A SCIENTIFIC FRAMEWORK FOR ASSESSING THE RISK PROFILE OF NGPs RELATIVE TO SMOKING

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Introduction

It is widely known that cigarette smoking causes diseases including cardiovascular disease, lung disease and cancer. Novel tobacco products, such as tobacco-heating products (THPs), snus and electronic cigarettes (ECs), hold great potential for reducing the harms associated with tobacco use. Health related claims on these novel products such as 'reduced exposure' and 'reduced risk' could be substantiated using a weight of evidence approach based on a comprehensive scientific assessment. The US Food and Drug Administration (FDA), has provided draft guidance outlining a framework to assess novel products as Modified Risk Tobacco Products (MRTP).

ECs deliver a vapour which is considerably less toxic than cigarette smoke due to reductions in exposure to chemical toxicant.[1] This has been supported by an independent scientific expert panel[2] which was recently endorsed by both Public Health England and the UK Royal College of Physicians.[3,4]

THPs comprise electronic devices that heat tobacco, typically to temperatures lower than 350ºC, rather than combusting it. Due to the absence of combustion, significantly fewer chemical toxicants are formed but nicotine is still released into the inhaled aerosol. There has been less public health and academic research on the properties of THPs compared to ECs, however, in-house assessments of the chemicals found in the aerosol from a novel THP (glo) revealed significant reductions in levels of many chemical toxicants when compared to those found in conventional cigarette (CC) smoke.[5,6]

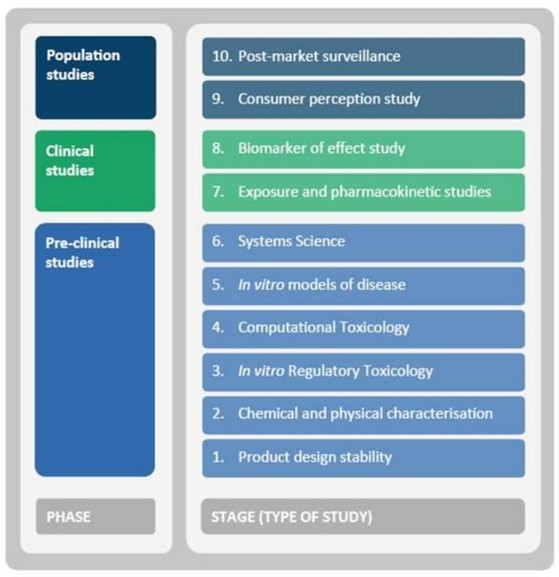

Figure 1 The approach used to assess NGPs

NGP Scientific Assessment

The approach used to assess NGPs is shown in Figure 1 comprises 3 main stages: Pre-Clinical Studies, Clinical Studies and Population Studies.[7]

Pre-clinical studies

The first stage involves Pre-clinical studies which includes assessment of the emissions from the glo THP. As shown in Figure 2, this shows substantial reductions in the levels of known cigarette smoke toxicants as listed by the WHO, Health Canada and the US FDA.[6] Figure 3 also shows substantial reductions in environmental emissions from glo when compared to cigarettes when used in a controlled environment.[8] These studies show that the particle concentrations from glo comply with WHO outdoor air quality standards.

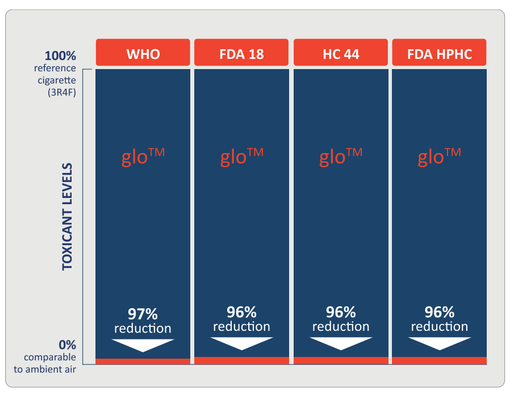

Figure 2. glo emissions relevant to regulatory lists were reduced by around 96–97%, relative to a scientific reference cigarette 3R4F

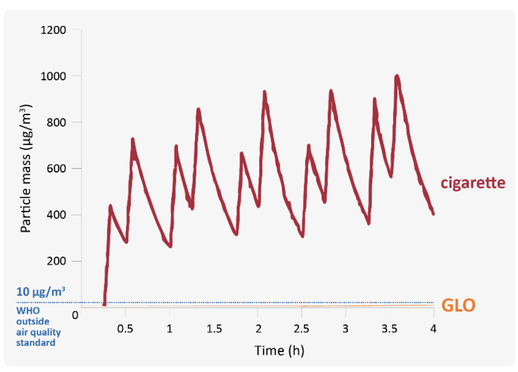

Figure 3. Social consideration: glo has less of an impact on environmental emissions relative to smoking

This stage also includes a combination of ***in vitro* regulatory and 21st Century toxicology.** Cigarette smoke was positive for all regulatory toxicological endpoints (mutagenicity, cytotoxicity, and tumour promotion),[9] whereas the emissions from glo did not produce a response in any of the tests, except the cytotoxicity assay, in which the response was only 3% of that compared to cigarette smoke.[10]

For *in vitro m*odels of disease, oxidative stress, CVD, COPD and Carcinogenesis models have shown reduced responses when exposed to glo when compared to CCs. Figure 4 shows the decreased response, in a COPD model using a systems biology approach. This study used Mucilair 3D lung tissue to investigate the changes in gene expression when exposed to glo compared to exposure to a CC.[11]

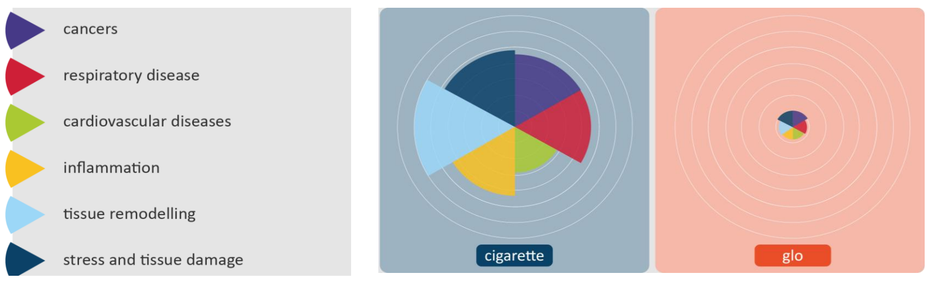

Figure 4. 3D cellular system (Mucilair) exposed to glo heated tobacco vapour and 3R4F cigarette smoke

Clinical Studies

Clinical studies on exposure are used as part of the second phase of the assessment programme. One such study was carried out in two sites in Japan (ISCTRN14301360 / UMIN000024988). The aim of this study was to determine whether reductions in machine yields for glo translate into a lowering of toxicant exposure, by measuring biomarkers of exposure (BoE) in a clinical confinement study.

Figure 5 below shows the results of a 7 day study where subjects smoked CCs for the first 2 days as a baseline period. They were then randomised to either continue to use CCs, the glo THP, or stop use of tobacco products completely for 5 days.[12,13]

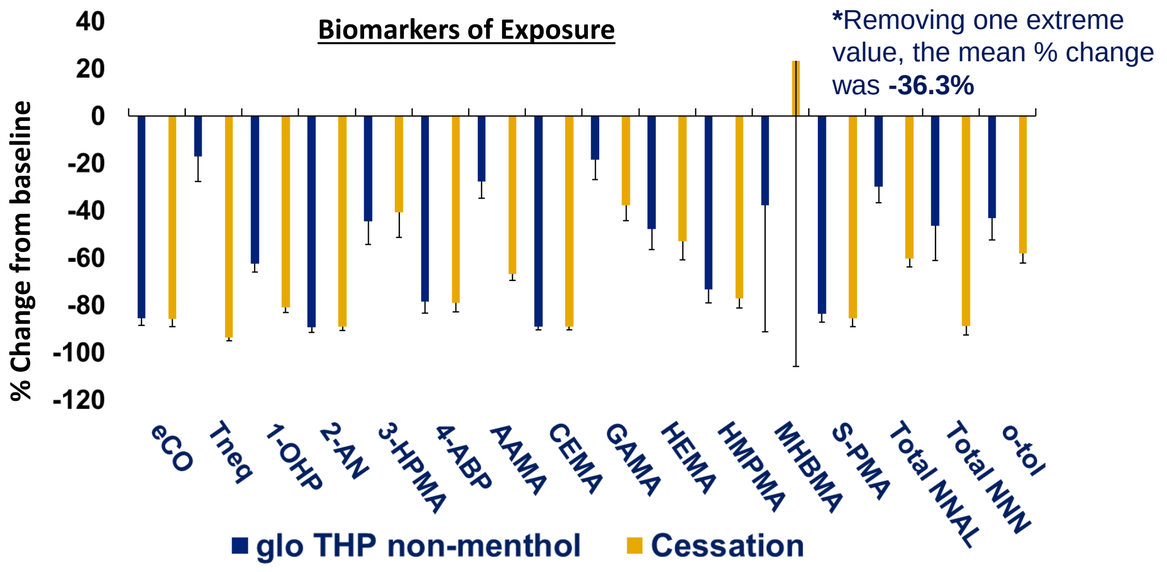

Figure 5. BoE Mean percent change from baseline at Day7

Biomarker Results – Within group comparisons

All urinary and exhaled BoE assessed following the switch from a CC to either a non-menthol variant of the glo THP, or to cessation were substantially and significantly decreased from baseline on Day 7 ($p < 0.05$). Figure 5 shows the arithmetic mean of all subjects' percentage change from baseline at Day 7, for each BoE assessed.

In addition, we have embarked on a clinical study investigating individual risk using Biomarkers of Effect to assess individual risk (ISRCTN81075760). This study will investigate health effect indicators when smokers switch to using glo.

Population Studies

Population studies incorporate consumer perception studies, use behaviour and post market surveillance (PMS). PMS will include passive surveillance which relies on data reported spontaneously by consumers and healthcare professionals, and active surveillance data collected through intervention and epidemiological studies and population wide surveillance.

The output from these studies will be used to model the population effect of switching to NGPs on morbidity and mortality as compared to using other products or quitting use of tobacco products.

Conclusion

glo is a novel THP which heats tobacco to around 240ºC, much lower than the combustion temperatures of >900ºC in CCs. As glo heats and does not burn tobacco, it produces a simpler aerosol than cigarette smoke and substantially (96 to 97%) reduced levels of toxicants.

This simpler aerosol elicits substantially reduced or no responses in regulatory and 21st Century toxicology and biological assays. Furthermore, when smokers switch from CC to glo, their levels of BoEs are reduced, in many cases to a similar level as cessation of tobacco products.

Longer term studies will assess if reduction in toxicant emissions and exposure leads to a reduction in individual and population risk.

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Disclosure

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Objective and Methods: A clinical study with 150 subjects was conducted to investigate changes in exposure to selected smoke toxicants when smokers switched to using NGPs. The study comprised of a 2-day baseline phase and a five day exposure phase, followed by a pharmacokinetic (PK) phase on the last day to investigate nicotine uptake. During the baseline phase all subjects smoked combustible cigarettes. This was followed by the exposure phase with the subjects randomised into groups where they either continued to smoke the combustible cigarettes, switched to using a NGPs, or abstained from any tobacco or nicotine product use, for five days. In these phases of the study 24-hour urine samples were collected for analyses of a range of BoE, and exhaled Carbon monoxide (eCO) was also measured daily. Finally, a PK phase was conducted with all subjects excluding the abstinence group. This comprised of a single use of the subjects' assigned product, with blood samples taken before, during and after product use for nicotine analysis.

Results: Levels of urinary BoE and eCO showed reductions of 25.5 to 93.1% in subjects who switched to an NGP for 5 days, and reductions of 69.3 to 95.5% in the levels in subjects who abstained from any tobacco or nicotine use for 5 days. These data show that UK smokers experience reductions in levels of exposure to the selected smoke toxicants when switched to a THP.

Conclusion: This data, supports our recently published framework which includes use of pre-clinical, clinical and population studies as a weight of evidence to assess the reduced risk potential of NGPs at the individual and population level. Longer term BoE and Biomarker of Biological Effect studies will be required demonstrate if these reductions in exposure are sustained, and if this translates into reductions in smoking-related health risks in subjects who switch to NGPs.

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