Methodology for Monitoring Adverse Event Reports for Potential Modified Risk Tobacco Products: Experience at Philip Morris International

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Introduction and Objectives

Philip Morris International (PMI) is developing potential Modified Risk Tobacco Products (MRTP) / Reduced Risk Products (RRPs) that present, are likely to present, or have the potential to present less risk of harm to adult smokers who switch to these products versus continued smoking.

PMI has a range of RRPs in various stages of development, scientific assessment and commercialization, such as heat-not-burn tobacco products and nicotine-containing products (e-cigarettes). For example, the Tobacco Heating System (THS), marketed as IQOS, is currently available in more than 30 countries outside the USA. This novel product does not burn tobacco, producing far lower quantities of harmful and potentially harmful constituents than found in cigarette smoke. As quoted from a recent publication, "*Nicotine, though not benign, is not directly responsible for the tobacco-related cancer, lung disease and heart disease. […] Other chemical compounds in tobacco, and in the smoke created by combustion are primarily to blame for such health harms*". [1]

PMI implemented an RRP assessment program (**Figure 1**) in which product safety surveillance is a key component.

Requirements for (post-market) safety data collection and reporting have emerged in Europe (Tobacco Product Directive, applicable since 2016) and in USA (FDA Draft Guidance on MRTP Applications 2012). [2,3]

Consistent with the FDA Draft Guidance on MRTP Applications, PMI has implemented a system for monitoring Adverse Events (AEs) aimed at detecting safety signals for any potentially new or different health risks associated with the use of RRPs.

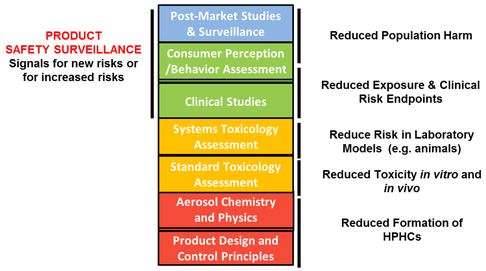
Objective of this presentation is to

- describe the product safety surveillance system in operation at PMI (Methods section),
- present a summary of pre-market safety data from THS completed studies and post-market safety surveillance data following the first two years of IQOS commercialization outside the US (Results section).

Methods

As part of the RRP assessment program (**Figure 1**), PMI conducts pre- and post-market safety assessments of RRPs using a number of processes according to the source of the safety reports. In randomized clinical studies, AEs are actively monitored as per international Good Clinical Practices[1]. In-study passive safety surveillance methods, derived from pharmacovigilance, are applied in consumer/behavioral studies. In the latter, the users spontaneously report health problems which they consider to be associated with product use. A similar post-market passive safety surveillance method is used in markets where PMI already commercializes RRPs. The overall goal of the product safety surveillance is to identify any new or increased risks associated with THS use and to communicate the RRP safety profile (e.g., Investigator's brochure, summary of product information, timely communication to call centers and available upon inquiry from a consumer).

Safety data is analyzed at the study level and is subject to a study-specific safety report. Post-market safety data is iteratively analyzed during the year. The findings are summarized in an annual safety update report.



[1]ICH E2A and ICH E6 Guidelines

Figure 1. Place of Safety Surveillance in PMI RRP Assessment Program.

In the absence of tobacco-specific standards, PMI proactively implemented a Quality Management System for RRP safety surveillance derived from well-established clinical & medical research and medicinal products standards with a set of customized standard operating procedures covering key safety operations (**Figure 2**). This approach allows a systematic way for collecting, entering data in a dedicated safety database, analyzing individual cases, performing regular safety signal management and reporting individual and aggregated safety data. Post-market safety data include AEs and Special Medical Conditions (SMC), such as pediatric and pregnancy cases.

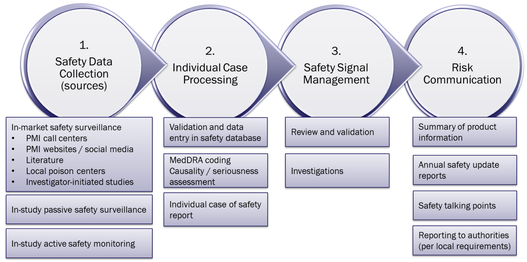


Figure 2. PMI Quality Management System for RRP Safety Surveillance.

Results

As an illustrative example of RRP safety surveillance outcomes, safety findings for THS are presented.

Solicited AEs from THS Clinical Studies (Jul-2013 to Oct-2014)

A total of 939 subjects were enrolled in 8 randomized clinical studies (4 single-use, crossover studies and 4 parallel group 1-week and 3-month studies) assessing THS (**Table 1**).

AEs were actively monitored throughout the studies.

Cross-over studies: 57 (22%) subjects had a total of 85 AEs, with 22 THS-related AEs in 19 subjects (nausea and vomiting, presyncope, dizziness, dysphoria, headache, pallor and abnormal hepatic function).

Parallel group studies: THS, Smoking Abstinence, continuing smoking Cigarettes: 278 (42%) of the randomized subjects experienced 526 AEs (all non-serious), with similar incidence rates in the 3 arms. A total of 266 AEs (8.6% assessed as THS-related) were reported in 44% of subjects randomized to THS. Overall, the incidence of the most frequent THS-related AEs was ≤4% for cough and ≤3% for abnormal spirometry, taking into account non-related corresponding AEs in the determination of these incidences.

Overall, 1/3 of subjects randomized to THS arm experienced one or more AEs temporarily associated with THS use, and 7.2% of subjects with medically-confirmed THS-related AEs.

Unsolicited AEs from THS Consumer Studies and from Perception and Behavior Assessment Studies (May-2014 to Jan-2016)

A total of 5948 participants (**Table 1**) were using THS in five 2- to 4-week consumer research studies (outside US) and in one 6-week actual use study (US). An in-study passive safety surveillance technique was applied, by collecting AEs spontaneously reported by participants.

5.7% of participants spontaneously reported AEs they think were THS-related (implied causality).

Headache was the most frequent AE (10% of all reported AEs, reporting rate 1%).

Unsolicited AEs from THS Post-Market Safety Surveillance (Period Nov-2014 to Dec-2016)

A total of 2717 unsolicited AEs and SMCs (AE MedDRA[2] preferred terms (PTs)) (1211 case reports) associated with THS were reported by consumers and by Health Care Professionals (HCP) (**Table 2**).

The most frequent AE (**Table 3**) was accidental ingestion of THS tobacco sticks by a child, with a reporting rate similar to published data for cigarettes/e-cigarettes (**Table 4**), with 20% of cases of accidental ingestion of THS tobacco sticks also reporting symptoms compatible with mild to moderate nicotine intoxication (with vomiting the most frequent symptom). Eight of these cases of accidental ingestion of THS tobacco sticks by a child were assessed as serious (required hospitalization for surveillance).

[2]MedDRA. Medical Dictionary for Regulatory Activities

Table 1. THS Adverse Events from Completed Human Studies.

Source of AEs	Solicited AEs	Unsolicited AEs
Type of Studies	Clinical studies (N=8)	Consumers studies (N=8) Behavior study (N=1)
Exposure to THS		
• Subjects (N)	566 (randomized)	5948
• Estimated subjects-days (N)	≈ 15268	≈ 134120
Number of Subjects with AEs	197 (34.8%)	340 (5.7%)
• With AEs related to THS	41 (7.2%)	340 (5.7%)
Total Number of AEs	351	653
• THS-related	45	653
• SAEs	-	24 (3.7% of all AEs)
• Fatal Cases	-	-

Table 2. THS Post-market Passive Safety Surveillance.

Passive Surveillance	Cumulative 31-Dec-2016
Source	Safety Update Report 2016
Estimated Exposure (millions IQOS HeatSticks)	5700
Safety cases (N)	1211
AEs and SMCs (n)	2717
• Including SAEs	41 (1.5% of all AEs)
• Fatal cases	-
AE Reporting Rate (AEs / 1 million IQOS HeatSticks)	0.48

Table 3. THS Post-market Most Frequent AEs.

5% or more of all AEs	n (%)
Accidental exposure by child	328 (12.1)
Device issue	240 (8.8)
Burning sensation / thermal burn	163 (6.0)

Table 4. Accidental Ingestion by Children – THS versus Cigarettes / e-Cigarettes.

	PMI Safety Surveillance	Literature
Source	IQOS safety database	Kamboj, et al 2016 [4] Cigarettes, e-cigarettes (National Poison Data System)
Period	Nov-2014 to Dec-2016	Jan-2012 to Apr-2015
Countries	Europe, Japan	USA
Cases (N)	328	29141
Cases with AEs (%)	20%	27.5%
SAE cases		
• Fatal	-	1 (e-cigarette)
• Life threatening	-	15
• Other cases	8	154
Risk (cases / million users)	94 (for 2016)	219 (average per year)
• Estimated denominator	3.5 million kits sold, assuming 1 kit = 1 IQOS consumer	40 million US smokers [PATH, NSDUH]

Discussion

Safety is an important building block for the assessment of RRPs and for demonstrating their potential for reducing the risk of tobacco-related diseases associated with cigarette smoking.

Leveraging methods and techniques established for medicinal products to RRPs is feasible.

Post-market safety surveillance is suitable for identifying acute/short-term AEs and risks associated with RRP use, while dedicated studies are necessary to assess the impact on long-term tobacco-related diseases.

The majority of RRP AEs are spontaneously reported by consumers, and not by HCPs, which may pose coding difficulties when translating verbatim local lay language into scientific terms.

The causality assessment remains a significant challenge for most of the safety cases temporarily associated with RRPs, necessitating the differentiation of health problems causally linked to the use of/exposure to an RRP from residual and delayed effects related to smoking history, and from RRP use in combination with one (dual use) or more (poly-use) other tobacco products/nicotine-containing products.

Conclusions

Leveraging standards and methods for safety monitoring and surveillance established for medicinal products to the safety assessment of tobacco products is feasible and has been successfully implemented at PMI. This allows PMI to identify and communicate any risks associated with RRPs.

References

[1] Gottlieb S. & Zeller M. (2017). A nicotine-focused framework for public health. NEJM; doi:10.1056/NEJMp1707409

[2] The European Parliament and the Council 2014. Tobacco Product Directive 2014/40/EU

[3] FDA 2012. Draft Guidance on Modified Risk Tobacco Product Applications

[4] Kamboj A. et al. Pediatric Exposure to E-Cigarettes, Nicotine, and Tobacco Products in the United States. Pediatrics. 2016;137(6)

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Declaration of Interest

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