in the report.

The **data provided** suffice to meet a number of requirements in order to allow the proper risk assessment of such novel tobacco product. These requirements can be summarized as:

1. Start and proceed with investigations according to a reasoned choice of substances from an established list of dangerous or potentially dangerous smoke/aerosol constituents to assess formation of such harmful constituents that might become available when using THS
2. Measure (in aerosol) those harmful constituents (see 1.) from actually heating THS

3. Demonstrate – at the same time – equivalence of nicotine delivery from THS compared to that from CC – despite reduction of harmful constituents
4. Demonstrate relevancy of exposure biomarkers that arise from harmful substances (see 1. and 3.)
5. Assess whether new product substantially lowers the amount of biomarkers of exposure from THS versus CC (see 4.)
6. Present results of toxicity testing
7. Present clinical evidence (including clinical risk biomarkers) in support of lowering the risk from THS.

Fulfillment of these requirements is needed to provide information on reduced toxicity from toxicological studies and on the reduced exposure of smokers to HPHCs resulting from their reduced formation, and on the addictiveness of THS driven by nicotine.

2.1.4 **Risk-benefit assessment**

The data presented in the PMI Technical and Scientific Dossier for THS, v 1.0 allows a proper risk assessment.

- These data provided allow to draw the conclusion of an overall positive risk-benefit assessment, where specific risk and specific benefit both contribute, notwithstanding public health intention to never start - or to refrain from - smoking tobacco. Public knowledge about the power of smoking habit (addiction) due to inhalation exposure of nicotine only lets one accept the "half-way house" of tobacco heat stick, whereby the act of tobacco use continues, but with much reduced danger, while maintaining nicotine exposure satisfying the addicition. It remains to be investigated in the future whether the switch from conventional cigarettes to THS will support cessation of smoking altogether, i.e. long-term cessation. Such can only be studied after marketing.

- *Risk needs to be seen in the light of never smoking, respectively long-term cessation of smoking.* Starting use of THS allows for elimination or reduction of the additional risk to be expected from continuation of smoking CC. Such concerns reversible and irreversible effects. Grosso modo, return to "zero risk" (i.e. status quo ante: baseline of such toxic effects due to never smoking conventional cigarettes) remains impossible, which implies that switching to THS only partially eliminates or reduces the incremental risk, which would arise from continuation of smoking CC. However, the goal of reaching the substantially lower risk connected to long-term cessation of smoking can be acomplished.

- *Benefit needs to be seen in the light of reduced exposure to HPHCs*, also represented and demonstrated by the corresponding biomarkers of exposure (and measured in urine, blood and exhaled air). Benefit arises from continuation of the satisfaction of craving / addiction (nicotine), thereby helping to prevent relapse back to using harmful CC. Benefit also arises from stopping the progression of irreversible risks and the initiation of the regress of reversible risks (to the extents possible – see scientific discussion beyond this report) from smoking CC (namely cardiovascular toxicity, COPD and cancer). This benefit grows over time, when replacement of smoking CC by THS resembles more and

more long-term cessation. Grosso modo, the remaining risks can be judged about equal to those after cessation of smoking.

- *Risk* arising from CC smoking is well defined as being caused by long-term exposure to HPHCs, which can be locally demonstrated by biomarkers. *Benefit* arising from never smoking leaves the frequency of such toxic effects at baseline. Baseline frequencies are due to many internal and external factors (e.g. passive smoking), and are well above zero frequencies/levels.

- *Benefit / risk arising from replacing smoking of CC by THS* is expected to follow that of cessation of smoking. Therefore, THS has a positive risk / benefit, despite expected persistence of those irreversible toxic effects of previous smoking of CC. It would be false to attribute these risks to THS. However, smokers should be informed that – due to the extent and duration of previous smoking – some risks might never become fully reversed. Smokers should also be informed that by exclusively using the THS (not anymore using CC) the decrease of further incremental risks incurred from stopping of smoking CC is expected to approach the benefit from the decrease after complete cessation of smoking *(which would need to be demonstrated in long-term epidemiological settings)*.

- *Benefit / risk as related to exposure to a major harmful toxicant being representative of smoke / aerosol* generated from smoking tobacco, *benzo[a]pyrene,* has been clearly identified. According to Boobis et al (2013) *"... Any alternative scenario will decrease levels of benzo[a]pyrene". "Therefore, benefit / risk assessment should stop after Tier 1 of assessment".* Such supports the conclusion of this report, which also is to stop at Tier 1 of Boobis et al. approach: *Individual assessment of benefits and risks.* Therefore, there is no suggestion to attempt quantification or probabilistic computation– as set out in Tiers 2 – 4 of the Boobis et al (2013) paper.

2.2 **Subject**

THS has been developed in order to dramatically reduce exposure to HPHCs as compared to CC where tobacco is burning. Documentation needs to be prepared for submission to Competent Authorities to satisfy legal provisions of "Notification/Authorization" according to current EU legislation (Directive 2014/40/EU) and Member States requirements.

The Notification/Authorization process includes a risk-benefit analysis, which is presented in this report.

The background for developing and notifying novel tobacco products for use in the European Union results from established knowledge about the negative individual and public health implications from smoking CC. Changing smoking habits, namely finding safer alternatives for CC, will improve public health. It has to be acknowledged that until that time, where no one will ever start smoking (preventing the problems of initiation and need for cessation),

any approach to reducing smoking and reduction of exposure to harmful substances generated from smoking remain a desirable option to improve public health in relation to continuation of smoking.

Appreciation can thus be shown for the approach taken by Philip Morris Products S.A.: development and assessment of a tobacco heating system, which will fulfill habit requirements like "cigarette-like appeal" and delivery of nicotine from puffing on such a device. Although this is still a tobacco product involving heat, HPHCs have been significantly reduced by avoiding the combustion of tobacco, i.e. burning at high temperatures.

2.2.1 State of the Art Approach to Performing Risk / Benefit Assessment

What is required to allow for proper risk / benefit assessment for THS?

The classical approach for a chemical or active pharmaceutical ingredient assessment would be to complete hazard identification studies (*in vitro/in vivo in appropriate models*). Then to characterize the hazard (dose response), perform exposure studies (under specified conditions) and then characterize the risk. However, there are additional challenges for a complex matrix of chemicals such as CC smoke, which causes adverse effects with no known adverse effect level.

While national guidelines for implementing the risk/benefit assessment requirements of Article 19 of the TPD are still lacking, it must be ascertained that the (scientific) state of the art is fulfilled through applying common sense and refering to known principles from several sources such as the German Federal Institute for Risk Assessment (BfR), the Benefit and risk-analysis for foods (BRAFO) (Vidry et al. 2013), and the consensus working group (Boobis et al. 2013), as well as other relevant literature The German BfR has published its comments towards implementation of the TPD on 30 July 2015. These comments do not specifically address novel tobacco products; however, by listing toxic (carcinogenic-mutagenic or reproduction toxic) substances, it needs to be taken into consideration when assessing the Philip Morris product THS. The BfR comments are taking stock of the "Guidance document for health assessments" of 2010, which has very limited application to tobacco products. However, their approach provides overall guidance for the risk/benefit assessment. This Expert Report is assessing available results from pre-clinical and clinical investigations including biomarkers of exposure following the identification and characterisation of hazards of smoking and provides characterisation of risk and potential benefit of the THS.

- **Identifying and characterizing the hazard**.
  Hazard from smoking conventional cigarettes is well understood. Any new product claiming superiority over conventional products will have to demonstrate at pre-marketing stage such superiority (related to risk and benefit).

- Harmful and Potentially Harmful Constituents (HPHCs) are chemicals that are found in tobacco products or tobacco smoke that cause or could cause harm to smokers or nonsmokers. There are a number of lists of HPHCs that have been developed by regulatory bodies such as Health Canada and the US FDA. These compounds have been linked to the most serious health effects of tobacco use (cancer, cardiovascular disease, respiratory effects, reproductive problems and addiction) and are considered to serve as a suitable basis for comparison of potential harm accross different types of products. Such listings are available for use. *These substances must be measured and compared in the aerosol. Requirement No. 1.*

- Among the tobacco smoke constituents that have been identified as HPHCs there are chemicals that cause or could cause harm to smokers, Nicotine also needs to be considered. Although it is listed as one of the harmful or potentially harmfull constituents, it's listing is linked to its addictive properties, not to toxicity as such - at the dose levels contained in cigarette smoke. It is necessary to be present in any smoking replacement product in order to prevent the craving and withdrawal symptoms when stopping conventional tobacco products. Tobacco products with reduced risk should be developed to retain and deliver nicotine in a similar manner to cigarettes, whilst reducing the delivery of other harmful constituents associated with toxic endpoints such as inflammation, tumor formation etc. *Thus nicotine delivery equivalency of the novel products to that of cigarretes needs to be demonstrated. Requirement No 2.*

- (Following identification and characterization,) recognised and established HPHCs from tobacco and tobacco smoke render themselves to becoming toxic (only), when exposure of smokers actually happens (notwithstanding passive exposure). This implies that the substances exiting cigarettes and becoming bioinhalable from the resulting aerosol and tobacco smoke must be measured.
  The delivery of harmful constituents in cigarette smoke can be measured using smoking machines operating to an agreed puffing regime. This does not totally mimic the puffing behavior of smokers, but does provide a first assessment of what potentially is delivered to a smoker's mouth - if they smoked according to the specified puffing regime. Such an approach does not provide a measure of exposure (i.e. what is taken into the body of a smoker when using a particular tobacco product), but allows for understanding the potential maximum exposure to harmful and potentially harmful substances – per puff, per cigarette, and per day. *Thus, the measurement of these HPHCs in the aerosol generated should be provided to compare the levels formed in THS compared to CC (and uptake into the body measured in clinical studies using biomarkers of exposure to known harmful constituents). Requirement No. 3.*

- Whereas these external ("in vitro") values tell us about the technically possible comparative formation, it is necessary to understand and measure "local" exposure – for actual exposure and for comparison: port of entry into the respiratory system and downstream to cells and their constituents. This area is the least standardized and regulated / amenable to regulation. Such tests and measurements are developed and introduced to serve various purposes, all in support of understanding "in vivo" exposure to harmful and potentially harmful substances and their potential toxic effects: *bio-exposure and bio-response*. ***Bio-exposure*** measures the substance(s) in question as close to the target as possible. ***Bio-response*** can be physiological and pharmacodynamics measurements (e.g. mode of action of nicotine), and can be indicative of pathological reactions to HPHCs.

  Bio-exposure and bio-response (under current nomenclature) are measured as "Biomarkers" and as "clinical endpoints" (which, in turn, may be established surrogate endpoints – which are also biomarkers), where those biomarkers, which point to risk, are especially important. Exposure to certain smoke constituents can be measured using biomarkers of exposure. Measuring biological response requires a different set of biomarkers which, if appropriate, can provide an indication of disease risk. Technical and technological opportunities have it, that often measurement is done of HPHCs and/or their metabolites at local levels (and/or their metabolites generated in vivo elsewhere or locally), and of interaction with target tissue, cell, or subcellular components.

  Irrespective of local interference and toxic action the specific biomarker may render itself available for measurement not at the same location, but (only) upon its excretion (urine, feces, exhalation). Here we are dealing not with "established" or "relevant", but rather with "suitable" biomarkers – usually of (local) exposure, present and measured (distant) in urine or blood.

  Ideally, most of the biomarkers of exposure (representing each one or more of the most important HPHCs) should come from the accepted listing of the recognized most harmful HPHCs , and be measured according to the state of the art. Requirement No. 4.

- It can be concluded that suitable biomarkers are available today, which measure the local exposure of some of the recognized relevant HPHCs – on behalf of their constituency. The many available accepted biomarkers of exposure also represent a broad range of chemical classes of harmful constituents found in tobacco smoke.

  The crux remains that no single harmful substance or biomarker in itself is sufficient to fully represent the risk from smoking and would allow for comparison with THS. As a result, multitudes of biomarkers must be chosen, which when evaluated together would become representative overall, and would allow for comparison. As the reaction of such multitude of biomarkers - employed

to compare conventional cigarettes and e.g. THS - may not be identical in qualitative and/or quantitative terms, assumptions made will always remain somewhat subjective – until a list of biomarkers of exposure has been internationally accepted and adopted – including their ranking for importance in comparing different tobacco products and disease endpoints.
Point 1: at this point in understanding and characterizing the clinical risk of different tobacco products, we remain focused on "exposure" (not on long-term toxicity).
Point 2: compared to pharmaceutical clinical studies there is no single primary biomarker endpoint available for nailing down smoking. Therefore, a study of the multitude of secondary biomarker endpoints representing different disease endpoints would then need to be sufficiently powered to have them statistically accepted as a combination primary endpoint marker. For smoking and for comparing different kinds of tobacco products this remains the only possibility to come to marketing decisions from pre-market data. As statistical proof may not be attempted, the "cumulative power" of the many biomarker results, however – moving in the same direction, i.e. indicating less exposure and approaching zero exposure – makes sense.
Point 3: Benzo(a) pyrene has been recognized as a main risk substance, which can be used for risk/benefit recognition alone (Boobis et al, 2013). This simplification is not relevant in the context of THS.

Therefore, a large panel of biomarkers of exposure, if found significantly decreased compared to smokers of conventional cigarettes ***and*** *values measured approach/reach those of non-smokers, will allow assumption that toxicity from smoking would be reduced. Requirement No. 5.*

- **Characterising the risk.**
  Risk from smoking conventional cigarettes is well understood. Any novel tobacco product claiming superiority over conventional products will have to reasonably demonstrate at pre-marketing stage such superiority.

  Smoking related diseases, e.g. cancer, cardiovascular and peripheral vascular disease, respiratory disease and COPD, which may become irreversible, occur (only) after long-term exposure of human smokers, and can then be measured as hard clinical endpoints. Such clinical epidemiological data cannot be made available before marketing of a novel tobacco product. As in other product developments, other endpoints must be used to provide sufficient data for risk assessment of novel versus conventional tobacco products. These range from classical in vitro and in vivo animal studies to clinical settings of short duration with relatively small numbers of trial participants - including measurement of surrogate endpoints (usually biomarkers). As in other product developments like pharmaceuticals it will be the totality of evidence generated from all studies including non-clinical and clinical studies, and employing any type of endpoint

(including surrogate endpoints from biomarkers), which when taken together will allow for risk characterization towards risk / benefit analysis and assessment.
For sake of simplification, it will be assumed in theory that there is a relationship lining up non-smokers, those who stopped smoking, those using novel tobacco products, and those smoking conventional cigarettes *versus* low, intermediate and high risk. This will allow to slot in novel tobacco products for comparison.

- In order to demonstrate that reduction of HPHCs generated/released from the novel tobacco product is related to lower/reduced toxicity compared to CC and approaching" non-smoking" levels of non-smoking individuals, such products should undergo a (complete) standard toxicity assessment (in vitro and in vivo). Mutagenicity/genotoxicity testing requires special attention, as comparable endpoints are usually not available from clinical studies. *Performance of Toxicity tests: Requirement No. 6.*

- As mentioned in the previous bullet novel tobacco products should also undergo further clinical studies. Also for ethical considerations only those studies will be performed, where smokers using CC switch to the novel tobacco product. No attempt may be made to turn non-smokers into smokers of novel tobacco or CC products.
Performance of proper clinical studies: Requirement No. 7.

2.2.2 **Conclusion**

In conclusion, the following requirements have to be met before attempting risk / benefit assessment of a novel tobacco product (and compare it to conventional cigarettes and/or cessation of smoking altogether)

1. Work according to an established list of smoke/aerosol constituents to confirm reduced formation of harmful constituents
2. Demonstrate nicotine delivery equivalency of the novel product to that of cigarettes
3. Measure the relevant harmful constituents (see 1.) in smoke / aerosol
4. Demonstrate relevancy of exposure biomarkers to arise from harmful substances (see 1. and 3.)
5. Assess new product substantially lowers the amount of exposure biomarkers (see 4.)
6. Present evidence from toxicity testing
7. Present clinical evidence (including clinical risk biomarkers)

2.3 **Evidence Documentation provided by Philip Morris Products S.A.**

NB: information presented below is considered to constitute trade secrets and confidential information provided to Expert only to allow preparation of an independent risk / benefit assessment. The report thus developed is based on confidential and legally protected material, which is described to some detail below. It remains under the responsibility of Philip Morris S.A. to disseminate this report. Without the following chapter

the reader would not be put into a position to fully grasp the complicated steps and conclusions to be drawn – as set out in the preceding chapter and in the subsequent ones.

2.3.1 **Characterization of "Tobacco Heating System"**

The characterization of the "Tobacco Heating system" is presented in several steps.

1. Physical build of the system, product formulation, manufacturing and properties – including the tobacco HeatStick manufacturing: *Such are considered developed according to technical standards, and validated. Their description in the Philip Morris Products S.A. document is considered sufficient, and will not be commented upon in this report. It is noted that the "Tobacco heating device" is CE-certified.*
2. Analysis of smoke generated from CC and the aerosol from THS
3. Results from using/smoking CC versus THS

The properties of THS are described in the PMI Technical and Scientific Dossier for THS, v 1.0, as follows.

- Chemical and physical characteristics of the THS aerosol, including:
  - Substantial reduction in the levels of harmful and potentially harmful substances as compared to CC
  - Nicotine yield similar to CC
  - Aerosol droplet size distribution within the respirable range similar to CC smoke
- Likelihood that adult consumers will accept the THS as a replacement for CC, including:
  - Physical design which ensures minimum disruption to the CCsmoking ritual
  - A use cycle which is similar to CC in terms of puff numbers and duration of a single HeatStick" use

Smoke / aerosol characterisation

One of the critical parameters of Philip Morris Products S.A. development is the "heat not burn" approach to developing a product with a potential to reduce risk to smokers.

Laboratory analysis of harmful and potentially harmful constituents

Generally, the evidence to support marketing of a tobacco product with the potential to reduce risk will come from three categories: health effects of the product when compared to CC, its addictive potential, and perceptions about the product. Laboratory analysis of the performance and of the constituents of tobacco products will be the first step in the evaluation of any new product. These analyses involve standard methods of extraction, sample preparation, analyte identification, and quantitation. There are important limitations to laboratory analysis of product performance and composition. First, laboratory analysis of constituents may not reflect constituent uptake under conditions of use. In particular, smoking machines do not replicate human smoking conditions. There is currently no proven way to replicate the many ways humans use tobacco. As such, it is crucial to describe the smoking regimen or other extraction methods employed. Second, there may be other unidentified compounds in tobacco that may contribute to adverse health effects. Also, seemingly innocuous compounds can exacerbate the effects of toxicants.

Nevertheless, such analysis and identification constitutes a major part for establishing the risk arising from a novel compared to conventional tobacco product. Without such information no reasonable risk-benefit assessment can be performed.

Table 1: Established list of the chemicals and chemical compounds identified by U.S. FDA as harmful and potentially harmful constituents in tobacco products and tobacco smoke.

Constituent	Carcinogen (CA), respiratory toxicant (RT), cardiovascular toxicant (CT), reproductive or developmental toxicant (RDT), addictive (AD)
Acetaldehyde	CA, RT, A
Acetamide	CA
Acetone	RT
Acrolein	RT, CT
Acrylamide	CA
Acrylonitrile	CA, RT
Aflatoxin B1	CA
4-Aminobiphenyl	CA
1-Aminonaphthalene	CA
2-Aminonaphthalene	CA
Ammonia	RT
Anabasine	AD
o-Anisidine	CA
Arsenic	CA, CT, RDT
A-a-C (2-Amino-9*H*-pyrido[2,3-*b*]indole)	CA
Benz[*a*]anthracene	CA, CT
Benz[*j*]aceanthrylene	CA
Benzene	CA, CT, RDT
Benzo[*b*]fluoranthene	CA, CT
Benzo[*k*]fluoranthene	CA, CT
Benzo[*b*]furan	CA
Benzo[*a*]pyrene	CA
Benzo[*c*]phenanthrene	CA
Beryllium	CA
1,3-Butadiene	CA, RT, RDT
Cadmium	CA, RT, RDT
Caffeic acid	CA
Carbon monoxide	RDT
Catechol	CA
Chlorinated dioxins/furans	CA, RDT
Chromium	CA, RT, RDT
Chrysene	CA, CT
Cobalt	CA, CT
Coumarin	Banned in food
Cresols (o-, m-, and p-cresol)	CA, RT
Crotonaldehyde	CA
Cyclopenta[*c,d*]pyrene	CA
Dibenz[*a,h*]anthracene	CA
Dibenzo[*a,e*]pyrene	CA

Dibenzo[*a,h*]pyrene ..... CA
Dibenzo[*a,i*]pyrene ..... CA
Dibenzo[*a,l*]pyrene ..... CA
2,6-Dimethylaniline ..... CA
Ethyl carbamate (urethane) ..... CA, RDT
Ethylbenzene ..... CA
Ethylene oxide ..... CA, RT, RDT
Formaldehyde ..... CA, RT
Furan ..... CA
Glu-P-1 (2-Amino-6-methyldipyrido[1,2-*a:*3',2'-*d*]imidazole) ..... CA
Glu-P-2 (2-Aminodipyrido[1,2-*a:*3',2'-*d*]imidazole) ..... CA
Hydrazine ..... CA, RT
Hydrogen cyanide ..... RT, CT
Indeno[*1,2,3-cd*]pyrene ..... CA
IQ (2-Amino-3-methylimidazo[4,5-*f*]quinoline) ..... CA
Isoprene ..... CA
Lead ..... CA, CT, RDT
MeA-a-C (2-Amino-3-methyl)-9*H*-pyrido[2,3-*b*]indole) ..... CA
Mercury ..... CA, RDT
Methyl ethyl ketone ..... RT
5-Methylchrysene ..... CA
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) ..... CA
Naphthalene ..... CA, RT
Nickel ..... CA, RT
Nicotine ..... RDT, AD
Nitrobenzene ..... CA, RT, RDT
Nitromethane ..... CA
2-Nitropropane ..... CA
N-Nitrosodiethanolamine (NDELA) ..... CA
N-Nitrosodiethylamine ..... CA
N-Nitrosodimethylamine (NDMA) ..... CA
N-Nitrosomethylethylamine ..... CA
N-Nitrosomorpholine (NMOR) ..... CA
N-Nitrosonornicotine (NNN) ..... CA
N-Nitrosopiperidine (NPIP) ..... CA
N-Nitrosopyrrolidine (NPYR) ..... CA
N-Nitrososarcosine (NSAR) ..... CA
Nornicotine ..... AD
Phenol ..... RT, CT
PhIP (2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine) ..... CA
Polonium-210 ..... CA
Propionaldehyde ..... RT, CT
Propylene oxide ..... CA, RT
Quinoline ..... CA
Selenium ..... RT
Styrene ..... CA
o-Toluidine ..... CA
Toluene ..... RT, RDT
Trp-P-1 (3-Amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole) ..... CA
Trp-P-2 (1-Methyl-3-amino-5*H*-pyrido[4,3-*b*]indole) ..... CA
Uranium-235 ..... CA, RT
Uranium-238 ..... CA, RT
Vinyl acetate ..... CA, RT
Vinyl chloride ..... CA

Aerosol Chemical Characterization:

Reducing the formation of Harmful and Potentially Harmful Constituents (HPHCs) and the users' exposure to them is a promising strategy to reduce risk and is one of the critical parameters of the Philip Morris Products S.A. "heat not burn" approach to developing products with a reduced risk to individual and population harm. In order to evaluate the validity of this approach, it is necessary to characterize and quantify the HPHC profiles of

both conventional combustible cigarettes and THS. Assessment is provided for the reduction in the levels of HPHCs on a per-unit or a per-unit-nicotine basis compared to CC.
Below are the criteria given by Philip Morris S.A. for selection of the 58 HPHCs :

- HPHCs based on ISO methods for aerosol analysis (ISO 3308 -Routine analytical cigarette-smoking machine -- Definitions and standard conditions)
- Priority toxicants in tobacco smoke as listed by regulatory bodies, or proposed by cognizant authorities.
- HPHCs with established biomarkers of exposure for clinical trials.
- Potentially harmful aerosol constituents which are predominately formed below 400°C. These were chosen on the basis of their classification by the International Agency for Research on Cancer (IARC) as Group 1 carcinogens (Carcinogenic to humans) and their abundance in mainstream aerosol.
- Potentially harmful aerosol constituents which are predominately formed above 400°C. These were also chosen on the basis of their Group 1 IARC classification and abundance in mainstream aerosol Product-specific analytes.

The fourth and fifth items on this list are important due to the design constraints for the THS in which tobacco should be heated, but not burnt. In this case, HPHCs are specifically identified which could also serve as indicators that the device actually is burning tobacco – opposite to the intention. Even if the tobacco is not combusted, pyrolysis (thermal degradation) occurs along a wide range of temperatures. Thus, some HPHCs are expected to be part of the aerosol (e.g., formaldehyde, acetaldehyde, acrylamide, ethylene oxide, propylene oxide) when temperatures are below 400°C, and some HPHCs should only be generated in very small amounts, as their formation occurs predominantely at temperatures above 400°C (e.g., 1,3-butadiene, benzo[a]pyrene, dibenz[a,h]anthracene, benz[a]anthracene, pyrene, hydrogen cyanide, isoprene, benzene, toluene, styrene).

List of relevant 58 HPHCs (see Section 5.1.1 in PMI Technical and Scientific Dossier for THS, v 1.0).

PMI List of 58 HPHCs			
HPHC	**CAS***	**HPHC**	**CAS***
Benzo(a)pyrene	50-32-8	Nitric oxide	10102-43-9
Carbon monoxide	630-08-0	N-nitrosoanabasine	1133-64-8
Nicotine	54-11-5	N-nitrosoanatabine	71267-22-6
Tar	N/A	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone	64091-91-4
Total particulate	N/A	N-nitrosonornicotine	15443-55-8

PMI List of 58 HPHCs			
HPHC	**CAS***	**HPHC**	**CAS***
matter (TPM)			
Water	7732-18-5	Nitrogen oxides	10102-44-0
1-aminonaphthalene	134-32-7	Phenol	108-95-2
2-aminonaphthalene	91-59-8	Pyridine	110-86-1
3-aminobiphenyl	2243-47-2	Quinoline	91-22-5
4-aminobiphenyl	92-67-1	Resorcinol	108-46-3
Acetaldehyde	75-07-0	Styrene	100-42-5
Acetone	67-64-1	Toluene	108-88-3
Acrylonitrile	107-13-1	Arsenic	7440-38-2
Acrolein	107-02-8	Cadmium	7440-43-9
Ammonia	7664-41-7	Chromium	7440-47-3
1,3-butadiene	106-99-0	Lead	7439-92-1
Benzene	71-43-2	Mercury	7439-97-6
Butyraldehyde	123-72-8	Nickel	7440-02-0
Catechol	120-80-9	Selenium	7782-49-2
m-cresol	108-39-4	Pyrene	129-00-0
p-cresol	106-44-5	*o*-Toluidine	95-53-4
o-Cresol	95-48-7	Acrylamide	79-06-1
Crotonaldehyde	123-73-9	Acetamide	60-35-5
Formaldehyde	50-00-0	Propylene oxide	75-56-9
Hydrogen cyanide	74-90-8	Ethylene oxide	75-21-8
Hydroquinone	123-31-9	Nitrobenzene	98-95-3
Isoprene	78-79-5	Vinyl chloride	75-01-4
Methyl ethyl ketone	78-93-3	Dibenz(a,h)anthracene	53-70-3
Propionaldehyde	123-38-6	Benz(a)anthracene	56-55-3

- **Choice of Comparator Products**

Characterization of the aerosol created by a potential reduced risk product requires both absolute measurements of HPHCs values and a comparison with conventional cigarettes. For development purposes, PMI currently uses 3R4F reference cigarette as a comparator. 3R4F is a reference cigarette supplied to the industry and other research organizations by the University of Kentucky. The chemical and in-vitro characteristics of the cigarette have been extensively examined and information on the cigarette's composition and physical characteristics are supplied by University of Kentucky.

- **Comparison of the THS with 3R4F Reference Cigarette for the PMI list of 58 HPHCs**
  The comparison of the yields of mainstream aerosol HPHCs of THS Regular and THS Menthol has been performed against the yields of the 3R4F Reference Cigarette. The results are presented on a 'per stick' basis and on a 'per mg nicotine' basis (see Section 5.1.1.2 in PMI Technical and Scientific Dossier for THS, v 1.0, v 1.0; Tables 2 and 3, and Figures 7 and 8).
  In both cases, the results demonstrate that THS provides a substantial reduction in the levels of HPHCs compared to the combustible cigarette.

- **Summary of Laboratory Analysis**
  The THS substantially reduces the formation of HPHCs available to the smoker and to the environment, which is demonstrated by the reduced levels of the relevant 58 harmful and potentially harmful constituents' profile when compared with a 3R4F reference cigarette, both on a mass per Tobacco Stick/cigarette or as mass per mg of nicotine. These results indicate that the THS" has the potential to drastically reduce exposure to HPHCs when used by adult consumers. Benzo[a]pyrene is present at approximately or less than 1% levels of that of the smoke of a reference cigarette. Benzo[a]pyrene is mentioned expressly here, as it has been investigated in the paper by Boobis et al (2013) to satisfy criteria for Tier 1 investigation for risk benefit assessment.

  The majority of the metals monitored were below the limit of quantification, both for the reference cigarette as well as for the THS.

In conclusion:

- THS produces levels of harmful and potentially harmful constituents, which are substantially below the conventional cigarette comparator, the 3R4F reference cigarette. The majority of the constituents are reduced by more than 80%. According to Boobis et al (2013) benzo[a]pyrene (determined at 1% or less than that of conventional cigarettes) satisfies the criteria of Tier 1 (stopping risk-benefit assessment right here and now).

- These data demonstrate that THS has the potential to reduce the users' exposure to HPHCs compared to continuation of smoking of conventional cigarettes.

➢ ***Expert Conclusion from Characterization Assessment:***

The THS produces and emits levels of harmful and potentially harmful substances, which are substantially below the standard cigarette comparator. Whereas 46 out of 58 constituents are reduced by more than 80%, the majority is found at a remaining range from 20% to zero% (also depending on analytical limitations). These data show that the THS has the potential to reduce exposure to harmful and potentially harmful substances.

Requirement No. 1: (setting up an accepted listing of harmful and potentially harmful substances for comparison): ***fulfilled***
Comparison of standard cigarette versus "THS has yielded drastic reduction of those substances, notwithstanding nicotine, which is retained at "normal" levels.
Requirement No.2: (nicotine delivery equivalency of the THS is determined): ***fulfilled***
Nicotine is contained in "Tobacco heat sticks" at 70% or more of the standard cigarette
Requirement No. 3: (determination of the harmful constituents exiting cigarettes and becoming bioavailable from the resulting aerosol and tobacco smoke): ***fulfilled***

2.3.2 Non-clinical Assessment

In the case of a potential novel tobacco product made to reduce risk from smoking, the first investigative step would be the analysis of harmful and potentially harmful constituents, as performed and discussed above. This would be followed by in vitro and in vivo non-clinical toxicity and genetic toxicology tests in bacterial and mammalian systems and animals. In these tests, extracts or fractions of the THS aerosol would be compared to standard conventional products: step 2 of investigation
(See Section 5.4 in PMI Technical and Scientific Dossier for THS, v 1.0).

Philip Morris Assessment:

Following determination and analysis of potentially harmful constituents in the aerosol of the THS versus CC (Requirements 1 – 3), aerosol fractions (containing HPHCs) were tested in a variety of in vitro and in vivo systems/animals. Cytotoxicity

was substantially reduced, and genotoxicity yielded negative Ames test and somewhat positive, but with lower potency positive mouse lymphoma assay. “Nose-only” sub-chronic exposure of rats to mainstream THS at three nicotine levels yielded lower respiratory tract toxicity compared to conventional cigarettes, and histomorphological changes without signs of tumourogenicity after 90 days of exposure.

Conclusion:
Non-clinical investigations of the the THS aerosol versus CC smoke demonstrated lower toxicity, and no relevant indication of cytotoxicity, genotoxicity or tumourogenicity.

The non-clinical assessment of the THS included the evaluation of aerosol chemistry, cytotoxicity (Neutral Red Uptake-NRU) and genotoxicity (Ames and Mouse Lymphoma Assay-MLA) in vitro and in vivo sub-chronic toxicity (90-day inhalation study) in comparison with 3R4F.

In detail

- **Cytotoxicity**
  For each in vitro study, the test system was exposed to different concentrations of both Total Particulate Matter (TPM) and Gas Vapor Phase (GVP).
  Neutral Red Uptake assay (NRU)
  Cytotoxicity was determined in the NRU assay. The study quality standards followed the OECD GLP principles. The reciprocal in vitro cytotoxicity (1/EC50) of TPM and GVP mainstream aerosol fractions generated from THS was reported on a per stick basis and a per nicotine basis, and compared with those from the 3R4F.
  Conclusion:
  The cytotoxicity of the aerosol fractions from the THS was substantially reduced when compared with that of the 3R4F smoke, as assessed in this NRU assay.

- **Genotoxicity**
  Bacterial Cell Reverse Mutation Assay (Ames Assay)

  Whereas for the reference cigarette 3R4F reproducible mutagenic responses were observed in bacterial strains TA98, TA100 and TA1537 in the presence of S9, the TPM from THS regular and THS menthol were not found to be mutagenic - in the presence or absence of S9. . In contrast, no biologically relevant mutagenicity was found with TA102 or TA1535 (data not shown).

  Conclusion:
  Under the assay conditions used, TPM from THS 2.2 regular and THS 2.2 menthol

did not show any mutagenic activity in the different strains tested irrespective of the presence or absence of S9.

Mammalian Cell Gene Mutation Assay (Mouse Lymphoma Assay (MLA))

Cells were exposed to TPM and GVP from both the reference cigarette 3R4F and from THS for 4 hours in the absence and presence of S9. All fractions showed mutagenic potential at variance between condition and test and reference chosen. Activity in the MLA, however, was lower by 10 to 30 fold in the THF compared to the reference cigarette both for TPM and for GVP.

Conclusion:

In conclusion, although the TPM and GVP aerosol fractions derived from THS 2.2 regular and THS 2.2 menthol displayed a mutagenic response in the MLA, their mutagenic potency *in vitro* was markedly lower compared to the corresponding fractions derived from 3R4F.

Conclusion:
Under the assay conditions used for the Ames test, TPM from THS regular and THS menthol did not show any mutagenic activity in different strains tested irrespective of the presence or absence of S9. Activity in the MLA was lower by 10 to 30 fold in the THF compared to the reference cigarette both for TPM and for GVP.

- **Subchronic Toxicity**
  90-day Inhalation Study
  Sprague-Dawley rats were exposed nose-only to mainstream aerosol from THS at three target nicotine concentrations (15, 23, and 50 µg/l) or mainstream smoke from 3R4F at three target nicotine concentrations (8, 15, and 23 µg/l) or filtered and conditioned air (sham exposure group). Measurement of aerosol constituents indicated lowered content of formaldehyde, acrolein, acetaldehyde, and carbon monoxide in the diluted aerosol from THS as compared to diluted smoke of 3R4F. The aerosol was taken up reproducibly by the animals as indicated by the measured carboxyhemoglobin (COHb), urinary nicotine metabolites, and urinary metabolites of selected aerosol constituents. While nicotine uptake was slightly higher for THS exposed animals than 3R4F exposed animals at corresponding target nicotine concentrations, COHb and the metabolites of selected aerosol constituents were substantially lower in the THS exposed animals as compared to the 3R4F exposed

animals, in line with the reduced concentrations of the corresponding aerosol constituents produced by THS as compared to 3R4F.
There were no differences in mortality, ocular findings, and gross pathology between THS- and 3R4F-exposed groups. There were no remarkable treatment-related in-life observations with the exception of a few incidences (no more than two animals per group per gender at each occurrence) of mild to moderate tremor occurring infrequently in rats exposed to high THS concentration. Aerosol-related histopathological findings in the respiratory tract included epithelial cell hyperplasia, squamous metaplasia, atrophy, and accumulation of pigmented alveolar macrophages and were also significantly reduced in THS, when compared to groups exposed to 3R4F. Accumulation of immune cells and pro-inflammatory and chemotactic cytokines in bronchioalveolar lavage fluid were also lower in THS as compared to 3R4F exposed groups, which indicates a reduction of lung inflammation in animals exposed to THS.
Gene expression measurements were performed in the nasal respiratory epithelium and lung tissue of all study groups and differential gene expression levels were derived from comparison of each 3R4F and THS exposure group to sham exposed animals. Both nasal respiratory epithelium and lung tissue exhibited a dose-dependent increase in inflammation, cell stress, cell proliferation, DNA damage and cell death network perturbation in 3R4F smoke exposed animals. In contrast, THS aerosol only induced a slight or no-significant perturbation of the cell stress network in the lung and the xenobiotic metabolism network in the nasal respiratory epithelium at high dose.

Conclusion:
The mainstream aerosol from THS shows in general a lower biological activity when compared to mainstream smoke from 3R4F. Systemic toxicity parameters responsive to 3R4F are lower in the THS groups. Histopathological analysis performed on the respiratory tract of THS exposed rats reveals reduced histomorphological changes when compared to 3R4F exposed rats. Inflammatory effects observed in the lungs are significantly reduced in the THS exposed rats. Systems Toxicology-based analysis of the gene expression in both nasal respiratory epithelium and lung tissue shows that biological mechanisms perturbed by smoke in 3R4F exposed rats are much less perturbed in THS aerosol exposed rats, even at the highest dose.

- ***Expert Conclusion from Non-clinical Assessment***

The results of non-clinical assessment (See Section 5.4 in PMI Technical and Scientific Dossier for THS, v 1.0) demonstrate that toxicity of THS is substantially reduced when compared to the 3R4F reference cigarette. This was evidenced by reductions in the levels of HPHC, markers for genotoxicity and cytotoxicity, as well as reduced sub-chronic inhalation toxicity.

Results from the overall non-clinical assessment program:

- confirm the potential of the THS to reduce risk;
- support the reduced risk potential of THS, indicating that a risk profile similar to smoking cessation is possible
- indicate, but do not establish, that by switching from CC to THS, smokers have the potential to reduce their exposure to HPHCs.

Characterization and Non-clinical Assessment: support for clinical investigations

Based on information of the product design and operating principles and the characterization and measurement of smoke and its components, the non-clinical studies and their results performed allow the conclusion that compared to conventional/reference cigarettes toxicity should be reduced overall and in many details studied. Especially from the subchronic inhalation study and genotoxicty tests it is justified (and has been used in this way by Philip Morris Products S.A.) to initiate clinical trials (under full GCP coverage). Such results have been presented to ethical review committees who also concluded that clinical investigations could be performed (for their performance and results see below).

Requirement no. 6: (non-clinical assessment presented): ***fulfilled***

Non-clinical assessment demonstrates that toxicity of the THS is reduced when compared to the 3R4F reference cigarette.

2.3.3 **Clinical Assessment**

In the case of a tobacco product with the potential to reduce risk, the first step would be the analysis of harmful and potentially harmful constituents as presented above. The second step would be vitro toxicity and genetic toxicology tests in bacterial and mammalian systems. Taken together, these results support ethical opportunity for

performing relevant clinical studies, which are presented here: step three (See Section 5.5 in PMI Technical and Scientific Dossier for THS, v 1.0).

Philip Morris Assessment:

Single and repeat use of tobacco heating system for pharmacokinetic/pharmacodynamics investigation of nicotine absorption parameters, and sophisticated clinical settings to investigate nicotine cmax and AUC showed that the profile of Tobacco Heating System was close to that of conventional smoking, and resembled results obtained non-clinically. Sophisticated GCP compliant clinical studies showed similar mean nicotine concentration-time curves, and reduction in the level of Biomarkers of Exposure and other biomarkers – comparing THS with CC arms.

- **Pharmacokinetics / Pharmacodynamics**
  In the PK/PD studies, THS nicotine pharmacokinetics is compared with CC and nicotine replacement therapy (NRT). Rate and extent of nicotine absorbed during single stick use of THS are measured and compared to CC and to NRT. These randomized cross-over, relative bioavailability, pharmacokinetic studies are part of the initial and basic characterization of THS after single use. They provide evidence following THS single use concerning the rate and the amount of nicotine absorbed and the suppression of urge to smoke in people who switch from CC. The short-term PK/PD studies provide initial safety data (e.g., data on vital signs, clinical biochemistry, hematology, spirometry, electrocardiogram, adverse events). These studies have been conducted in the EU, Japan, and the U.S.

- **Reduced Exposure (Confined)**
  The Reduced Exposure studies investigate reduction of biomarkers of exposure to HPHCs following switching from CC to THS in an optimal, clinical laboratory setting. The study staff monitors product consumption, and participating adult smokers are controlled for product compliance in a confinement setting. The adult smokers used THS without restriction (ad libitum), but dual use of CC and THS was not allowed. These comparative 3-arm, randomized parallel study designs included THS, CC, and smoking abstinence (SA) arms. Exposure to nicotine, to various HPHCs, as well as subjective effects (craving, withdrawal symptoms, and product satisfaction) were assessed over a period of confinement of one week. These studies have been conducted in Europe and Japan.

- **Reduced Exposure (Confined and Ambulatory)**

Reduced Exposure studies have two distinct periods with a confinement period followed by an ambulatory period. These 3-arm, randomized, parallel study designs include THS, CC and SA arms. The confinement period of these studies is similar to the short-term Reduced Exposure studies, in that subjects (current CC users) are confined for a week. In the ambulatory period of the study, subjects are followed over a three months period in an ambulatory setting including (three) monthly ambulatory visits. In this study, biomarkers of exposure to HPHCs, to nicotine, and biological and functional risk endpoints are measured.
The ambulatory period increases the understanding of product use and acceptance, as well as the achieved exposure reduction by THS use, either exclusively consumed or in combination with CC.
These studies have been conducted in Japan and the U.S., and the results are in the reporting phase.

- **ZRHR PK-01-EU Clinical Study Summary**
  The study was conducted in Northern Ireland from November to December 2013. Principles as defined in International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and in the Declaration of Helsinki, as well as additional applicable national regulations were followed. The study protocol was assessed and approved by an Institutional Ethics Committee (IEC), and the subjects received complete information about the study and signed an informed consent form (ICF).

  Summary of Results:

  Primary Endpoint

  The overall shape of the mean nicotine concentration-time curves was similar for THS and CC, although the concentration of nicotine appeared to be lower throughout the 24 hours following single use for THS. The plasma concentration versus time profiles following single use of THS and CC were characterized by a rapid absorption phase, with Cmax reached at approximately the same time post-product use (6 minutes). The full summary of results is provided in Appendix 7 in PMI Technical and Scientific Dossier for THS, v 1.0)

In detail

- **ZRHR REXC-03-EU Clinical Study**

The study was conducted in Poland from June to September 2013. Principles as defined in the International Conference on Harmonization (ICH) Good Clinical Practice (GCP), and in the Declaration of Helsinki as well as additional applicable national regulations were followed. The study protocol was assessed and approved by an “Institutional

Review Board" (IRB), and the subjects received complete information about the study and signed an informed consent form (ICF).

Summary of Results

Primary Endpoints:

The primary endpoints for this study were assessed on Day 5 (evening) for the biomarkers of exposure (BoExp) COHb blood (% saturation of hemoglobin); MHBMA urinary concentration adjusted for creatinine (pg/mg creat); 3-HPMA urinary concentration adjusted for creatinine (ng/mg creat); and S-PMA urinary concentration adjusted for creatinine (pg/mg creat). Reductions were seen in the level of each BoExp assessed as a primary endpoint for the THS arm compared to the CC arm, with reductions of approximately 77% in COHb (whole blood), 92% in MHBMA urinary concentration adjusted for creatinine, 58% in 3-HPMA urinary concentration adjusted for creatinine, and 94% in S-PMA urinary concentration adjusted for creatinine.

These results were consistent with the study hypothesis and evaluation criteria in demonstrating a > 50% reduction in biomarkers. COHb, MHBMA, 3 HPMA, and S-PMA in the THS arm compared to the CC arm. The full summary of results is provided in Appendix 9 in PMI Technical and Scientific Dossier for THS, v 1.0.

- ***Expert Conclusions from Clinical Investigations and Biomarker Experiments***

Based on detailed description of the system and assessment of substances released from the tobacco heating system, and on detailed non-clinical investigations, clinical studies have been performed comparing conventional cigarettes and the tobacco heating system and smoking abstinence.

The focus of clinical investigations is to view aspects of nicotine behaviour comparing the tobacco heating system with other forms of smoking. This is due to the well-reasoned understanding that sufficient provision of nicotine in a "cigarette-like environment" can serve the purpose to give up smoking of conventional cigarettes. This has been done successfully.

In addition numerous studies/measurements show that the exposure to harmful and potentially harmful substances generated and provided for inhalation is lowered) quite drastically (although not consistent across the board – as is to be expected). Substance measurements, kinetic investigations, bioavailability, excretion and numerous biomarkers are in support of tobacco heating system being less dangerous and risky compared to

conventional cigarettes – and on a theoretical linear scale possibly almost to the point of cessation of smoking.

In addition there were no new safety signals arising from the use of tobacco heating system.

Requirement No. 2: (nicotine delivery equivalency): supportive evidence: ***fulfilled***

Requirement No. 4: (relationship of biomarkers of exposure to harmful substances): ***fulfilled***

Requirement No. 5: (significant reduction of exposure biomarkers from "Tobacco heat stick" use): ***fulfilled***

Requirement No 7: (relevant evidence from short and longer term clinical studies under GCP conditions): ***fulfilled***

2.4 State of the Art Approach to Performing Risk / Benefit Assessment

The totality of evidence generated is holisticly assessed as part of the risk / benefit analysis

Requirement No. 1: (setting up an accepted listing of harmful and potentially harmful substances for comparison): ***fulfilled***

Comparison of CC versus "THS has yielded drastic reduction of those substances, notwithstanding nicotine, which is retained at "normal" levels.

Requirement No.2: (nicotine delivery equivalency of the THS is determined): ***fulfilled;*** supportive evidence: ***fulfilled***
Nicotine delivered by the THS HeatStick is at 70% or more of the CC

Requirement No. 3: (measurement of relevant substances exiting cigarettes and becoming bioavailable from the resulting aerosol and tobacco smoke): ***fulfilled***

Requirement No. 4: (relevancy of biomarkers of exposure to HPHCs constituents): ***fulfilled***

Requirement No. 5: (significant reduction of biomarkers of exposure after the THS use): ***fulfilled***

Requirement no. 6: Evidence from toxicity testing presented and assessed): ***fulfilled***

Non-clinical assessment demonstrates that toxicity of the THS is reduced when compared to the 3R4F reference cigarette.

Requirement No 7: (relevant evidence from short and longer term clinical studies under GCP conditions): ***fulfilled***

Expert Conclusion: Data and results provided in the PMI Technical and Scientific Dossier for THS, v 1.0 do fulfill the requirements developed and set out in the chapter on "State of the art approach to perform risk/benefit assessment".

- ***Expert Conclusions on the Heated Tobacco Product***

Rationale for developing THS product

- **Smoking tobacco products** constitutes an important risk factor for various and many diseases including early death. Smoking can both be prevented and avoided. Once started and accustomed, personal psychological status and stamina will influence chances to quit. From experience we know that many smokers remain unable to quit.

- **Smokers and those wanting to quit**, but remaining unable to do so, would constitute important populations world wide amenable to less than perfect options. Such have been introduced over time. They span from nicotine chewing gum or applying nicotine patches to the skin (satisfying the quest for smoking without involving the burning of tobacco), to providing courses of varenicline or cytisine tablets over limited periods of time (thus diminishing the craving developed under smoking tobacco (and where nicotine is held mainly responsible); these are established medicinal products to be used under medical supervision. Also homeopathy and Chinese traditional medicine have been employed – partially successful, but often not. Relatedly, psychotherapy has been used case by case. In many scenarios appearance of serious untoward cardiovascular reactions to smoking tobacco products, e.g. smoker's leg, helped discontinuation of smoking tobacco. The impact of public health initiatives (including drastic labelling and limiting the availability of tobacco products) has been discussed elsewhere.

- **Public health initiatives** have impacted on the number of young people who start to smoke tobacco and have increased the starting age. Nevertheless numerous humans become addicted to smoking tobacco products and are prone to suffer –later- from the identified well-known adverse reactions – causing immense cost to public health as well as personal disease. It is for these populations that new approaches towards improvement of personal health are needed and are being developed. This is shown by recent European legislative changes, which now include "smokeless tobacco products" and "novel tobacco products" (and set forth requirements and conditions for their marketing). It is in this region that Philip Morris has developed a product including "tobacco sheets", which are subject to electric heating, thus providing (standardized "normal") amounts of nicotine in the inhalant from employing lower temperatures than those attained from actually burning tobacco, various recognized and measurable (potentially) dangerous substances or molecules inhaled from smoking (burning) tobacco are drastically reduced.

- **The Philip Morris Products S.A. tobacco product**, the Tobacco Heating System which electrically heats tobacco falls under Article 19 of Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014. The use of this product as compared to conventional cigarette reduces smokers' exposure to harmful and potentially harmful consituents while providing smokers' satisfaction and delivering nicotine in a way similar to conventional cigarettes.

- As an expert in this field, I have come to these conclusions on the risk-benefit of THS, however, the national competent authority will assess the sufficiency of Philip Morris' scientific results as presented in the PMI Technical and Scientific Dossier for THS, v 1.0, and the scientific value of this expertise independently. This report comes to the conclusion that based on the totality of data from different areas of research the THS has a distinctly different health profile as compared to CC. The "Guidance document for health assessment" published by the German BfR in 2010 provides a useful framework for the risk/benefit analysis. In this framework the "Gold standard" of lowest possible risk and highest possible benefit are non-smoking and long-term cessation of smoking was taken into account in this review. This implies that the use of THS continues building a risk higher than that from non-smoking. Compared to cessation of smoking, THS is assumed to approach.the same **risk/benefit**, which remains to be proven. If THS leads to reduction of **risk** equal to smoking cessation (per ex-smoker), and at the same time offers same or better frequencies in permanently quitting conventional cigarettes (per ex-smoker population), THS might even show a better risk/**benefit** compared to cessation, which has a poor long-term success rate. The absolute proof may be achieved with long term epidemiological studies and sufficient prevalence of use of the product over time. Other endpoints including biomarkers need to be assessed further for their suitability to replace such long term studies.

2.5 **Overall Conclusion**

- Smoking is a cause of severe diseases and is addictive.
- Once started, it is highly recommended to quit smoking (as early as possible).
- If quitting is not an option, any support available should be approached.
- Tobacco heating system (THS) could be an alternative to smoking for those adult smokers not willing/able to quit. "Tobacco heating system" has been investigated by Philip Morris Products S.A. according to a recognized set of state of the art requirements needed to be fulfilled for performing proper risk / benefit assessment.
- Risk / benefit assessment has been performed by independent expert.
- Risk / benefit assessment leads to the conclusion that benefit of exclusive use of THS prevails over the risk in the context of broad use of conventional combustible cigarettes and the expert recommends the use of the THS as a possible alternative and support to refrain from smoking conventional cigarettes.
- The THS does not add any known or new safety issue.

- The THS generates harmful and potentially harmful constituents at levels very much reduced compared to conventional cigarettes; therefore, the use of the THS demonstrates the effects which are close and parallel those observed upon smoking cessation.
- It remains to be shown that by using THS a larger proportion of those smoking conventional cigarettes will remin "off" long-term than those quitting. Determination of such long-term benefits may be assessed after product marketing and collection of additional epidemiological data.

Berlin, 9 May 2016

(Signature)

Prof. Dr. Rolf Bass, FFPM (Hon)

Acknowledgement:
I would like to honour my late colleague, Dr. Klaus Olejniczak, for his early involvement in this work until he became terminally ill and could no longer contribute.

His input is retained, and he would have loved to continue this work.

He has always been a perfect mate, in work and as a friend, and I shall not forget him.

Disclaimer:
The expertise provided is based on the PMI Technical and Scientific Dossier for THS, v 1.0 as provided. No attempt has been undertaken to re-check the dossier content against the original study reports nor their compliance with international standards.

3 CV OF EXPERT FOR RISK-BENEFIT ASSESSMENT

[redacted]

Rolf Bass is German and was born in Berlin in 1941. He is married and has three children.

Rolf Bass qualified as physician in 1967 and holds a medical degree (Dr. med. – magna cum laude) from the Free University of Berlin. Following pre-doctoral work in 1966/67 with Prof. Diether Neubert at the Free University of Berlin – Dept. of Pharmacology, and postdoctoral work for three years at The Johns Hopkins University, School of Medicine – Dept. of Physiological Chemistry with Prof. Albert L. Lehninger in Baltimore, Maryland, he did research in pharmacology, prenatal toxicology and clinical pharmacology at the Dept. of Toxicology and Prenatal Pharmacology of the Free University with Prof. Diether Neubert, where he was appointed Adjunct Professor (Ausserplanmäßiger Professor) in 1984. In 1998 Rolf Bass was awarded an honorary degree (FFPM hon) from the Faculty of Pharmaceutical Medicine of the three Royal Colleges of Medicine (Edinburgh, Glasgow and London). In 2007 he was awarded with the "Walter-Cyran-Medaille" of the German Society for Drug Regulatory Affairs (DGRA), and he held the "Annual-Award-Lecture" at the 2007 Annual Meeting of the European Teratology Society Meeting (ETS). In 2009 he received the "Distinguished Career Award" of the DIA.

Rolf Bass in 1979 joined the German Health Authority (BGA) as Head of the newly created Pre-Clinical Department at its Drug Institute in Berlin. He became Chairman of CPMP´s Safety Working Party in 1984, where he was in charge of the pre-clinical ICH program; he created the tripartite ICH guideline on "Testing for Reproductive Toxicity", and was responsible for the development and implementation of a full set of European toxicological guidelines.

From 1995 to 2000 he was Head of the Human Medicines Unit at the EMEA (now EMA) in London. He was responsible for developing and running the EMEA regulatory business and procedures concerning medicines for human use including herbal medicinal products: pre-approval aspects (scientific advice, regulatory affairs, CPMP Secretariat, European Commission- and ICH-liaison), post-marketing issues (pharmacovigilance, variations and extensions, and renewals), external contacts (the press, trade associations, health professionals and patient associations), and supporting designated Central and Eastern European Countries Drug Regulatory Authorities (CADREAC) towards accession of their countries to the European Union.

Following his return to Germany in 2000 Rolf Bass was given the task of managing the "Nachzulassung" (re-registration) of all "old" medicines to be scrutinised for their adherence to EU-standards (prompted by intervention of the European Commission). In August 2000 he was appointed member to the CPMP (now CHMP), and set up the new Department for European and International Business of the Federal Institute for Drugs and Medical Devices (BfArM), first in Berlin and then in Bonn. He officially retired from this position at the BfArM mid-2006.

Rolf Bass was chosen by the Polish Government to lead two EU-"Twinning projects" as Resident Twinning Advisor, whereby the Polish drug regulatory authorities (URPL: for marketing authorization and pharmacovigilance, and GIF: for GMP inspections) attached to the Ministry of Health were supported and trained to achieve and maintain EU-Standards (the "acquis communautaire"). From 2003 to 2006 the German (Federal and Laender) Regulatory/Inspection Authorities and the central Polish Authorities (URPL and GIF) - both in Warsaw – and the Polish Wojewods Inspectorates have been working together to develop and strengthen the Polish institutions in the areas of inspection, namely GMP (focusing on GMP inspections), the implementation of QA system (throughout), market surveillance, sampling and testing, rapid alerts, the distribution chain, and advertising), and GCP (focusing on setting up the expertise), regulatory and scientific handling and assessment of marketing authorization dossiers (medicines for human use), update of marketing authorizations obtained previous to joining the EU, and pharmacovigilance.

He was appointed Visiting Professor for Pharmaceutical Medicine at the University of Basel, Switzerland, in December 2007 (serving until 2014). He was in charge of the development of postgraduate Master curricula for Regulatory Affairs within Pharmaceutical Medicine (imi PharmaTrain programme (PPP) between EFPIA and EurCom. He has advised the Kosovo Department of Health (Kosovo Medicines Agency) striving to achieve EU standards (2009/12). He has also advised the Government of Georgia for their future medicines market and control.

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