Module 8 : Postmarket Information

8.2 Adverse Experience Reports

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1. SAFETY DATA REVIEW

The *IQOS* System[1], which corresponds to the Authorized *IQOS* System, was commercialized in countries outside the U.S. for the first time in November 2014 while the *IQOS* 3 System was introduced only in November 2018, four years later. Up to the end of November 2019, the Authorized *IQOS* System has been commercialized in 52 countries and the *IQOS* 3 System in 50 countries. With the exception of Mexico and the U.S., the *IQOS* 3 System has been commercialized in the same countries as the Authorized *IQOS* System.

This section presents a summary of relevant Adverse Experiences (AEs) potentially attributed to the *IQOS* System (corresponding to the Authorized *IQOS* System) and the *IQOS* 3 System in countries outside the U.S., reported to Philip Morris International (PMI) by the *IQOS* users, derived from the PMI's global safety database for *IQOS*. Of note, the majority of the spontaneous reports received by PMI are not medically confirmed, *i.e.*, they are reported directly by consumers and not by healthcare professionals.

A query of the PMI safety database for *IQOS* was performed on January 28, 2020 using the following search criteria:

- Period: December 01, 2018 to November 30, 2019
- Report types: spontaneous reports

A total of 26,569 spontaneous cases potentially attributed to any *IQOS* System and reported during the period from December 01, 2018 to November 30, 2019, were retrieved from the PMI's safety database. Based on sales data for *HeatSticks*[2] the estimated total number of *IQOS* consumers was above 10 million worldwide during the reporting period. Therefore, case reporting rate was estimated to be 2.66 cases per 1,000 consumers.

Unlike with *HeatSticks*, where it is possible to estimate the number of consumers based on the sales data, it is not possible to make such estimation based on sales data for the *IQOS* Systems because direct correlation between the sales data for the *IQOS* Systems and number of consumers cannot be established. Indeed, the number of the Authorized *IQOS* Systems and the *IQOS* 3 Systems sold in the reporting period do not directly correspond to the number of consumers using each version of the *IQOS* System (for instance a consumer using the Authorized *IQOS* System or the *IQOS* 3 System during the reporting period might have bought it before December 01, 2018).

In 4,162 cases (15.7% of the total number of reported cases), the version of the *IQOS* System used was not reported by the consumer and was therefore coded as "*IQOS* unspecified".

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[1] Spontaneous Adverse Experiences (AEs) presented and discussed as attributed to the Authorized *IQOS* System comprise combined inputs for two *IQOS* Systems commercialized internationally **(b) (4)**

[2] In countries outside the U.S. *HeatSticks* are sold under the brand name *HEETS*.

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1.1. Summary of safety data for the Authorized *IQOS* System and the *IQOS* 3 System

Of the 26,569 cases retrieved from the PMI's safety database, 17,417 cases (reporting 31,241 AEs[3]) were attributed to the Authorized *IQOS* System and 4,061 cases (reporting 8,643 AEs) were attributed to the *IQOS* 3 System. Cases which were not attributed to the Authorized *IQOS* System, the *IQOS* 3 System or to the *IQOS* unspecified category, were associated with the use of other versions of the System.[4]

Of the 17,417 cases associated with the Authorized *IQOS* System use, 556 cases (3.2 %) were considered serious and 16,861 cases were considered non-serious. Of the 4,061 cases reported for the *IQOS* 3 System as the suspected product, 118 cases were considered serious (2.9 %) and 3,943 were considered non-serious.

The number of cases reported in association with the Authorized *IQOS* System is higher when compared with the *IQOS* 3 System because the Authorized *IQOS* System has been in the market for a longer period of time, than the *IQOS* 3 System. Indeed, the Authorized *IQOS* System was launched for the first time in November 2014 while the *IQOS* 3 System was marketed for the first time in November 2018, four years later.

Table 1 and Table 2 show the number of cases reported during the reference period per version of the System for the top 5 countries. The differences in the percentage of cases between countries is attributable to different number of users and varying reporting behaviors between countries.

Table 1 Authorized *IQOS* System cases in top 5 countries

Country	Number of cases (%)
Russia	6,078 (34.9)
Italy	1,434 (8.2)
Romania	1,172 (6.7)
Greece	894 (5.1)
South Korea	864 (5.0)

[3] One case can comprise more than one Adverse Experience (AE), therefore the number of reported cases does not match the number of AEs.

[4] Additional versions of the *IQOS* system, (b) (4) (b) (4) have been commercialized worldwide outside the U.S.

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Table 2 *IQOS* 3 System cases in top 5 countries

Country	Number of cases (%)
South Korea	940 (23.1)
Russia	425 (10.5)
Japan	370 (9.1)
Germany	302 (7.4)
Hungary	290 (7.1)

1.1.1. *Most frequently reported adverse experiences*

Table 3 presents the most frequently reported MedDRA System Organ Class (SOCs) per version of the System during the reporting interval.

Table 3 Most frequently reported AEs (>5%) by SOCs

MedDRA SOC	Authorized *IQOS* System	*IQOS* 3 System
	Number of adverse experiences (%)	Number of adverse experiences (%)
Respiratory, thoracic and mediastinal disorders	8,250 (26.4)	2,065 (23.9)
Gastrointestinal disorders	5,795 (18.5)	1,878 (21.7)
Injury, poisoning and procedural complications	3,941 (12.6)	846 (9.8)
Nervous system disorders	3,617 (11.6)	943 (10.9)
Product issues	3,340 (10.7)	952 (11.0)
General disorders and administration site conditions	3,033 (9.7)	979 (11.3)

The table above shows that the most frequently reported SOCs are the same for both versions of the *IQOS* System and have similar proportions of AEs (count of AEs for a given SOC/total count of AEs in all SOCs for each version of the *IQOS* System).

Table 4 presents the most frequently reported MedDRA Preferred Terms (PTs) per version of the *IQOS* System during the reporting period.

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Table 4 Most frequently reported AEs (>5%) by PTs

MedDRA PT	Authorized *IQOS* System	*IQOS* 3 System
	Number of Adverse Experiences (%)	Number of Adverse Experiences (%)
Thermal burn	3,055 (9.8)	632 (7.3)
Cough	2,596 (8.3)	461 (5.3)
Headache	1,812 (5.8)	442 (5.1)
Device physical property issue	1,617 (5.2)	420 (4.9)

The above table shows that the most frequently reported PTs are similar for both version of the *IQOS* System, in terms of proportions (count of a given AE / total count of AEs).

Table 5 presents the most frequently reported Serious Adverse Experiences (SAEs) by MedDRA Preferred Terms (PTs) per version of the *IQOS* System during the reporting period.

Table 5 Most frequently reported SAEs (>5% of SAEs) by PTs

MedDRA PT	Authorized *IQOS* System	*IQOS* 3 System
	Number of Serious Adverse Experiences (%)	Number of Serious Adverse Experiences (%)
Hypersensitivity	180 (24.1)	28 (16.6)
Angina pectoris	131 (17.5)	25 (14.8)

The above table shows that the most frequently reported SAEs by PTs are similar for both versions of the *IQOS* System, in term of proportions (count of a given SAE/ count of SAEs).

Hypersensitivity is a common AE (≥1/100, <1/10) with Nicotine Replacement Therapies (e.g. Nicorette Inhalator).

The suspected cases of angina pectoris were poorly documented and none of them was medically confirmed, meaning that they have been reported by consumers and not by healthcare professionals. In the vast majority of cases of angina pectoris, the corresponding verbatim was "pain in the heart", "cardiac pain" or "stabbing pain in the heart". Indeed, angina pectoris is the appropriate MeDRA PT to code such verbatims.

1.2. Discussion and conclusions

A total of 26,569 cases were retrieved from the safety database during the period from December 01, 2018 to November 30, 2019. From the 26,569 cases, 17,417 cases (3.2% being

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serious) were attributed to the Authorized *IQOS* System and 4,061 cases (2.9% being serious) to the *IQOS* 3 System.

The analysis of these cases showed that the most reported SOCs were the same for both versions of the *IQOS* System, as well as the most reported PTs.

"Thermal burn" is the most frequently reported PT for both versions of the *IQOS* System. For most of the cases reporting "thermal burn", the corresponding MedDRA Lower Level Term (LLT) was "Burn of unspecified degree of lips" (78.5% of the cases for the Authorized *IQOS* System and 72.2% of the cases for the *IQOS* 3 System). The water in the aerosol may make the aerosol temperature feels very warm under hot and humid weather conditions. **(b) (4)**

(b) (4)

"Headache" is known to be a very common AE (≥1/10) and "Cough" a common AE (≥1/100, <1/10) with nicotine replacement therapies (e.g. Nicorette Inhalator).

The AE "Device physical property issue" is the corresponding PT to complaints reporting an issue with the *IQOS* System, such as System overheating or System being hot. For both *IQOS* Systems, this AE "Device physical property issue" was most commonly associated with the PT "Thermal burn". The corresponding LLT for the PT "Thermal burn" associated with "Device physical property issue" was "Burn of unspecified degree of lips" in 78.6 % of cases for the Authorized *IQOS* System and 71.4% of cases for the *IQOS* 3 System. While acknowledging a comparable reporting rate for this AE, **(b) (4)**

(b) (4)

(b) (4)

Hypersensitivity and angina pectoris were the most frequently reported SAEs.

Hypersensitivity is also a common AE (≥1/100, <1/10) with Nicotine Replacement Therapies (e.g. Nicorette Inhalator).

The suspected cases of angina pectoris were poorly documented and none of them was medically confirmed, meaning that they have been reported by consumers and not by healthcare professionals. In the vast majority of cases of angina pectoris, the corresponding verbatim was "pain in the heart", "cardiac pain" or "stabbing pain in the heart". Among the 131 cases allegedly associated with the Authorized *IQOS* System, four cases required hospitalization and among the 25 cases potentially associated with the *IQOS* 3 System, one case required hospitalization. As mentioned above, none of these cases have been reported by healthcare professionals, therefore it was not possible to contact the healthcare provider to confirm the hospitalization and conduct any futher follow-up. The mean age of consumers reporting such verbatim was 34.0 years for the Authorized *IQOS* System and 34.4 years for the

(b) (4)

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IQOS 3 System. When the information was provided, the mean time period between the start of the *IQOS* System use and the onset of the AE was 18.1 days for the Authorized *IQOS* System and 25.6 days for the *IQOS* 3 System. Taking into account the mean age of the consumers, the short mean time period between the start of the *IQOS* System use and the onset of the AE, and also the fact that most of these cases did not lead to hospitalization and that the cases (verbatims) were reported by a person without medical background, it is very likely that most of these cases of angina pectoris refer in fact to chest pain or chest discomfort. Chest pain and chest discomfort are also associated with use of nicotine replacement therapies (e.g. Nicorette Inhalator) and are classified as uncommon AEs (≥1/1000, <1/100).

Overall, the analysis of the available data shows that the Authorized *IQOS* System and the *IQOS* 3 System have a similar safety profile.

In addition, to address any potential concerns that the Agency may have in relation to the outbreak of lung injury associated with electronic cigarettes (EVALI), a retrieval of AEs pertaining to the Standardised MedDRA Query "Interstitial lung disease" (Broad) was performed for the reporting period, namely from December 01, 2018 to November 30, 2019 in coutries outside the U.S. Out of the 17,417 cases associated with the Authorized *IQOS* System, 9 cases with 10 AEs were retrieved and out of the 4,061 cases associated with the *IQOS* 3 System, no cases were retrieved.

None of the 9 cases was medically confirmed. In addition these cases had little to no information on medical history, important risk factor or on smoking or other tobacco or nicotine use history.

Out of the 10 AEs retrieved, there were 3 potential SAEs (1 experience of Pneumonitis, 1 experience of Pulmonary sarcoidosis and 1 experience of Sarcoidosis, all leading to hospitalization) and 7 non-SAEs (5 experiences of Pneumonitis, 1 experience of Cystic lung disease and 1 experience of Alveolitis).

The SAE of pneumonitis that led to hospitalization has been reported by the consumer herself, a 37 year-old female who started using the Authorized *IQOS* System on September 02, 2018. There was no information reported on concomitant medication and medical history. She reported that she had been admitted to hospital on two occasions after using the Authorized *IQOS* System. Reason for hospital admission was reported as "accelerated inflammation of lungs to the point that she could not breath". She reported that the events started on November 03, 2018. The consumer considered that the events were life-threatening. According to the consumer, the specialists that treated her established that "the device caused the event." She was prescribed with unspecified medicines to control the inflammation. It was reported that the Authorized *IQOS* System was discontinued after the occurrence of the event. Outcome of the event was not resolved at the time of reporting. Given the temporal relationship, PMI concluded that a causal role of the Authorized *IQOS* System could not be excluded.

The SAEs of pulmonary sarcoidosis and sarcoidosis that led to hospitalization, were reported in the same case. This case has been reported by the consumer himself, a 22 year-old male

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who started using the Authorized *IQOS* System on February 25, 2019. There was no information reported on concomitant medication and medical history. He reported that on March 20, 2019 (after 24 days of usage) he experienced shortness of breath and dizziness and was hospitalized. According to the consumer, he developed symptoms of pulmonary sarcoidosis; some nodes were found on his legs, and as a consequence of the sarcoidosis he developed erythema nodosum on his legs. After reducing the use of the product the symptoms started improving. According to the consumer, the event reappeared once he started using the Authorized *IQOS* System again. At the time of reporting, the outcome of the events was that the consumer was recovering. Considering the time between the start of the product use and the onset of the events, and taking into consideration the implication of environmental agents and infectious organisms in the aetiology of sarcoidosis and the genetic predisposition, PMI concluded that a causality between the use of the product and the reported SAEs could reasonably be excluded in this nonmedically confirmed case.

These 9 cases represent 0.05 % of the cases associated with the Authorized *IQOS* System. As mentioned above, no cases pertaining to the Standardized MedDRA Query "Interstitial lung disease" (Broad) were retrieved for the *IQOS* 3 System.

Of note, Vitamin E acetate (CAS #58-95-7) is not used as an ingredient or additive in the production of *HeatSticks*.

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