Appendix J:
Population Health Impact Model (PHIM)

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1. INTRODUCTION

The Population Health Impact Model (PHIM) is used to assess the population health effects of introducing a new Reduced-Risk Product (RRP) as a function of the risk of the product to the individual user, and the prevalence and patterns of product use. The model allows the exploration of a wide range of scenarios assessing the possible effect of RRP introduction on the prevalence of CC and RRP use, individually and in combination. By comparing mortality attributable in a scenario where RRP is introduced (Business Case scenario) on the U.S. market in 1990 with one (Null scenario) where it is not, the model estimated the mortality attributable to CCs and RRP, as well as the reduction in deaths over a twenty-year period following the introduction of a new product. The simulations are built on a number of assumptions. The robustness of the results is investigated in terms of sensitivity analyses.

The overall reduction in smoking attributable deaths from lung cancer (LC), ischemic heart disease (IHD), stroke, and chronic obstructive pulmonary disease (COPD) for men and women combined was estimated varied from 70,274 to 90,155 assuming that switching to RRP had an effect in risk reduction equivalent to 70% - 90% of effect of quitting. This drop in deaths is associated with a scenario where within 10 years of product introduction in U.S., 17% of smoking population will move to use of RRP (15% exclusive RRP users and 2% dual users of CCs and the RRP). Sensitivity analyses included variation in rates of initiation, cessation, and dual use.

The Technical Project Lead (TPL) Report provides that the PHIM "population modelling projections are not particularity informative to the overall assessment" for the following reasons:

- The projected population health effects may be overstated if assumptions about tobacco use behavior and risks are not realized in the actual population
    - *e.g.*, if exclusive use of *IQOS* is lower than predicted,
- Predicted mortality over a 20-year period does not allow for adequate consideration of the long-term health effects of tobacco use initiation among youth and young adults,
- It is unclear if the modelling took into account the effect of marketing the product with modified risk claims.

Further, the "Modified Risk Granted Orders - Exposure Modification" concluded that future population health impact modelling of *IQOS* System must include data from PMSS studies, in particular:

- % of former smokers initiating *IQOS,*
- % of current smokers initiating *IQOS* and becoming dual users,
- % of current smokers initiating *IQOS* and becoming exclusive users,
- % of youth and young adults below legal age of purchase who initiate *IQOS,*

- % of initiating *IQOS* who then initiate or re-initiate cigarette smoking,
- The latest information on acute and long-term health effects of using *IQOS* relative to combusted cigarette smoking.

In addition, the annual PMSS report will include:

- A description of the methodological approach used in the model, including statistical, mathematical, and computational components of the model,
- A copy of the model or its underlying code, and all associated supporting code, such that FDA can independently run and verify the model inputs and outputs,
- Documentation directly related to model development and implementation, including scientific literature,
- A description of all model inputs, including the justification for input values and how they were derived from postmarket data and information,
- A summary of the modeling results and their implications for assessing whether the MRTPs continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole.

2. UPDATE OF THE POPULATION HEALTH IMPACT MODEL

PHIM used for the FDA submission was version 6. Subsequent improvements to the model have been incorporated and the current version of PHIM is 8.2. PHIM version 8.2 anticipated many of the comments made in the TPL Report, such that the requirements outlined above have already been implemented. In addition, an age-period-cohort model is incorporated in PHIM 8.2 to predict future rates for four smoking attributable diseases (lung cancer, ischaemic heart disease, stroke and COPD) based on the available mortality data. This allows forecasting future trends of reduction in deaths following the introduction of a new product into a market. In particular, the long-term population health effects (for example, for the period 2000-2040 or 2025-2065) of introducing a new product can be estimated. Other updates include prediction based on probabilistic models rather than simulations (in version 6, the Markov chain stochastic process is simulated based on the hypothetical population), f-factor varying by disease (version 6 used the same f-factor applied to all diseases) and the expansion of the number of products that can be considered from 4 to 10.