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6.5. Effect on the Population as a Whole

Prior to introducing a Modified Risk Tobacco Product (MRTP) into a market, population-level data on consumer behaviors and use of such product can in general not be collected. The impact of marketing such a product on the health of the population as a whole therefore cannot be fully assessed. PMI has implemented a scientifically-based, systematic approach to pre-market product assessment, as well as a thorough post-market assessment program to assess the longer-term effects of the products and to monitor the impact of marketing the product on the population. In addition, PMI has developed a Population Health Impact Model (PHIM), to quantify, in the absence of epidemiological data, the effect that marketing an MRTP may have on the health of the population as a whole.

6.5.1. The Population Health Impact Model (PHIM)

The PHIM was developed using a general approach to population health impact assessment. More specifically, it was designed to assess the impact of an MRTP on population harm as a function of the risk or toxicity of the product to the individual user, and the prevalence of use in the population (Figure 1).

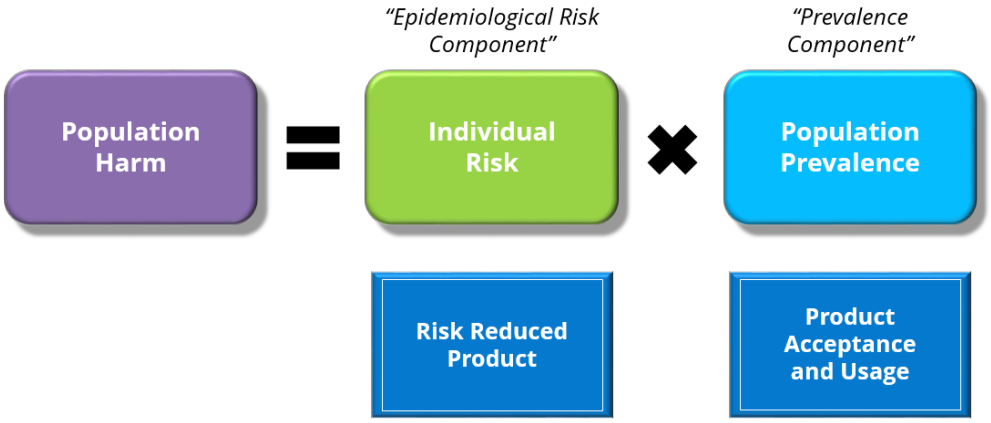


Figure 1 Approach to Assessing Population Harm. Population harm is a function of the individual risk to the user and the population prevalence of use

The PHIM represents PMI's approach to assessing the population health impact of introducing an MRTP and is described in detail in a recent publication (Weitkunat 2015). The PHIM involves two components: the "Epidemiological Risk Component" and the "Prevalence Component".

The Prevalence Component starts with a defined set of individuals of a given sex and range of ages with a known initial distribution of cigarette smoking pattern that is representative of the US population at a given point in time. Two complete tobacco use histories are built up for each individual under two scenarios. Under the "Null Scenario" the MRTP is not introduced into the market, and the Null tobacco transition probabilities (TTPs) relate to changes between three smoking behaviors (never smoking, current smoking, and former smoking). Under the "MRTP Scenario" the MRTP is introduced into the market, and the

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MRTP TTPs relate to changes between five tobacco use behaviors (never smoking, current cigarette smoking, current MRTP use, current dual use, and former use). The hypothetical population is separately followed through time under the two Scenarios by considering successive small time intervals (one year), during which each individual can change their smoking behavior according to defined TTPs. Each individual is allowed only one change in their smoking behavior in each time interval, which is sufficient to describe at a population level the overall smoking trajectories.

For clarification a "current cigarette smoker" is an individual whose tobacco use pattern consists mainly of cigarette use, a "current MRTP user" is an individual whose tobacco use pattern consists mainly of MRTP use, and a "current dual user" is an individual whose tobacco use pattern consists of a substantial use of both products. In this model the term "tobacco use" relates only to use of cigarettes and the MRTP, and does not incorporate or account for the use of other tobacco products.

The Epidemiological Risk Component uses the age and sex-specific tobacco use histories generated by the Prevalence Component, for each individual and year during the simulation, and estimates of the relative risks (RRs) of smoking compared to never smoking, of each of the four major smoking-related diseases – lung cancer, ischemic heart disease (IHD), stroke and chronic obstructive pulmonary disease (COPD) – under each of the two Scenarios. The PHIM uses an extension of the negative exponential function to estimate the RRs by quantifying the decline in excess relative risk (ERR=RR-1) by time since quitting smoking. It has been shown that the negative exponential function provides a good fit to cessation data for each of the four smoking related diseases (Fry 2013, Lee 2012b, Lee 2014a, and Lee 2014b). These publications provide disease-specific estimates of the time after cessation when the ERR reaches half of that for continuing to smoke (the half-life of the ERR). Taking the exposure to be 1 when smoking and 0 when not smoking (cessation), the negative exponential model can be extended to allow the ERR to be estimated for a "reduction in exposure", as described in Lee 2015a. The Lee 2015 paper demonstrates the adequacy of the extension to fit data on the reduction in lung cancer risk following a reduction in daily cigarette consumption. The adaptation can therefore be used to describe the decline in risk on switching to an MRTP, based on an estimate of the relative exposure (f), as compared to cigarette smoking. The negative exponential model can further be extended to address more complex smoking behaviors, such as an individual that undergoes multiple changes in their tobacco use over time.

For each year during the follow-up, and for each of the four diseases, the RR estimates for individuals of a given sex and age group can be averaged under each Scenario, and used to estimate proportions of tobacco-attributable deaths. This can then be converted to estimates of tobacco-attributable deaths, based on national data on total deaths. Differences between the estimates (e.g., number and proportion) of attributable deaths between the two Scenarios (with and without the introduction of the MRTP) are used to quantify the impact due to the introduction of the MRTP.

This model was used in order to predict the population impact of introducing THS into the US market. These simulations required product-specific information, including assumptions on the following:

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- The relative exposure of THS compared to smoking cigarettes (f)
- The rate of uptake of THS in the US market
- The probabilities of initiation, re-initiation and cessation (TTPs)
- The probabilities that an individual will transition between the different tobacco use patterns (TTPs)

The PHIM is flexible and can be used to consider a wide range of situations, including plausible and implausible. The summary here focuses on a limited set of the simulations and analysis that quantify the type of impact that may be observed following the marketing of THS in the US market. However, there is a much more detailed report in Section 7.4 "PHIM Simulations and Sensitivity Analysis Report" that provides a more comprehensive exercise in defining and testing the model. As well, a more detailed description of the PHIM and each of the components are presented in a recent publication (Weitkunat 2015) and there is a report to describe the modeling approach used to estimate the relative exposure of THS compared to smoking cigarettes (the f-value) in Section 7.4 "f-value Sampling Report".

6.5.2. The Population

6.5.2.1. Considerations Related to the Prevalence Component

The Prevalence Component of the model was primarily designed to support the Epidemiological Risk Component. The model limits the age of the smoking population to a maximum of 79, and does not account for changes in daily cigarette consumption patterns (a cigarette smoker that remains a cigarette smoker, but reduces the number of cigarettes per day by 50%).

Length of follow-up. The Prevalence Component allows for follow-up of a hypothetical population over a follow-up period of up to 20 years. Although the PHIM could be extended to longer periods, such projections are less reliable and therefore were not included in the model. The testing of the model under the Null Scenario below in Section 6.5.3.5, show that over a 20 year period the PHIM was able to fairly closely replicate the smoking prevalences from the International Smoking Statistics database (ISS).

Age range. The Epidemiological Risk Component estimates risks only for the age range from 30 to 79 years, because there is little if any risk of smoking-attributable deaths below age 30 and because attributing deaths to specific diseases above age 79 is unreliable. As prevalence data are required for the age range 30-79 years at the end of the follow-up period (maximum of 20 years), the Prevalence Component simulations start with the youngest age group being 10-14 years of age, and follows individuals until they reach age 79 years or the end of the follow-up period.

Amount smoked. The model does not consider the level of consumption of an individual or changes in the level of consumption within an individual. However, the model is flexible and we could substitute reduced consumption into the current model as a tobacco use pattern (e.g., removing or combining with dual use). Currently reduced consumption can only be considered within a tobacco use patterns, in future work this could be expanded.

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Products other than CC or MRTP. The Prevalence Component only accounts for the use of cigarettes and an MRTP, and does not consider other tobacco products, such as cigars, pipes or smokeless tobacco. Failure to do so might cause some bias in estimating the reduction in deaths attributable to an MRTP if CC smokers switching to an MRTP tend to change their use of these other products. However, unless evidence emerges that this occurs to any material extent, no attempt will be made to account for this possibility, as this would make the estimation process extremely complex and highly unreliable due to the number of assumptions required and the interactions between the smoking statuses.

6.5.2.2. The Baseline Population (1990)

All of the modeling simulations presented within this section are based on a counterfactual approach with a fixed baseline population for each sex. The baseline populations were generated as representative samples of the US population in 1990 and then followed-up over a period of 20 years under both Scenarios: (1) assuming either THS was introduced in that year (the "MRTP Scenario") and (2) assuming that THS was not introduced at all during the follow-up period (the "Null Scenario").

The baseline populations (male and female) generated were aged 10 to 79 years of age in 1990. At baseline, each individual in the population was randomly assigned an age, based on the age- distribution of the US population in 1990 using the sex-specific data provided on the United Nations website (United Nations 2013). Then, given the sex and age of the individual, they were randomly assigned to a smoking status (never smoker, current smoker or former smoker), based on the published data on the relative frequencies of these smoking patterns (Forey 2002a, Forey 2002b, Lee 2009). Former smokers in the population were also randomly assigned an age of cessation, assuming that it could not have been prior to the age of 18 years, based on data for 2006 from the National Health Interview Survey (www.cdc.gov/nchs/nhis.htm). Further, to fully define the full smoking history of individuals, including the history prior to the start of the simulation, individuals that enter the simulation as current and former smokers in 1990 were assumed to have initiated smoking at 16 years of age, with no periods of cessation and re-initiation between when they initiated smoking and their entry (in 1990) into the baseline population.

In 1990, the US Population consisted of approximately 210 million people (aged 10 to 79) with over 51 million of them being smokers and approximately 46 million of them being former smokers. Table 1 presents the sex and age-specific distributions of smoking patterns that was used to generate the baseline hypothetical populations of 10,000 male and 10,000 females for the modeling exercise.

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Table 1 United States 1990 Distribution of Sex- and Age- Specific Smoking Patterns

Sex	Age	Population (hundreds)	% Current smokers	% Former smokers	Distribution of time of quit (years)[a]					
					0	1-2	3-5	6-10	11-20	21+
Males	10-14	90413	0.0	0.0	-	-	-	-	-	-
	15-19	93115	20.0	4.4	69.4	30.6	-	-	-	-
	20-24	99492	30.7	9.1	30.2	40.3	29.5	-	-	-
	25-29	107776	35.1	14.4	27.3	30.2	21.1	21.4	-	-
	30-34	111413	34.7	19.7	20.3	15.4	36.7	23.7	3.9	-
	35-39	101077	33.0	24.8	10.2	11.3	18.5	29.6	30.4	-
	40-44	89185	31.9	30.5	8.8	5.1	13.5	15.9	56.7	-
	45-49	68739	32.0	36.6	7.2	6.3	10.6	17.5	35.8	22.6
	50-54	57142	30.1	42.2	8.6	6.8	11.0	8.7	33.4	31.5
	55-59	51965	28.5	46.9	7.7	6.5	12.9	17.4	22.2	33.3
	60-64	50602	25.8	51.5	2.5	3.6	7.7	13.0	30.9	42.3
	65-69	45859	21.6	56.1	1.8	4.6	8.7	12.9	28.3	43.7
	70-74	34917	18.6	60.6	0.6	1.5	14.8	8.7	27.2	47.2
	75-79	24601	15.2	55.7	1.8	4.9	2.8	6.3	29.7	54.5
Females	10-14	86055	0.0	0.0	-	-	-	-	-	-
	15-19	88397	18.5	5.0	60.2	39.8	-	-	-	-
	20-24	96369	26.9	12.8	34.1	34.0	31.9	-	-	-
	25-29	107257	29.2	15.9	17.3	19.9	31.1	31.7	-	-
	30-34	112405	29.5	18.8	20.1	22.8	19.7	26.7	10.7	-
	35-39	102936	26.6	21.5	10.0	12.6	20.3	24.2	32.9	-
	40-44	92403	26.4	22.1	10.7	16.7	19.9	20.6	32.1	-
	45-49	71777	26.7	23.2	9.1	7.8	11.1	20.2	32.9	19.0
	50-54	60079	25.5	24.8	5.6	9.8	9.9	20.9	26.2	27.6
	55-59	55797	22.4	26.7	4.5	5.6	8.4	11.2	28.9	41.4
	60-64	57949	20.4	28.5	2.7	5.0	9.1	11.6	33.2	38.4
	65-69	56485	15.8	30.3	4.1	3.2	7.9	12.8	22.5	49.5
	70-74	46881	14.1	32.1	0.5	3.4	2.6	11.8	25.8	55.9
	75-79	38036	10.0	19.6	1.2	1.9	3.1	6.3	28.3	59.1

[a] The data presented for "Distribution of time of quit (years) is grouped differently from the original presentation which was broken out with more granularity

6.5.2.3. The Tobacco Transition Probabilities – Null Scenario

Under the Null Scenario, the smoking history only considers transitions to and from cigarette smoking, because the MRTP is not introduced in this Scenario. Therefore this Scenario is much simpler and more straightforward than the MRTP Scenario. There are only a few possible transitions and although assumptions are required for the TTPs, there are longer term studies of smoking patterns on which these assumptions can be based (Figure 2):

- P_{NC} = Probability of a never-smoker starting to smoke (initiation);
- P_{FC} = Probability of a former-smoker starting to smoke again (re-initiation).
- P_{CF} = Probability of a smoker quitting smoking (cessation)

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		Start of the Interval		
		N	**C**	**F**
End of the Interval	**N**	P_{NN} (= 1-P_{NC})	0	0
	C	P_{NC}	P_{CC} (= 1-P_{CF})	P_{FC}
	F	0	P_{CF}	P_{FF} (= 1-P_{Fc})

Figure 2 Matrix of possible Tobacco Transition Probabilities under the Null Scenario

Where the smoking patterns for the Null Scenario are defined as N=never-smoker, C=current-smoker, and F=former-smoker and the required Tobacco Transition Probabilities are P_{NC}=probability of initiating smoking, P_{FC}=probability of re-initiating smoking, and P_{CF}=probability of cessation. Under this Scenario the probabilities of individuals not transitioning within an interval can be calculated as the complement of the probabilities of the transitions from that group.

The TTPs used for the Null Scenario are a set of assumptions that were derived from minimal empirical data, and compared with estimates in a recent publication (Weinberger 2014), which reported on a follow-up of a representative US sample. The comparison suggested that our original estimates of initiation and cessation rates were reasonable, however, the estimates of re-initiation rates were too low. The TTPs shown below (Table 2) include the re-initiation rates that were revised according to the recent publication cited above.

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Table 2 The Monthly Tobacco Transition Probabilities (per million) under the Null Scenario

Age	Initiation P_{NC}	Cessation P_{CF}	Re-initiation P_{FC}
10-14	2000	500	240
15-19	3500	1500	720
20-24	2000	2000	960
25-29	1000	2000	960
30-34	500	2000	960
35-54	0	2000	960
55-64	0	2500	1200
65-69	0	3000	1440
70-74	0	3500	1680
75-79	0	4000	1920

The probability of transition between the three states N = never, C = current and F = former, is described by P followed by two subscripts, the first representing the state changed from, and the second the state changed to.

Although the model is flexible and allows the TTPs to vary by time, in the simulations presented here we make the following assumptions for the TTPs included in the Null Scenario:

- The TTPs are independent of period and sex.
- The initiation rates, which are reported to be almost non-existent in adult population over 30 years of age, have been assumed to be zero over 35 years of age. (Prevention 2016)
- The re-initiation rates are 48% of the cessation rates. (Weinberger 2014)
- Smokers who have made a recent quit attempt, are more likely to quit again. Therefore we assumed that the probability of cessation is two times more likely in smokers who have recently made a quit attempt.
- Recent quitters are more likely to re-initiate than are long-term quitters. Therefore we assumed that the probability of re-initiation is two times more likely in quitters who have quit in the last 2 years, compared to those who have quit for more than 2 years.

6.5.2.4. The Tobacco Transition Probabilities – The THS Scenario

As we are specifically considering the introduction of THS into the US market, we refer to the MRTP Scenario as the "THS Scenario". In the THS Scenario, the set of TTPs are much more complex than in the Null Scenario. This is because the model considers three patterns of tobacco product use: cigarette smoking, THS use, and dual use. Therefore three distinct transition rates are required for each of the following: initiation, re-initiation, and cessation. In addition six transitions are required to describe the transitions between the tobacco

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products, making a total of 15 TTPs (Figure 3) that need to be accounted for in the THS Scenario.

		Start of the Interval				
		N	**C_C**	**C_T**	**C_D**	**F**
End of the Interval	**N**	P_{NN}	0	0	0	0
	C_C	P_{NC}	P_{CC}	P_{TC}	P_{DC}	P_{FC}
	C_T	P_{NT}	P_{CT}	P_{TT}	P_{DT}	P_{FT}
	C_D	P_{ND}	P_{CD}	P_{TD}	P_{DD}	P_{FD}
	F	0	P_{CF}	P_{TF}	P_{DF}	P_{FF}

Figure 3 Matrix of Possible Tobacco Transition Probabilities (TTPs) under the THS Scenario

Where the tobacco use patterns for the THS Scenario are defined as N=never-smoker, CC=current cigarette smoker, CT=current THS user, CD=current dual user, and F=former tobacco user. The six Tobacco Transition Probabilities are =probability of switching product use =probability of initiating, =probability of re-initiating, and =probability of cessation. Under this Scenario the probabilities of individuals not transitioning within an interval can be calculated as the complement of the probabilities of a transitions from that group.

Prior to marketing THS, the results from our Clinical Assessment and Perception and Behavioral Assessment Programs were evaluated to provide information on the TTPs required by the PHIM. Although in the pre-market studies, the majority of subjects assigned to use THS mainly used THS, there were individuals that dual used (i.e., combined use of both cigarettes and THS). Because these studies were conducted in a pre-market setting with study subjects and not with consumers of THS, most of the studies did not include the product messaging and/or claims that are intended to support the transition of cigarette smokers to exclusive users of THS. The results from these studies were used to characterize the patterns of tobacco use that were observed and therefore needed to be addressed in the simulations to ensure that the model could assess the impact of introducing THS in the US market.

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The ingoing assumptions (the "Business Case") for the THS Scenario TTPs were aligned with some of the potential PMI forecasts. This allows us to quantify the impact on the population as a whole, if PMI were to achieve the forecast. Table 3 and Table 4 present the TTPs for the THS Scenario. These are one set of TTPs but, in order to present them in a readable format, they were split into two tables, with Table 3 presenting the initiation, cessation and re-initiation rates and Table 4 presenting the switching rates between tobacco products. The Prevalence Component simulations from the Business Case provide insight into the impact of introducing THS on the prevalence of tobacco use at a population level.

The simulations presented here make the following assumptions for the TTPs included in the THS Scenario:

- Based on one potential forecast, the "Business Case" defines the uptake of THS in the market. The aim is that within 10 years of marketing THS in the US market, 17% of the smoking population will be using THS (with approximately 15% THS users, and 2% dual users).
- Based on the experience with cigarettes, we assume that product use transitions, including transitions to THS, will be more likely in the middle age segment of the population. In the younger segment of the population transitions to THS will be less likely for reasons such as the investment cost to purchase the device. In the older segment of the population transitions to THS will also be less likely due to the fact that this segment is, in general, less likely to make a switch.
- From the pre-market Perception and Behavioral Assessment studies (Section 7.3), we found that in general, never and former smokers were not interested in trying THS. Therefore in the Business Case we assume that the introduction of THS into the US market will not change the overall rates of initiation, re-initiation or cessation from the Null Scenario. The introduction of THS will only change the distribution of initiation, re-initiation and cessation between the different products on the market (cigarettes, THS, dual use).
- Similar to the Null Scenario, the following assumptions are assumed to hold for the different products on the market (cigarettes, THS, dual use):
    - Initiation rates from age 35 years are zero.
    - The re-initiation rates are higher in the middle age than in the younger segment of the population, and are 48% of cessation rates.
    - Cessation rates are two-times higher in those who have recently attempted to quit.
    - The re-initiation rates are two-times higher in quitters who have quit within the last 2 years.
- After one year of continuous THS use, it is assumed that individuals are unlikely to switch back to cigarettes or start dual use.

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Table 3 Monthly Tobacco Transition Probabilities (per million) under the Target THS Scenario – Probabilities of Initiation, Cessation and Re-Initiation

Period of follow-up	Age	Initiation			Cessation			Re-initiation		
		P_{NC}	P_{NT}	P_{ND}	P_{CF}	P_{TF}	P_{DF}	P_{FC}	P_{FT}	P_{FD}
1-24	10-14	1660	260	80	500	500	500	144	48	48
	15-19	2905	455	140	1500	1500	1500	432	144	144
	20-24	1660	260	80	2000	2000	2000	576	192	192
	25-29	830	130	40	2000	2000	2000	576	192	192
	30-34	415	65	20	2000	2000	2000	576	192	192
	35-39	0	0	0	2000	2000	2000	576	192	192
	40-44	0	0	0	2000	2000	2000	576	192	192
	45-49	0	0	0	2000	2000	2000	576	192	192
	50-54	0	0	0	2000	2000	2000	576	192	192
	55-59	0	0	0	2500	2500	2500	720	240	240
	60-64	0	0	0	2500	2500	2500	720	240	240
	65-69	0	0	0	3000	3000	3000	864	288	288
	70-74	0	0	0	3500	3500	3500	1008	336	336
	75-79	0	0	0	4000	4000	4000	1152	384	384
25+	10-14	1416	484	100	500	500	500	96	96	48
	15-19	2478	842	180	1500	1500	1500	288	288	144
	20-24	1416	484	100	2000	2000	2000	384	384	192
	25-29	708	230	60	2000	2000	2000	384	384	192
	30-34	354	116	30	2000	2000	2000	384	384	192
	35-39	0	0	0	2000	2000	2000	384	384	192
	40-44	0	0	0	2000	2000	2000	384	384	192
	45-49	0	0	0	2000	2000	2000	384	384	192
	50-54	0	0	0	2000	2000	2000	384	384	192
	55-59	0	0	0	2500	2500	2500	480	480	240
	60-64	0	0	0	2500	2500	2500	480	480	240
	65-69	0	0	0	3000	3000	3000	576	576	288
	70-74	0	0	0	3500	3500	3500	672	672	336
	75-79	0	0	0	4000	4000	4000	768	768	384

The probability of transition between the five states N = never, C = current cigarette smoking, T = current THS use, D = current dual use, and F = former, is described by P followed by two subscripts, the first representing the state changed from, and the second the state changed to.

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Table 4 Monthly Tobacco Transition Probabilities (per million) under the Target THS Scenario – Probabilities of Product Switching

Period of follow-up	Age	Switching within current tobacco use groups					
		P_{CT}	P_{CD}	P_{TC}	P_{TD}	P_{DC}	P_{DT}
Any	10-14	600	1	600	1	100000	400
	15-19	600	1	600	1	100000	400
	20-24	600	1	600	1	100000	400
	25-29	1200	1	600	1	100000	400
	30-34	1200	1	600	1	100000	400
	35-39	1200	1	600	1	100000	400
	40-44	1200	1	600	1	100000	400
	45-49	1200	1	600	1	100000	400
	50-54	1200	1	600	1	100000	400
	55-59	1200	1	600	1	100000	400
	60-64	1200	1	600	1	100000	400
	65-69	1200	1	600	1	100000	400
	70-74	1200	1	600	1	100000	400
	75-79	1200	1	600	1	100000	400

The probability of transition between the five states N = never, C = current CC, T = current THS, D = current dual, and F = former, is described by P followed by two subscripts, the first representing the state changed from, and the second the state changed to.
If the individual has used THS continuously for more than 1 year P_{TC} and P_{TD} are multiplied by 0, indicating that they are unlikely to switch to cigarette use or dual use.

6.5.2.5. The Follow-Up Population - Over the 20-Year Simulation (2009)

The output from the Prevalence Component is the complete set of sex and age-specific annual smoking histories for the hypothetical population over the 20 years of transitions following each of the two Scenarios (Null and THS Scenarios). Figure 4 below displays distribution of smoking histories under the Null Scenario for the male population aged 30-79 in 2009 (at the end of the simulation) as well as over time, while Figure 5 displays the same information for the female population.

It is interesting to note some of the differences in the smoking histories between the male and female populations, as these differences at the population-level may later influence the smoking-attributable mortality within the population. In the male population, we observe a reduction in the proportion of never smokers with age, which is replaced by an increase in the proportion of former smokers within the higher age groups and a fairly constant rate of smokers across the age groups.

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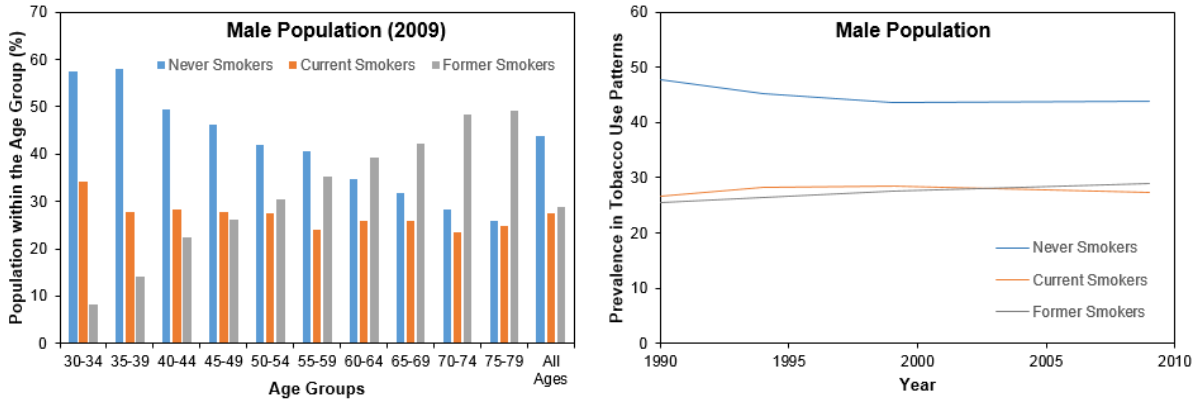


Figure 4 Distribution of Smoking Patterns in the Null Scenario in the Male Population

Left: Prevalence of product use patterns within age-groups in the male population after 20 years of follow-up (2009). Note that since the model starts with 10-14 year olds that at the end of the simulation the younger end of the population is 30-34 years old. Right: Changes in the overall prevalence of the product use patterns through the 20 year follow-up period

This age related trend in smoking seen in 2009 for the male population is not replicated for the female population, where we see that the proportion of never smokers fluctuates slightly between the age groups, but overall remains fairly constant, with a slight increase in the proportion of former smokers because of the decrease in current smokers. We also see that the trend over time in never smokers, current smokers and former smokers is very similar between men and women, the only notable difference being that there are over 10% more never smokers in women than in men which results in an approximately equally distributed reduction in current and former smokers (approximately 5% reduction in each group).

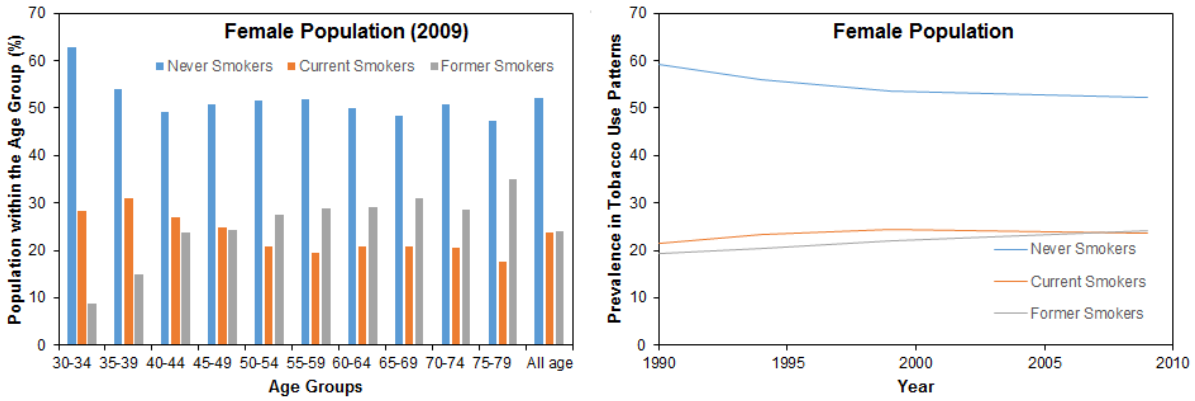


Figure 5 Distribution of Smoking Patterns in the Null Scenario in the Female Population

Left: Prevalence of product use patterns within age-groups in the female population after 20 years of follow-up (2009). Note that since the model starts with 10-14 year olds that at the end of the simulation the younger end of the population is 30-34 years old. Right: Changes in the overall prevalence of the product use patterns through the 20 year follow-up period

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Figure 6 displays the distribution of smoking histories under the THS Scenario for the male population aged 30-79 in 2009 (at the end of the simulation), as well as over time (1990, 1994, 1999, and 2009). Figure 7 displays the same information for the female population. The differences in the 2009 smoking patterns between men and women that were noted under the Null Scenario are also present in the THS Scenario, although THS and dual use appear to not be influenced in the same manner. In line with the ingoing assumption, the introduction of THS does not impact the prevalence of never smokers or former smokers, while the current smoker population is reduced over time to allow for THS use.

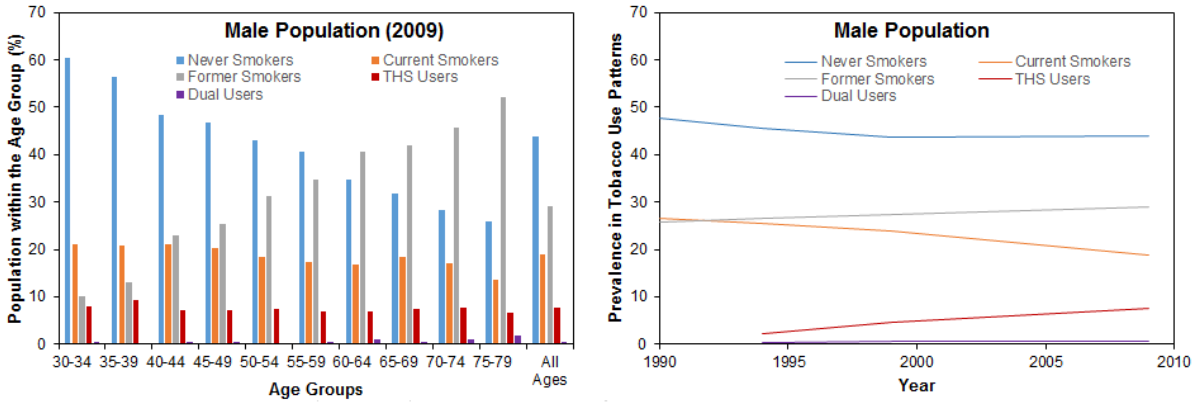


Figure 6 Distribution of Smoking Patterns in the THS Scenario in the Male Population

Left: Prevalence of product use patterns within age-groups in the male population after 20 years of follow-up (2009). Note that since the model starts with 10-14 year olds that at the end of the simulation the younger end of the population is 30-34 years old. Right: Changes in the overall prevalence of the product use patterns through the 20 year follow-up period

As in the Null Scenario the changes in the product use patterns over the 20 year follow-up period are very similar between the male and female populations, with the same reduction of approximately 10% more never smokers in women than in men which results in an approximately equally distributed reduction in current smokers and former users (approximately 5% reduction in each group).

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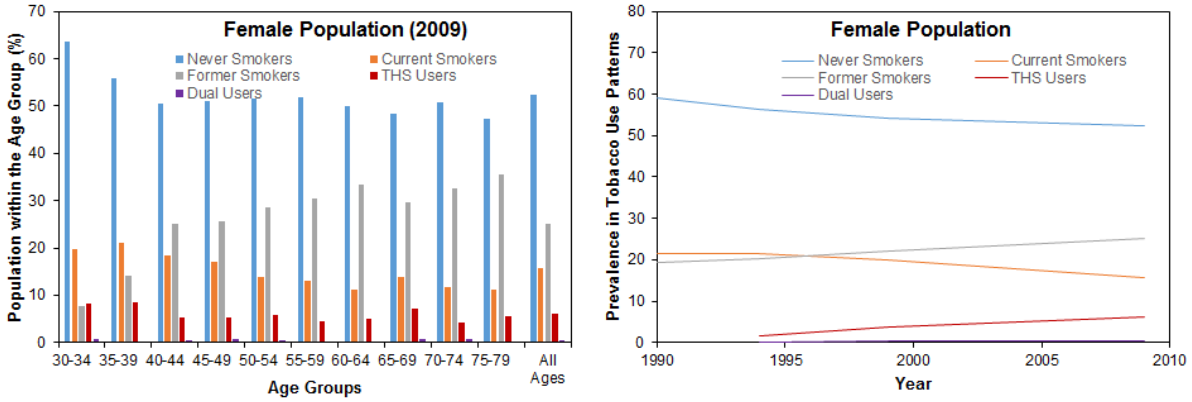


Figure 7 Distribution of Smoking Patterns in the THS Scenario in the Female Population

Left: Prevalence of product use patterns within age-groups in the female population after 20 years of follow-up (2009). Note that since the model starts with 10-14 year olds that at the end of the simulation the younger end of the population is 30-34 years old. Right: Changes in the overall prevalence of the product use patterns through the 20 year follow-up period

When comparing the simulations across the two Scenarios, we see a very consistent trend across all of the age groups and in both sexes, namely:

- In 1990, in the male population, the prevalence of tobacco product use was 26.6% (cigarettes), which did not notably change over the 20 year period for either Scenario resulting in 27.0% tobacco product use under the THS Scenario and 27.4% cigarette use under the Null Scenario. In the female population, this change was slightly larger with the prevalence of tobacco product use in 1990 being 21.6% increasing to 23.7% under the Null Scenario, while remaining fairly constant in the THS Scenario (22.3%).
- By 2009 THS users make up almost 30% of the male tobacco users (8.1% of the overall population), while in women THS use accounts for more than 29% of all tobacco consumption (6.5% of the overall population).
- In the male population, there is a clear reduction in the prevalence of never smokers with age which increases with an increasing length of follow-up due to the fact that fewer of the more recently born cohorts smoke. This pattern is not as clear in women, where although the prevalence of never smokers does decrease with increasing follow-up, there is also no clear trend with age and the rate of never smokers appears to stay fairly constant over the age groups.
- There are some slight increases in the prevalence of former users by age groups, but essentially the prevalence of former users is not affected by the introduction of THS into the market at the overall population-level.

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6.5.3. Impact on the Population Health

6.5.3.1. Considerations for the Epidemiological Risk Component

No Monte-Carlo simulation in E-Component. No attempt was made to allow for variation in the number of subjects with a given tobacco history and underlying rate that actually die. Thus, though the Prevalence Component involves Monte-Carlo simulation to generate samples of smoking history distribution, the Epidemiological Risk Component does not involve simulation.

Restriction to four diseases. The PHIM considers deaths from lung cancer, COPD, IHD and stroke. These are the four most common smoking-related diseases, and there is a substantial amount of data for each of these diseases to provide estimates of the relative risk (of smokers compared to never smokers) and of the half-life of excess risk following cessation from smoking. Ezzati and Lopez concluded that in industrialized countries in 2000 there were a total of 2,427,000 smoking-attributable deaths (1,815,000 in men and 612,000 in women) and, of these, 1,853,000 (76%), of the smoking attributable deaths (1,361,000 in men and 492,000 in women), were from lung cancer, COPD and cardiovascular diseases (CVD) (Ezzati 2003). Even after adjusting for the fact that IHD and stroke only account for about 75% of the estimated CVD deaths associated with smoking, the four diseases incorporated into the model still account for approximately 66% of all estimated smoking attributable deaths. Provided the reduction in risk due to the introduction of THS is similar between the diseases included in the model and the diseases not included in the model, the PHIM estimates of deaths saved from the introduction of THS would be a conservative estimate and would need to be multiplied by a factor of about 1.52 (1.55 in men, 1.44 in women) to give an overall estimate for all smoking-related diseases (Weitkunat 2015).

Environmental tobacco smoke (ETS) exposure. When estimating the reduction in the number of deaths associated with the introduction of THS, the PHIM does not account for ETS exposure. Recent meta-analyses on ETS and lung cancer (Lee 2016), COPD (Lee 2013a), IHD (Lee 2015b) and stroke (Lee 2013b) show that, for these diseases, the RRs associated with ETS exposure in never smokers is much lower than the corresponding RRs for current smoking. This suggests that any impact of ETS will not have a substantial effect on the estimates of cases saved from these diseases.

THS-related reductions in risk may occur even when disease rates rise. The Epidemiological Risk Component may estimate THS-related reductions in deaths from some diseases even when the actual rate of disease rises. This is not indicative of an error, but merely reflects an underlying adverse trend in the risk factors associated with the disease other than cigarettes (e.g., obesity). In this situation, the estimate would suggest that had THS not been introduced, the rise in mortality from these diseases would have been greater.

6.5.3.2. Risks Associated with the Tobacco Use Histories

The method of estimating the excess relative risk for each disease depends on first calculating what an “equivalent dose” is at each age, and then multiplying this by the excess relative risk for a smoker continuing to cigarette at that age. The equivalent dose for an individual is derived from relative exposures relating to tobacco use patterns (as defined in

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Table 5) at different ages. The equivalent dose will be 0 at birth, as all individuals are then non-smokers, and so long as the individual does not start to smoke their equivalent dose will remain at 0. Once an individual starts to use a tobacco product, their relative exposure will increase, and their equivalent dose will gradually move (following a negative exponential model) towards the relative exposure related to their specific tobacco product use pattern. Subsequently, further switches in tobacco product use will result in further changes in relative exposure, with their equivalent dose gradually moving in the direction of the new relative exposure.

Formally, the method can be defined as follows. Assume that, at each year of age, an individual's relative exposure is F(a) and the half-life is H(a). First, calculate the negative exponential factor for a single year as $N(a) = \exp(-\log_e(2) / H(a))$. The equivalent dose, ED(1), is taken as 0, and subsequent values of are then calculated by the formula

$$ED(a) = N(a)\, ED(a\text{-}1) + (1\text{-}N(a))\, F(a) \qquad (1)$$

Thus, the equivalent dose is calculated based on the estimate from the previous year, and the effective exposure in the year. Note that though values of H(a) were derived from data on cessation, where the change in relative exposure is from 1 to 0, H(a) is used more generally in relation to any change in relative exposure, including initiation, re-initiation and upward or downward dose-switching.

Table 5 Relative Exposures by Tobacco Product Use Pattern

Tobacco Product Use Pattern	Relative Exposure
Non Smoker (never or former tobacco product user)	0
Current Smoker	1
THS User	f
Dual User	$(1+f)/2$

Dual use is assumed to be half way between THS and smoking,

The estimates of relative risks for continued smoking and the half-lives (H) of excess risk following smoking cessation, by disease and age are presented in Table 6. These estimates were all derived from meta-analyses of published data. Age-dependent estimates are included only if there is strong evidence that the RRs and/or half-lives varies with age. Although there are variations in the relative risk within individual studies, there is currently very little evidence that either the RRs or half-lives vary by sex, so the estimates have been taken to apply to both sexes.

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Table 6 Estimated Relative Risks for Continued Smoking and Half-Life (H) of Excess Relative Risk - by Disease

		Disease			
	Age	**Lung Cancer**	**IHD**	**Stroke**	**COPD**
Relative risks[1]	Any	11.68			4.56
	to 54		3.38	2.48	
	55 to 64		2.32	2.13	
	65 to 74		1.70	1.39	
	75 to 79		1.27	1.06	
Half-life[2]	Any			4.78	13.32
	to 49	6.98	1.47		
	50 to 59	10.39	5.32		
	60 to 69	10.60	7.48		
	70 to 79	12.99	13.77		

[1] Sources for relative risks: Lung cancer: (Lee 2012a) Table 8; COPD: (Forey 2011) Table 7; IHD and Stroke (Lee 2016 – not yet published).
[2] Sources for half-lives: Lung cancer: (Fry 2013) Table 6; COPD: (Lee 2014a) Table 4; IHD: (Lee 2012b) Table 5; Stroke: (Lee 2014b) Table 5

From this information the PHIM is able to estimate an individual's relative risk profile by age based on the tobacco product use pattern over time. Figure 8 below illustrates the impact of changes in relative exposure on changes in relative risk. In this example the individual:

- Enters the simulation at 18 years of age as a smoker (with initiation at 16)
- Switches to dual use (cigarettes and THS) at the age of 25
- Converts to THS use at the age of 35
- Quits THS use at the age of 40
- Re-initiates smoking cigarettes at the age of 50.

We can see in this example that during both of the periods of smoking cigarettes the individual's estimated relative risk rises. We also observe a lesser reduction in the estimated relative risk with dual use than we see with the use of THS. In the Epidemiological Risk Component of the model, this information is generated for each individual in the hypothetical population (each smoking history produced in the Prevalence Component).

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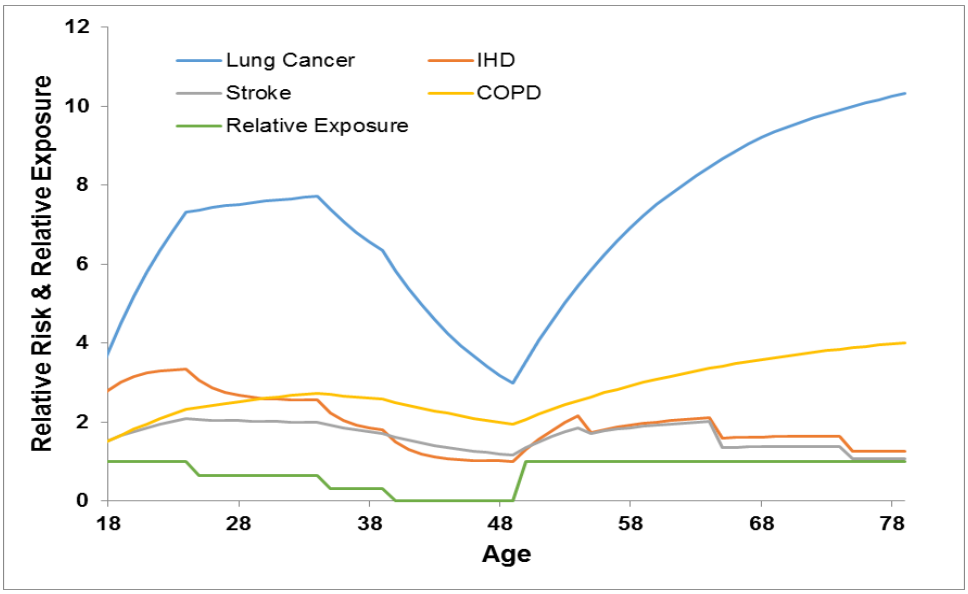


Figure 8 Illustration of the Increase and Decrease in Estimated Relative Risk by Age with Changing Tobacco Product Use Patterns

Each individual in the population will have a curve like this of relative exposure by age. In this example we assume an *f* for THS of 0.3 (for illustrative purposes), which results in a dual use relative exposure = 0.65. The individual started smoking at the age of 16, switched to dual use at age 25, and then became an THS user at the age of 35 before quitting at the age 40 and re-initiating smoking at the age of 50

In examining the absolute risk profile generated by the PHIM, we see that, consistent with the literature, the absolute risk of disease mortality is a function of age, years of smoking and age at the time of cessation. Below in Figure 9 we compare patterns of absolute risk of lung cancer in an individual that never smokes (green line) and in three individuals who initiate smoking at the age of 20 and who either continue to smoke (red line), quit at age 40 (orange line) or quit at age 30 (blue line). There is a clear difference in risk within a few years of quitting, illustrating the reduction of risk from smoking cessation. However the risk that is accumulated with years smoked prior to cessation is not overcome with years quit. The younger a person is when they quit smoking (or switch to a lower risk product), the lower their risk of developing lung cancer (or other smoking related disease).

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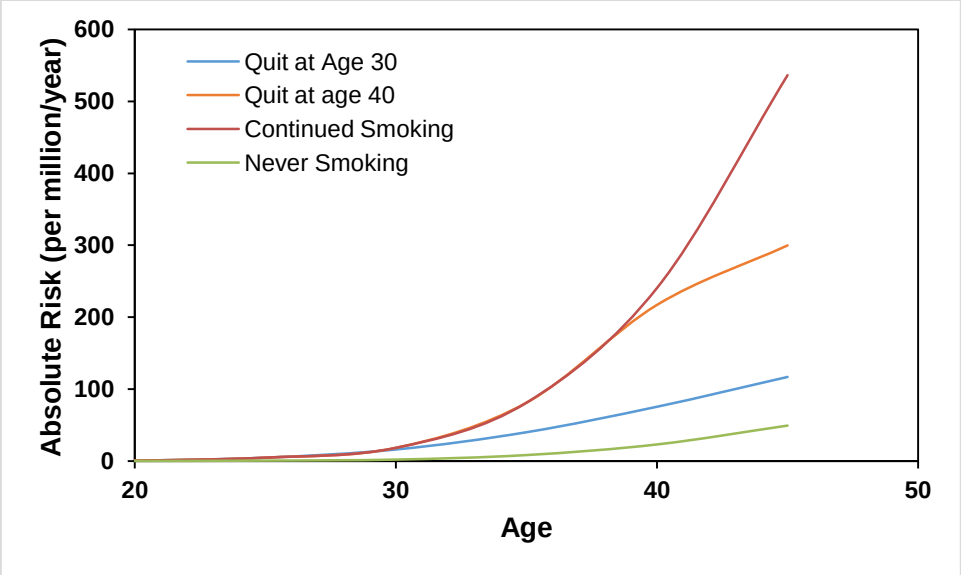


Figure 9 Illustration of the Increase in the Estimated Absolute Risk of Lung Cancer with Increased Age and Years of Smoking

This compares the absolute risk profile of smokers initiate smoking at the age of 20 and continue to smoke or quit at ages 30 and 40. Never smokers are shown as a reference. The data are approximate because the absolute data collected from the literature is presented in risk by 5 year age groups

6.5.3.3. The *f*-value for THS

The *f*-value is the parameter in the Epidemiological Risk Component for the product-specific (THS-specific) relative exposure. In the absence of long term health outcome studies of a marketed product, this parameter cannot be empirically measured. Therefore in the pre-market setting an assumption (or set of assumptions) is required to estimate the THS-specific *f*-value.

In the Epidemiological Risk Component, the relative risk for an individual switching from cigarettes (C) to THS is estimated by

$$RR_{THS}(a,t) = 1 + (RR_C(a) - 1)\,(f + (1-f)\exp(-t\ln(2)/H)).$$

where the subscripts define the tobacco product, t is the time since switching to the product, H is the disease-specific half-life of the excess relative risk, and a is age.

In order to derive an estimate of *f*, the non-clinical and clinical data collected during the product assessment programs were examined. PMI developed a multivariate *f*-value distribution based on objective Bayesian statistics. The details of this approach can be found in Section 7.4 "*f*-value Sampling Report".

After testing the model with the non-clinical and clinical data separately, the resulting distribution of estimated *f* –values were similar for both sets of data, therefore we derived the estimates for this summary using data from the Reduced Exposure studies to compare the effects of continued smoking, with the effect of switching to THS. Also included in these

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studies, to provide context for the magnitude of the change after switching to THS, was a study arm that switched individuals from smoking to smoking cessation (the "gold standard" for harm reduction).

The data from studies in a confinement setting (ZRHR-REXC-03-EU and ZRHR-REXC-04-JP) and in an ambulatory setting (ZRHM-REXA-07-JP and ZRHM-REXA-08-US) were evaluated to determine the relative change (RC) in each parameter (X):

$$\doteq \frac{(\ |\ )-(\ |\ )}{(\ |\ )-(\ |\ )}$$ (where *i* is the index to identify each parameter)

In the absence of data to inform the model, we assumed that the f-value is uniformly distributed between 0 (smoking cessation) and 1 (continued smoking). To inform the model distribution of the f-values, we looked at the set of biomarkers of exposure (BoExp) and clinical risk endpoints collected in the studies. The assumptions for the model were:

- Normality of the conditional distribution of each biomarker given the product use.
- The effect of the MRTP must lie between the effect of continued smoking and the effect of cessation.
- The relative changes in the parameters provide information on the f-value using a link function of an unknown multi-endpoint biomarker that ensures the sufficiency of the selected set of biomarkers.
- The set of markers is adequate to provide information on the f-value.

The distribution of f-values from the estimates of the probability distributions of RC (for a given link function) requires various assumptions on the sufficiency and necessity of the set of biomarkers collected in the pre-market studies.

Due to the types of biomarkers and length of follow-up that were available in the Reduced Exposure studies, the level of sufficiency and necessity were both set to 0.5 and from the resulting distribution of the estimated f-values a sample of 99 were drawn at random to generate the f-value that would be used in the Epidemiological Risk Component (Figure 10). From the sample of 99 f-values, we see that the distribution is left weighted. Although the values range from 0.02 to 0.95, almost 60% of the observations are less than 0.375, with the mean f-value of 0.35 (95%CI: 0.3, 0.4) and the median f-value of 0.30.

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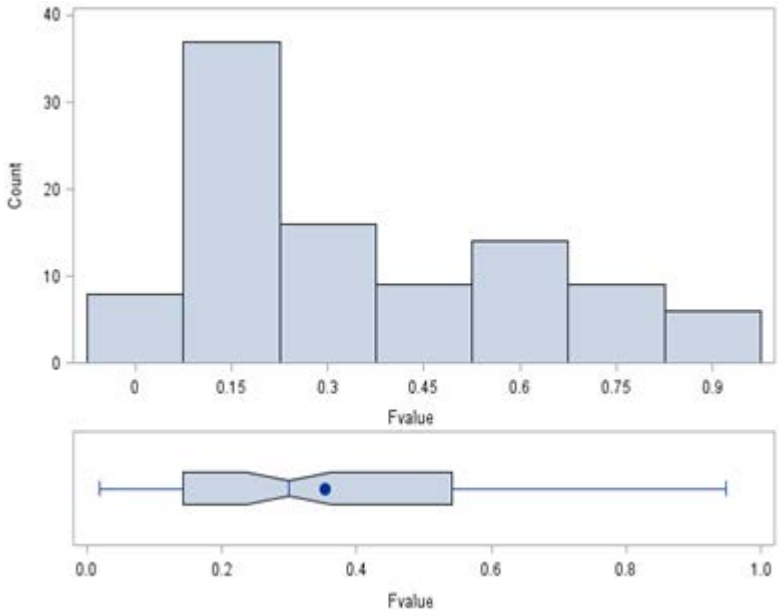


Figure 10 Distribution of the sample of f-values

For the purposes of this modeling exercise a collection of 99 f-values we sampled from the distribution f with a lack of sufficiency= 0.5 and a necessity of 0.5

To examine the impact of THS on the health of the population after the introduction of THS into the US market, the simulations of the Epidemiological Risk Component of the PHIM were all run with following f-values.

- $f = 0$, to interpret the impact of THS, it is important to put the results in the context of the maximal achievable impact on health, the 'gold standard' effect of cessation, under the scenario defined by the Prevalence Component.
- $f = 0.10$, because for THS the results of the aerosol chemistry showed a reduction of more than 90% in the levels of HPHCs formed and the Reduced Exposure studies demonstrated that 90% of the effects of cessation are achieved in those who switched to THS. Therefore, it is important to understand the impact of THS if this directly translates to disease reduction.
- $f = 0.15$, because for the f-value distribution it is the value where the probability mass function takes its maximum value.
- $f = 0.30$, because it is the median of the f-value distribution.

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6.5.3.4. Definition of the Business Case

Parameter	Definition
Country	USA
Sex	Males and Females (separate analysis)
Year of start	1990
Months of follow-up	240 months (20 years)
Follow-up interval length	12 months (1 year)
Lower age for risk estimation	10
Upper age for risk estimation	79
Relative exposure for THS use (f-value)	0, 0.10, 0.15, 0.30
Relative exposure for dual use	0.50, 0.55, 0.575, 0.65
Factor 1 : Probability that a THS user will relapse to cigarettes is X times higher if the individual previously was a cigarette smoker	Not applicable
Factor 2 : Probability that a current smoker, THS user, or dual user will quit X times higher if the individual has previously quit	X=2
Factor 3 : Probability that a former tobacco user will start smoking cigarettes, start using THS or start being a dual users is X times higher if the individual is a short-term quitters	X=2
Definition of a short term quitter (less than X years ago)	X=2 years
Factor 4 : Probability that a THS user will switch to cigarettes or dual use becomes X if the individual is a continuous user of the THS *Note: if this factor (Factor 4) is applied Factor 1 above is not applied.*	X=0
Definition of continuous user of THS is more than X years of THS use	1 year
Number in population simulated	10,000
Number of simulations	1
Source for population data	UN [1]
Source for current smoking prevalence data	ISS [2]
Source for former smoking prevalence data	ISS [2]
Source for quit-time distribution data	NHIS [3]
Source for deaths by cause	WHO [4]
Source for relative risks	Table 6
Source for half-lives	Table 6
TTPs in Null Scenario	Table 2
TTPs in MRTP Scenario	Table 3 and Table 4
Adjustment for population size	None

[1] UN = The United Nations website (United Nations 2013).
[2] ISS = International Smoking Statistics, (Forey 2006-2013).
[3] NHIS = National Health Interview Survey for 2006 (www.cdc.gov/nchs/nhis htm).
[4] WHO = World Health Organization data downloaded on December 2014 (World Health Organization 2013).

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6.5.3.5. Testing the Appropriateness of the Null Scenario

Assessment of the Prevalence Component

The appropriateness of the Prevalence Component under the Null Scenario was tested by comparing the International Smoking Statistics estimates of smoking prevalence (current and former smokers) for ages 30-34, 50-54 and 70-74 in 1995, 2000, 2005 and 2010 with those predicted from the PHIM (Figure 11).

The simulated prevalence for the years 1990 and 1995 agree quite well with the International Smoking Statistics database (ISS) estimate, though for later years the correspondence is not as strong. It is also better for ages 30-34 and 50-54 than for ages 70-74 years. Exact correspondence between these two estimates was not expected for various reasons, such as variation due to the simulation process, inaccuracies in the ISS estimates and ISS estimates for the US population not being available past 2005 (so that 2005 estimates were used for later years). Also the modelling assumes that the initial sample survives throughout follow-up, with no account taken of differential mortality by smoking pattern, or of immigration or emigration. Although it would have been possible to modify the set of TTPs used to improve the fit, for example by allowing the TTPs to vary by time, it was considered, based on the sensitivity analyses Section 7.4 “PHIM Simulations and Sensitivity Analysis Report”., that these adaptions to the model would be unlikely to affect the assessment of population health.

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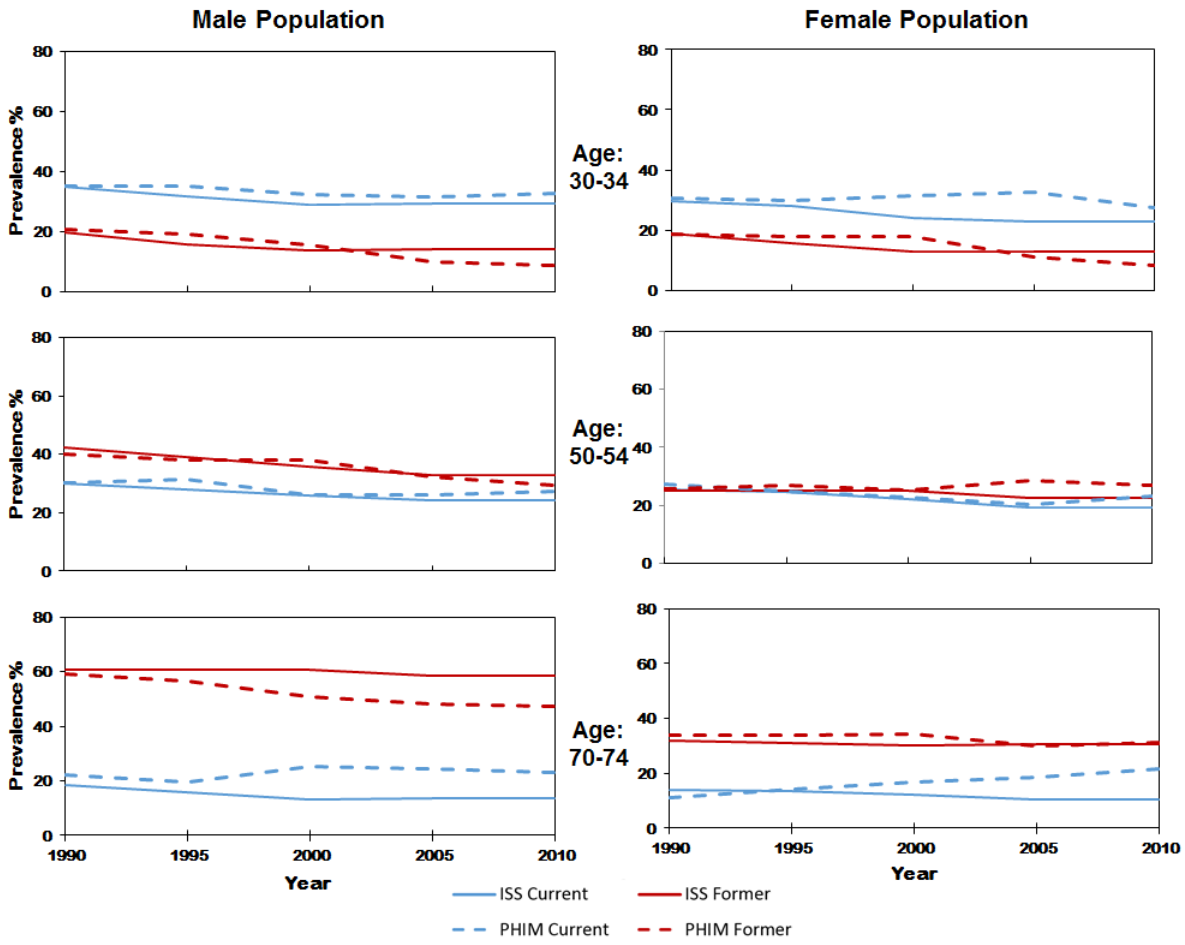


Figure 11 Comparison of PHIM "Prevalence Component" Estimates of Current Smokers and Former Smokers under in Null Scenario as Compared to the International Smoking Statistics Estimates

Assessment of the Epidemiological Risk Component

The appropriateness of the Epidemiological Risk Component, under the Null Scenario was also tested. To test the Epidemiological Risk Component, the estimate of smoking attributable deaths predicted from the PHIM was compared with the published estimates from the US Surgeon General Report (2014) for 2005-2009 and the Morbidity and Mortality Weekly Report (Anonymous 1993) for 1990 (Table 7).

The results for most diseases are quite similar between PHIM and the published data, especially when compared with the Surgeon General estimates. However, there is a notable difference for COPD, with the Null Scenario estimates much lower in both sexes. This difference mainly arises due to the much lower current smoking RRs estimate incorporated in the PHIM.

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- PHIM estimate of RR for COPD = 4.56 (male and female)
- Morbidity and Mortality Weekly Report (MMWR) estimate of RR for COPD = 9.7 (male) and 10.5 (female)
- Surgeon General estimate of RR for COPD (age 65-74) = 29.69 (males) and 38.89 (female)

Given that the PHIM estimate was based on a published meta-analysis (Forey 2011) involving 39 North American studies, with the 95% confidence interval for our estimate as narrow as 3.69 to 5.62, it seems possible that the US Surgeon General published RR estimates may be too high.

Table 7 Comparison of Estimates of Smoking Attributable Deaths between PHIM – Null Scenario and Published Estimates

		MMWR [1]	PHIM Null Scenario			USSURG [2]
Sex	**Disease**	**1990**	**1990**	**2005**	**2009**	**2005-09**
Estimates of Smoking Attributable Deaths expressed as % of All Deaths from the Specified Cause(s)[3]						
Male	Lung cancer	89.3	80.5	77.5	76.8	83.7
	IHD	26.0	22.4	21.4	21.5	28.2
	Stroke	26.8	14.0	13.7	14.1	15.3
	COPD	81.5	57.1	53.5	52.5	82.0
	Four diseases	45.0	39.7	39.5	39.9	46.1
Female	Lung cancer	71.4	71.8	72.9	72.7	80.7
	IHD	14.2	12.8	15.2	15.9	19.4
	Stroke	9.6	9.5	10.5	10.9	8.7
	COPD	66.4	43.7	46.8	46.7	75.7
	Four diseases	24.9	28.7	36.4	38.6	36.8
Estimates of Smoking Attributable Deaths expressed as % of Total Smoking-attributable Deaths for the Four Smoking Related Diseases Combined						
Male	Lung cancer	40.3	50.4	51.0	51.1	38.2
	IHD	32.5	30.5	27.0	26.0	31.7
	Stroke	7.4	3.6	3.7	3.8	4.2
	COPD	19.7	15.4	18.3	19.1	25.9
Female	Lung cancer	35.1	53.5	55.3	55.8	37.3
	IHD	33.0	22.0	16.0	14.2	24.8
	Stroke	8.2	5.6	4.3	4.1	4.7
	COPD	23.7	18.9	24.4	25.9	33.2

[1] Morbidity and Mortality Weekly Report (MMWR) data are from Anonymous (1993) and for age 35+. ICD-9 codes used are: lung cancer 162, IHD 410-414, stroke 430-438, COPD 491-492, 496.

[2] US Surgeon General (USSURG) data are from US Surgeon General (2014) and also for age 35+. ICD-10 codes are used: lung cancer C33-C34, IHD I20-I25, Stroke I60-I69, COPD J40- J44.

[3] Total numbers of deaths by cause for age 35+ were not given, so, in order to calculate the percentage presented as a % of deaths for all causes, the World Health Organization (2013) data were used. From the WHO data the COPD definition used differed somewhat (ICD-9 490-493, 495, 496).

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6.5.3.6. The Impact of THS on the Population

When looking at the cumulative lives saved (over the 20 year follow-up period), for the four diseases combined (lung cancer, IHD, stroke and COPD) it is first important to understand the maximal contribution to lives saved that could be achieved for the Business Case prevalence assumptions. Therefore if all individuals that transitioned to THS user had instead successfully quit smoking (f-value=0) at the time they would have switched to THS, the total number of lives saved could have reached a maximum of 100,234 (67,151 in the male population and 33,083 in the female population).

In the Business Case simulations the introduction of THS is associated with a drop of 47,649 to 60,586 deaths in male population and 22,625 to 29,569 deaths in the female population (using f-values between 0.1 and 0.3). This represents, a 0.82-1.04% reduction in all deaths (2.1-2.7% in smoking-attributable deaths) in the male population and a 0.58-0.76% reduction in all deaths (1.7-2.3% in smoking-attributable deaths) in the female population. This means that over the 20 year simulation, the introduction of THS could save in total between 70,274 and 90,155 out of a total potential of 100,234 lives, if the individuals that switched to THS in the simulation would have quit. Table 8 provides a more detailed summary of the results by each disease and overall for all four disease combined.

Table 8 Cumulative Impact of THS Introduction on the Disease-Specific Mortalities 20 Years after the Introduction of THS, by Disease, Sex and f-value for all Ages Combined

Diseases	Sex	f-value	Drop in deaths	% drop in deaths	% drop in attributable deaths
All Diseases	Male	0	67151	1.155	2.954
		0.1	60586	1.042	2.665
		0.15	57329	0.986	2.522
		0.3	47649	0.820	2.096
	Female	0	33083	0.848	2.540
		0.1	29569	0.758	2.271
		0.15	27823	0.713	2.136
		0.3	22625	0.580	1.737

(table continues)

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Diseases	Sex	f-value	Drop in deaths	% drop in deaths	% drop in attributable deaths
Lung cancer	Male	0	14215	0.963	1.225
		0.1	12882	0.873	1.111
		0.15	12223	0.828	1.054
		0.3	10270	0.696	0.885
	Female	0	9320	0.950	1.309
		0.1	8287	0.845	1.164
		0.15	7776	0.793	1.092
		0.3	6259	0.638	0.879
IHD	Male	0	38046	1.270	5.960
		0.1	34158	1.140	5.351
		0.15	32228	1.075	5.049
		0.3	26494	0.884	4.150
	Female	0	13725	0.831	5.904
		0.1	12363	0.749	5.318
		0.15	11685	0.708	5.026
		0.3	9666	0.586	4.158
Stroke	Male	0	5827	0.928	6.899
		0.1	5255	0.837	6.223
		0.15	4971	0.791	5.886
		0.3	4122	0.656	4.881
	Female	0	4225	0.678	6.894
		0.1	3820	0.613	6.233
		0.15	3618	0.580	5.903
		0.3	3014	0.484	4.919
COPD	Male	0	9062	1.272	2.321
		0.1	8289	1.163	2.123
		0.15	7905	1.109	2.025
		0.3	6761	0.949	1.732
	Female	0	5812	0.900	1.959
		0.1	5098	0.790	1.719
		0.15	4743	0.735	1.599
		0.3	3684	0.571	1.242

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When looking solely at the number of deaths, the reductions in mortality are greatest for IHD in both sexes, and least for stroke. However, when considering the change as a percentage of attributable deaths, the impact of THS is clearly greater for both cardiovascular diseases (IHD and stroke) as compared to lung cancer and COPD; this difference reflects the shorter half-life of excess risk for the cardiovascular diseases.

The percent reductions in total deaths are fairly similar for the four diseases, despite the differences in the numbers of deaths and percent of the deaths attributable to THS use. The effects of the introduction of THS, increase by increased years of follow-up as seen in Figure 12. This reflects both an increase in prevalence of THS use over time and a reduction in the estimated excess relative risk over time. Interesting to note is that for f-values within the range of 0-0.3, the temporal effect is stronger than that of the relative exposure. In this simulation, by 2009, 20 years after introducing THS, there would be 8,775 to 11,160 lives saved annually (approximately 24-31 lives per day).

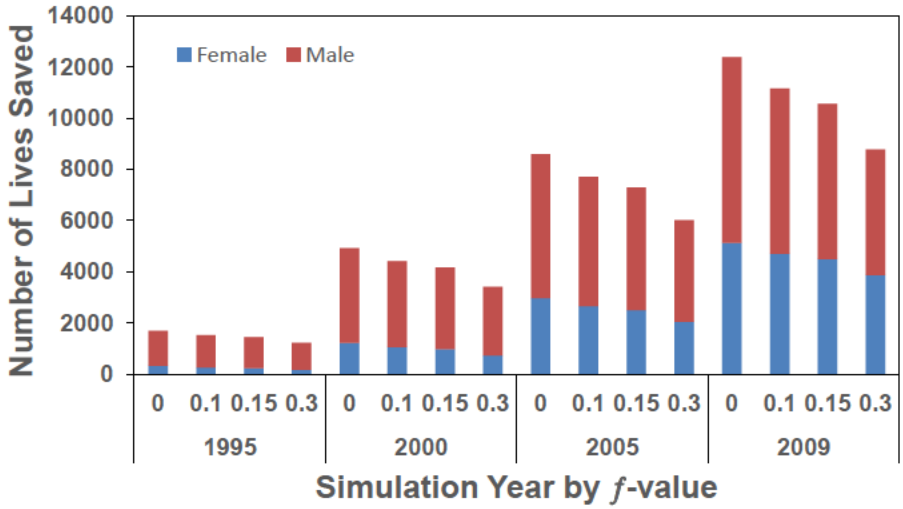


Figure 12 Annual Number of Lives Saved Across all Four Diseases Combined and all Ages

Presented by Simulation and f-value

6.5.4. Sensitivity Analysis and Simulations

The information presented above examines the impact that THS will have on the US population, given that the uptake and patterns of use of THS (e.g., dual vs. exclusive use) are in line with the PMI forecast. To better understand the potential impact that THS could have on the population, a whole series of simulations and sensitivity analyses were run. To see the detailed report, see Section 7.4 "PHIM Simulations and Sensitivity Analysis Report". Below we briefly look at some of the ingoing assumptions, and some variability associated with the assumptions.

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6.5.4.1. Changes in the Business Case

(1) Ingoing Assumption: the introduction of THS will not change the initiation and or cessation rates.

Alternative assumption 1 – the introduction of THS will increase THS-specific initiation or decrease the THS-specific cessation rates.

To examine the impact of this alternative, we looked at two possibilities: (1) doubling the probabilities of initiating with THS or with dual use, and (2) halving the probability of cessation from THS or dual use.

After 20 years in the market, doubling of the initiation rates with THS has a bigger effect on prevalence of use than on mortality rates. After 20 years there are about 1.6% fewer never smokers in the population due to the increased initiation rate. The reduction in never smokers is directly related to the increase in THS users and dual users, with only a minimal shift in the prevalence of cigarette smokers (decreased <0.1%) and former use (increased about 0.4 %) (Table 9). The overall trend in the prevalence of tobacco use decreasing between 1999 and 2009 does not change due to increase initiation, however the rate of decline is less.

Decreasing the cessation rate from THS, does not affect the prevalence of never smoker or current smokers. However, over the 20 year simulation we see a direct reduction (~1%) in the number of former users, which is replaced by an increase in THS users and dual users combined.

In both situations there are fairly significant number of lives saved across the four diseases, namely – 69,711 to 89,879 (47,332 to 60,449 in the male population and 22,378 to 29,429 in the female population), with the increased initiation of THS use. This compares with a potential of 100,110 lives saved if the THS users had quit smoking instead of switching to THS (in this situation with increased initiation). The decreased cessation rates in THS user results in 66,756 to 88,207 lives saved with the introduction of THS (45,587 to 59,463 in the male population and 21,168 to 28,743 in the female population). This compares with 70,274 to 90,155 for the Business Case analysis and 99,093 potential lives saved if the THS users had quit smoking instead of switching to THS (in this situation with decreased cessation).

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Table 9 Effect on Tobacco Use Prevalence in 2009 of Doubling Initiation Rates to THS or Halving Cessation Rates from THS Double Initiation with Cigarettes

		Never Smokers	Current Smokers	Former Users	THS Users	Dual Users
Male	**Business Case**	**43.89**	**18.92**	**29.08**	**7.56**	**0.55**
	Increased Initiation	42.29	18.96	29.47	8.65	0.63
	Decreased Cessation	43.89	18.92	28.00	8.56	0.63
Female	**Business Case**	**52.52**	**15.75**	**25.20**	**6.10**	**0.44**
	Increased Initiation	50.97	15.76	25.63	7.16	0.49
	Decreased Cessation	52.52	15.73	24.28	6.98	0.49

Note: percentages presented in this table are percentage of the adult population, not percentage of the smoking population.

Alternative Assumption 2 - the introduction of THS will increase the overall rate of initiation or decrease the overall cessation rates.

For these simulations we assumed that the introduction of THS leads to (1) a doubling in all the initiation probabilities including the initiation of cigarettes, or (2) a halving the cessation probabilities for all products (i.e., cigarettes, THS, and dual use).

In the simulation, 20 years after doubling of the initiation rate of tobacco products in the population, there is a big reduction in the number of never smokers in the population (>5.1% reduction). This reduction results in an increase across the use of other tobacco use patterns including former users (Table 10).

A scenario that halves the overall cessation rates from all tobacco use had no impact on the prevalence of never smokers. However, unlike the alternative that only considered cessation from THS, this alternative has a larger impact on the current smoking rate. We see a >5% reduction in the number of former smokers in the population as a results of a >4% increase in the prevalence of cigarette smokers and a >1% increase in the prevalence of THS use (including dual use).

Within the simulation's 20 year follow-up, the impact of the increased initiation cannot be fully demonstrated because initiation occurs in the younger segment of the population and the simulation is not long enough to experience more than a minimal mortality associated with the this segment of the population within 20 years. As a result, there are still a fairly significant number of lives saved across the four diseases, 65,809 to 85,886 lives saved (44,867-57,918 in the male population and 20,942-27,968 in the female population), as compared to 96,070 lives saved if the THS users had quit smoking.

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The impact of decreasing the cessation rates has a much bigger effect on the number of lives saved within the simulation, as compared to the Business Case. The majority of the change is due to the increase in the number of cigarette smokers in the population. But even despite this fairly significant change (5% increase in the number of tobacco users, 4% of whom are smoking cigarettes rather than consumers of THS, or other modified risk tobacco products) in population level dynamics, the introduction of THS still results in 3,326 to 23,883 lives saved (as compared to 34,309 lives saved if the THS users has quit smoking).

Table 10 Effect on Tobacco Use Prevalence in 2009 of Doubling all Initiation Rates or Halving all Cessation Rates

		Never Smoker	Current Smokers	Former Users	THS Users	Dual Users
Male	**Business Case**	**43.89**	**18.92**	**29.08**	**7.56**	**0.55**
	Increased Initiation	38.87	21.20	30.45	8.92	0.56
	Decreased Cessation	43.89	23.14	23.44	8.93	0.60
Female	**Business Case**	**52.52**	**15.75**	**25.20**	**6.10**	**0.44**
	Increased Initiation	47.18	18.18	26.39	7.73	0.53
	Decreased Cessation	52.52	19.73	20.03	7.30	0.42

Note: percentages presented in this table are percentage of the adult population, not percentage of the smoking population.

Population changes as large as those presented in these simulation have not been experienced, and are unlikely to be experienced with the introduction of a single new product in a market. However, to fully assess the types of impacts that may be experienced it is important to understand whether or not there is a negative impact of introducing THS even under these fairly extreme situations.

As smoking harm reduction is not the only goal of the Family Smoking Prevention and Tobacco Control Act, it will be important to have a Post-Market surveillance program in place to monitor the changes in smoking prevalence following the introduction of THS. This will allow both the manufacturers and regulators to understand the impact of marketing the product and take the necessary actions in time to prevent changes in tobacco use before they are extreme enough to truly impact the population health.

(2) Ingoing Assumption: the sales of THS will be in line with the forecasts for the product (as stated above).

Based on forecast, the "Business Case" defining the uptake of THS in the market. The aim is that within 10 years of marketing THS in the US market, 17% of the smoking population will be using THS (with approximately 15% THS users, and 2% dual users). (Section 6.5.2.4)

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It is important to note that the THS Scenario is very complex and there are many different ways in which the forecast can be achieved. THS can be introduced into the market in different ways that can impact population prevalence and therefore population harm slightly differently. Although, many alternatives have been run, and the outcomes were all slightly different, in the end the trends were very similar.

Alternative Assumption 1 – THS uptake targets are met (17% of the smoking population is using THS within 10 years) but the rate of dual usage is higher than expected.

It will be important that consumers of THS (or any modified risk tobacco product) understand that the product is more effective when it is not combined with cigarettes. Therefore this alternative looks at the situation where dual use rates are higher than expected.

Two variations in the assumptions for Alternative 1 were considered.

(1) "Slight Increase in Dual Use": A slight increase in prevalence dual use. In this scenario, after 10 years of the simulation, there are 17% THS use in the smoking population but this is made up of 12.4% THS users and 4.4% dual users in the male population and 12.0% THS users and 4.0% dual users in the female population. This compares to the Business Case which included 1.9% dual use in the male population and 1.5% dual use in the female population (Table 11).

(2) "Extreme Increase in Dual Use": A more extreme change in the prevalence of dual use. In this scenario, the majority of THS use occurs in a dual use pattern. After 10 years, there are still 17% THS use in the smoking population, however in this situation 4.8% of the males and 5.1% of the females are mainly using THS, while 12.4% of males and 12.9% of females are dual using THS with cigarettes (Table 11).

Because variations in the assumptions for Alternative 1 do not impact initiation or cessation rates, changes in the prevalence of never smokers and former users, are minimal, in both variations. The main impact is the increase in the prevalence of dual users at the expense of exclusive THS users.

Given the increased relative exposure for dual use (f-value of 0.55-0.65) as compared with THS use (f-value of 0.10-0.30), these situations obviously results in fewer lives saved and the higher the prevalence of dual use, the fewer lives that are saved.

Despite this increase in the prevalence of dual use, we still see lives saved under both variations in the assumptions for Alternative 1:

- Slight Increase in Dual Use results in 61,249-78,766 lives saved compared to the 87,630 lives saved, if the THS use is replaced with not smoking
- Extreme Increase in Dual Use results in 45,802-59,840 lives saved compared to 66,921 lives saved, if THS use is replaced with not smoking.

Importantly, in these alternative scenarios, when the dual use prevalence is higher, the number of lives saved is not as large even under the scenario when THS use is replaced by smoking cessation. This is because in the group of "dual users", use of a combination of THS

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and cigarettes, when THS is replaced by cessation, the individuals in this group are still exposed to cigarettes, with a resulting effective dose of 0.5.

Table 11 Effect on Tobacco Use Prevalence in 2009 if dual use is increased

		Never Smoker	Current Smokers	Former Users	THS Users	Dual Users
Male	**Business Case**	**43.89**	**18.92**	**29.08**	**7.56**	**0.55**
	Slight Increase in Dual Use	43.89	19.82	28.76	6.08	1.44
	Extremes Increase in Dual Use	43.89	20.98	28.62	2.33	4.17
Female	**Business Case**	**52.52**	**15.75**	**25.20**	**6.10**	**0.44**
	Slight Increase in Dual Use	52.52	16.56	24.98	4.76	1.19
	Extremes Increase in Dual Use	52.52	17.75	24.36	1.93	3.45

Note: percentages presented in this table are percentage of the adult population, not percentage of the smoking population.

Alternative Assumption 2 – The THS uptake targets are not met in the targeted timelines (17% of the smoking population is using THS within 10 years). Instead it takes closer to 20 years to reach this level of market uptake.

In this alternative, THS is in the market for 10 years but there is approximately 10% THS use in the smoking population (males: 8.3% THS use plus 1.7% dual use; females: 7.6% THS use plus 1.3% dual use). After 20 years on the market THS use reaches levels of approximately 16% of the smoking population (including almost 2% dual use). In this alternative, the dual use is similar to the Business Case, however the THS use is 3.6% lower in the male population and 3.8% lower in the female population (Table 12).

Again, as with the previous alternative, there is very little impact on initiation or cessation rates, and therefore there are no real changes in the prevalence of never smokers or former users. Because the reduction in THS use is replaced by an increase in cigarette smoking, the prevalence of cigarette smokers is higher under this alternative.

Since the relative exposure for cigarette smoking (f-value = 1.0) is higher than for THS use (f-value = 0.1-0.3), and there is an increased proportion of the population smoking cigarettes, this alternative results in fewer lives saved due to the introduction of THS than was seen for the Business Case. Despite this reduction, we still see 40,562 to 51, 798 lives saved, which is

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still a significant improvement at the population level and can be compared to the 57,456 lives that would have been save if THS users had switched to cessation

Table 12 Effect on Tobacco Use Prevalence if Objective met after 20 years

		Never Smoker	Current Smokers	Former Users	THS Users	Dual Users
Male	**Business Case**	**43.89**	**18.92**	**29.08**	**7.56**	**0.55**
	Decreased Uptake of THS	43.89	22.95	28.79	3.91	0.46
Female	**Business Case**	**52.52**	**15.75**	**25.20**	**6.10**	**0.44**
	Decreased Uptake of THS	52.5253.62	19.04	24.80	3.25	0.39

Note: percentages presented in this table are percentage of the adult population, not percentage of the smoking population.

Alternative Assumption 3 – The THS uptake targets are exceeded within the targeted timelines (17% of the smoking population is using THS within 10 years), instead the level of market uptake is doubled.

In this alternative, THS users makes up over 50% of the smoking population 20 years after launching the product. At the full adult population level, this results in 13.1% THS use plus 1.6% dual use in the male population and 11.5% THS use plus 1.3% dual use in the female population (Table 13).

As with the previous alternatives, because there is very little impact on initiation or cessation rates, there is no real change in the prevalence of never smokers or former users. The change to the scenario only really impacts the prevalence of THS use (more than 6% increase in the population). This change comes directly from the population of cigarette smokers who, in this scenario, transition to THS (therefore resulting in a close to 6% decrease in the number of cigarette smokers).

This alternative results in a reduction in the overall relative exposure for the population as the relative exposure for THS use (f-value = 0.1-0.3) is less than that for cigarette smokers (f-value = 1), this alternative translates to more lives saved than currently predicted from the business forecast. This means between 134,728 and 175,534 lives saved (out of a maximum of 196,540 achievable if THS users had quit smoking) and represents an improvement of more than doubling of the number of lives saved compared to the ingoing Business Case assumptions.

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Table 13 Effect on Tobacco Use Prevalence if the Level of Market Uptake is Doubled

		Never Smoker	Current Smokers	Former Users	THS Users	Dual Users
Male	**Business Case**	**43.89**	**18.92**	**29.08**	**7.56**	**0.55**
	Exceed Targets	43.89	12.37	28.98	13.14	1.62
Female	**Business Case**	**52.52**	**15.75**	**25.20**	**6.10**	**0.44**
	Exceed Targets	52.52	10.36	24.32	11.49	1.31

Note: percentages presented in this table are percentage of the adult population, not percentage of the smoking population.

Changes in product use patterns affect the relative exposure, and hence the overall cumulative exposure of an individual. Whenever a significant portion of the population switch from a higher to a lower relative exposure product there is an improvement in population health, and the greater the reduction in exposure the larger is the public health impact. As long as enough smokers switch to a lower risk product the population can withstand some increase in the prevalence of the higher risk products before the benefit from introducing the lower exposure product would be outweighed. Again a Post-Market surveillance program would need to be in place to monitor changes in smoking prevalence following the introduction of THS. This will allow both the manufacturers and regulators to understand the impact of marketing the product and take the necessary actions in real-time, to ensure that the impacts on the population are going to positive, thereby prevent changes in tobacco use before they are extreme enough to have a negative impact the population.

6.5.4.2. Changes in the Risk Assumptions

Note: the following simulation were conducted as part of a thorough and systematic simulation and sensitivity analysis. For this analysis the tobacco use prevalence is the same as discussed above for the Null Scenario, however for the THS Scenario the TTPs were different and for the Epidemiological Risk Component the assumption on the relative exposure was not based on the *f*-Factor modeling project (which resulted in f=0.3), but was an assumption for the purposes of testing the model (f=0.2). As this was the sensitivity analysis for the purpose of testing and understanding the model, the interpretation of the model itself was not impacted by these differences, however the outcomes are based on different assumptions and therefore the results cannot be compared directly with the scenarios above.

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The Half-Life of the Smoking Related Diseases

Using longer estimates of the half-life of disease reduces the estimated number of deaths saved as a result of introducing THS into the market.

The PHIM uses half-life estimates derived from a thorough literature review and fitting a negative exponential model to the data. For myocardial infarction and coronary heart disease, the half-lives used in the PHIM (Table 6) are longer than those indicated by the US Surgeon General's Report (2014), which claims that the risk falls rapidly following cessation, decreasing by about one-half in one year. For COPD and lung cancer, however, the PHIM estimates of half-life are consistent with those of the US Surgeon General's Report (2014).

Lung Cancer: "after 10 years of abstinence, the estimated risk of lung cancer is about 30–50% of the risk for continuing smokers; with further abstinence, the risk continues to decline"

COPD: "20 years after cessation, COPD risk still remains elevated in comparison with never smokers" – where our estimate of the half-life implies that 35.3% of the excess risk would still exist after 20 years of smoking cessation.

Had we used the half-life estimates suggested by the Surgeon General, instead of using our own estimates derived from comprehensive meta-analyses, it appears that the estimated reduction in deaths associated with the introduction of THS would have been greater than we estimated, particularly for heart disease.

The Relative Risk of Smoking Related Diseases

Increasing the estimated relative risk of disease increases the estimated reduction of deaths as a results of introducing THS. This was particularly true in male population, where using relative risk estimates from the US Surgeon General increased the estimated number of lives saved. This was due to changes in deaths from cardiovascular disease (IHD and stroke), but not from lung cancer and COPD, where the relationship was in the opposite direction.

Note that modifying the relative risk estimates affects the estimated mortality in both the Null Scenario and the THS Scenario, implying that for lung cancer and COPD, the rise in attributable deaths as RR increases is less than for the Null Scenario.

The Relative Exposures

Increasing relative exposure estimates for THS and/or dual use decreases the number of lives saved from the introduction of THS, whether these estimates are considered on their own or in combination. This is most clearly evident when the relative exposure are set to vary concomitantly, with dual users having relative exposure that is the average of cigarette smoking and THS. With this assumption, the decline in the number of saved cases is quite linear, and would extrapolate to approximately zero if relative exposure for THS was equal to that of smoking cigarettes (=1).

Note that relative exposure can only exceed 1 if it is assumed that an individual increases their overall consumption (e.g., a value of 1.2 would be equivalent to an individual who smoked 20 cigarettes per day and, following introduction of the new product, also used 20 THS per day). Because these types of patterns of product use were not seen in the pre-market

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Perception and Behavior Assessment and Clinical Assessment programs, even when the THS were distributed within the study these types of patterns were not considered.

Zero Benefit Simulations

To try to determine which set(s) of assumptions would be able to eliminate the reduction in deaths associated with the introduction of THS into the market, we ran simulations focused on increasing the relative exposure of dual users, increasing the rate of re-initiation with tobacco products among former users, and decreasing the cessation rates from cigarettes, because these parameters have the largest effect on the mortality rate. First we determined what level each of the parameters would have to change on their own to eliminate the risk reductions associated with the introduction of THS, then we examined different combinations of the three.

While it is clear that in theory the effects from the introduction of THS in the market can be reduced and in extreme product use scenarios, even eliminated, whether or not such scenarios are likely to occur in the market is open to question, and one that would have to be monitored in the post-market setting. From this simulation exercise, we were able to develop a variety of combinations of the parameters that could eliminate the beneficial effects from the introduction of THS (Table 14). The scenarios presented below show that the positive effects of the introduction of THS on the population health are present until the assumptions on the relative exposure for dual use reach about 1.5, and are combined with increased initiation (40-50% increase in initiation compared to the Basic Case) and decreased cessation (15-18% reduction in cessation compared to the Basic Case). However, based on the product use data that we have to date these alternative situations are fairly extreme (a 50% to 70% increase in exposure compared to smoking cigarettes) and considered to be unrealistic.

Table 14 Alternative Situations Considered in the Simulation Exercise (f=0.2) to determine the Zero Effect Point

	Parameters varied			Drops in deaths	
Alternative	Relative Exposure for Dual Use	Re-initiation Rate	Rate of smoking cessation	Males	Females
Basic Case[1]	0.60	Basic	Basic	35206	16403
1	0.82	x1.1	x0.964	27486	8303
2	1.04	x1.2	x0.928	18402	2123
3	1.26	x1.3	x0.892	7984	-3433
4	1.48	x1.4	x0.856	-5838	-8284
5	1.70	x1.5	x0.820	-14022	-13139

[1] the Basic Case is not the same as the Business Case and the full set of assumptions for these simulations are as defined in Section 7.4 “PHIM Simulations and Sensitivity Analysis Report

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6.5.5. Discussion

The PHIM described above differs slightly from the model that was initially described (Weitkunat 2015). In the THS Scenario, we now allow for five categories of tobacco use, not just four, by also considering the possibility that there will be individuals who use THS in combination with cigarettes (dual users). The method of estimating relative risks from the individual tobacco use histories is based on the negative exponential model, and has been described in detail (Lee 2015a). In simpler applications, such as cessation or reduction in dose, the formulae we used are the same as described in that publication. However, the formulae we used when an individual makes multiple changes in exposure (see Section 6.5.3.2) are not those described in Lee 2015a, which proved to produce rather implausible time patterns of relative risk in some situations. Though the predictions of the model we used here require testing based on data from a large study involving extensive information on changes in tobacco use over time, such data are currently not available to us.

Some features of the modelling approach deserve additional comment

- We only account for smoking cigarettes and/or using THS in the model, and do not specifically account for other forms of tobacco use or nicotine consumption. Smokeless tobacco and nicotine replacement therapy were not included, as these products are believed to have little or no effect on risk of the diseases studied. Ignoring e-cigarettes may also not have a big impact on the model outcomes if claims (Nutt 2014) that any health effects are less than 5% of those from cigarettes are correct. Ignoring cigar and pipe smoking may seem more relevant. However if the prevalence of the use of e-cigarettes continues to increase, it will be important to expand the model to account for this tobacco use behavior. In the model these are lumped together with cigarette smoking therefore our methods effectively assume that cigar and pipe smoking carry the same risk as cigarette smoking, as the initial smoking status of the populations followed is based on the prevalence of smoking rather than smoking only cigarettes. Had we allocated initial smoking status based on estimates of prevalence of cigarette smoking, we would instead have effectively assumed that cigar and pipe smokers have the same risk as never smokers, which would clearly be inaccurate. The problem, of course, is that extending the tobacco groups to include pipe and cigar smokers (and possibly also cigarette smokers with differing consumption levels) would require estimation of a huge number of transition probabilities, which would be difficult or impossible to estimate reliably.
- Also we do not account for environmental tobacco smoke exposure, where we showed earlier (Weitkunat 2015) that, whether or not the MRTP reduces the risk from ETS exposure would have little effect on the estimated drop in mortality associated with MRTP introduction.
- In the absence of reliable available estimates on relative risk and half-lives for all the diseases associated with smoking, we have limited attention to the four major smoking-associated diseases. We estimated earlier (Weitkunat 2015) that overall estimates of deaths saved due to the introduction of THS would have to be increased about 50% to give an estimate for all smoking-related diseases combined.

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- Our estimates of deaths saved may be in error if those who switch from cigarette smoking to THS use tend to be atypical in some ways (e.g., having a duration of smoking markedly different from those who do not switch) or change their distribution of other risk factors (e.g., their degree of alcohol consumption).
- Probably more relevant is that our analyses have limited attention to 20 years follow-up, particularly if the introduction of THS has an effect on the initiation of tobacco use by adolescents and young men and women. While the increase in prevalence would be clear after 20 years, any effect on mortality would be minimal, as the great majority of the additional tobacco users would be less than 50 years old.

The FDA MRTP Draft Guidance (FDA 2012) highlights seven population segments and exposure patterns that should be considered when submitting an application for a new MRTP. The PHIM considers all but two of these. One that is not considered is the segment which relates to environmental tobacco smoke exposure, already discussed above. The other is the segment which relates to use of the MRTP rather than an FDA approved cessation medication. This is not considered as the PHIM does not consider switching to products other than cigarettes or THS. In theory, one could use the PHIM, replacing dual use with a tobacco cessation medication scenario (and an appropriate relative exposure). However more research would have to be done to determine transition rates to and from these products.

Despite these reservations we believe that the results summarized here provide insight into the extent to which the THS introduction might affect the distribution of tobacco use and the number of deaths associated with tobacco, as well as clarifying those assumptions most critical to the predictions.

6.5.6. Conclusion

In accordance with the MRTP draft guidance we have developed, implemented, validated, applied, and explored a comprehensive dynamic simulation model which aims to assess the potential impact that marketing THS may have on the health of the population as a whole with respect to tobacco-related diseases. The work related to the population health impact model (PHIM) commenced years before the draft guidance was issued, and included conceptual work as well as population demographic, smoking behavior and risk data collection, analysis, and integration. The rationale for developing the PHIM is that, while a large body of original product-specific primary empirical data has been collected throughout years of research at various levels (ranging from aerosol chemistry to clinical studies on disease risk markers), the evidence so obtained – while serving as a foundation for health-risk assessment – cannot by itself directly quantify health risks. Whereas, as detailed in previous sections of Module 6, the available original data coherently indicate a substantially reduced *likelihood* of contracting smoking-related diseases upon switching from cigarettes to THS, and even indicate similarity to quitting tobacco use altogether, it is not possible to empirically quantify the reduction in disease *incidence* (or mortality) rates (risks) themselves related to that switch, even at the individual level. Such empirical risk quantification is only possible once the product has been used by a sufficient number of individuals over a period of time sufficiently long to cover the induction period of chronic smoking-related diseases, i.e., only through post market epidemiological studies.

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Short of the possibility of empirical risk quantification, the objective of the PHIM development was to be able to assess the potential population-level mortality impact of the policy of marketing THS in a specific population, i.e. in the US in this context, by making use of data available prior to market launch. In essence, model-based health impact assessment addresses the "what if THS was marketed" question in a relative manner, i.e., through comparison of scenarios. Indeed, such comparisons are the essence of the health impact analyses described throughout Module 6. At the product level, the comparisons include those of the effects of THS-exposure against the effects relating to continued cigarette smoking on the one hand and of quitting all tobacco use on the other. At the behavioral level, the comparisons ultimately aim at assessing actual levels of THS use against that of existing tobacco products. In essence, the PHIM-based evaluation is based on comparison of the actual 1990-2010 US population mortality burden due to cigarette smoking with an estimate of the mortality burden over the same period had THS been marketed. Thus, the comparison is between factual mortality (with THS not being available in the past) and counterfactual mortality (assuming THS availability in the past) over the same 20 year period and in the same population and context. This allows assessment of the specific public health effect of only introducing THS, counter to the historical facts, over the simulation period, all other things being equal. While the PHIM approach is technically capable of predicting future mortality, the approach used avoids assumptions about future trends in any number of influences, known and unknown.

The main rationale behind the comparison of simulations over historical periods is that while the resulting estimates may differ in magnitude from the actual future effects when THS is actually marketed, the patterns of estimates so obtained (under varying assumptions regarding modeling variables, including tobacco-use transition rates and product-specific risk modification factors) can be compared and assessed against each other under maximal protection from those unknown and uncertain influences that may affect future predictions (e.g., overall trends in mortality, or in factors affecting these trends, like economic prosperity). In the absence of reliable epidemiological risk estimates for disease incidence for less prevalent smoking-related health outcomes, we have limited attention to mortality from the four cigarette smoking-related chronic diseases that are most relevant to public health: lung cancer, ischemic heart disease, stroke, and chronic obstructive pulmonary disease.

While the key objective, when building a PHIM to assess the effects of introducing THS into the US market, was to minimize uncertainty due to unknown future influences on mortality, another major objective was to minimize the number of assumptions required, and to present as transparently as possible those which cannot be avoided. In order to achieve this, a large number of modeling approaches were dismissed upfront. A number of decisions were made early on when building the PHIM: 1. Generally accepted epidemiological concepts (including attributable risk) should be used; 2. Comprehensive and publicly available population data should be used, both on the prevalence of cigarette smoking and on risks (compared to never smoking) relating to cigarette smoking and cessation; 3. Comprehensive empirical evidence should be used to estimate unknown parameters (including the product-specific risk modification factor); 4. A quality management system and validation program covering all model structures, algorithms and processes of model implementation should be implemented and executed; 5. All methodological and implementation-related details should be

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comprehensively laid out for the scientific community to review. These would include publishing the underlying data and estimates (including the disease-specific excess relative risk estimates related to cigarette smoking, and their decreasing time functions after cessation), as well as details of the model development and architecture, and also the modeling results (including findings from sensitivity analyses). Also, the simulator would be made accessible to external scientists for purposes of replication, as well as extension of modeling scope and applications (including impact estimation for other populations).

The sex- and age-specific smoking transition rates were derived from published collections of US and international smoking statistics data and from individual large-scale survey data by applying assumptions relating to the age-specific transition patterns between smoking groups. One conclusion from our work is that predictions of the current and former smoking prevalence of the US population during the 1990-2010 period, based on these transition rate estimates, were in good agreement with data from the International Smoking Statistics database. In the age groups up to 54 years the annual differences were generally below 5% over the 20 year prediction period. In addition to predicting the secular trend in actual US smoking prevalence, the Null scenario (in which THS is assumed not to be marketed) also delivered disease-specific estimates of deaths attributable to smoking (for the four diseases considered). Another conclusion was that these estimates, both combined and individually, were reasonably well in line with those presented in available authoritative sources, including the 2014 Surgeon General's report. While the latter reported higher numbers for COPD than those predicted by the PHIM, the difference was explained by the higher relative risk estimates used by the Surgeon General (which stemmed mainly from one US cohort study) compared to those used by the PHIM, which were based on comprehensive meta-analyses. The reliability of the PHIM predictions was assessed through repeated runs over multiple simulation samples representative of the 1990 US population with regard to sex, age, smoking status and age of cessation of former smokers; the standard errors of the smoking prevalence estimates were below 1% of the point estimates and although somewhat greater for the estimated drop in numbers of deaths, single runs based on a simulation sample of 10,000 individuals were found to be sufficiently accurate to be relied on.

Both regarding smoking prevalence and smoking-related mortality impact, the closeness of the model-based predictions to actual epidemiological and authoritative statistics provides a solid basis for assessing the impact of THS introduction at the beginning of the simulation period (the THS scenario). Thus, the resulting population health impact estimates can be trusted with regard to the model specification, reliability and functioning, rendering them essentially dependent only on the soundness of the specific assumptions made under the THS scenario. Where these assumptions are reasonable, the predictions appear likely to correctly reflect the population health impact, relative to the Null scenario.

Instead of there being three monthly age-specific tobacco use transition probabilities (TTPs) in the Null scenario, there are 15 in the THS scenario. Those used were based on initial estimates which were updated based on recent literature for the Null scenario, as well as on a set of specific constraints (described in Section 6.5.4.) which served to ensure comparability between the two scenarios. In the "business case analysis" the TTPs were designed to produce a breakdown of current tobacco use 10 years after THS introduction of approximately 83% CC smokers, 15% THS users and 2% dual users. In the "basic analysis",

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used in some detailed sensitivity analyses reported in detail separately in Section 7.4 "PHIM Simulation and Sensitivity Analysis Report", the breakdown was 84% CC smokers, 10% THS users and 6% dual users.

From changes in biomarker levels observed in clinical studies 90 days after switching from cigarettes to THS, a Bayesian modeling approach was used to derive both relative changes for these biomarkers and also the related posterior distribution of the THS-specific effective dose factor (Section 7.4, "f-value Sampling Report"). This was based on specific assumptions to account for lack of knowledge regarding the dose-response relationships of the biomarkers with disease incidence and mortality. The resultant THS-specific effective dose factor ranging from 0 to 0.3, and the associated effective dose factor ranging from 0.5 to 0.65 for dual use were used as inputs to the PHIM for the Business Case analysis, enabling estimation of the reduction in lives lost by introducing THS over the 20 year simulation period. In the basic analysis, the effective dose factors used were 0.2 for THS and 0.6 for dual use.

Although the biomarkers measure in the clinical studies were carefully selected (as defined in Section 6.1.3) and can be expected to cover a large extent of the involved pathogenic pathways, not all of the resulting uncertainties and limitations can be accounted for. Since the model does not account for this uncertainty, the necessity and sufficiency of the set of biomarkers had to be quantified.

In addition to the distribution of the effective dose factor estimated from the Bayesian model, additional effective dose factors were evaluated to fully examine the impact of THS on the health of the population following the introduction of THS into the US market. These were $f = 0$ (the 'gold standard' effect of cessation), $f = 0.10$ (preserved effect of cessation on the biomarkers of risk), $f = 0.15$, (value where the probability mass function takes its maximum value), $f = 0.30$ (median of the f-value distribution).

In the Business Case analysis as detailed in Sections 6.5.3.6 and 6.5.4, the prevalence of former smokers was hardly affected by the introduction of THS. In men the prevalence of tobacco use was quite stable under the Business Case THS scenario, slightly changing from 25.6% in the beginning to 29.0% at the end of the 20 year simulation period, compared to 28.9% under the Null scenario. In women, the prevalence changed from 19.3% to 25.2% under the THS and to 25.0% under the Null scenario. At the end of the simulation interval, THS users accounted for more than 29% of male and female tobacco product users.

The Business Case analysis estimated that, over the 20 year simulation period, there would be a reduction in deaths in 30-79 year olds of 47,649 to 60,586 in men and 22,625 to 29,569 in women attributable to the introduction of THS at the beginning of the period. To put these figures into context, the maximal impact on lives saved can be considered when the effective dose related to the product would be equivalent to smoking cessation (effective dose = 0). In this case the maximal lives saved would be 67,151 in men and 33,083 in women.

The majority of these saved lives is accounted for by the reductions in ischemic heart disease-related mortality (almost 55% and 42% in men and women, respectively). This reflects the shorter half-lives for cardiovascular as compared to respiratory diseases, including lung cancer. It is evident that over a period of beyond 20 years, reduced mortality related to these diseases would increasingly contribute to the reduction in deaths. Partly this

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would be due to increasing THS use, and partly because substitution of cigarette smoking by THS use in younger age groups would largely manifest itself more than 20 years after THS introduction, due to the long latency of most of the adverse health impacts of smoking. Finally, as previously estimated (Section 6.5.3.1), the estimated numbers of lives saved would have to be increased by about 50% when accounting for all smoking-related diseases.

To put the reduction in mortality due to THS introduction into perspective, some extreme alternatives to the basic THS scenario of the sensitivity analyses (Section 7.4, "PHIM Simulation and Sensitivity Analysis Report") were considered. In that basic analysis, the number of deaths saved over the 20 year period was estimated as 35,206 in men and 16,403 in women. These numbers can be compared with those in the extreme alternative most beneficial to public health, where all smokers quit at the beginning of the simulation period, with no subsequent uptake of smoking (or other products). Here the number of lives saved was estimated as 605,321 in men and 333,027 in women. A very substantial reduction in mortality would also occur in an alternative where smoking is totally replaced by THS following its introduction, where the number of deaths saved would be 443,627 in men and 244,615 in women. In another alternative, the whole population (smokers and nonsmokers) initiates exclusive THS use at baseline and no further cigarette smoking, dual use or cessation occurs. In this alternative, which balances reductions in exposure for current cigarette smokers and shorter-term quitters, and increases in exposure for never smokers and longer-term quitters, the reductions in deaths would be less, 121,258 in men and 10,500 in women.

In the basic analysis (Section 7.4, "PHIM Simulation and Sensitivity Analysis Report"), extensive sensitivity analyses were conducted on the effect variations in initiation, re-initiation, cessation and switching might have on the prevalence of tobacco use. A number of conclusions were clear, which would also apply to the business case analysis. Thus, increasing initiation rates had stronger effects at younger age groups, while increasing re-initiation rates had more effects at older age groups. While changing the smoking cessation rate clearly affected tobacco use prevalence, even quite large changes in the cessation rates for THS and dual users had little effect. Varying switching rates between the three current tobacco use groups while affecting their distribution, little affected the prevalence of never and former users.

Effects of varying sensitivity analysis parameters on smoking-related mortality were generally in the same direction for each of the diseases and overall. Changes in mortality reductions resulting from variations in relative risks and half-lives were, as expected, clearly evident. The largest variations in mortality reduction resulted from varying the effective dose factor of THS, while varying the dual use exposure factor had a moderate effect. Generally estimated reductions in mortality were approximately proportional to the reduction in the factor. Thus, for example, the 70% reduction implied by an effective dose factor of 0.3, would predict about twice the reduction in deaths associated with a 35% reduction in dose (to 0.65).

Increasing switching to THS in one sensitivity analysis or from cigarette smoking in another sensitivity analysis, both had far more effect than did other switches (which changed the individual's exposure less). Even a very large increase in the transition rates from THS and dual use to cigarette smoking would not eliminate completely the estimated drop in deaths

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associated with THS introduction. Increased numbers of deaths in the THS scenario, compared to the Null scenario, could theoretically occur if cigarette smoking cessation were eliminated or drastically reduced, or if re-initiation rates were very substantially increased.

There were three situations where the mortality benefit associated with THS introduction might be eliminated – if there are fairly significant changes in the rates of cessation from cigarettes (decrease), initiation or re-initiation (increased), and if there is a substantial increase in consumption among dual users. Zero benefit analyses suggested that even if all three situations occurred, the extent of change required would be unlikely to occur in practice.

In summary, by applying the model described above, an overall assessment was undertaken of the effect that the product's introduction to the US market might have on tobacco product use and on tobacco-related mortality, both disease-specific and overall. The methods used take into account various relevant possibilities: dual use of THS and cigarettes, non-smokers initiating with THS, and THS users switching back to cigarettes. They also allow for a range of possibilities to be compared, for example cigarette smokers switching to THS rather than cessation.

The simulation results demonstrated reduced cigarette smoking compared to the Null scenario. Mortality was markedly reduced, both for tobacco-related diseases combined and for the major specific diseases. Additionally, the population health benefit of the THS compared to the NULL scenario was robust over a range of situations, both when compared to the business case THS scenario or the basic THS scenario used to conduct a wide range of sensitivity analyses. The simulation results were found to be robust in sensitivity analyses increasing transition rates into tobacco use, reducing transition rates into non tobacco use, reducing product-specific risk reduction factor estimates, and varying relative risk and half-life estimates within reasonable ranges, individually and in various combinations. Generally, the effects of parameter variations on reductions in deaths were in the same direction for all four diseases studied. Only under quite improbable parameter constellations was the THS-associated mortality reduction eliminated, as shown in "zero-benefit" analyses. It would require the introduction of THS to lead to a substantial increase in re-initiation of cigarette smoking or a substantial decrease in smoking cessation, for the THS-related reduction in mortality not to occur. Overall, based on the modeling results and scenario specifications, introducing THS into the US population appears to lead to a sizeable public health benefit in terms of reduced cigarette smoking and tobacco-related mortality. Variation in the model parameter estimates within reasonable ranges would not materially change these conclusions.

In the sensitivity analysis where it was assumed the prevalence of THS use could reach levels that are double that of the forecast, meaning that THS users make up 50% of the smoking population within 20 years of marketing the product, 134,728 to 175,534 lives could be saved (out of a maximum of 196,540 achievable if THS users had instead quit smoking). From the full extent of the simulations and sensitivity analyses it becomes obvious that there are three key prevalence related factors to achieve a maximum public health impact in terms of reducing smoking related mortality: maximizing the number of smokers switching to THS, minimizing the number of dual users, and accelerating the adoption process to maximize the excess relative risk reduction distribution.

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