7.4 Executive Summary: Population Health Impact Model studies

A Population Health Impact Model (PHIM) has been developed to estimate the reduction in mortality from the four major smoking-related diseases (lung cancer, IHD, stroke and COPD) that would occur over a period following the introduction of a Modified Risk Tobacco Product (MRTP).
The modelling approach has been described in Weitkunat et al., 2015.

The model consists of two components, the Prevalence (P) and Epidemiological (E) Risk Component. The P-Component starts with a defined group of individuals of a given sex and age range with a known initial distribution of conventional cigarette (CC) smoking habits that is representative of the population at a given time point. The population is then followed over a number of discrete time intervals under two Scenarios. In the Null Scenario, MRTPs are not introduced and the smoking status of each individual (never, current, former) is updated at each interval based on assumed CC tobacco use transition probabilities (TTPs). In the MRTP Scenario, the MRTP is introduced and the status of each individual (never, current CC, current MRTP, current dual use, former) is updated at each interval based on assumed MRTP TTPs.

In the E-Component, the tobacco histories are used to estimate relative risks (RR), compared to never tobacco users, of the four major smoking-related diseases - LC, IHD, stroke, and COPD - under the two Scenarios. For each individual, and for each period of follow-up, the RR is estimated using the negative exponential model (NEM). The model was originally used to describe the decline in excess relative risk (ERR = RR−1) by time quit, and it has been shown to provide a good fit to data for the four smoking-related diseases (Fry et al., 2013; Lee et al., 2014a; Lee et al., 2012; Lee et al., 2014b). These publications provided estimates for each disease of the half-life (H) of the ERR, that is the time after quitting when the ERR reaches half that for continuing smokers. Quitting may be regarded as switching from a relative exposure (RE) of 1 unit to 0 unit, and a simple adaptation of the NEM allows the ERR to be estimated for switching to a reduced exposure, and has been shown (Lee et al., 2015) to adequately describe reductions in risk of lung cancer following reductions in amount smoked (Fry et al., 2013).

For MRTP Scenario, the effective dose relative to CC smoking for MRTP use (F-factor) and for dual use (G-factor) was estimated. F-factor represents the reduction of the excess risk due to smoking if one switches to the MRTP. Its value is 1 if switching to MRTP has an excess risk similar to that of smoking and is 0 if switching to MRTP has an excess risk similar to that of smoking cessation. Currently, there is no epidemiological data allowing the direct estimation of the F-factor. Nevertheless, clinical studies are available and key markers measured during these studies are used to estimate the difference between subjects switching to an MRTP and those quitting smoking relative to the difference between subjects continuing smoking and those

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quitting smoking. By using Bayesian statistics, the uncertainty related to these relative changes (RCs) are also estimated. A link function is then required to translate the various RCs and their uncertainty into the F-factor. Given the lack of knowledge to determine a reasonable link function, we introduce a family of them defined on a parameter space that can be uniformly sampled. The concepts of 'sufficiency' and 'necessity' are introduced to estimate our degree of belief that the panel of biomarkers investigated during clinical studies can be considered as representative of the final disease endpoint. At the end of the process, a distribution of potential F-factors representing various sources of uncertainty is obtained and can be used as an input to the PHIM. Sensitivity analysis is also performed to investigate the impact of the 'sufficiency' and 'necessity' parameters on the distribution of potential F-factors and its impact on the PHIM. The "G-Factor" takes a value between F and 1+F. It is the effective dose associated with dual use. If the subject uses the same amount of CC + MRTP then the G-Factor should be taken as a value close to 1 + F, whereas if the subject uses fewer CC and replaces some of their CC with MRTP the factor should be taken to be between F and 1. In the model, unless otherwise specified, the dual use assumption will be based on the situation that dual users do not alter their overall consumption, and use equal numbers of each product, so the G-Factor will be set as (1+F)/2.

All the simulation analyses described in this work are based on simulated samples of the US population aged 10-79 years, which in 1990 had a distribution of conventional cigarette (CC) smoking habits based on national data, individual smoking histories then being updated annually for 20 years using Tobacco Transition Probabilities (TTPs) under two alternative scenarios. In the NULL Scenario, where the MRTP is not introduced, there are three smoking groups (never, current, former smokers) and three TTPs (initiation, cessation and re-initiation). In the MRTP Scenario, there are five tobacco use groups (never, current CC, current MRTP, current dual, former) and 15 TTPs, three each for initiation, quitting and re-initiation and six for switching between current tobacco use groups. (Note that in this Executive Summary we use the terms "MRTP users" and "CC smokers" to refer to those who predominantly use the relevant product, with "dual users" being those with a substantial use of both products. Note also that tobacco use refers only to the use of the two products of interest, CCs and MRTPs.)

Based on these simulated tobacco use histories, downloaded national data on population size and mortality, published estimates of the current smoking relative risk and the half-life for quitting (the time following quitting when the excess risk associated with continuing smoking is halved), and estimates of the effective dose relative to CC smoking for MRTP use (F-factor) and for dual use (G-factor), the number of deaths associated with smoking at age 30-79 years can then be estimated under the NULL and MRTP scenarios. The difference between the two estimates then represents the reduction in mortality associated with the introduction of the specific MRTP over the first 20 years of it's introduction.

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For the NULL Scenario, predictions of national smoking prevalence up to 2010 derived using the TTPs were shown to be reasonably consistent with published estimates of smoking prevalence over this period from International Smoking Statistics (ISS). Differences observed may partly be due to lack of representativeness in a simulated population followed for 20 years and assumed not to die. The overall percentages of deaths from the four causes of interest which were attributable to smoking estimated by PHIM for the NULL Scenario were also reasonably consistent with estimates published in 2014 by the US Surgeon General's Report. The proportion of lung cancer and COPD deaths that are projected from the PHIM were lower, because the US Surgeon General's Report includes deaths from individuals 80 years of age and older, and uses relative risk estimates from the American Cancer Society CPS-II prospective study, which are unusually high, particularly for COPD, compared to the RRs we derived from meta-analyses. The differences do not invalidate the PHIM, seem unlikely to affect conclusions from the simulation and sensitivity analyses, and do not cast doubt on the parameter estimates used for the NULL Scenario.

The sensitivity analyses conducted tested the effect on the estimated reduction in mortality associated with MRTP introduction of varying a wide range of parameters. These included the effective dose factors, the relative risks, the half-lives, the factors by which TTPs are affected by previous tobacco use history, as well as the TTPs used in the MRTP Scenario. The TTPs used in the NULL Scenario, which were found to predict smoking distributions reasonably consistent with national data, were not varied.

A basic analysis used a set of parameters which does not relate to any specific MRTP, but is thought to be a suitable starting point from which to evaluate the effect of parameter changes in the sensitivity analyses. The parameters considered in the basic analysis include an 80% reduction in effective dose for MRTP use (F-factor = 0.2) and a 40% reduction for dual use (G-factor = 0.6, consistent with dual users smoking 50% CCs and 50% MRTPs with no increase in total consumption), relative risk and half-life estimates derived from published meta-analyses, and a set of assumed values of the TTPs in the MRTP Scenario derived, in the absence of empirical data, The magnitude of effect on tobacco use prevalence in the basic analysis is illustrated by men aged 50-54 years in 1990, at which time there were 29.6% never smokers, 30.3% current smokers and 40.1% former smokers. By 2010, when the men were aged 70-74 years, the proportions of never users in the NULL and MRTP Scenarios remained the same, and the proportions of former users were similar 47.3% NULL and 45.8% MRTP). However, the make-up of current users was different (23.1% CC in the NULL Scenario, and 17.9% CC, 4.6% MRTP and 2.1% dual in the MRTP Scenario).

If the introduction of the hypothetical MRTP would result in a scenario where all CC smokers are replaced by MRTP users, the introduction of this MRTP would be associated with a reduction in deaths from the four smoking-associated diseases totalling 443,627 in males and 244,615 in females, representing, respectively 19.5% and 18.7% of all deaths attributable to

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smoking during 1990-2009 in the US population aged 30-79 years. This compares with a reduction of 605,321 (26.6%) in males and 333,027 (25.5%) in females in the situation where all smokers quit, with no further initiation or re-initiation. The difference between these reductions in deaths arises because switching to the MRTP involves an 80% reduction in exposure, whereas quitting involves a 100% reduction. The reductions would be expected to continue to increase as the proportion of the population that ever smoked CCs decline and are replaced by MRTP use over the years.

In the sensitivity analyses one or more parameters were varied from the values assumed in the basic analysis. Some sensitivity analyses (e.g. varying relative risks) did not affect smoking prevalence in the MRTP Scenario but, in those that did, the effects were much as would be expected *a priori*. Thus, increasing initiation rates had most effect on tobacco use prevalence at younger ages, while increasing re-initiation rates had most effect at older ages. Varying rates of quitting and switching between products had a much greater effect on tobacco use distributions than did varying the factors by which TTPs are affected by previous tobacco use, these factors only being applied when multiple changes in tobacco use status occurred.

The largest increases in the estimated reductions in mortality associated with MRTP introduction resulted from decreasing the effective dose factors F and G, increasing rates of switching to MRTP (from CC or dual use), decreasing rates of switching to CC (from MRTP or dual use), and quitting. Effects of varying relative risk and half-life estimates and re-initiation rates were also clearly seen. In analyses involving 4-fold variations in multiple parameters, decreasing the effective dose factor, F, and increasing the rate of switching to MRTP caused the largest increases in the estimated reductions in mortality, larger than those resulting from decreasing the rate of switching to CC or increasing the rate of quitting from MRTP.

Analyses were also conducted to determine what changes in parameter values might possibly eliminate the estimated reduction in deaths associated with MRTP introduction. Leaving aside the cases where the effective dose for MRTP use and CC smoking is identical, or where there is no uptake of MRTP, which would clearly totally eliminate the reduction in deaths, there were three situations where variation in a parameter might in theory fully eliminate the reduction, but none of these seemed likely to occur in practice. One was where the G-factor, the effective dose for dual users, was increased to 2.8, consistent with 20 a day CC smokers before MRTP introduction becoming users of almost 100 a day (half CC, half MRTP) afterwards. The second was where re-initiation rates increased 2-fold. The third was where quitting rates of CC smokers decreased by about 35%.

Increasing initiation rates 8-fold had a moderate effect on the reduction in deaths, the number of death reduced was 24,541 in males and 9,537 in females. It should be noted that initiation was assumed only to occur at age <35 years, so that over the 20-year follow-up period increasing initiation rates would have no effect at all on those aged 55 years or over, where most deaths

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occur. It should be noted that an 8-fold increase in initiation rates would massively affect the smoking distribution in 30-34 year olds. Thus, comparing 1990 and 2010, the proportion of never users would reduce in males from 44.5% to 2.6%, and in females from 50.8% to 3.0%, while the proportion of current users would increase in males from 34.9% (all CC) to 70.0% (48.4% CC, 13.3% MRTP, 8.3% dual), and in females from 30.5% (all CC) to 72.3% (50.2% CC, 12.4% MRTP, 9.7% dual). Had the follow-up period been longer than 20 years, the effect of such a large, though implausible, increase in initiation rates on the reduction in deaths would clearly have been greater than seen in our analyses.

Compared to increasing the initiation rates, decreasing quitting rates of CC smokers and increasing re-initiation rates has a greater effect, and substantial and rather implausible changes in these would in theory eliminate the reduction in deaths associated with MRTP introduction. While the reduction could in theory be eliminated by making simultaneous multiple smaller changes in these parameters, even these smaller changes seem rather improbable. The fact that MRTP introduction is unlikely to cause an increase in deaths is emphasised by the results of an analysis involving an extreme situation in which, as soon as MRTP was introduced, smokers and non-smokers alike all became continuing MRTP users. Here the effect of MRTP introduction was clearly beneficial in males, and somewhat so in females, the reduction in risk for those who were smokers at the time of the introduction outweighing the increase in risk for those who were non-smokers.

The FDA MRTP guidelines highlight seven population segments and exposure patterns, two of which (**"Tobacco users who opt to use the proposed product rather than an FDA approved tobacco cessation medication"** and **"Non-users who experience health risks from the product"**) are outside the present scope of the model. The analyses presented in this report do, however, provide relevant information on the other segments. Thus **"Tobacco users who switch from other commercially marketed tobacco products to the proposed product"** relates to switching from CCs to MRTPs, **"Tobacco users and non-users who, after adopting the proposed product, switch to or switch back to other tobacco products that may present higher levels of individual health risk"** relates to switching from MRTPs to CCs, **"Non-users who initiate tobacco use with the proposed product, such as youth, never users, former users"** relates to both initiation and re-initiation to MRTPs, and **"Tobacco users who use the product in conjunction with other tobacco products"** relates to dual use and the effective dose for dual users, all well covered by the sensitivity analyses conducted. **"Tobacco users who opt to use the proposed product rather than cease tobacco use altogether"** was considered by a specific analysis in which current CC smokers who would otherwise have switched to MRTP or to dual use quit instead. Here, the reduction in deaths associated with MRTP introduction was estimated to be about 11 times greater in males and about 13 times greater in females than that for the basic analysis.

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Overall, we confirm that, given MRTPs have a low effective dose and given a reasonable rate of uptake by smokers, a clear reduction in mortality would be achieved by their introduction, and the detailed results provide estimates of the initial magnitude of this reduction in various alternative situations. The results also show that a reduction in mortality would still occur given levels of increases in cigarette consumption, risk in dual users, rates of initiation, switching or re-initiation to CC smoking, or reductions in rates of quitting which might plausibly be associated with MRTP introduction.

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