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A novel approach to assess the population health impact of introducing a Modified Risk Tobacco Product

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ABSTRACT

Based on the Food and Drug Administration's Modified Risk Tobacco Product (MRTP) Application draft guideline, Philip Morris International (PMI) has developed a Population Health Impact Model to estimate the reduction in the number of deaths over a period following the introduction of an MRTP. Such a model is necessary to assess the effect that its introduction would have on population health, given the lack of epidemiological data available prior to marketing authorization on any risks from MRTPs. The model is based on publicly available data on smoking prevalence and on the relationships between smoking-related disease-specific mortality and various aspects of the smoking of conventional cigarettes (CCs), together with an estimate of exposure from the MRTP relative to that from CCs, and allows the exploration of possible scenarios regarding the effect of MRTP introduction on the prevalence of CC and MRTP use, individually and in combination. By comparing mortality attributable in a scenario where the MRTP is introduced with one where it is not, the model can estimate the mortality attributable to CCs and the MRTP, as well as the reduction in the deaths attributable to the introduction of the MRTP.

1. Introduction

To obtain a risk modification order under the United States Food and Drug Administration's draft guidance (FDA, 2012), the applicant must demonstrate that the Modified Risk Tobacco Product (MRTP) benefits the health of the population as a whole, accounting for current, former and never smokers. Given the lack of population-level data available prior to marketing an MRTP on its risks or the level of uptake, Philip Morris International (PMI) is, in accordance with Section VI.B.4 of the draft guidance, developing a Population Health Impact Model to estimate the impact of the introduction of the product on mortality given assumptions concerning the exposure to the smoker from the MRTP relative to that from conventional cigarettes (CCs), and on the rate of uptake of the MRTP. The model estimates the impact on mortality in a population which survives until a specific time after the introduction of the MRTP on the market. Although the model was developed with focus on the US, it is also intended to be used for population health impact assessment in other countries, such as the UK, Germany, and Japan, for which the required data are available.

To predict the potential impact from the introduction of an MRTP, the model will allow the exploration of a wide range of scenarios assessing the possible effect of MRTP introduction on the prevalence of CC and MRTP use, individually and in combination. The input data are extracted from publicly available databases and the scientific literature, and are country-specific where available and applicable. The attributable deaths under the "MRTP Scenario" (with the introduction of the MRTP) will be compared with those under the "Null Scenario" (without the introduction of the MRTP) to estimate the reduction in attributable deaths. The purpose of this article is to describe, in detail, the data sources, modeling methodology, rationale and approach to the assessment of the potential impact from the introduction of an MRTP.

Abbreviations: CCs, conventional cigarettes; COPD, chronic obstructive pulmonary disease; E-component, epidemiological risk component; ER, excess risk; ETS, environmental tobacco smoke; IHD, ischemic heart disease; LC, lung cancer; MRTP, Modified Risk Tobacco Products; P-component, prevalence component; PMI, Philip Morris International; STPs, smoking transition probabilities; RR, relative risk.

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2. Methods

2.1. Prevalence (P)-component

The P-component is a Markov chain state-transition model to estimate changes in the distribution of CC and/or MRTP use occurring in a hypothetical population of a given size over a defined period, separately for the Null and MRTP Scenarios. Before the MRTP is introduced, the population has a country-specific distribution of CC smoking habits (current, former [by years since quitting] and never smoking). The population is followed over the simulation period by considering successive small time intervals, typically one year, during which only one change in smoking habits can occur. Smoking transition probabilities (STPs) are applied to each member of the population to determine whether they stay in the same group or change to a different one by the end of each interval. The STPs can vary based on the time since introduction of the MRTP and/or the time that the population member has spent in their current state. Thus, by the end of the simulation period, each member will have a complete smoking history, updated age, and (for former smokers) updated time since quitting.

Under the Null Scenario, the smoking histories relate only to use or non-use of CCs. Thus the possible STPs relate to never smokers starting to smoke CCs, current CC smokers quitting CCs, and former CC smokers reinitiating CCs. Under the MRTP Scenario, both CCs and the MRTP are available, increasing the complexity of the STPs. The possible STPs relate to never smokers starting to use the MRTP or CCs, former smokers re-initiating with the use of the MRTP or CCs, and current users of the MRTP or CCs quitting use of the product, or switching to the other product.

2.1.1. Data and data sources

The P-component will be populated with the distribution of CC smoking for twelve countries (Austria, Canada, France, Germany, Hungary, Italy, Japan, Poland, Sweden, Switzerland, the United Kingdom and the United States from 1986 onwards), but is expandable to allow the inclusion of additional data from future years and/or additional countries and regions.

2.1.1.1. Current and former smoking prevalence data. Prevalence data on current CC smoking will be extracted from International Smoking Statistics (ISS; Forey et al., 2002; Forey and Lee, 2002). Smoking prevalence data specific for sex-, age (in 5-year groups) and period (in 5-year groups) are available from all twelve countries up to at least 2005 (Forey et al., 2006–2013; Forey et al., 2007).

Age- and sex-specific prevalence data on former CC smokers, extracted from the same sources used for the ISS database, are readily available (Lee et al., 2009) for Austria, Canada, Germany, the United Kingdom and the United States. Data for Italy and Japan have been extracted, but are not yet published. Data extraction is planned for France, Hungary, Poland, Sweden and Switzerland, to ensure that there is prevalence data on former smokers from the same countries as the data on current CC smokers.

2.1.1.2. Distribution of former smokers by years quit. National age- and sex-specific data on the distribution of former smokers (by years since quitting) are also required. Preliminary investigations found data for all the countries, except Poland, but the publications vary in scope and quality, some using broad grouping of years since quitting, some presenting results only for limited age groups, and some being based on small samples. Further attempts will be made to obtain data by concentrating on data sources allowing customized analysis. Where relevant data cannot be found for a given country, the distribution may be estimated using the data for other countries that are similar with respect to economic and cultural aspects, including tobacco use history.

2.1.1.3. Estimating STPs for CCs from smoking distributions. Data on the prevalence of current and former CC smoking within the same birth cohort in successive periods do not allow direct estimation of STPs. This can be seen when examining the changes in the proportion of former CC smokers between periods. An increase from 36% in period 1 to 39% in period 2 could reflect 3% of the current CC smokers quitting smoking during the period, but cannot be distinguished from a scenario where 6% of former smokers re-initiated CC smoking, while 9% of CC smokers quit. Therefore, national data on the re-initiation rates of former smokers are required to estimate the STPs more precisely.

2.1.1.4. Estimating STPs for the MRTP. In the pre-market setting, STP estimates for the MRTP Scenario will be based on assumptions and product use patterns from controlled studies that cannot be validated with regard to post-market actual use. After the introduction of the MRTP, the preliminary STP estimates can be replaced by estimates derived using the data from a series of longitudinal cross-sectional surveys that are planned to initiate at the time of product launch. These cross-sectional surveys will also provide data on re-initiation rates for CCs.

2.1.2. Smoking histories

The smoking histories will be modeled starting with a large hypothetical population sample (e.g., 10,000). The start year is assumed to be before the introduction of the MRTP, so the population will be initially subdivided according to the sex-, age- and country-specific distribution of CC smoking status (current, former [by time since quitting], never) for that year. The population will then be followed up at successive small time intervals (typically one year) over a defined period. During any interval, the smoking status of each population member may change, assuming that smoking status can only change once per interval because the length of the time interval is sufficiently short to ignore multiple changes. The probabilities of these transitions are defined by the STPs. Although it is expected that the STPs will remain constant from year to year, the model will allow the STPs to vary over the period. At the end of the period, each population member will have a history of tobacco use. These histories will then be used to determine the distributions of CC and MRTP use at any time following the introduction of the MRTP and so allow the estimation of disease risks.

Where the end of the period is a recent year, the STP values for the Null Scenario can be selected based on time trends in smoking habits obtained from the data on current and former CC smoker prevalence. The smoking distribution predicted by the P-component at the end of the follow-up period should be closely aligned with its known distribution. The effects of alternative assumptions concerning the trends in smoking distributions and the choice of STPs will be considered in sensitivity analyses.

Fig. 1 shows the matrix of STPs required for the Null Scenario. Determining how smoking habits change in an interval requires knowledge of three STPs, P_{NC} = the probability that a never smoker (N) becomes a current smoker (C), P_{CF} = the probability that a current smoker (C) becomes a former smoker (F), and P_{FC} = the probability that a former smoker (F) becomes a current smoker (C).

The diagonal of the matrix running from the top left to bottom right reflects a situation without change in smoking habits. The cells marked with a zero are excluded because for two of these (a current or former smoker becoming a never smoker) the transition is impossible, while for the other (a never smoker becoming a former smoker) the transition requires multiple changes which